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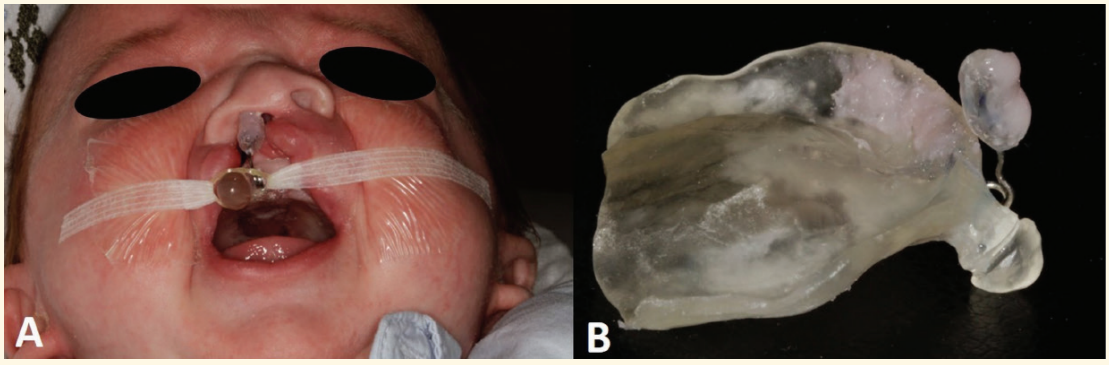

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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

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Editorial

Dear Journal of Pediatric Research Readers,

We are so proud and happy to welcome you to the first issue of The Journal of Pediatric Research in 2022.

This issue consists of 16 valuable studies of which 15 are research articles and 1 is a case report from different disciplines. The first research we present evaluates the oximetry-derived perfusion index in neonatal brachial plexus injury. We hope that you will be interested in reading the studies that evaluate the anxiety and related factors in parents about COVID-19 for children, the effect of diagnostic disease activity index on current myocardial function in pediatric inflammatory bowel disease patients, relationship between body mass index and dental health. Also this issue includes some different topics such as vaccination in children, home accidents in preschool children, vesicoureteral reflux, cleft lip and palate, salivary secretory IgA levels, asthma, congenital hypothyroidism, cervical lymphadenitis, fetal MRI-based tissue analysis and Watson's Model of Human Care Theory.

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We would like to thank all the editorial board, reviewers, authors and Galenos Publishing House for their efforts in creating this issue. We look forward to seeing your valuable scientific contributions in our coming issues.

Best wishes,
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Original Article

Alterations of Oximetry-Derived Perfusion Index in Neonatal Brachial Plexus Injury

Emre Dincer[1], Sevilay Topçuoğlu[1], Adil Umut Zübarioğlu[2], Güner Karatekin[1]

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ABSTRACT

Aim: As we know, the perfusion index (PI) increases in nerve blocked areas in regional anesthesia and this is used to predict successful intervention, we hypothesized that, in neonatal brachial plexus palsy (NBPP), PI may alter in the affected arm.

Materials and Methods: Prospectively, 11 patients with defective Moro reflex diagnosed as NBPP were included in this study. Their demographic data were collected and perfusion indices were measured from both the affected and non-affected limbs in the 24th hour of postnatal life. These measurements were statistically compared. The increased rate of PI was also calculated and the increment of PI in patients with and without clavicle fracture was compared.

Results: PI values were statistically higher in affected extremities compared to not-affected extremities (mean ± standard deviation, 2.47±0.74, 1.83±0.66 respectively, p=0.0003). There was no difference in patients with or without clavicle fracture.

Conclusion: In the future, PI may be evaluated as a prognostic factor for neurologic dysfunction in NBPP and be used as a predictor for early surgical intervention.

Keywords: Perfusion index, neonatal brachial plexus injury, newborn, peripheral nerve

Introduction

Neonatal brachial plexus palsy (NBPP) is uncommon with an incidence of 0.05-0.3% but it can cause permanent functional problems in up to 20-30% of affected individuals (1). Even though many risk factors have been widely investigated, no antepartum or intrapartum risk factors have been reported to be reliable except for shoulder dystocia. Consequently, NBPP is still regarded as a non-predictable situation (2).

Although NBPP is easily recognizable in infants with loss of Moro reflex or movements in the affected extremity, different diagnostic modalities such as electromyography, magnetic resonance imaging, and ultrasonography are needed to investigate its localization, severity, and prognosis. However, these diagnostic tools need highly qualified personnel, expensive equipment, and even anesthetic interventions ranging from sedation to general anesthesia, which may cause complications (3).

Perfusion index (PI) is a non-invasive marker of pulse strength provided by new generation pulse-oximeters. It is calculated as the ratio of pulsatile and non-pulsatile blood flow and is related to cardiac output and tissue vascular resistance (4). Previously, it has been suggested that lower values of PI values are associated with neonatal pathologies

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caused by hypoperfusion (5) and correlate with disease severity (6).

Given its efficacy, the use of PI has been investigated in different conditions such as the screening for congenital heart diseases (7), patent ductus arteriosus (8), and tissue perfusion after red blood cell transfusions (9), and it has been reported to be an effective parameter.

Recent studies in adults have reported that PI, measured on the extremities after central and peripheral nerve blocks, increased due to vasodilation as a result of the cessation of alpha-adrenergic stimuli during regional anesthesia (10).

PI is an easy, fast, and user-independent measurement. We hypothesized that PI values may be higher on the affected extremity due to the cessation of α-adrenergic stimuli as a result of nerve injury in NBPP.

Materials and Methods

This prospective observatory study was conducted in a tertiary Maternity and Children's Training and Research Hospital between January 2016 and July 2017. Local Ethics Committee approval was received from University of Health Sciences Turkey, İstanbul Zeynep Kamil Women and Children Diseases Training and Research Hospital (approval no: 136, date: 24.06.2016) and written informed consent was obtained from all patients. Babies with defective Moro reflex in one limb or "waiter's tip" posture diagnosed with NBPP were included in the study. Those babies who had a limited range of movement (thought to be affected in utero or by other musculoskeletal problems), cardiovascular or respiratory impairment, birth asphyxia (pH <7.1 or base excess >12), sepsis, or congenital anomalies including congenital heart diseases were excluded from this study.

Those babies diagnosed with NBPP were evaluated via chest X-ray for clavicle fracture. On the 24th hour of postnatal life, the baby's oxygen saturation, heart rate, arterial pressures, and PI were recorded on both their right and left upper extremities.

Their demographic data such as gestational age, birth weight, maternal age and type of delivery, and usage of auxiliary birth instruments were recorded.

The values of the affected limb were compared with other extremity values. To test our main hypothesis that PI is higher in the arm with palsy, we used pairwise Student's t-test to identify if there was a difference between the affected and unaffected arms of the same patient. To explore further, if the fracture had a different impact rather than just brachial plexus injury, we calculated the PI difference ratios between the affected and unaffected sides. Following this, we compared these ratios between the patient groups with and without clavicle fracture again via Welch's two sample t-test. A two-sided p-value smaller than 0.05 was accepted as significant.

Results

Fifteen patients were diagnosed as NBPP during the study period and four of them were excluded from the study due to a diagnosis of birth asphyxia. The median gestational age was 40 weeks (Q1: 38 - Q3: 40 weeks) and the median birth weight was 4,050 grams (Q1: 3,810 - Q3: 4,360 grams) (Table I). In seven babies, NBPP was on the left side and in four patients, NBPP was on the right extremitie. In eight patients, there was a loss of Moro reflex and in three of the patients, Moro reflexes were weak. All babies had higher PI levels on the extremity with NBPP, independent of being right (preductal) or left (postductal). The clinical features and PI measurements of the patients are given in Table II. The PI measured on the side with palsy [mean ± standard deviation (SD): 2.47±0.74] was significantly higher than for the unaffected arm (1.83±0.66); [t(10)=5.25, p=0.0003]. The ratio of PI differences was not statistically different between the group with brachial plexus only (mean ± SD: 25.68±13.42) and the group with clavicle fracture (mean ± SD: 22.94±14.16); [t(8)=0.31, p=0.76].

Discussion

In this study, we hypothesized that the nerve injury in NBPP may cause vasodilatation in the affected arm of the neonate and this can be shown with PI measured by a pulse-oximeter. We found statistically significant increased PI values in the affected extremities of the neonates.

Table I. Demographic features of the patients

	Patients (n=11)
Gestational age (weeks)	40* (Q1-Q3; 38-40)
Birth weight (grams)	4050* (Q1-Q3; 3810-4360)
Gender (n)	Female: 4 (36%) Male: 7 (64%)
Delivery mode (n)	Vaginal: 10 (91%) Cesarean: 1 (9%)
Affected extremity (n)	Left: 7 (64%) Right: 4 (36)
Clavicle fracture (n)	6 (54%)

Values not normally distributed are given as median and quartile 1-3 and marked with*

Table II. Clinical features and perfusion index measurements of patients

	Gestational age	Birth weight	Affected limb	Moro reflex on affected side	Clavicle fracture	Perfusion index on affected extremity	Perfusion index on non-affected extremity
Baby 1	40	4440	Left	No	Yes	1.1	0.55
Baby 2	34	2670	Left	No	Yes	1.6	1.3
Baby 3	37	3730	Right	No	Yes	2.4	1.8
Baby 4	41	4050	Left	Weak	No	3.2	1.8
Baby 5	39	3890	Left	No	Yes	2.4	2.1
Baby 6	36	3140	Right	Weak	No	1.9	1.3
Baby 7	40	4350	Left	No	Yes	2.8	1.5
Baby 8	41	4290	Right	No	No	2.8	2.6
Baby 9	40	4320	Left	No	Yes	2.5	2.2
Baby 10	39	3980	Right	Weak	No	3.8	2.9
Baby 11	40	4120	Left	No	No	2.7	2.1

In previous studies, PI was widely investigated for detecting nerve blockage. Vasodilatation occurs in the nerve-blocked part of the body as a result of the cessation of α-adrenergic stimuli (10). As there is no parasympathetic innervation of arteries/arterioles, blockage of the related nerve results in a loss of sympathetic tone below the level of the blockage and so vasodilatation occurs. With respect to this mechanism, it was investigated whether PI can be used to determine nerve blockage in regional anesthesia and if it is useful in different anesthesia modalities, such as infraclavicular and supraclavicular brachial plexus (11-13).

PI has been shown to be an effective tool for evaluating perfusion (4). Studies about PI have shown that PI values are correlated with superior vena cava flow, which reflects the cerebral blood flow (14) and also with left ventricle output (15). Lower values of PI give information about hypoperfusion, so it can be used in screening for congenital heart diseases (5), detecting patent ductus arteriosus (8), or grading the severity of illness in neonates (6,8). It is also reported that red blood cell transfusions provide increased PI (9) and surfactant treatment improves PI values (16).

PI can be affected by patent ductus arteriosus and studies have shown that in the first three days of life, PI values are lower in the left hand (postductal) than in the right hand (preductal) of the neonate (17). In our study, even though postductal PI levels (the left extremity) were expected to be lower than preductal PI levels (the right extremity) at the 24th hour of life, it was observed that even if NBPP is on the left extremity of the neonate, PI levels are higher than in the unaffected extremity.

On the other hand, as aforementioned, PI has been used in evaluating the severity of neonatal illness (6) and has been correlated with cardiac output (15). However, in the light of our findings, in cases of NBPP, monitoring the neonate from the affected extremity may show higher levels of PI on pulse-oximeter. This situation may lead to issues with fluid replacement or inotrope therapies so it may be logical to consider measurements taken from the unaffected arm for treatment plans.

NBPP is still a problem in neonatal medicine, causing functional problems in one-fourth of affected neonates. Even though NBPP can be easily diagnosed via physical examination after birth, further studies need to be done to clarify the condition. The gold standard for the evaluation of the NBPP is electro-diagnostic studies. These studies have been shown to be superior to imaging studies regarding localization and severity. However, when it comes to the issue of determining prognosis or predicting the need for microsurgery, no single imaging study has been shown to be sufficient (1,2,5,18). In addition to diagnostic studies, the presence of Horner syndrome or lower scores on the "Active Movement Scale" are predictors for early microsurgical intervention (19). Due to all this ongoing controversy, a combination of more parameters is helpful in the evaluation of NBPP. To evaluate the correlation of prognosis and increase in PI levels compared to the unaffected extremity, it was planned to follow-up the neonates in our study for three years. However, only three of the babies were brought to follow-up and it was not possible to calculate the correlation of increase in PI with prognosis. Pleasingly, all three of these patients had no disability in three years of follow-up. In future studies, we think that evaluating PI

after the third day of life may eliminate the effect of ductus arteriosus in the left arm.

Study Limitations

One limitation of our study is that our sample size was small. Although the number of patients was small, we found significantly higher levels of PI in the affected limbs of the patients. Future studies are needed to evaluate the duration of PI alteration and, its correlation with other diagnostic studies, and its usefulness in long-term follow-up.

Conclusion

In conclusion, PI levels are higher in the affected extremities of newborns with NBPP compared to the unaffected side but this finding needs to be studied to determine whether it has a correlation with prognosis and whether it can be used as a predictor for early microsurgical intervention. In the future, this finding may be combined with other diagnostic modalities if further studies are carried out.

Ethics

Ethics Committee Approval: Local Ethics Committee approval was received from University of Health Sciences Turkey, İstanbul Zeynep Kamil Women and Children Diseases Training and Research Hospital (approval no: 136, date: 24.06.2016).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Extrenally and internally peer-reviewed.

Authorship Contributions

Design: E.D., S.T., Data Collection or Processing: E.D., Analysis or Interpretation: S.T., G.K., Literature Search: E.D., A.U.Z., G.K., Writing: A.U.Z.

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References

1. Smith BW, Daunter AK, Yang LJ, Wilson TJ. An Update on the Management of Neonatal Brachial Plexus Palsy-Replacing Old Paradigms: A Review. JAMA Pediatr 2018; 172:585-91. https://doi.org/10.1001/jamapediatrics.2018.0124
2. Yang LJ. Neonatal brachial plexus palsy--management and prognostic factors Semin Perinatol 2014; 38:222-34.
3. Selcen D. Neonatal brachial plexus palsy. UpToDate, Inc. https://www.uptodate.com/contents/neonatal-brachial-plexus-palsy. Access date, December, 2020.
4. Piasek CZ, Van Bel F, Sola A. Perfusion index in newborn infants: a noninvasive tool for neonatal monitoring. Acta Paediatr 2014; 103:468-73.
5. Granelli AD, Ostman-Smith I. Noninvasive peripheral perfusion index as a possible tool for screening for critical left heart obstruction. Acta Paediatr 2007; 96:1455-9.
6. De Felice C, Latini G, Vacca P, Kopotic RJ. The pulse oximeter perfusion index as a predictor for high illness severity in neonates. Eur J Pediatr 2002; 161:561-2.
7. Siefkes H, Kair L, Tancredi DJ, et al. Oxygen Saturation and Perfusion Index-Based Enhanced Critical Congenital Heart Disease Screening. Am J Perinatol 2020; 37:158-65.
8. Nitzan I, Hammerman C, Fink D, Nitzan M, Koppel R, Bromiker R. The effect of patent ductus arteriosus on pre-ductal and post-ductal perfusion index in preterm neonates. Physiol Meas 2018; 20;39:075006.
9. Ibonia KT, Bada HS, Westgate PM, et al. Blood transfusions in preterm infants: changes on perfusion index and intermittent hypoxemia. Transfusion 2018; 58:2538-44.
10. Abdelhamid B, Emam M, Mostafa M, et al. The ability of perfusion index to detect segmental ulnar nerve sparing after supraclavicular nerve block. J Clin Monit Comput 2020; 34:1185-91.
11. inosar Y, Weiniger CF, Meroz Y, et al. Pulse oximeter perfusion index as an early indicator of sympathectomy after epidural anesthesia. Acta Anaesthesiol Scand 2009; 53:1018-26.
12. Abdelnasser A, Abdelhamid B, Elsonbaty A, Hasanin A, Rady A. Predicting successful supraclavicular brachial plexus block using pulse oximeter perfusion index. Br J Anaesth 2017; 119:276-80.
13. Kus A, Gurkan Y, Gormus SK, Solak M, Toker K. Usefulness of perfusion index to detect the effect of brachial plexus block. J Clin Monit Comput 2013; 27:325-8.
14. Takahashi S, Kakiuchi S, Nanba Y, Tsukamoto K, Nakamura T, Ito Y. The perfusion index derived from a pulse oximeter for predicting low superior vena cava flow in very low birth weight infants. J Perinatol 2010; 30:265-9.
15. Janaillac M, Beausoleil TP, Barrington KJ, et al. Correlations between near-infrared spectroscopy, perfusion index, and cardiac outputs in extremely preterm infants in the first 72 h of life. Eur J Pediatr 2018; 177:541-50.
16. Karadag N, Dilli D, Zenciroglu A, Aydin B, Beken S, Okumus N. Perfusion index variability in preterm infants treated with two different natural surfactants for respiratory distress syndrome. Am J Perinatol 2014; 31:1015-22.
17. Hakan N, Dilli D, Zenciroglu A, Aydin M, Okumus N. Reference values of perfusion indices in hemodynamically stable newborns during the early neonatal period. Eur J Pediatr 2014; 173:597-602.
18. Pitt M. Why wait 3 months before doing electromyography in obstetric brachial plexus lesions? Challenging the norm. Dev Med Child Neurol 2012; 54:682. https://doi.org/10.1111/j.1469-8749.2012.04326.x.
19. Andersen J, Watt J, Olson J,Van Aerde J. Perinatal brachial plexus palsy. Paediatr Child Health 2006; 11:93-100.

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Original Article

Anxiety and Related Factors in Parents About Coronavirus Disease-2019 for Children

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ABSTRACT

Aim: The aim of study was to determine the anxiety and related factors in parents about new Coronavirus disease-2019 (COVID-19).

Materials and Methods: The sample of the descriptive study consisted of 494 parents with children aged 0-18. The data were collected during April-May 2020 with tools that were prepared via Google Docs, an online study. The link to the questionnaires was shared via social media. The volunteers were agreed to participate in the survey.

Results: In the study, 94.5% of the parents participating are mothers, 69.5% are between the ages of 31-40 and 59.6% have one child. 31.8% of the parents stated that they worked during the COVID-19 pandemic, 90.3% applied social isolation or quarantine. The most frequent feeling that 83.6% of the parents was concern/anxiety, 69.0% used kitchen activities such as cooking and baking cakes as coping mechanisms, 68.4% used games, and painting activities with children.

Conclusion: In this study, it was determined that parents' anxiety levels were mild. It is recommended that social and health initiatives be created to prevent and alleviate the psychosocial effects of the pandemic, and to develop programs that will reduce parents' anxiety.

Keywords: COVID-19, pandemic, anxiety, parent, children

Introduction

Coronavirus disease-2019 (COVID-19) was identified as a disease which caused respiratory problems in December 2019 (1). This virus has a high and rapid contagiousness. It is transmitted from person to person (2). The World Health Organization (WHO) declared a coronavirus to be a pandemic on March 11th, 2020, and named this disease 2019-new coronavirus (2019-nCoV) (3,4). In Turkey, COVID-19 started to be seen as of March 19, 2020. The WHO recommended that millions of people "stay home and socially isolated to avoid" COVID-19 transmission (5). The Ministry of Health in Turkey has also launched a stay-at-home campaign with the motto "Life Fits into Home" immediately after the incidents began to appear in our country. In this context, the whole community started to stay at home except for mandatory needs (6). The effects of infectious diseases-related outbreaks and social isolation on community mental health were included in many studies (7-10). It was stated that such outbreaks could cause psychological situations. These can include stress, depression, fear, and anxiety (10,11).

In China, the first country affected by coronavirus, people were reported to show signs of stress, depression, and anxiety (12). Especially in those people who were in quarantine, fear, irritability, sadness, and feelings of guilt are found to be

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common negative emotions during this process (13). No study investigating the effects of the COVID-19 pandemic on the child and family were found in the literature. In a simple study, it was stated that families face stress factors such as commuting to work, bringing home viruses, and meeting their children's increased educational and care needs (14). Mothers and fathers should pay attention to their children's health and illnesses. Besides this, they have to deal with some of the uncertainties surrounding their family during COVID-19 isolation (15). Nurses, as well as families, have important roles and responsibilities in the protection and development of children, family, and community health (16). Also, nurses working in the field of paediatric nursing, family health nursing or public health nursing should have a responsibility for the management of the health of the family.

It is thought that the global COVID-19 outbreak will lead to deep psychological effects on families. Evidence-based strategies should be developed to reduce any negative psychological effects, psychiatric symptoms, or anxiety during the epidemic. Determining the anxiety levels and their related factors experienced by children who are one of the risk groups in infectious diseases, and therefore their families is important for better management of the situation. This study was carried out to identify the anxiety and related factors of parents associated with COVID-19.

Materials and Methods

This study has a descriptive design. The data was collected with an online survey during April and May 2020. The increase in the number of people using the Internet means that researchers have the opportunity to recruit participants from different backgrounds and different geographical regions that would not otherwise be possible (17). As it helps to reach the hard-to-reach segments of the general population by taking advantage of this feature of the Internet, also with the effect of the pandemic, the link for the questionnaires was shared via social networking sites such as Facebook, Twitter, Instagram, blogs, and forums.

The focus of the research was parents who have children between 0-18 years old, and also use social media and agreed to participate in the research. Since the number of elements in the universe is unknown, the number of samples was calculated with the formula n=t2pq/d2 (n=number of individuals to be sampled, t=1.96, p=0.50, q=050, d=0.05). According to this formula, the sample size was determined to be at least 385 (95% confidence interval in the calculation, the α value for the significance level is taken to be 0.05) (18). The number of parents included in the study was 498. Four parents who were not voluntary or who answered the questionnaire incomplete were excluded from the sample. The final sample was 494 parents.

Ethical Considerations

İzmir Bakırçay University, Non-Interventional Clinical Research Ethics Committee's written permission was taken (approval number: 21/21, approval date: 20.04.2020) to conduct the research.

The consents of the individuals were taken and then they were allowed to answer the questions after the consent.

Data Collection

The data collection tools were prepared using the Google Docs website. The study was conducted via the internet by means of social media. The social media tools were Facebook, Twitter, Instagram, blogs, and forums. The link for the questionnaires was distributed. The parents agreed to participate in the survey voluntarily.

Information Form Introducing the Child and Family: This is a form consisting of 8 questions including questions regarding the sociodemographic characteristics (age, gender, education, etc.) of the child and the family.

Questionnaire of Anxiety and Related Factors: There are 14 questions in this form that include anxiety factors related to coronavirus using the literature. The questions are about the symptoms of infectious diseases of children and other family members, social isolation, frequent feelings and coping skills of the parents, transportation preferences, and prevention methods (19-21).

Beck Anxiety Inventory: This twenty-one item Likert-type self-assessing scale was developed for anxiety by Beck in 1988. Likert (sum of degrees) provides type measurement. There are 4 options in each of the twenty-one symptom categories. Each item is given points between 0 and 3. The person is asked to assess the signs within the last week including the day of the questionnaire. Each symptom is evaluated as none, mild, moderate, or severe. The final score ranges from 0 to 63. The value of the score obtained from the scale shows the anxiety experienced by an individual. The Turkish language validity and reliability study of this scale were conducted. A result of 8-15 points shows mild anxiety, 16-25 shows moderate anxiety, and 26-63 shows severe anxiety. The Cronbach's alpha value for this scale was 0.93. The scale has two subgroups: "Subjective Anxiety" and "Somatic Symptoms". The subjective anxiety sub-dimension contains 13 items (1,4,5,7-11,14-17,19) and the score is between

0 and 39, the somatic symptoms sub-dimension is 8 items (2,3,6,12,13,18,20,21) and its score varies between 0 and 24 (22).

Statistical Analysis

Analysis of the data to be obtained from the research was carried out through the SPSS 26.0 package program. Descriptive statistics in the analysis of the research data were calculated as a number, percentage, average, and standard deviation. Additionally, Shapiro-Wilk/Kolmogorov-Smirnov (K-S) was carried out to determine the suitability of the data for normal distribution. If the data were suitable for normal distribution, Student's t-test, and One-Way ANOVA were used. If it was not suitable for normal distribution, the Mann-Whitney U test, and the Kruskal-Wallis test were used. Multiple linear regressions analysis was performed to determine the effect of various independent variables on the parents' anxiety level scores during the pandemic process. The results are presented as estimated β (Standard Error), p-values, and R2 value. The significance level was accepted as 0.05.

Validity, Reliability, and Rigour

The data instruments were selected by the researchers for their relevance to the study population. All data collection tools demonstrated reliability and validity for the Turkish population. The researchers received preliminary online education on Google Documents data collection. Interpretation of the survey content was also included in the education content to ensure the accuracy and consistency of the data.

Results

Almost all the 494 participants were mothers (94.5%) and the average age of 69.5% was between 31-40 years. Sixty-point nine percent of the participants were bachelor, 67.8% were working, 45.3% of the income assessment was in the medium level. 56.9% had 1 child and 37.3% had 2 children. The Beck Anxiety Inventory mean score of the participants was found to be 11.77±10.36 and this was considered as mild level. The Subjective Anxiety Subscale mean score was 8.93±7.47, and the Somatic symptoms subscale mean score was 2.84±3.42 (Table I).

Before the COVID-19 pandemic, 95.1% had never been to another country and 92.5% had never had any guests from another country. During the COVID-19 pandemic, 83.4% of the parents took care of their children themselves. 33.6% of participants had a family member with a chronic disease. A statistically significant difference was found between family members with and without chronic disease (p=0.003). The anxiety score average of those with chronic diseases in their family was found to be higher. 87.0% of participants did not have a condition requiring constant hospitalization (follow-up, treatment, etc.), only 8.5% had a person who was constantly taking medication within their family members. A statistically significant difference was found between those families with or without members taking regular medication (p=0.047). The anxiety score average for those with a member of their family taking medication was found to be higher. 75.3% of parents had not received training on infectious diseases and prevention methods. During the COVID-19 pandemic, 90.3% of participants implemented social isolation or quarantine (Table II).

Considering the participants' use of vehicles during the pandemic, 83.6% used their own private car for transportation. A statistically significant difference was found between those who used private cars and those who did not (p=0.042). The anxiety score average of those who used their private car was found to be lower. According to information source used to obtain developments regarding COVID-19, it was reported that 90.7% of participants preferred the internet/social media, while 56.5% preferred television/radio. While there was no significant difference between those who preferred the internet-social media as a news source about COVID-19 and those who did not (p=0.105), a difference was found between those who preferred TV-radio and those who did not (p<0.001). The anxiety score average of those who preferred TV-radio was found to be lower. In the first place was the difference between those participants who preferred using a mask (96.0%) and keeping a social-distance (1 meter) as a protection method. The most common emotions about COVID-19 experienced by parents were concern/anxiety (83.6%), fear (38.5%), sadness (33.8%), and difficulty in coping (21.7%). When the parents' anxiety scores were compared with emotions such as fear, sadness, and difficulty in coping, a statistically significant difference was found between those who experienced these feelings and those who did not (p<0.001, p<0.001, p<0.001). The anxiety score average of those parents who experienced these emotions was higher than those who did not. The parents' methods of coping during social isolation included kitchen activities (cooking, baking cake, etc.) (69.0%), games and painting with their children (68.4%), home cleaning (65.8%), and reading (40.5%). A statistically significant difference was found between those who preferred the reading method and those who did not (p=0.034). The

anxiety score average of those who preferred to read books was lower (Table III).

Several factors could be seen to significantly affect the anxiety scores of the parents in the pandemic when regression analysis was performed; the employment status of the parents, the presence of an individual with a chronic disease in the family, the person caring for the child during the pandemic process, the most common feelings of anxiety, fear, sadness, and difficulties in coping are included in these. These variables explain 23% of the anxiety level of the parents during the COVID-19 pandemic (Table IV).

Table I. Comparison of participants' socio-demographic characteristics and anxiety

Variables	**N**	**%**	**BAI**	**Significance**		
	494	**100**	**X ± SD**	**Mean Rank**	**Test**	**p-value**
Parents						
Mother	467	94.5	12.15±0.48	253.41	Z=-3,834	<0.001
Father	27	5.5	5.29±1.20	145.20		
Age						
19-30	58	11.7	13.01±1.43	264.12	χ^2=3,026	0.220
31-40	343	69.5	11.85±0.55	250.48		
41 and above	93	18.8	10.70±1.10	226.13		
Education						
First-secondary education	5	1.0	11.40±3.58	258.00	χ^2=0.650	0.885
High school	46	9.3	11.73±1.71	235.55		
Bachelor	301	60.9	12.03±0.60	251.05		
Graduate	142	28.8	11.25±0.80	243.47		
Profession						
Unemployed	55	11.1	11.41±1.25	247.79	χ^2=0.094	0.954
Health employee	20	4.0	10.75±2.10	237.95		
Other professional groups	419	84.9	11.87±0.51	247.92		
Working status						
Working	335	67.8	10.73±9.83	233.49	Z=-3,170	0.002
Not working	159	32.2	13.96±11.11	277.02		
Economic situation assessment						
Low level	104	21.1	14.52±1.21	276.01	χ^2=5,326	0.070
Intermediate level	224	45.3	11.25±0.66	241.39		
High level	166	33.6	10.75±0.70	237.88		
Number of children						
1	281	56.9	12.11±0.61	255.58	χ^2=3,512	0.173
2	187	37.8	11.03±0.77	232.50		
3 and above	26	5.3	12.76±1.84	268.04		
Beck Anxiety Inventory mean score	494	100.0	11.77±10.36	9.00 (0-53) Median (Min.-Max.)		
Subjective Anxiety Subscale mean score	494	100.0	8.93±7.47	7.00 (0-34) Median (Min.-Max.)		
Somatic Symptoms Subscale mean score	494	100.0	2.84±3.42	2.00 (0-19) Median (Min.-Max.)		

X: Average, SD: Standard deviation, BAI: Beck anxiety inventory, Min.: Minimum, Max.: Maximum

Discussion

It has been seen that there has been a rapid rise in the number of cases and deaths in the COVID-19 pandemic in the world. This situation has led to psychological effects such as stress, depression, and anxiety in people. Fear of uncertainty has been reported to cause negative behaviour (23). It was also emphasized with the proposal of WHO that the quarantine decisions and curfews made by most countries might increase stress, anxiety, and depression (13,24). It was found that the quarantine measures applied in the severe acute respiratory syndrome and Middle East respiratory syndrome (MERS) outbreaks were associated with psychosocial problems. These were depressive signs, post-traumatic stress, anxiety, stress, social isolation, loneliness, and stigma, and the most important determinants were the length of the quarantine and loss of income (25).

Also, insufficient and fake news about COVID-19 has led to increased anxiety and fear regarding the situation in this process (2). The WHO suggested that people should only receive news on COVID-19 from reliable sources. In this study, most of the participants used social media as their news source. However, the anxiety scores of those who preferred TV news as their news source were found to be lower.

In a study conducted on 1,210 people in China examining the psychological effects of coronavirus, it was reported that 28.8% of the people in the community showed moderate or severe anxiety, 16.5% showed moderate or severe depression, and 8.1% showed moderate or severe stress (12). A study in Canada found that one-third of 1,354 Canadian adults were concerned about the coronavirus and 7% were "very worried" (26). In Spain, while the signs of depression, stress, and anxiety were low in the early stages of the

Table II. Comparison of participants' COVID-19 characteristics and anxiety scores

Variables	N	%	BAI	Significance		
	494	100	X ± SD	Mean Rank	Test	p-value
Going to another country before the COVID-19 pandemic						
Yes	24	4.9	8.79±2.07	194.15	Z=-1,879	0.060
No	470	95.1	11.92±047	250.22		
Guest arrival from another country before COVID-19 pandemic						
Yes	37	7.5	12.21±1.41	266.09	Z=-0.825	0.410
No	457	92.5	11.74±0.49	245.99		
Caregiver for children in the COVID-19 pandemic						
Mother/Father	412	83.4	11.98±0.51	250.90	χ^2=2,982	0.394
Caregiver	28	5.7	9.21±1.49	220.57		
Grandma/grandfather	46	9.3	11.00±1.67	226.08		
Other (family elders, relatives, etc.)	8	1.6	14.50±3.84	290.00		
Presence of chronic disease in family members (Diabetes, heart disease, kidney disease, etc.)						
Yes	166	33.6	13.73±0.86	273.92	Z=-2,930	0.003
No	328	66.4	10.78±0.54	234.13		
Presence of a condition requiring constant hospitalization in family members (follow-up, treatment, etc.)						
Yes	64	13.0	13.25±1.46	263.64	Z=-0.971	0.332
No	430	87.0	11.55±0.48	245.10		
The presence of a person constantly taking medication in family members						
Yes	42	8.5	14.92±1.77	289.35	Z=-1,988	0.047
No	452	91.5	11.48±0.48	243.61		
Training status on infectious diseases and prevention methods						
Yes	122	24.7	10.87±0.98	228.80	Z=-1,670	0.095
No	372	75.3	12.07±0.52	253.63		
Social isolation or quarantine status in the COVID-19 pandemic						
Yes	446	90.3	11.86±0.48	250.16	Z=-1,265	0.206
No	48	9.7	11.00±1.74	222.77		

X: Average, SD: Standard deviation, BAI: Beck anxiety inventory, COVID-19: Coronavirus disease-2019

Table III. Comparison of participants' coping methods and problems during the pandemic and their anxiety scores

Variables		N	%	BAI	Significance		
		494	100	X ± SD	Mean Rank	Test	p-value
Type of transportation use							
Personal car	Yes No	413 81	83.6 16.4	11.27±0.49 11.93±1.28	241.73 276.93	Z=-2,032	0.042
Public transportation (bus, minibus)	Yes No	24 470	4.9 95.1	10.91±2.50 11.82±0.47	221.38 248.83	Z=-0.920	0.357
Taxi	Yes No	14 480	2.8 97.2	13.57±3.18 11.72±0.47	267.46 246.92	Z=-0.531	0.595
Other (bicycle, motorcycle, subway)	Yes No	12 482	2.4 97.6	12.08±3.37 11.76±0.47	239.75 247.69	Z=-0.191	0.849
The information source of developments regarding COVID-19							
Internet-social media	Yes No	448 46	90.7 9.3	11.87±0.47 10.80±1.81	250.83 215.09	Z=-1,619	0.105
Television-radio	Yes No	279 215	56.5 43.5	10.48±0.59 13.46±0.72	227.27 273.75	Z=-3,592	<0.001
Health professionals	Yes No	122 372	24.7 75.3	11.22±1.00 11.95±0.52	234.47 251.77	Z=-1,163	0.245
Other (newspaper, friend, neighbor)	Yes No	50 444	10.1 89.9	11.94±1.64 11.75±0.48	237.80 248.59	Z=-0.507	0.507
Preferred preventive measure							
Mask	Yes No	474 20	96.0 4.0	11.93±0.47 8.15±1.83	249.80 192.93	Z=-1,747	0.081
Distance (1 meter)	Yes No	445 49	90.1 9.9	11.90±0.49 10.63±1.40	249.44 229.88	Z=-0.912	0.362
Disinfectant	Yes No	270 224	54.7 45.3	11.94±0.61 11.57±0.71	253.34 240.46	Z=-1,000	0.317
Glove	Yes No	259 235	52.4 47.6	11.97±0.65 11.56±0.67	250.16 244.57	Z=-0.435	0.663
Cologne	Yes No	229 265	46.4 53.6	12.84±0.72 10.85±0.59	260.99 235.84	Z=-1,955	0.051
Other (soap, visor, napkin, cleaning water)	Yes No	15 479	3.0 97.0	12.40±2.36 11.75±0.47	266.47 246.91	Z=-0.523	0.601
The most common emotion about COVID-19							
Concern	Yes No	413 81	83.6 16.4	12.04±0.51 10.39±1.04	251.09 229.19	Z=-1,264	0.206
Fear	Yes No	190 304	38.5 61.5	16.10±0.84 9.07±0.48	305.05 211.53	Z=-7,092	<0.001
Sadness	Yes No	167 327	33.8 66.2	14.21±0.85 10.53±0.53	281.94 229.91	Z=-3,837	<0.001
Difficulty in coping	Yes No	107 387	21.7 78.3	19.08±1.12 9.75±0.45	343.80 220.87	Z=-7,893	<0.001
Other (communication difficulties, confusion, uncertainty, anger)	Yes No	38 456	7.7 92.3	12.92±1.70 11.68±0.48	262.38 246.26	Z=-0.670	0.503
Coping methods in social isolation							
Kitchen activities (food, cake, etc.)	Yes No	341 153	69.0 31.0	11.93±0.54 11.42±0.90	253.00 235.24	Z=-1.281	0.200

Table III. Continued

Variables		N	%	BAI	Significance		
		494	100	X ± SD	Mean rank	Test	p-value
Game and painting activities with children	Yes No	338 106	68.4 31.6	11.95±0.56 11.38±0.84	250.62 240.73	Z=-0.717	0.473
Home cleaning	Yes No	325 169	65.8 34.2	12.20±057 10.94±0.78	254.54 233.97	Z=-1,521	0.128
Reading	Yes No	200 294	40.5 59.5	10.67±0.70 12.52±0.61	230.99 258.73	Z=-2,123	0.034
Professional activities (working from home)	Yes No	159 335	32.2 67.8	11.13±0.76 12.08±0.58	241.64 250.28	Z=-0.629	0.529
Individual hobbies (guitar, stone painting, mandala, sports events)	Yes No	116 378	23.5 76.5	11.59±0.89 11.83±0.54	248.64 247.15	Z=-0.099	0.921

X: Average, SD: Standard deviation, BAI: Beck anxiety inventory, COVID-19: Coronavirus disease-2019

Table IV. The effect of some parents-related variables on their anxiety scores (n=494)

Dependent variable: the anxiety level				
Independent variables: working status, chronic disease, caregiver, most common emotions	**B**	**SE**	**β**	**p***
Constant	**41,542**	**3,605**	-	-
Working status (Working Not working)	1,335	0.943	0.060	0.157
Presence of chronic disease in family members (Yes No)	-2,226	0.875	-0.102	0.011
Caregiver for children in the COVID-19 pandemic (Mother/Father Caregiver Grandma/grandfather Other)	0.039	0.341	0.005	0.910
The most common emotion about COVID-19 Concern (Yes No)	-1,640	1,117	-0.059	0.143
The most common emotion about COVID-19 Fear (Yes No)	-4,517	0.906	-0.212	<0.001
The most common emotion about COVID-19 Sadness (Yes No)	-2,666	0.905	-0.122	0.003
The most common emotion about COVID-19 Difficulty in coping (Yes No)	-7,992	1.036	-0.318	<0.001
R	0.484			
R^2	0.234			
F	21,230			
p*	**<0.001**			

*p<0.05.
B: Fixed value/regression load (Sabit değer/regresyon yükü), SE: Standard error, Beta: Standardized regression load (Standartlaştırılmış regresyon yükü), COVID-19: Coronavirus Disease-2019

COVID-19 pandemic, these symptoms levels increased after quarantine (27). Restrictive prevention and isolation can be confusing, and not well understood for children (15). It is considered common for children and their families to experience anxiety, panic, and fear, both for themselves and their families, friends, loved ones, and relatives (28). In this study, the most common emotions experienced by parents in the process of COVID-19 were concern/anxiety (83.6%), fear (38.5%), sadness (33.8%), and difficulty in coping (21.7%). In studies on this subject, it has been stated that the features seen in individuals in the process of COVID-19 are often paranoia, sadness, fear, anxiety, anger, and depression (13,29,30). In this study, 90.3% of parents stayed at home (social isolation or quarantine). In a study on global

epidemics, it was stated that people who were isolated for 2 weeks because they were in contact with MERS showed anxiety signs and anger such as fear, isolation, and social withdrawal (31). In addition to isolation or quarantine, anxiety levels were found to be high in both parents and their children during the pandemic in cases of chronic illness and long-term regular medication.

If parents experience situations such as anxiety, fear, sadness, and difficulty in coping, it can negatively affect their children's health. In this situation, families are advised to talk to their children about how they keep them safe and to try to manage any stress they feel (19). In this study, the coping mechanism of the parents during their stay at home to manage their anxiety for themselves included kitchen activities (cooking, baking cake, etc.) (69.0%), games and painting activities with their children (68.4%), home cleaning (65.8%), and reading (40.5%). The anxiety score average of those parents who preferred reading was lower. In another study, similarly, it was stated that children prefer activities such as physical entertainment or reading during the epidemic process (28). Additionally, it is recommended that parents teach their children hand-washing techniques or how to apply hand disinfectants and regularly wash any contacted surfaces with house cleaning materials so that the children and parents can cope with this process (19). In this study, it was found that parents preferred masks, social-distancing (1 meter), disinfectants, gloves, and cologne as first-line methods of protection. In another study, it was also found that parents attach importance to physical distancing especially in interpersonal relationships (29). Since diseases that are transmitted by the respiratory way require a specific intimacy between people, social-distancing reduces transmission (32). UNICEF has prepared a guide especially for those parents with small children during the COVID-19 period. This guide contains topics such as the importance of handwashing, the importance of not touching faces with dirty hands, the use of masks, keeping one meter social distance, and avoiding crowded environments (33).

Study Limitations

This study was cross-sectional and it had some limitations. The study particularly focused on those parents who used social media and the sample was limited only to those who used social media; therefore, homogeneity of the participants could not be achieved. Some parents may have limited internet access or not have had time due to their children.

Conclusion

In this study, it was found that the most common emotion experienced by the parents was fear, anxiety, sadness, and difficulty in coping and mild anxiety levels. It is important to research the psychological effects of international epidemics on populations and to create strategies for reducing negative psychological effects. It is recommended to develop programs to support parents during quarantine to prevent and alleviate the psychological effects of the pandemic by starting social and medical initiatives. As the COVID-19 pandemic affects the whole of society, it also affects children and their parents who are one of the risk groups by creating fear and anxiety. It is thought that planning studies, intervention programs, and training that will strengthen the mental health of their children can be effective in managing any negative effects. Nurses working in the field of paediatric nursing, family health nursing or public health nursing should have a responsibility in this part. It is recommended to conduct studies that can identify the causes of anxiety and stress in order to be prepared for situations such as epidemics that negatively affect children, families and society. In addition, studies which determine the problems faced by people during the quarantine process will be effective in examining this issue in depth.

Ethics

Ethics Committee Approval: İzmir Bakırçay University, Non-Interventional Clinical Research Ethics Committee's written permission was taken (approval number: 21/21, approval date: 20.04.2020) to conduct the research.

Informed Consent: The consents of the individuals were taken and then they were allowed to answer the questions after the consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.B.Y., A.K., M.G., Design: Ş.B.Y., A.K., M.G., Data Collection or Processing: Ş.B.Y., A.K., M.G., Analysis or Interpretation: Ş.B.Y., Writing: Ş.B.Y., A.K., M.G. Critical Revision: Ş.B.Y., A.K., M.G.

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References

1. Adhikari SP, Meng S, Wu YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control

of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infect Dis Poverty 2020; 9:29.

2. Li Y, Guo F, Cao Y, Li L, Guo Y. Insight into COVID-2019 for pediatricians. Pediatric Pulmonology 2020; 55:1-4.
3. WHO. Technical guidance, 2020a. 18 March 2020 archived at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it).
4. Mahase E. China coronavirus: WHO declares international emergency as death toll exceeds 200. BMJ 2020; 368:408.
5. Horton R. Offline: 2019-nCoV- "A desperate plea". Lancet 2020; 395:400.
6. Ministry of Health. Life Fits Home, 2020. (30 April 2020 archived at https://covid19bilgi.saglik.gov.tr/tr/videolar.html)
7. Ko CH, Yen CF, Yen JY, Yang MJ. Psychosocial impact among the public of the severe acute respiratory syndrome epidemic in Taiwan. Psychiatry Clin Neurosci 2006; 60:397-403.
8. Peng EY, Lee MB, Tsai ST, et al. Population-based post-crisis psychological distress: an example from the SARS outbreak in Taiwan. J Formos Med Assoc 2010; 109:524-32.
9. Taha SA, Matheson K, Anisman H. H1N1 was not all that scary: Uncertainty and stressor appraisals predict anxiety related to a coming viral threat. Stress Health 2014; 30:149-57.
10. Hawryluck L, Gold WL, Robinson S, Pogorski S, Galea S, Styra R. SARS Control and Psychological Effects of Quarantine, Toronto, Canada. Emerg Infect Dis 2004; 10:1206-12.
11. Shultz JM, Baingana F, Neria Y. The 2014 Ebola outbreak and mental health: current status and recommended response. JAMA 2015; 313:567-8.
12. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the ınitial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health 2020; 17:1729.
13. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. Lancet 2020; 395:912-20.
14. Coyne LW, Gould ER, Grimaldi M, Wilson KG, Baffuto G, Biglan A. First Things First: Parent Psychological Flexibility and Self-Compassion During COVID-19. Behav Anal Pract 2020; 14:1092-8.
15. Vessey JA, Betz CL. Everything old is new again: COVID-19 and public health. J Pediatr Nurs 2020; 52:7-8.
16. Fraser S, Grant J, Mannix T. The role and experience of child and family health nurses in developed countries: a review of the literature. Neonatal, Paediatric and Child Health Nursing 2014; 17:2-10.
17. Coulson N. Online Research Methods for Psychologists. Red Globe Press, 2015.
18. Qualtrics. Determining Sample Size: How to Ensure You Get the Correct Sample Size. (21 April 2020, archived at https://www.qualtrics.com/experience-management/research/determine-sample-size/)
19. Thompson LA, Rasmussen SA. What does the Coronavirus Disease 2019 (COVID-19) mean for families? JAMA Pediatr 2020; 174:628.
20. WHO. Technical guidance, 2020b. (18 March 2020, archived at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it Accessed)
21. WHO. Coronavirus disease Situation Report 58, 2020c. (18 March 2020, archived at https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200318-sitrep-58-covid-19.pdf?sfvrsn=20876712_2)
22. Ulusoy M. Sahin NH, Erkmen H. Turkish version of the Beck Anxiety Inventory: Psychometric Properties. Journal of Cognitive Psychotherapy 1998; 12:163-72.
23. Shigemura J, Ursano RJ, Morganstein JC, Kurosawa M, Benedek DM. Public responses to the novel 2019 coronavirus (2019-nCoV) in Japan: Mental health consequences and target populations. Psychiatry Clin Neurosci 2020; 74:281-2.
24. Cava MA, Fay KE, Beanlands HJ, McCay EA, Wignall R. The experience of quarantine for individuals affected by SARS in Toronto. Public Health Nurs 2005; 22:398-406.
25. Röhr S, Müller F, Jung F, Apfelbacher C, Seidler A, Riedel-Heller SG. Psychosocial impact of quarantine measures during serious coronavirus outbreaks: A rapid review. Psychiatr Prax 2020; 47:179-89.
26. Asmundson GJG, Taylor S. Chronophobia: Fear and the 2019-nCoV outbreak. J Anxiety Disord 2020; 70:102-96.
27. Ozamiz-Etxebarria N, Dosil-Santamaria M, Picaza-Gorrochategui M, Idoiaga-Mondragon N. Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain. Cad Saude Publica 2020; 36:e00054020
28. Jiao WY, Wang LN, Liu J, et al. Behavioral and Emotional Disorders in Children during the COVID-19. Epidemic. Journal Pediatr 2020; 221:264-6.
29. Kundu B, Bhowmik D. Societal impact of novel coronavirus (COVID-19 pandemic) in India. 2020. DOI: 10.31235/osf.io/vm5rz
30. Nicomedes CJC, Avila RMA. An Analysis on the Panic of Filipinos during COVID-19 Pandemic in the Philippines. Journal of Economic Studies 2020. DOI: 10.13140/RG.2.2.17355.54565.
31. Jeong H, Yim HW, Song YJ, et al. Mental health status of people isolated due to Middle East Respiratory Syndrome. Epidemiol Health 2016; 38:e2016048.
32. Wilder-Smith A, Freedman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the novel coronavirus (2019-nCoV) outbreak. J Travel Med 2020; 27:taa020. doi: 10.1093/jtm/taaa020
33. UNICEF. Coronavirus Explained to Parents of Young Children, 2020. (30 April 2020, archived at https://www.unicef.org/southafrica/media/2801/file/ZAF-COVID-19-explained-to-parents-of-young-children-2020-ENG.pdf)

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Original Article

Is Body Mass Index for-age Related with Dental Caries in Children?

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ABSTRACT

Aim: Nutrition has a significant impact on dental health. The aim of this study was to investigate the relationship between dental caries and body mass index (BMI)-for-age.

Materials and Methods: Four hundred and fifty-one children who were 5-14 years were included in this study. The children were examined according to dmft/DMFT indexes with mirror - sound and panoramic radiography. After taking weight and height measurements, the BMI-for-age calculation, age, weight and height status were entered into the World Health Organization AnthroPlus Software program in order to obtain a z-score for each child. The children were grouped according to their z-scores as Group 1: normal; Group 2: overweight; Group 3: fat/obese; Group 4: underweight; and Group 5: severely underweight. Data were analyzed using SPSS software 22, correlation, frequency and independent sample t-tests.

Results: The mean age of the children was 9.1±2.5 years. The mean DMFT/dmft values were 6.97±3.79. 55% of the children were of normal weight, 16.2% were overweight, 11.8% were fat/obese, 12.2% were underweight and 4.8% were severely underweight. In terms of DMFT/dmft, when the groups were compared, a statistically significant difference was found between Group 3 and Groups 1, 4 and 5 ($p<0.05$).

Conclusion: The risk of caries increased as the weight increased in the children participating in this study. Obesity can be considered as an important risk factor for dental health. Informing parents about children's poor eating habits can have an impact on dental health.

Keywords: Dental caries, body mass index by age, obesity

Introduction

Proper nutrition has a significant impact on oral and dental health as well as on physical and cognitive health (1,2). Dental caries are a multifactorial disease that is caused by cariogenic bacteria, a carbohydrate-rich diet and high host susceptibility (3-5).

Obesity and tooth decay have common and variable features such as diet and lifestyle (1). Being overweight and obesity are among the health problems that are increasing in our country as well as worldwide (6). Today, obesity, which is increasing rapidly in adults and adolescents, is called "obeziteus" in Latin and means "due to eating" (7). It is a multifactorial disease characterized by stored fat as a result of an increase in the amount of fatty and carbohydrate foods consumed resulting from having more calories entering the body than the number of calories expended (8). It is also known as an energy metabolism disorder that can cause physical and psychological problems (6,9). The main causes of obesity, defined by the World Health

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Organization (WHO) as a global epidemic, are considered to be environmental factors such as practical living conditions, immobility, eating habits, in addition to genetic and physical factors (7).

The nutritional habits of children are among the most important causes of both childhood obesity and dental caries. Some children who experience early tooth loss may face problems such as weight gain due to incomplete digestion resulting from a decrease in chewing function (1). Tooth loss and caries may also be associated with both obesity and weakness. Weight loss can be seen in children who have difficulty feeding due to early tooth loss and painful teeth. Severe dental caries can reduce the action of eating and thus cause weight loss (10).

Among the obesity criteria of the WHO is the body mass index (BMI), also called the Quetelet index. BMI is calculated by dividing an individual's body weight by the square of his/her height (BMI=kg/m^2). The classification of children and adolescents is different from adults and "z-score" values are used (4). As growth and development continues in children, body fat changes; therefore, the assessment of BMI in children and adolescents is made by BMI-for-age; those who are in the 5th percentile and below are considered as "underweight", those who are in the 85th percentile and above are at risk of being "overweight" and those who are in the 95th percentile and above are considered as "overweight" (11).

In many studies relating to obesity and dental caries, the relationship between BMI and caries in the child age group has been evaluated (2,10,12-14). García Pérez et al. (15) used BMI-for-age in their study and examined the relationship between the caries experience and obesity in Mexican 8-12 year-old school children. The aim of the current study was to investigate the relationship between dental caries and BMI-for-age (normal, overweight, obese, underweight and severely underweight) in a group of 5-14 year-old Turkish children. Secondly, it was hypothesized that the results obtained from evaluating caries with BMI-for-age might be different from results obtained using BMI.

Materials and Methods

According to the power analysis, the n value was calculated to be 451 with a confidence interval of α=0.05 and β=0.95. Those children between the ages of 5-14 who applied to the Department of Pedodontics in Erciyes University were included in this study. Ethics committee approval was received for this study from Erciyes University Faculty of Medicine (approval no: 2020/60, date: 29.01.2020).

Those patients with systemic diseases which may affect growth and development were excluded from this study. After obtaining consent forms from the patients and their parents stating that they want to participate in the study, the demographic information (age, gender, etc.) of the patients was recorded.

Study Design

The participants were asked to remove their shoes in order to record their body weight and height measurements; a Tanita® scale (Bc601 model) with integrated stadiometer was used to perform both measurements. The BMI-for-age calculation was made by entering the age, weight and height measurements into the WHO AnthroPlus Software program and the z-score was obtained. The children were grouped according to their z-scores as Group 1: normal, Group 2: overweight, Group 3: fat/obese, Group 4: underweight, and Group 5: severely underweight. The calculations of anthropometric evaluations were made by a nutritionist and dietetics specialist.

Intraoral examination was made after the teeth were air-dried by a research assistant dentist with the help of a mouth mirror and dental probe. The measurements were recorded by another dentist. According to the criteria determined by the WHO, the DMFT (decay, missing, and filled teeth) index was used to determine the number of caries in permanent teeth and the dmft index was used in primary teeth. The existing periapical and panoramic radiographs of the patients were used in the diagnosis of interface caries.

The data were analyzed by correlation, frequency and independent sample t-tests using the IBM SPSS Statistic (v.22) software.

Results

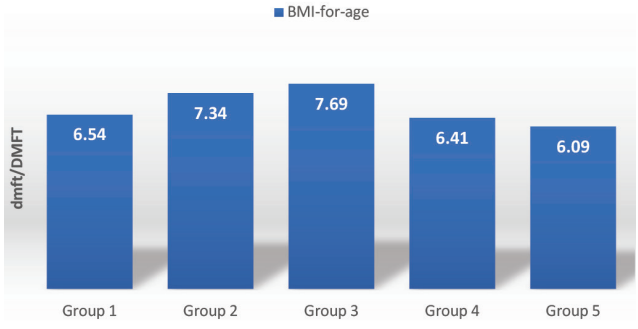
The average age of the children who participated in this study was 9.1±2.5 years. Of these, 52% (n=234) were female and 48% (n=217) were male. Average DMFT/dmft values were found to be 6.97±3.79. It was found that 425 of the children in the study group had at least 1 caries. The caries percentages of the females and males were 91% and 97%, respectively. There was no significant difference in the number of caries between the two groups (p>0.05). When the children were grouped according to their BMI-for-age values, 55% of them were found to be normal (n=248), 16.2% were overweight (n=73), 11.8% were obese (n=53), 12.2% were underweight, (n=55) and 4.8% were severely underweight (n=22). Overweight and obese participants constituted 24% of the group. 45% (n=24) of Group 3

were girls and 54% (n=29) were boys (Table I). There was no significant relationship between gender and obesity (p>0.05). In terms of the DMFT/dmft index, when groups were compared according to their BMI-for-age (Graph 1), no difference was observed between obese participants and overweight participants (p>0.05). A statistically significant difference was found between Group 3 and the other 3 groups (Group 1, Group 4 and Group 5) (p<0.05). There was no significant difference observed when the other groups were compared with each other (p>0.05). No relation was observed between the risk of caries and being underweight (p>0.05). The risk of caries increased as weight increased in those children who participated in this study.

Table I. The frequency and percentage distribution of children based on BMI-for-age

BMI-for-age		n	%
Group 1	Female	131	52.8
	Male	117	47.2
	Total	248	100
Group 2	Female	35	47.9
	Male	38	52.1
	Total	73	100
Group 3	Female	24	45.3
	Male	29	54.7
	Total	53	100
Group 4	Female	33	60
	Male	22	40
	Total	55	100
Group 5	Female	11	50
	Male	11	50
	Total	22	100

Group 1: Normal, Group 2: Overweight, Group 3: Fat/obese, Group 4: Underweight, Group 5: Severely underweight, BMI: Body mass index



Graph 1. Diagram showing mean DMFT/dmft among children with different body weights

Group 1: Normal, Group 2: Overweight, Group 3: Fat/obese, Group 4: Underweight, Group 5: Severely underweight *[a-b]Different letters denote the statistical differences (p<0.05)*

Discussion

In recent years, there has been an increase in overweight and obesity rates due to an increase in over-nutrition habits of children. It has also started to come into prominence in studies investigating the relationship between tooth decay and weight, which are both closely related to dietary habits (14,16,17).

Obesity and overweight status can be measured using the BMI. However, BMI is calculated by dividing body weight (kg) by the square of the height (m), and it does not take into account variable values such as age, gender, and body fat percentage (18). Since growth is on-going in children and adolescents, body fat is in the process of change; for this reason, the evaluation of BMI in children and adolescents according to age will give more accurate results. Therefore, in our study, the BMI-for-age calculation was made by obtaining z-scores by entering age, weight and height measurements into the AnthroPlus Software, as recommended by the WHO for children under the age of 18 years. In many studies, only obesity or severely underweight conditions were evaluated (10,15,19,20). In our study, not only obese and overweight children, but also underweight, severely underweight and normal children were included in the evaluation.

A study in Mexico found that approximately one-fifth of students were obese, and the proportion of overweight and obese children constituted 37.7%. of the whole group (15). In our study, 11.8% of the children who participated were found to be obese, and the overweight and obese groups together constituted 24%. Comparing these two studies, the lower values obtained in our study may stem from different eating habits within our country. We believe that it is possible to provide data to explain any differences by an evaluation of the nutritional habits of children by dietetic and nutritionist specialists.

Bafti et al. (8) found that tooth decay in the primary teeth of children was inversely proportional to an increase in their body weight. In another study, Benzian et al. (10) investigated the relationship between BMI and dental caries in underweight children and found a significant correlation between BMI and dental caries in low-weight children. On the other hand, Mitrakul et al. (19) and Dikshit et al. (14) argued that there was no significant relationship between dental caries and BMI.

In many studies, the risk of dental caries was found to be higher in overweight and obese children (21-23). Cheng et al. (24) showed that the frequency of dental caries among primary and secondary school children is related to gender, school type, region and BMI. They claimed that extensive studies are needed to confirm the findings of their study and to address existing oral health problems (24). The study conducted by Barrington et al. (25) focused on the incidence of the relationship between obesity and caries. However, they emphasized that sugar and carbohydrate consumption status are factors that should be evaluated primarily for both (25).

Karki et al. (16) declared that children with low or high BMI, regardless of their age, are at risk of developing caries. They emphasized that both underweight and overweight or obese children have common risk factors relating to their diet (16).

Another related study conducted by Willerhausen et al. (2) also found a significant relationship between being overweight and caries. According to the results of our study, a positive relationship was found between obesity and caries and these results support the findings of the study conducted by Willerhausen et al. (2).

In addition, in the study conducted by García Pérez et al. (15), in which BMI-for-age evaluations were used as in our study, it was reported that there was an inversely proportional relationship between obesity and caries as was also seen in other studies using BMI (8,10). However, it was emphasized that caries is a complex process including a contribution of various factors such as fluoride consumption, sugar intake, and brushing teeth, none of which should be ignored (18). In our results, there was no significant relationship between underweight children and the incidence of caries, which is in contrast to the results given by García Pérez et al. (15). We presume that this situation may be due to the low number of underweight children in our study group or to different eating habits among countries.

However, as mentioned in the results of some studies, explaining the relationship between caries and BMI by various factors such as poor eating habits, frequency and times of sugar consumption, malnutrition, frequency of brushing teeth, fluoride intake or a sedentary lifestyle is a complex process (26,27).

Study Limitations

One of the limitations of this study was that the sugar and carbohydrate consumption of children was not evaluated together with BMIs-for-age. The small sample size for severely underweight children was another limitation for our study.

Nkambule et al. (17) stated that the incidence of caries is associated with an availability of access to health services rather than to other factors. In our study, we tried to eliminate this parameter by means of a working group who could access health services in our clinic. However, it should not be forgotten that field studies may reveal different results.

Conclusion

Why this paper is important to pediatric dentists/ pediatricians:

- Within the limitations of this study, no relationship between the risk of caries and being underweight was found.

- Obesity was found to be an important risk factor for oral and dental health.

- Parents should be informed that their child's body-mass-index for age has an impact on oral and dental health.

Ethics

Ethics Committee Approval: This study was approved by the ethics committee of Erciyes University, Faculty of Medicine Clinical Research Ethics Committee (number: 2020/60, date: 29.01.2020).

Informed Consent: Informed consent was obtained from all of the parents included in the present study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept and Design: E.K., C.D., B.D., B.A., Data Collection or Processing: C.D., B.D., Analysis Interpretation: E.K., B.A., Drafting of Manuscript: E.K., C.D., B.D., B.A., Critical Revision: E.K.

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References

1. Hooley M, Skouteris H, Boganin C, Satur J, Kilpatrick N. Body mass index and dental caries in children and adolescents: a systematic review of literature published 2004 to 2011. Syst Rev 2012; 1:57.

2. Willerhausen B, Blettner M, Kasaj A, Hohenfellner K. Association between body mass index and dental health in 1,290 children of elementary schools in a German city. Clin Oral Investig 2007; 11:195-200.

3. Sheiham A, James WP. Diet and Dental Caries: The Pivotal Role of Free Sugars Reemphasized. J Dent Res 2015; 94:1341-7.

4. Pitts NB, Zero DT, Marsh PD, et al. Dental caries. Nat Rev Dis Primers 2017; 3:17030.

5. Hilgers KK, Kinane DE, Scheetz JP. Association between childhood obesity and smooth-surface caries in posterior teeth: a preliminary study. Pediatr Dent 2006; 28:23-8.

6. Lee EY, Yoon KH. Epidemic obesity in children and adolescents: risk factors and prevention. Front Med 2018; 12:658-66.

7. No authors listed. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000; 894:1-253.

8. Bafti LS, Hashemipour MA, Poureslami H, Hoseinian Z. Relationship between Body Mass Index and Tooth Decay in a Population of 3-6-Year-Old Children in Iran. Int J Dent 2015; 2015:126530.

9. Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. Int J Behav Nutr Phys Act 2017; 14:42.

10. Benzian H, Monse B, Heinrich-Weltzien R, Hobdell M, Mulder J, van Palenstein Helderman W. Untreated severe dental decay: a neglected determinant of low Body Mass Index in 12-year-old Filipino children. BMC Public Health 2011; 11:558.

11. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl 2006; 450:76-85.

12. Basha S, Mohamed RN, Swamy HS, Ramamurthy PH, Sexena V. Caries Incidence Among Obese Adolescents: A 3-year Prospective Study. Oral Health Prev Dent 2017; 15:65-71.

13. Cinar AB, Christensen LB, Hede B. Clustering of obesity and dental caries with lifestyle factors among Danish adolescents. Oral Health Prev Dent 2011; 9:123-30.

14. Dikshit P, Limbu S, Bhattarai R. Relationship of Body Mass Index with Dental Caries among Children attending Pediatric Dental Department in an Institute. JNMA J Nepal Med Assoc 2018; 56:582-6.

15. García Pérez A, Barrera Ortega CC, González-Aragón Pineda ÁE, Villanueva Gutiérrez T, Pérez Pérez NG, Calderon Uriostegui D. An inverse relationship between obesity and dental caries in Mexican schoolchildren: a cross-sectional study. Public Health 2020; 80:163-7.

16. Karki S, Päkkilä J, Ryhänen T, et al. Body mass index and dental caries experience in Nepalese schoolchildren. Community Dent Oral Epidemiol 2019; 47:346-57.

17. Nkambule NR, Madiba TK, Bhayat A. Dental Caries, Body Mass Index, and Diet among Learners at Selected Primary Schools in Pretoria, Gauteng Province, South Africa. J Contemp Dent Pract 2019; 20:1241-8.

18. Cantekin K, Gurbuz T, Demirbuga S, Demirci T, Duruk G. Dental caries and body mass index in a sample of 12-year-old eastern Turkish children. J Dent Sci 2012; 7:77-80.

19. Mitrakul K, Arunakul M, Asvanund Y, Laisirireoungrai T, Praneechotiros T, Tevavichulada P. Diet, Body Mass Index And Dental Caries Among Thai Children Aged 3 To 5 Years. Southeast Asian J Trop Med Public Health 2017; 48:466-72.

20. Serrano-Piña R, Aguilar-Ayala FJ, Scougall-Vilchis RJ, Trujillo-Güiza ML, Mendieta-Zerón H. Prevalence of Obesity in Elementary School Children and its Association with Dental Caries. Oral Health Prev Dent 2020; 18:35-42.

21. Costacurta M, Di Renzo L, Bianchi A, Fabiocchi F, De Lorenzo A, Docimo R. Obesity and dental caries in paediatric patients. A cross-sectional study. Eur J Paediatr Dent 2011; 12:112-6.

22. Gerdin EW, Angbratt M, Aronsson K, Eriksson E, Johansson I. Dental caries and body mass index by socio-economic status in Swedish children. Community Dent Oral Epidemiol 2008; 36:459-65.

23. Sharma A, Hegde AM. Relationship between body mass index, caries experience and dietary preferences in children. J Clin Pediatr Dent 2009; 34:49-52.

24. Cheng YH, Liao Y, Chen DY, Wang Y, Wu Y. Prevalence of dental caries and its association with body mass index among school-age children in Shenzhen, China. BMC Oral Health 2019; 19:270.

25. Barrington G, Khan S, Kent K, Brennan DS, Crocombe LA, Bettiol S. Obesity, dietary sugar and dental caries in Australian adults. Int Dent J 2019; 69:383-91.

26. Palacios C, Rivas-Tumanyan S, Morou-Bermúdez E, Colon AM, Torres RY, Elías-Boneta AR. Association between Type, Amount, and Pattern of Carbohydrate Consumption with Dental Caries in 12-Year-Olds in Puerto Rico. Caries Res 2016;50:560-70.

27. Trumbo PR, Rivers CR. Systematic review of the evidence for an association between sugar-sweetened beverage consumption and risk of obesity. Nutr Rev 2014; 72:566-74.

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Original Article

Is There Any Effect of Diagnostic Disease Activity Index on Current Myocardial Function in Pediatric Inflammatory Bowel Disease Patients?

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ABSTRACT

Aim: Inflammatory bowel disease (IBD): [Crohn's disease (CD) or ulcerative colitis (UC)] is characterised by chronic inflammation with multisystemic effects. Myocardial dysfunction may occur during active disease due to increased inflammation. The aim of our study is to evaluate the effect of disease activity index at diagnosis on myocardial functions in children with IBD in remission.

Materials and Methods: The study consisted of 34 IBD patients and 21 healty children. Patients were divided into two groups according to disease activity at the diagnosis as mild and severe disease activity. Conventional echocardiography and strain echocardiography was performed for all study patients.

Results: In IBD patients with severe disease activity at diagnosis, global longitudinal strain of left ventricle (GLLV), longitudinal strain (AP3) and (AP4) were lower than patients with mild disease activity at the diagnosis (p=0.043, p=0.032, p=0.028, respectively). Disease activity at the diagnosis was inversely correlated to ejection fraction (%), strain values of GLLV, left ventricle apical chamber (LVAP) 3, LVAP2 in UC patients. (p=0.047, p=0.016, p=0.029, p=0.011, respectively). Mitral E, DT was lower in IBD patients than control patients (p=0.05, p=0.04). Strain value of LVAP4 was lower in CD patients, than UC patients (p=0.046). Strain values of GLLV, LVAP3, LVAP4 was decreased in CD patients than control patients (p=0.046, p=0.046, p=0.048). Mitral E and desceleration time were found to be decreased in IBD patients than control patients (p=0.05, p=0.04 respectively).

Conclusion: Our study revealed that the severity of disease activity at diagnosis has long-term effects on myocardial functions.

Keywords: Inflammation, left ventricular function, strain echocardiography

Introduction

Inflammatory bowel disease (IBD): [Crohn's disease (CD) or ulcerative colitis (UC)] is the result of an immune response in individuals with genetic predisposition. It is thought that luminal antigens cause systemic immunoreaction due to increased intestinal permeability. Triggered systemic inflammation results in fibrosis and dysfunction in the extraintestinal organs (1,2). Inflammation has effects on

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cardiac structures either in an occult or overt manner. In acute exacerbation periods, pericarditis, myocarditis, arteritis, valvular regurgitation and tromboembolic events can be seen (3-5). Subtle myocardial involvement was shown in a few studies due to ongoing chronic low grade inflammation (6-8). We studied myocardial functions with conventional echocardiography and strain echocardiography, which gives more reliable information about global and segmental myocardial function. We investigated the effect of the severity of disease activity at the time of diagnosis on current myocardial functions by strain echocardiography. Patients in a remission period were chosen to exclude the effects of any increased inflammation of the active disease on myocardium.

Materials and Methods

Of the 42 IBD patients followed up in two different paediatric gastroenterology centres, 34 patients in remission were included in this study. Additionally, twenty-one healthy children were evaluated as a control group. The control group comprised patients referred to a paediatric gastroenterology clinic with non-specific abdominal pain with no systemic or cardiovascular disease. The diagnosis of 16 patients in the study group was CD and 18 of them were UC. The inclusion criteria of the study group was being in a remission period. IBD diagnosis was made based on clinical symptoms, radiological, endoscopic, and histopathological features according to the Montreal Classification and revised Porto Criteria (9,10). Paediatric CD activity index and paediatric UC activity index were recorded from the patients' medical records (11,12). The actual height, weight and blood pressure of all the patients were recorded. Body mass index (BMI) was obtained by means of the formula weight (kg)/ height^2 (m). Patients groups were established according to disease activity at the time of diagnosis as either mild or severe disease activity. There were no patients with moderate disease activity at the time of diagnosis. Written consent for the study was obtained from the parents of all the patients and this study was approved by the local ethics committee of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval no: 06, date: 29.06.2018).

Echocardiographic Protocols and Definitions

Echocardiographic evaluation was performed using a Philips Affiniti 50C (Release 2.0.2 3000 Minuteman Road Andover, MA 01810 USA) echocardiography machine and 8-4 Mhz transducer in all subjects. Left ventricular diameters and systolic functions were assessed by M-mode echocardiography at a parasternal long axis view. Pulsed wave Doppler was performed to determine the mitral inflow parameters, namely, mitral E velocity, mitral A velocity, interventricular contraction time and deceleration time (DT).

For strain analysis, standard 2D grayscale images of LV were performed. Apical 4-chamber, 3-chamber and 2-chamber (AP4, AP3 AP2, respectively) views were obtained for the longitudinal strain of LV as previously described (13). Circumferential strain was obtained by parasternal short-axis views at the mitral valve plane, papillary muscle plane and apical plane (SAXB, SAXM, SAXA, respectively).

Synchronized with continuous electrocardiography, five consecutive cardiac cycles were recorded with frame rate of 60 and 90 frames per second. At end-systole, seven segments for longitudinal strain and six segments for circumferential strain were assessed by tracing the endocardial border line manually. Global longitudinal strain was obtained from the apical four-three-two chamber views and circumferential strain was obtained from the basal, mid-cavity, apical short axis views using speckle-tracking echocardiography software package (QLAB advanced ultrasound quantification soft release 10.4).

Statistical Analysis

Twenty-two software package (IBM Corp., Armonk, NY, USA) was used for the analysis of the data. The Kolmogorov-Smirnov test was used to determine the distribution of normality. Data is expressed as mean ± standard deviation for variables; number and percentages (%) are given for categorical variables, Mann-Whitney U and Student's t-test were used for the comparison of groups, whichever being more appropriate. For the analysis of correlations, the Spearman rank correlation coefficient was used. Statistical significance was considered at a p-value <0.05.

Results

This study consisted of 34 IBD patients (median: 11 years, range: 5-17 years, 10.9±3.9 years of age; 16 CD and 18 UC) and 21 healthy children (median: 12.5 years, range: 5-18 years, 11.6±4 years of age) as a control group (p=0.15). All patients in the IBD and control groups and in the subgroups of severe or mild disease activity were comparable in terms of age, sex, height, weight and BMI. Their demographic data is shown in Table I.

Eleven patients were undergoing mesalamine therapy, 23 patients were receiving mesalamine and azathiopurine therapy, 3 patients were being treated with mesalamine

and infliximab and 1 patient was receiving treatment with mesalamine, azathiopurine and infliximab. The duration of the disease was 29.4±23.4 months (median: 28 months; range: 3-96 months), the duration of treatment was 23.8±19.8 months (median: 23 months; range: 1-84 months), the activity index at the time of diagnosis was 51.3±12.8 (median: 50; range: 35-85), the activity index at the time of test was 7.1±8.4 (median: 5; range: 0-30). There were 3 patients who had perianal disease, 4 patients who had extra intestinal disease, and one patient who had perianal and extra intestinal disease.

Four CD and 12 UC patients had mild activity index and 12 CD and 6 UC patients had severe activity index at the time of diagnosis.

There were no statistically significant differences between the groups and subgroups in terms of left ventricular diameters, ejection fraction (EF%), and shortening fraction (SF%). Mitral inflow parameters revealed decreased mitral E and DT in IBD patients in comparison to the control patients (p=0.05, p=0.04) (Table II). DT was lower in IBD patients with severe disease activity in comparison to the control group and those IBD patients with mild disease activity (p=0.006, p=0.05) (Table III). Mitral E was lower in CD patients than in the control patients (p=0.038) and DT was lower in UC patients than in the control patients (p=0.02). Other conventional echocardiographic parameters were not statistically significantly different between the UC, CD and control group patients (Table IV).

Strain Echocardiography

There was no statistical difference between the IBD and control patients in terms of the strain parameters of the left ventricle (Table II).

The strain value of LVAP4 was lower in those patients with CD (-17.1±3.3) than in patients with UC (-19.1±2.3) (p=0.046) (Table IV). The GLLV, LVAP4, and LVAP3 strain values were lower in the CD group than in the control patients (p=0.046, p=0.048, p=0.046 respectively).

In patients with severe disease activity at diagnosis, the strain values of GLLV (-17.1±2.9 vs -18.7±1.79), LVAP3 (-16.4±3.24 vs -19±2.8) and LVAP4 (-17.8±3.5 vs -19±2.5) were lower than in those patients with mild disease activity at the time of diagnosis (p=0.043, p=0.032, p=0.028, respectively). In addition, the strain values of GLLV (-17.1±2.9, vs -18±2.04) LVAP3 (-16.4±3.24 vs -17.7±2.7), and LVAP4 (-17.8±3.5 vs -18.5±2.1) were lower in those IBD patients with severe disease activity than in the control patients (p=0.044, p=0.018, p=0.028, respectively) (Table III).

Disease activity at the time of diagnosis was inversely correlated to EF (%) (p=0.047 r=-0.50) and the strain values of GLLV (p=0.016, r=-0.57), LVAP3 (p=0.029, r=-0.53), and LVAP2 (p=0.011, r=-0.53) in UC patients.

Discussion

IBD is a chronic inflammatory immune mediated disease with acute exacerbation and remission periods. Chronic inflammation exists systemically, extending beyond the gut in addition to local inflammation. The status of chronic inflammation is the main cause of extra intestinal manifestations. Cardiac involvement is often in the form of pericarditis and myocarditis during acute exacerbation periods (14-16). Endocarditis, atrioventricular block and arrhythmias are the other forms of cardiac involvement in IBD (17,18). Subtle myocardial involvement in IBD patients was shown in a few studies via strain echocardiography

Table I. Demographic and echocardiographic features of study patients

	Demographic features of study patients					
	Mild disease activity	**Severe disease activity**	**Control**	**p-value**	**p***	**p†**
Gender (M/F)	8/7	10/9	10/11	0.57	0.35	0.47
Age (years)	9.9±2.3	11.9±2.8	11.6±4.02	0.15	0.23	0.68
Weight (kg)	38±10	38.8±9.5	39.4±17	0.25	0.75	0.46
Height (cm)	139±24	141.3±19.4	145.3±22.8	0.54	0.64	0.37
BMI	15.9±2.4	16.8±1.7	17.6±2.8	0.10	0.35	0.78
SBP (mmHg)	98±7.8	105±6.7	101±9.7	0.19	0.44	0.62
DBP (mmHg)	59±8.9	62±9.2	60.4±10.4	0.09	0.12	0.38
Pulse Pressure	41±6.7	40.9±5.8	42.6±6.4	0.23	0.35	0.17

p: p-value for mild disease activity vs severe disease activity, p*: p-value for severe disease activity vs control, p†: p-value for mild disease activity vs control
M/F: Male/Female, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

(6-8). Subclinical myocardial involvement cannot be shown by standard conventional echocardiography because of its limitations, such as being angle and geometry dependent and also being affected by volume load. Strain echocardiography provides segmental myocardial wall functions and is not dependent on the angle or the user.

Hensel et al. (6) showed that the global strain rate was depressed in paediatric IBD patients who were in active or remission periods in comparison to control patients. We demonstrated that children with severe disease activity at diagnosis had worse global longitudinal strain than those children with mild disease activity at diagnosis.

It was revealed that the disease activity index of CD was inversely correlated to the global longitudinal strain of LV in adult IBD patients (7). In adult patients with CD and UC disease, the activity index was correlated inversely to the global longitudinal strain (7,8). Hensel et al. (6) found no difference in terms of myocardial functions shown by strain echocardiography between CD and UC patients. However, we showed that the longitudinal strain parameters were depressed in CD in comparison to both the control patients and the UC patients. On the other hand, we found that disease activity at diagnosis was inversely correlated to the EF% and global strain value of the left ventricle in paediatric UC patients.

Table II. Conventional and strain echocardiographic features of IBD and control patients

Demographic features of study patients			
	IBD	**Control**	**p-value**
M-Mod echocardiography			
IVSd/m^2 (mm)	6±1.33	5.8±1.32	0.82
LVDd/m^2 (mm)	35.4±7.24	35.6±8.1	0.80
LVDs/m^2 (mm)	22.9±5.1	22.2±4	0.70
LVPwd/m^2 (mm)	42.8±0.73	43.4±0.86	0.47
SF (%)	34.8±3.72	37.4±5.8	0.13
EF (%)	64±4.26	67.4±5.74	0.07
Mitral ınflow parameters			
Mitral E (cm/s)	90.6±14.4	98.4±16.3	0.05
Mitral A (cm/s)	63.3±15.8	59.4±12.4	0.22
DT (s)	149±0.32	177±0.37	0.04
IVRT (s)	64.7±15.5	61.9±6.8	0.26
Strain echocardiography measurements			
LVAP4 (%)	-18.3±3.03	-18.5±2.1	0.70
LVAP3 (%)	-17.8±3.5	-17.7±2.7	0.97
LVAP2 (%)	-17.7±3.07	-18.1±2.8	0.54
GLLV (%)	-17.9±2.7	-18±2.04	0.50
SAXB (%)	-18.1±4.4	-20.7±5.1	0.90
SAXM (%)	-20.7±5.2	-23.4±5.3	0.11
SAXA (%)	-24.7±8	-25.6±6.1	0.69
GLSAX (%)	-23.4±9.1	-23.2±3.04	0.95

IBD: Inflammatory bowel disease, m^2: body surface area, IVSd: Interventricular septal defect, LVDd: Left ventricular diastolic diameter, LVDs: Left ventricular systolic diameter, SF (%): Shortening fraction, EF (%): Ejection fraction, DT: Desceleration time, IVRT: Isovolumetric relaxation time

Chronic inflammation is associated with increased collagen type I, III, and V in IBD patients (19-23). The increased synthesis of procollagen type 3 also plays a role in the fibrosis process of other organs such as the pancreas, lungs and liver in IBD (23-25). Abnormal collagen deposition (increased serum procollagen 3 peptides) in peripheral circulation and the degradation of type I collagen was shown in IBD cases (19,20). Increased procollagen type 3 is a marker used in the follow-up and prediction of the prognosis in dilated cardiomyopathy and heart failure (26,27). In the adult group, the risk of cardiac disease-related hospitalization was found to be 37%, especially in the acute exacerbation phase of the disease (28). Acute hyperinflammation is another important risk factor for myocardial decompensation. Fibrosis and fibrosis related abnormal collagen composition may be the cause of ventricular volume increases and myocardial dysfunction. Thickening of the mitral valve and mitral valve prolapse may be associated with this finding in IBD patients (29).

Altered endothelial dysfunction was shown in the gut of IBD patients (30). Endothelial dysfunction is not restricted to the gut endothelium, but it is seen in the entire endothelium as a marker of the systemic extent of the inflammation (31,32).

Decreased mitral E and DT shows impairment in the early filling of the left ventricle, especially in those patients with severe disease activity. The effect of both chronic inflammation and flares of acute exacerbations on myocardial function and cardiovascular health has been shown in studies in adult IBD patients. It has been shown that adult IBD patients have coronary microvascular dysfunction leading to myocardial systolic and diastolic dysfunction (33). A study conducted with the adult population revealed that for myocardial infarction, having IBD is an independent risk factor (34).

We demonstrated the effect of disease severity at the time of diagnosis on long-term myocardial function. In paediatric patients, the negative effects of systemic inflammation on myocardium at the time of diagnosis

Table III. Echocardiographic features and strain echocardiographic measurements in IBD patients with mild disease activity, IBD patients with severe disease activity and control patients

	Mild disease activity	Severe disease activity	Control	p-value	p*	p†
IVSd/m²	5.7±1.43	6.3±1.21	5.8±1.32	0.64	0.65	0.39
LVDd/m²	34.4±7.1	37.8±4.8	35.6±8.1	0.43	0.23	0.43
LVSd/m²	22.5±3.1	23.3±4.4	22.2±4.1	0.56	0.85	0.21
LVPwd/m²	4.4±0.61	4.11±0.64	4.34±0.86	0.22	0.47	0.19
SF%	35.6±2.72	33.5±3.9	37.4±5.8	0.36	0.09	0.09
EF%	66±3.16	62±3.41	67.4±5.74	0.22	0.07	0.78
Mitral E	93.7±12.4	89.4±14.5	98.4±16.3	0.54	0.89	0.79
Mitral A	64.2±14.5	61.5±13.2	59.4±12.4	0.65	0.63	0.53
DT	167±5.2	131±4.9	177±3.7	0.05	0.006	0.46
IVRT	63.7±14.5	65.3±13.3	61.9±6.8	0.77	0.44	0.63
LVAP4	-19±2.5	-17.8±3.5	-18.5±2.1	0.028	0.028	0.43
LVAP3	-19±2.8	-16.4±3.24	-17.7±2.7	0.032	0.018	0.76
LVAP2	-18.2±1.98	-17.4±3.5	-18.1±2.8	0,65	0.08	0.91
GLLV	-18.7±1.79	-17.1±2.9	-18±2.04	0,043	0.044	0.54
SAXB	-18.3±4.1	-18.6±3.1	-20.7±5.1	0.55	0.67	0.58
SAXM	-20.6±5.1	-21±5.9	-23.4±5.3	0.63	0.71	0.51
SAXA	-25.6±6.5	-23.6±9	-25.6±6.1	0.39	0.61	0.48
GLSAX	-21.7±3.9	-25.1±1.24	-23.2±3.04	0.83	0.72	0.63

LVAP: Left ventricle apical chamber, GLLV: Global longitudinal left ventricle strain, SAXB: Short axis basal strain (mitral valve plane), SAXM: Short axis medial strain (papillary muscle plane), SAXA: Short axis apical strain, GLSAX: Global short axis strain, IBD: Inflammatory bowel disease
p: P-value for mild disease activity vs severe disease activity
p*: P-value for severe disease activity vs control
p†: P-value for mild disease activity vs control

Table IV. Strain echocardiographic measurements of ulcerative colitis, Crohn's disease and control patients

	UC	CD	Control	p-value	p*	p†
M-mod echocardiography						
IVSd/m²	6.5±1.38	6.1±1.1	5.9±1.3	0.12	0.09	0.08
LVDd/m²	38±7.4	37.4±7.7	35±8.1	0.45	0.089	0.067
LVSd/m²	25.1±4.4	23.3±3.9	22.2±4	0.54	0.61	0.86
LVPwd/m²	4.6±0.7	4.4±0.3	4.3±0.8	0.61	0.77	0.43
SF (%)	34.9±3.5	36±3.7	37.4±5	0.21	0.32	0.27
EF (%)	64.5±4.5	64±3.9	67.4±5.7	0.27	0.33	0.41
Mitral inflow parameters						
Mitral E	92.8±15.9	86.7±18.5	97.4±14.3	0.08	0.038	0.62
Mitral A	64±17	58.5±17	59.4±12	0.21	0.66	0.12
DT	142±34	130±49	149±28	0.09	0.63	0.02
IVRT	60±11	69±18	62±18	0.15	0.09	0.28
Strain echocardiography measurements						
LVAP4	-19.1±2.3	-17.1±3.3	-19±1.9	0.046	0.048	0.65

Table IV. Continued

	UC	CD	Control	p-value	p*	p†
LVAP3	-18.3±3.02	-17.2±4.1	-19.2±2.1	0.48	0.046	0.51
LVAP2	-18.3±2.3	-17±3.7	-18.4±2.3	0,38	0.41	0.76
GLLV	-18.6±1.82	-17.06±3.3	-19±2.1	0,15	0.046	0.57
SAXB	-18.1±3.6	-18.1±5.2	18.5±1.99	0.90	0.75	0.69
SAXM	-19.5±5.2	-22.1±5.1	-21.8±4.8	0.17	0.53	0.46
SAXA	-25.1±8.2	-24.1±7.9	-24.2±5	0.73	0.67	0.71
GLSAX	-22.6±6.9	-24.2±11.3	-21.4±3.7	0.65	0.58	0.72

p: P-value for Crohn's disease vs ulserative colitis
p*: P-value for Crohn's disease vs control
p†: P-value for ulserative colitis vs control
UC: Ulserative colitis, CD: Crohn's disease, LVAP: Left ventricle apical chamber, GLLV: Global longitudinal left ventricle strain, SAXB: Short axis basal strain (mitral valve plane), SAXM: Short axis medial strain (papillary muscle plane), SAXA: Short axis apical strain, GLSAX: Global short axis strain

continue even after the patient is in remission. In our study, the myocardial functions of children with severe disease activity at the time of diagnosis, ascertained via strain echocardiography, were found to be impaired compared to those with mild disease activity at the time of diagnosis. We could not find any difference between the IBD and control patients in terms of myocardial functions via strain echocardiography. This may be due to the shortness of the follow-up period and the fact that the patients were in remission. We can conclude that "the more severe the inflammation is at the time of diagnosis, the more subclinical myocardial dysfunction there is in the long term".

Conclusion

Our study revealed that the severity of disease activity at the time of diagnosis has long-lasting effects on myocardial functions in those children with IBD. In this study, the systolic dysfunction of our patients was assessed after a rather short follow-up period. A longer term follow-up study to observe myocardial functions in IBD patients with both mild and severe disease activity is needed in future studies.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee in University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital (approval number: 06, date: 29.06.2018).

Informed Consent: Written consents for the study were taken from the parents of the all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: E.P., E.E., N.G., H.A.C., Data Collection or Processing: N.G., H.A.C., Analysis or Interpretation: E.E., Literature Search: E.E., Writing: E.P., E.E.

Conflict of Interest: The authors declare that they have no conflict of interest.

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References

1. Levine JS, Burakoff R. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2011; 7:235-41.
2. Harbord M, Annese V, Vavricka SR, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. J Crohns Colitis 2016; 10:239-54.
3. Filimon AM, Negreanu L, Doca M, Ciobanu A, Preda CM, Vinereanu D. Cardiovascular involvement in inflammatory bowel disease: Dangerous liaisons. World J Gastroenterol 2015; 21:9688-92.
4. Gaduputi V, Tariq H, Kanneganti K. Abdominal aortitis associated with Crohn disease. Can J Gastroenterol Hepatol 2014; 28:69-70.
5. Andrade AR, Barros LL, Azevedo MFC, et al. Risk of thrombosis and mortality in inflammatory bowel disease. Clin Transl Gastroenterol 2018; 9:142.
6. Hensel KO, Abellan Schneyder FE, Wilke L, Heusch A, Wirth S, Jenke AC. Speckle Tracking Stress Echocardiography Uncovers Early Subclinical Cardiac Involvement in Pediatric Patients with Inflammatory Bowel Diseases. Sci Rep 2017; 7:2966.
7. Kivrak T, Sunbul M, Cincin A, et al. Two-dimensional speckle tracking echocardiography is useful in early detection of left ventricular impairment in patients with Crohn's disease. Eur Rev Med Pharmacol Sci 2016; 20:3249-54.
8. Cincin A, Sunbul M, Kivrak T, et al. Evaluation of cardiac function by two-dimensional speckle tracking echocardiography in ulcerative colitis patients. Dig Dis Sci 2014; 59:3004-11.

9. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014; 58:795-806.

10. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011; 17:1314-21.

11. Dotson JL, Crandall WV, Zhang P, et al. Feasibility and validity of the pediatric ulcerative colitis activity index in routine clinical practice. J Pediatr Gastroenterol Nutr 2015; 60:200-4.

12. Turner D, Levine A, Walters TD, et al. Which PCDAI Version Best Reflects Intestinal Inflammation in Pediatric Crohn Disease? J Pediatr Gastroenterol Nutr 2017; 64:254-60.

13. Hensel KO, Wilke L, Heusch A. Transthoracic Speckle Tracking Echocardiography for the Quantitative Assessment of Left Ventricular Myocardial Deformation. J Vis Exp 2016; 54736.

14. Aarestrup J, Jess T, Kobylecki CJ, Nordestgaard BG, Allin KH. Cardiovascular Risk Profile Among Patients With Inflammatory Bowel Disease: A Population-based Study of More Than 100 000 Individuals. J Crohns Colitis 2019; 13:319-23.

15. Freeman HJ, Salh B. Recurrent myopericarditis with extensive ulcerative colitis. Can J Cardiol 2010; 26:549-50.

16. Uchida W, Mutsuga M, Ito H, Oshima H, Usui A. Nonbacterial Thrombotic Endocarditis Associated With Crohn Disease. Ann Thorac Surg 2018; 105:199-201.

17. Efe TH, Cimen T, Ertem AG, et al. Atrial Electromechanical Properties in Inflammatory Bowel Disease. Echocardiography 2016; 33:1309-16.

18. Curione M, Barbato M, Amato S, et al. Atrioventricular block associated with Crohn's relapsing colitis in a 12-year-old child. Inflamm Bowel Dis 2010; 16:373-4.

19. Stallmach A, Schuppan D, Riese HH, Matthes H, Riecken EO. Increased collagen type III synthesis by fibroblasts isolated from strictures of patients with Crohn's disease. Gastroenterology 1992; 102:1920-9.

20. Kjeldsen J, Schaffalitzky de Muckadell OB, Junker P. Seromarkers of collagen I and III metabolism in active Crohn's disease. Relation to disease activity and response to therapy. Gut 1995; 37:805-10.

21. Kjeldsen J, Rasmussen M, Schaffalitzky de Muckadell OB, Kronborg O, Junker P. Collagen metabolites in the peripheral and splanchnic circulation of patients with Crohn disease. Scand J Gastroenterol 2001; 36:1193-7.

22. De Simone M, Cioffi U, Contessini-Avesani E, et al. Elevated serum procollagen type III peptide in splanchnic and peripheral circulation of patients with inflammatory bowel disease submitted to surgery. BMC Gastroenterol 2004; 4:29.

23. Leidenius MH, Risteli LT, Risteli JP, Taskinen EI, Kellokumpu IH, Höckerstedt KA. Serum aminoterminal propeptide of type III procollagen (S-PIIINP) and hepatobiliary dysfunction in patients with ulcerative colitis. Scand J Clin Lab Invest 1997; 57:297-305.

24. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2003; 9:104-15.

25. Ramos LR, Sachar DB, DiMaio CJ, Colombel JF, Torres J. Inflammatory Bowel Disease and Pancreatitis: A Review. J Crohns Colitis 2016; 10:95-104.

26. Kaufman BD, Videon N, Zhang X, Harris MA, Shaddy RE, Goldmuntz E. Procollagen type III amino-terminal propeptide: a serum biomarker of left ventricular remodelling in paediatric dilated cardiomyopathy. Cardiol Young 2015; 25:228-36.

27. Dupuy AM, Kuster N, Curinier C, et al. Exploring collagen remodeling and regulation as prognosis biomarkers in stable heart failure. Clin Chim Acta 2019; 490:167-71.

28. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure: a Danish Nationwide Cohort study. Circ Heart Fail 2014; 7:717-22.

29. Vizzardi E, Sciatti E, Bonadei I, et al. Subclinical cardiac involvement in Crohn's disease and ulcerative colitis: an echocardiographic case-control study. Panminerva Med 2016; 58:115-20.

30. Hatoum OA, Binion DG, Otterson MF, Gutterman DD. Acquired microvascular dysfunction in inflammatory bowel disease: Loss of nitric oxide-mediated vasodilation. Gastroenterology 2003; 125:58-69.

31. Roifman I, Sun YC, Fedwick JP, et al. Evidence of endothelial dysfunction in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2009; 7:175-82.

32. Winderman R, Rabinowitz SS, Vaidy K, Schwarz SM. Measurement of Microvascular Function in Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr 2019; 68:662-8.

33. Caliskan Z, Keles N, Gokturk HS, et al. Is activation in inflammatory bowel diseases associated with further impairment of coronary microcirculation? Int J Cardiol 2016; 223:176-81.

34. Aniwan S, Pardi DS, Tremaine WJ, Loftus EV Jr. Increased Risk of Acute Myocardial Infarction and Heart Failure in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2018; 16:1607-15.

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Original Article

Endoscopic Management of Vesicoureteral Reflux in Duplex Renal Collecting Systems

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ABSTRACT

Aim: Standardization of an optimal treatment protocol for vesicoureteral reflux (VUR) correlated with duplex kidney systems remains controversial. In this study, we reviewed our experience in endoscopic subureteric injection to correct reflux in duplex systems with documented indications, in an aim to confirm its position as an alternative means of open surgery.

Materials and Methods: The hospital records of complete renal duplex system patients who had experienced endoscopic subureteric injection for VUR between 2009 and 2018 were reviewed. The indications for the amelioration of VUR included breakthrough urinary tract infection (UTI) along with the presence of renal scarring.

Results: A total of 24 patients (18 girls, 6 boys) with refluxing renal duplex systems were included in the study. The mean age at first injection was 46.4±28.8 months (5-160) and the mean duration of follow-up was 47.25±27.7 months. The success rate with the initial injection was 83.3% (20/24). The mean volume of material injected was 0.68±0.49 mL per duplex system.

Conclusion: Management of reflux in duplex systems is still controversial with insufficient data. Our results suggest that endoscopic management should be considered as an alternative to open ureteral reimplantation in refluxing duplex renal collecting systems. Major open surgery and accompanying discomfort can be avoided by an endoscopic injection which can be performed as an outpatient procedure in most of the reflux patients with duplex system who have an indication for surgical management.

Keywords: Vesicoureteral reflux, duplex renal systems, endoscopic reflux treatment, subureteric injection, pediatric

Introduction

The management of vesicoureteral reflux (VUR) in complete renal duplex systems remains a controversial issue. In this patient group, the spontaneous resolution of VUR (1), urinary tract infection (UTI) incidence (2,3), reflux grade, and the success of surgical treatment (4,5) are affected by certain anatomic factors. Endoscopic management of VUR has reached worldwide popularity because it is easy to apply, and has short hospital stay with superior patient comfort in children, with the inclusion of duplex systems (6-9). In this study, we reviewed our experience in an aim to evaluate the safety and efficacy of endoscopic subureteric injection to correct VUR in complete duplex systems with documented indications for anti-reflux surgery.

Materials and Methods

The hospital records of complete renal duplex system patients who underwent endoscopic subureteric injection for VUR between 2009 and 2018 were reviewed. Those patients with partial duplication of the ureter(s) or documented bladder-sphincter dysfunction were excluded.

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The indications for VUR correction included breakthrough UTI or the existence of renal scarring. Breakthrough UTI was defined as one with fever (>38 °C) and proven with a catheter collected urine culture that happened during a course of antibiotic prophylaxis. Lower UT (LUT) functions were evaluated by detailed anamnesis (such as constipation, storage/voiding symptoms), voiding frequency/volume chart, uroflow studies, bladder wall thickness, and post-void residual measurement for those children who had voluntary control over their LUT function. If the child was <5 years of age and did not have voluntary control, LUT function was accepted as normal if the bladder wall thickness and post-void residual measurements were in range. Invasive urodynamic studies were not routinely used to evaluate LUT function. All families were informed about VUR treatment options and the expectations regarding their success rates in duplex systems. The choice of an open or endoscopic method was left to the family as a treatment method. Those who elected for open surgery were not included in this study. Informed consent was obtained from the parents/legal guardians of the patients before the procedure. Data including preoperative and postoperative VUR grades, the presence of contralateral VUR, the presence of ureterocele, the site of refluxing renal moiety, the amount of injected material, patient demographics, and the success rates following endoscopic treatment were recorded.

Reflux classification was made according to the International Reflux Study in Children, also known as the International Classification (10). The procedure was performed via 9.5 Fr., 0° cystoscope (Storz, Tuttlingen, Germany) under general anesthesia. Polyacrylate polyalcohol copolymer (PPC) (Vantris®, Promedon, Argentina) was applied submucosally at the most suitable position(s) of the ureteral orifices until the creation of a significant bulge using a Williams cystoscopic injection needle (Cook Medical®, Bloomington, USA). A standard method was not applied for subureteric injection, and injections were made at the appropriate place(s) and in the appropriate number according to the anatomical features. All procedures were performed according to the outpatient protocol and complete resolution of reflux in voiding cystourethrogram (VCUG) obtained at least three months after injection was defined as the success criterion. If persistent reflux was detected, the injection was repeated, or open surgery was performed depending on clinical features and parental choice.

Ultrasound examinations were carried out at the first, third, and sixth months for post-operative control, and afterward, performed yearly for the follow-up of findings such as increased or newly developed hydroureteronephrosis suggesting obstruction. The approval for this study was obtained from the Ethics Committee of Ege University Faculty of Medicine, under the number 20-5.1T/27.

Results

Twenty-four patients (18 girls, 6 boys) with refluxing duplex kidneys were involved in the study. The mean age was 46.4±28.8 months (5-160) at first injection, and the mean duration of follow-up was 47.25±27.7 months. Pre-operative scintigraphic examination revealed a loss of function in 14 patients and localized scarring in 6 patients. The success rate with the initial injection was 83.3% (20/24). The success rates for grade IV and grade V reflux in duplex systems were 80% and 83.3%, respectively. The mean material volume injected was 0.68±0.49 mL per duplex system at the first injection. A flowchart showing the overall management steps for the study group is summarized in Figure 1.

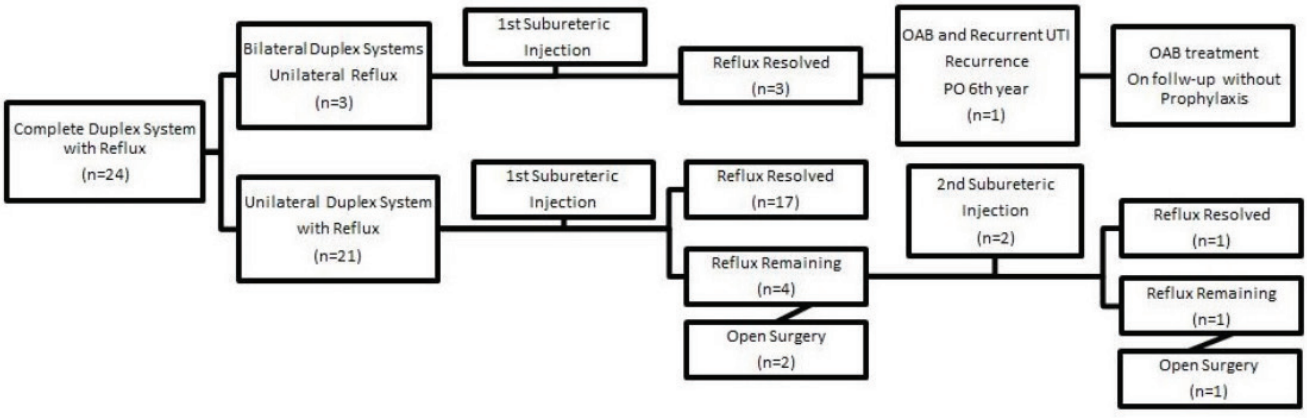

Figure 1. The steps of overall management for the study group
OAB: Overactive bladder, UTI: Urinary tract infection

Twenty-one of the 24 patients had unilateral, and 3 had bilateral duplex systems with unilateral reflux. Fourteen patients had reflux to the left and 10 patients to the right kidney. Eighteen patients had reflux to the lower moiety, one patient only had reflux to the upper moiety, and 5 patients had reflux to both upper and lower moieties. Six ureters had grade V reflux, 10 had grade IV reflux, 8 had grade III reflux, and 5 had grade II reflux. Twelve patients had a unilateral refluxing duplex system coexisting with contralateral reflux into a single system, and all refluxing units were treated successfully with a single injection in these patients.

Twenty of the 24 patients (83.3%) were treated successfully at the first injection. Two of 4 patients were treated with a second endoscopic subureteric injection, and only one of these succeeded. Two of the 4 patients whose first subureteric injection failed had metachronous contralateral reflux. Eventually, 3 patients had an open surgical procedure for persistent VUR. In these cases, ureteroneocystostomy was performed in line with the choices of the families. During the open surgeries, subureteric injection materials did not complicate ureteric dissection.

Two of the patients had incised ureteroceles, and reflux (one to the upper moiety and the other one to the lower moiety) was treated successfully with the first subureteric injection in both cases. One of them had recurrent UTI in the postoperative 6th year. She also had complaints of overactive bladder (OAB). VCUG revealed recurrent grade III VUR to the upper moiety. OAB was treated with anticholinergics, and she did not have any subsequent UTI on the follow-up without prophylaxis. Our patients did not have gross hematuria or urinary retention, and neither early post-operative febrile UTI episodes nor new-onset hydronephrosis were seen on follow-up.

Discussion

Renal duplication, which is the UT's most common congenital abnormality, has an incidence of 0.8% to 2% (3 4,11,12). Duplex systems can be associated with nearly 8% of children admitted to the hospital with febrile UTIs (9,13,14), and VUR is present in 70% of these children (2-4,12). VUR has an incidence of 56% in patients with a duplex system and occurs in the lower moieties in 75% of cases (1). As compatible with the literature, 18 of 24 patients (75%) had reflux into the lower moiety in our study.

In VUR patients, long-term antibiotic prophylaxis is not without concerns, such as increased bacterial resistance, and a high rate of recurrent UTI (1,4,15). On the other hand, the spontaneous resolution rate, especially of high-grade VUR in duplex systems, is lower in comparison to single renal systems due to the anatomic configuration of the region (1,4,7,8), and these patients have a greater likelihood of recurrent UTI and renal parenchymal scarring (4,8,13). Hunziker et al. (4) reported a febrile UTI rate of 4.1% in their study, with Dextranomer/Hyaluronic acid (Dx/HA) injection for VUR in duplex system patients. In our study, one patient (4.1%) had recurrent febrile UTI in the follow-up, and she was the only patient who had new renal scarring and long-term recurrence of VUR despite initially successful endoscopic treatment.

While open surgery is accepted as the gold standard with a success rate of over 95%, it is more complex and carries a higher risk of complications than for single-system cases due to anatomical variations (8,16). Similar to those with single-system reflux, the advantages of the STING procedure in a refluxing duplex system are that it can be performed with a short anesthesia time and is well tolerated so that it can be performed as an outpatient procedure (6,7,16). STING is currently recommended for use in complex VUR, including duplex systems (16). In our study group, breakthrough UTI and renal parenchymal scarring were the indications for surgical treatment. The families were informed about open and endoscopic surgical techniques, and they were allowed to decide on the surgical treatment method.

There are controversies regarding endoscopic treatment. Repeated injections for unsuccessful attempts increase the number of anesthesia sessions. Furthermore, its success rate may decrease with time, and the treatment may even become ineffective at long-term follow-up (16). In a multicenter trial, between 6 months and 3 years, the late recurrence rate was 21% after subureteric Dx/HA injection for VUR treatment (17,18). Only one of our patients who presented with OAB and recurrent UTI complaints and was treated medically had recurrent reflux during 6 years of follow-up. Since we do not perform routine VCUG in our patients without symptoms during long-term follow-up, we cannot give a figure regarding reflux recurrence rates over a long-term in our series.

The overall ratio of VUR resolution increases with multiple endoscopic injections (9). In our series, the families of 4 patients with unsuccessful first injections were given repeat injection or open surgery options. Only two families preferred the second injection, and the other two preferred open surgery. One of the two patients was successfully treated with a second injection, and the other patient

needed open surgery after the second failure via injection. The resolution rate of reflux in our patients was 83.3% (20 of 24 patients) after the first injection and this increased to 87.5% after the second injection.

In a systemic review of published studies on the endoscopic management of VUR in patients with the duplex systems, the predicted probability of success was reported to be 68% for the single system and 64% for the duplex system (4,8). In our series, the success rate with the first injection was higher than for similar studies in the literature. Since subureteric injections in our patients were not performed by a single surgeon or with a standardized method, the reason for this high success may be related to the injected material.

Kocherov et al. (19), in a multicenter survey study, found the success rate to be 93.8% (759 of 809 renal units) after the first PPC injection, including both primary and complex VUR patients. Furthermore, Tekin et al. (20) obtained a higher success rate for the first injection in the PPC group (90.5%) than in the Dx/HA group (62.4%) in their study which included 260 primary and secondary VUR patients. These high success rates published in the literature show that our high success rates in endoscopic VUR treatment in duplex systems may be related to the material used for subureteric injection. Although PPC is known to have a relatively high success rate in the treatment of endoscopic VUR, postoperative obstruction was also reported in relation to the amount of material used (above 2 mL) at a rate of 11% requiring treatment and 5.6% requiring open surgical treatment in the study of De Badiola et al. (21) in 2013. The postoperative obstruction rate was only 0.7% after subureteric injection of Dx/HA up to 1 ml in the study of Vandersteen et al. (22) in 2006. Urinary obstruction was not observed in any of our patients in the follow-up of mean 47 months; thus, the mean volume injected per duplex system was 0.68 mL in our study. Hunziker et al. (4) reported the success rate to be 67.2% with grade IV and 45.5% with grade V reflux in complete duplex systems. In our study, the success rate for grade IV reflux in duplex systems was 80%, and for grade V reflux, it was 83.3%. These high success rates support the idea that subureteric injection therapy can be preferred in duplex system patients with high-grade reflux. Moreover, in 5 patients with upper and lower moiety reflux, the success rate was as high as 80% with the first injection and 100% with the second.

Study Limitations

Our study has some limitations. It was a retrospective study and we did not have a control group. In duplex systems, the distance between the anatomic features and the location of duplicated ureteral orifices may differ. Although the puncture site of the needle can be standardized in the STING method for single system ureters, this is not easy to achieve for duplex systems. The injection number per operation or method could not be analyzed statistically in this study due to the low number of patients in the groups.

Although there are studies with higher patient numbers, the high success rate of our study is noteworthy (3,6). While the parents were routinely informed, the possibility that some parents did not report the occurrence of febrile UTI after recovery from VUR should be considered. Prospective randomized studies are required to confirm our results.

Conclusion

The management of reflux in duplex systems is still controversial and there is insufficient data. Our results suggest that endoscopic management should be considered as an alternative to open ureteral re-implantation in refluxing duplex renal collecting systems. Major open surgery and its accompanying discomfort can be avoided by an endoscopic injection, which can be performed as an outpatient procedure in most reflux patients with a duplex system who have an indication for surgical management.

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Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval date: 29.05.2020; approval no: 20-5.1T/27).

Informed Consent: Informed consent was obtained from the parents/legal guardians of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.Ç., A.T., Design: H.Ç., İ.U., Data Collection or Processing: Ö.K., İ.Z.A., H.Ç., Analysis or Interpretation: A.T., A.A., İ.U., Literature Search: H.Ç., İ.U., Writing: H.Ç., A.T., İ.U..

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References

1. Bartoli F, Niglio F, Pastore V, et al. Polydimethylsiloxane (macroplastique) injection for vesicoureteral reflux in duplex ureters: A comparison with single renal systems. J Pediatr Urol 2011; 7:516-9.
2. Thomas JC. Vesicoureteral reflux and duplex systems. Adv Urol 2008; 2008:651891.
3. Privett JT, Jeans WD, Roylance J. The Incidence and Importance of Renal Duplication. Clin Radiol 1976; 27:521-30.
4. Hunziker M, Mohanan N, Puri P. Dextranomer/Hyaluronic Acid Endoscopic Injection is Effective in the Treatment of Intermediate and High Grade Vesicoureteral Reflux in Patients with Complete Duplex Systems. J Urol 2013; 189:1876-81.
5. Elder JS, Peters CA, Arant BS Jr, et al. Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report on the Management of Primary Vesicoureteral Reflux in Children. J Urol 1997; 157:1846-51.
6. Steinbrecher HA, Edwards B, Malone PS. The STING in the Refluxing Duplex System. Br J Urol 1995; 76:165-8.
7. Miyakita H, Ninan GK, Puri P. Endoscopic Correction of Vesico-Ureteric Reflux in Duplex Systems. Eur Urol 1993; 24:111-5.
8. Hensle TW, Reiley EA, Ritch C, Murphy A. The clinical utility and safety of the endoscopic treatment of vesicoureteral reflux in patients with duplex ureters. J Pediatr Urol 2010; 6:15-22.
9. Rossini CJ, Moriarty KP, Courtney RA, Tashjian DB. Endoscopic Treatment With Deflux for Refluxing Duplex Systems. J Laparoendosc Adv Surg Tech A 2009; 19:679-82.
10. Weiss RA, Spitzer A. Vesicoureteral Reflux and Reflux Nephropathy. In: Suki WN, Massry SG (eds). Suki and Massry's therapy of renal diseases and related disorders. Boston, MA, Springer, 1998.
11. Molitierno JA Jr, Scherz HC, Kirsch AJ. Endoscopic injection of dextranomer hyaluronic acid copolymer for the treatment of vesicoureteral reflux in duplex ureters. J Pediatr Urol 2008; 4:372-6.
12. Hunziker M, Mohanan N, Menezes M, Puri P. Prevalence of duplex collecting systems in familial vesicoureteral reflux. Pediatr Surg Int 2010; 26:115-7.
13. Bisset GS 3rd, Strife JL. The Duplex Collecting System in Girls With Urinary Tract Infection: Prevalence and Significance. AJR Am J Roentgenol 1987; 148:497-500.
14. Visuri S, Jahnukainen T, Taskinen S. Prenatal complicated duplex collecting system and ureterocele-Important risk factors for urinary tract infection. J Pediatr Surg 2018; 53:813-7.
15. Hensle TW, Grogg AL. Part 1: Vesicoureteral reflux treatment: The past, present, and future. Curr Med Res Opin 2007; 23(Suppl 4):1-5.
16. Yu TJ, Chang LC. Use of Collagen for Endoscopic Correction in Complicated Vesicoureteral Reflux. Scand J Urol Nephrol 2007; 41:58-65.
17. Schmedding A, Zeeh U, Huebner U, Krause M, Lorenz C. Sx IN – Prospective multicenter survey of subureteric injection in children. Presented at international conference on vesicoureteral reflex in children, June 4e6, Goteborg, Sweden, 2009.
18. Chertin B, Kocherov S. Long-term results of endoscopic treatment of vesicoureteric reflux with different tissue-augmenting substances. J Pediatr Urol 2010; 6:251-6.
19. Kocherov S, Ulman I, Nikolaev S, et al. Multicenter Survey of Endoscopic Treatment of Vesicoureteral Reflux Using Polyacrylate-Polyalcohol Bulking Copolymer (Vantris). Urology 2014; 84:689-93.
20. Tekin A, Yagmur I, Tiryaki S, Dokumcu Z, Ulman I, Avanoglu A. Changing bulking agent may require change in injection volume for endoscopic treatment of vesicoureteral reflux. Int Braz J Urol 2018; 44:1194-9.
21. De Badiola FI, Soria R, Vagni RL, Ormaechea MN, Moldes JM, Benmaor C. Results of Treatment of Grades IV and V Vesicoureteral Reflux with Endoscopic Injection of Polyacrylate Polyalcohol Copolymer. Front Pediatr 2013; 1:32.
22. Vandersteen DR, Routh JC, Kirsch AJ, et al. Postoperative ureteral obstruction after subureteral injection of dextranomer/hyaluronic Acid copolymer. J Urol 2006; 176:1593-5.

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Original Article

Pediatricians' Knowledge and Awareness on Pre-surgical Orthopedics in Newborns with Cleft Lip and Palate

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ABSTRACT

Aim: The aim of this study is to determine the level of knowledge and awareness of pediatricians about pre-surgical orthopedic treatment and nasoalveolar molding (NAM) of newborns with cleft lip and/or palate (CL/P).

Materials and Methods: We conducted a 10-item questionnaire and sent emails to 600 pediatricians in Türkiye. The title, professional experience, institution of employment of the participants and their knowledge level about preoperative maxillary orthopedic treatment and NAM practices of newborns with CL/P were evaluated.

Results: One hundred-twelve pediatricians responded to the questionnaire. There was no statistically significant difference in the knowledge level regarding the preoperative treatment of newborns with CL/P between experienced and inexperienced pediatricians ($p>0.05$). When the knowledge levels about preoperative treatment and NAM applications of newborns with CL/P were evaluated, no statistically significant difference was found between pediatricians with more or less than 5 years' experience ($p>0.05$). All pediatricians who participated in the questionnaire reported that they referred newborns with CL/P to at least one specialist (orthodontist, dentist or plastic surgeons). The most frequently referred specialist group was plastic surgeons (84%), followed by orthodontists (52%) and dentists (39%). A linear regression was found between the number of cases seen and the professional experience year of pediatricians.

Conclusion: Increasing the awareness and knowledge of pediatricians about NAM, pre-surgical orthopedic and other treatment alternatives in newborns with CL/P is very important for the success of CL/P treatment. Newborns with CL/P should be referred to an orthodontist by pediatricians as soon as possible after birth to initiate the treatment process.

Keywords: Cleft lip and palate, nasoalveolar molding, pediatrician, newborn

Introduction

Non-syndromic cleft lip/palate (CL/P) is one of the most common congenital craniofacial abnormalities worldwide. Non-syndromic CL/P's etiology is multifactorial based on the interaction of genetic and environmental factors (1). CL/P may be associated with one of many syndromes, as approximately 275 syndromes with orofacial clefts as a primary feature have been identified. Etiologies include mutation of a single genetic locus, teratogenic factors, and chromosomal abnormalities (2). The development of facial structures occurs between the fourth and twelfth weeks of pregnancy, with the left and right sides of the facial structures fusing in the middle of the fetus' body during this time; however, if the parts of the face do not fuse properly due genetic or environmental factors, craniofacial clefts will occur (3-5).

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CL/P should be treated with a multidisciplinary approach involving many specialists including pediatricians, obstetrician-gynecologists, speech therapists, plastic surgeons, orthodontists, and dentists. The first and most important obstacle in the treatment of infants born with CL/P is nutrition. As a general method, this problem is addressed with passive feeding plates. It is also possible to approximate the cleft segments closer to each other and to extend the columella by making active regulatory additions to the feeding plates. This is the best method to improve facial aesthetics to date (3). The treatment approach of the clinical team following the patient will determine the individual treatment protocol. Although newborns with CL/P undergo many reconstructive surgeries throughout their lives, they may continue to have aesthetic challenges as they grow up. Therefore, determining the right treatment approach is one of the most important missions of the clinical team. The basic treatment protocol for patients with CL/P consists of pre-surgical orthopedic appliances, surgical repair of the lip and palate, and treatment of associated complications such as speech, otology, and dental anomalies. Pre-surgical orthopedics have many important advantages which include: reducing the gap between the alveolar and maxillary segments, aligning and correcting the nasal cartilage, lengthening the columella, minimizing the formation of scar tissue after surgery due to the cleft segments being closer to each other, reducing the need for secondary surgery, enabling the surgeon to perform gingival perioplasty and ultimately preventing the need for secondary alveolar grafting, and producing more consistent postoperative results (6-9).

Nasoalveolar molding (NAM) is one of the important pre-surgical orthopedic techniques (10,11) (Figure 1). Matsuo et al. (12) introduced a pre-surgical orthopedic technique that first focused on molding the cartilage. Grayson and Maull (13) applied the theory that newborn cartilaginous tissues are softer and their plasticity higher due to the level of estrogen transferred from the mother to the nasal cartilages of newborns with CL/P, introducing the NAM appliance and its benefits (3,8).

Pediatricians are physicians who are responsible for monitoring the overall health of newborns, infants, and children. The early diagnosis of various dental conditions is critical in the success of patient treatment. Pediatricians who encounter patients with CL/P play an important role in determining and forming the appropriate multidisciplinary team care (2,14). It is important to direct the parents of newborns with CL/P to a specialist as soon as possible for the purpose of applying a NAM appliance. This responsibility falls to pediatricians, who are usually the first clinicians to encounter newborns with CL/P.

The purpose of this study was to determine the level of knowledge and awareness of pediatricians regarding NAM and the pre-surgical orthopedic treatment of newborns with CL/P.

Materials and Methods

We performed a questionnaire study on pediatricians who were randomly selected from all over Türkiye. The study was approved by the Clinical Research Ethics Committee of Ordu University (no: 2021/9). The survey was specifically designed by the researchers using Google Forms©. Emails were sent to 600 pediatricians. Of the 600 pediatricians, 112 agreed to participate in the study. The sample size was calculated in the G*Power (version 3.1.9.2; Axel Buchner, Universität Düsseldorf, Düsseldorf, Germany) program and the total sample size required to detect a medium-sized effect with 90% power (effect size: 0.60) was found to

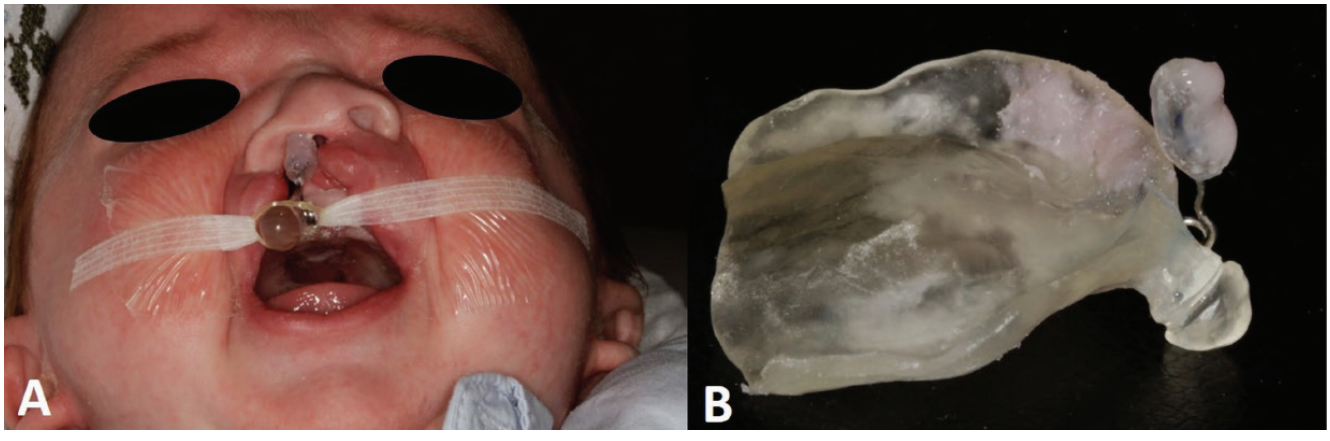

Figure 1. Nasoalveolar molding appliance

be 98 for this study. The questionnaire consisted of 10 questions in 2 parts. First, demographic information such as title, workplace, and years of experience was recorded. Pediatricians who had greater than 5 years' experience in pediatrics were described as experienced, while those who had 5 or less than 5 years of pediatric experience were described as inexperienced. In the second part, participants were queried about their knowledge of CL/P and the NAM appliance.

Statistical Analysis

Statistical analysis was performed using the SPSS software (SPSS for Windows version 20.0; SPSS Inc, Chicago, Illinois). Descriptive statistics were determined for the evaluated parameters. For categorical variables, percentages were calculated. Pearson chi-square and Fisher's exact tests were used to compare the pediatricians' level of knowledge about pre-surgical orthopedic treatment and the NAM appliance. Logistic regression analyses were performed to evaluate the effect of gender and years in practice on knowledge and referral to specialists for pre-surgical orthopedics and NAM therapy. Gender, years of experience, number of cases seen, and workplace served as the independent variables, while knowledge and referral to specialists were the dependent variables. Model fit was checked using the Hosmer-Lemeshow test. Statistical significance was accepted at $p<0.05$.

Results

A total of 112 pediatricians responded to the questionnaire, with a higher number of females (72.3%) than males (27.7%). Of the participants, 50% reported working as pediatricians for less than 5 years, and 50% reported working for more than 5 years. Most of the respondents reported working in a university hospital (50%), while 32.1% reported working in a state hospital and 17.9% reported working in a private hospital/practice. The demographic characteristics of pediatricians as well as their knowledge of NAM can be seen in Table I. There was a statistically significant number of pediatricians who had encountered newborns with CL/P and had knowledge of NAM therapy ($p<0.001$).

In the questionnaire, 84% of pediatricians reported that they redirect newborns with CL/P to plastic and reconstructive plastic surgeons, 52% redirect to an orthodontist, and 39% redirect to a dentist. All respondents reported referring newborns with CL/P to at least one of these three departments (Figure 2).

There was a statistically significant difference in the knowledge level regarding the preoperative treatment of newborns with CL/P between experienced and inexperienced pediatricians ($p>0.05$). Moreover, there was a statistically significant difference between experienced and inexperienced pediatricians in the number of newborns with CL/P examined ($p<0.05$). The difference in knowledge level regarding NAM treatment and applications for newborns with CL/P between experienced and inexperienced pediatricians was not statistically significant ($p>0.05$) (Table II).

According to the results of multivariate analysis for the effect of gender, workplace, experience, and number of

Table I. Demographic characteristics of pediatricians about the knowing NAM therapy

	Parameter	%	Yes	No	p-value
Gender	Male	27.7	12	19	0.775[α]
	Female	72.3	29	52	
Number of cases	None	8.9	1	9	0.001[β]
	0-10	68.8	23	54	
	11-20	12.5	9	5	
	>20	9.8	8	3	
Experience	5 or less than 5 years	50	17	39	0.170[α]
	More than 5 years	50	24	32	
Workplace	University hospital	50	23	33	0.409[α]
	State hospital	32.1	10	26	
	Private practice	17.9	8	12	

[α]Pearson chi-square test results; [β]Fischer's Exact test results
NAM: Nasoalveolar molding

cases encountered on knowledge of NAM therapy, a linear regression was only seen between the number of cases encountered and years of experience (Table III). There was no correlation between years of experience and the level of knowledge about the NAM appliance.

Discussion

CL/P is one of the most common orofacial malformations, with orofacial clefts occurring in approximately 1 in 700 live births (15,16). Pediatricians play an important role in forming the multidisciplinary treatment team for patients with CL/P. Our study aimed to measure the level of pediatrician awareness regarding NAM therapy, which is one of the most prevalent pre-surgical orthopedic treatments for CL/P.

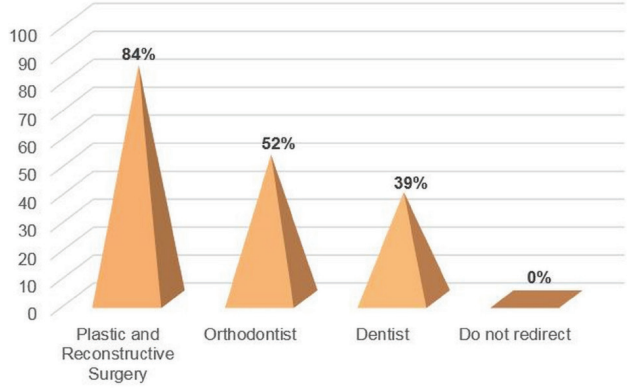

Figure 2. The % distributions of the pediatricians redirect CL/P newborns related departments for NAM

NAM: Nasoalveolar molding

Orofacial clefts are one of the most common congenital anomalies, with a higher prevalence than neural tube defects, though the prevalence of cardiovascular malformations is higher (17,18). In the present study, 10 pediatricians (9%) reported having never been at the birth of a newborn with CL/P, while 11 pediatricians reported taking part in the birth of more than 20 newborns with CL/P. Experienced pediatricians were found to have seen more cases of CL/P than inexperienced pediatricians, and this difference was statistically significant.

In the 1950s, modern methods of pre-surgical orthopedics began with the acrylic plates used by McNeil (19) in patients with CL/P. McNeil (19) used these plates to reduce the space between the hard palate and the alveolar segments. Many modifications of this appliance have since been used for orthopedic treatment before surgery, being used either actively or passively depending on the indication for its use. Grayson and Maull (13) introduced the NAM appliance that was based on the shaping of the nasoalveolar segments in the first weeks after a newborn's birth, and this is now one of the most up-to-date appliances used for pre-surgical orthopedic treatment. The NAM appliance is one of the latest and most important treatment techniques as it enables the surgeon and patient to benefit from a cleft deformity repair that is of minimal severity (3,7,13). While approximately 67% of the pediatricians who participated in the survey stated that they had knowledge of pre-surgical orthopedic treatments, the remaining participants stated that they did not have any knowledge on this subject. Of the pediatricians

Table II. Responses of pediatricians according to their level of knowledge about preoperative treatment of CL/P

	Answer	Experience less than 5 years	Experience more than 5 years	p-value
Do you have any information about presurgical orthopedics performed before surgical treatment in CL/P newborns?	Yes	33	42	0.071[α]
	No	23	14	
How many CL/P newborn patients have you examined?	None	7	3	0.021[β]
	0-10	43	34	
	11-20	4	10	
	>20	2	9	
Have you heard about the use NAM therapy in newborns with CL/P?	Yes	38	43	0.291[α]
	No	15	13	
Do you know what NAM and its' purpose?	Yes	17	24	0.170[α]
	No	39	32	
Do you know who performed the NAM therapy?	Yes	18	27	0.083[α]
	No	38	29	

[α]Pearson chi-square test results, [β]Fischer's Exact test results
CL/P: Cleft lip and/or palate, NAM: Nasoalveolar molding

without knowledge of pre-surgical orthopedic treatment, 62% consisted of pediatricians with less than 5 years of experience.

When asked about NAM and its purpose in patients with CL/P, 41 providers (37%) stated that they had knowledge of this appliance and its purpose, while 71 providers (63%) stated that they did not have any knowledge of NAM. There was no statistical difference between the experienced and inexperienced groups regarding this question. According to this result, pediatricians in Turkey do not have enough knowledge of NAM therapy and its purpose. Such a low rate of awareness is surprising, as the NAM appliance is used quite frequently in pre-surgical orthopedic treatment for patients with CL/P. In a previous study that aimed to measure the attitude of cleft care specialists working in Africa towards the NAM appliance, NAM was only used by orthodontists and consequently, orthodontists had a stronger positive attitude towards pre-surgical orthopedics than other specialists (general surgeons, plastic surgeons, oral and maxillofacial surgeons, otolaryngologists, anesthetists, and general nurses). Similar to the results of our study, the popularity of NAM was limited among pediatricians (20).

We could not identify any other survey study assessing pediatrician awareness and knowledge of pre-surgical orthopedic treatment and the NAM appliance in the literature, which limited the comparisons with our study findings. When asked if providers knew who performed NAM applications, 45 providers (40%) stated that they knew, while 67 providers (60%) stated that they did not know. This was a similar response to the response we received to the previous question.

Another question asked to pediatricians in the questionnaire was, "Who do you refer the newborns with CL/P to?" All pediatricians reported that they direct patients to at least one specialist, 84% to plastic and reconstructive surgeons, 52% to orthodontists, and 39% to dentists. CL/P should be treated by a multidisciplinary team and this approach involves many specialists

Table III. Multivariate analysis for the effect gender, workplace, experience and number of cases on knowledge NAM therapy

	Parameter		**p-value**	**OR**	**95% CI**
Do you have any information about orthopedic applications performed before surgical treatment of lip-palate cleft in newborn with lip-palate cleft?	Gender	F*	0.457	0.69	0.26-1.82
		M			
	Experience	Less than 5 years	0.293	1.57	0.68-3.61
		More than 5 years*			
	Number of cases	None*			
		0-10	0.012	23.33	1.99-273.29
		11-20	0.245	3.51	0.42-29.17
		>20	0.416	2.73	0.24-30.66
	Workplace	University hospital*			
		State hospital	0.457	1.60	0.46-5.53
		Private practice	0.396	1.76	0.48-6.49
Do you know what NAM and its' purpose?	Gender	F*	0.775	0.88	0.38-2.07
		M			
	Experience	Less than 5 years	0.171	1.72	0.79-3.74
		More than 5 years*			
	Number of cases	None*			
		0-10	0.011	24.00	2.06-279.62
		11-20	0.011	6.26	1.52-25.74
		>20	0.654	1.48	0.27-8.27
	Workplace	University hospital*			
		State hospital	0.933	0.96	0.34-2.71
		Private practice	0.350	1.73	0.55-5.50

*Reference parameter, OD: Odds ratio, CI: Confidence interval, F: Female, M: Male, NAM: Nasoalveolar molding

including obstetrician-gynecologists, pediatricians, speech therapists, plastic surgeons, orthodontists, and dentists. Pediatricians, along with obstetrician-gynecologists, are usually the first step in the treatment chain. Pediatricians' increased knowledge about pre-surgical treatment options affects the success of the treatment. Pre-surgical orthopedic applications are recommended to begin within the first few days after birth because the plasticity of the tissues is at its highest. The authors reported that the cartilaginous tissues of a newborn are softer, and their plasticity is higher due to the level of estrogen transferred from the mother (3,8). Therefore, pediatricians should direct the family to the right specialist during this period.

Patients with CL/P should be treated with a multidisciplinary approach that involves many specialists, with pediatricians being one of the most important. Narrowing of the cleft region and an unchanged sagittal dimension, reduction in the number of soft tissue revision and alveolar grafting surgeries, and achievement of excellent facial esthetics with minimal scar tissue are some of the main benefits of this therapy (3,8,21).

Study Limitations

The present study has some limitations. This study was performed on pediatricians in a single country. It is important to obtain more global results can be achieved with larger sample numbers, including pediatricians from different countries.

Conclusion

It is critical to begin the pre-surgical orthopedic treatment process as soon as possible after birth to enhance treatment success. The results of our study indicate that pediatricians do not have sufficient knowledge of NAM and its purpose. Consequently, it is important to increase pediatrician awareness and knowledge regarding treatment alternatives for patients with CL/P, including NAM and pre-surgical orthopedic treatment.

Ethics

Ethics Committee Approval: The study was approved by the Ordu University Clinical Research Ethics Committee with approval number: 2021/09 and date: 07.01.2021.

Informed Consent: For this type of this study, the informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.K.D., S.K.B., T.A., Data Collection or Processing: T.A., Analysis or Interpretation: S.K.B., Writing: K.K.D.

Conflict of Interest: The authors declared no conflict of interest.

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References

1. Imani MM, Golchin N, Safaei M, et al. Methylenetetrahydrofolate reductase C677T polymorphism is not associated with the risk of nonsyndromic cleft lip/palate: An updated meta-analysis. Sci Rep 2020; 10:1531.
2. Lewis CW, Jacob LS, Lehmann CU; SECTION ON ORAL HEALTH. The primary care pediatrician and the care of children with cleft lip and/or cleft palate. Pediatrics 2017; 139:e20170628.
3. Altuğ AT. Presurgical Nasoalveolar Molding of Bilateral Cleft Lip and Palate Infants: An Orthodontist's Point of View. Turk J Orthod 2017; 30:118-25.
4. Ji Y, Garland MA, Sun B, et al. Cellular and developmental basis of orofacial clefts. Birth Defects Res 2020; 112:1558-87.
5. Garland MA, Reynolds K, Zhou CJ. Environmental mechanisms of orofacial clefts. Birth Defects Res 2020; 112:1660-98.
6. Nakajima T, Yoshimura Y, Sakakibara A. Augmentation of the nostril splint for retaining the corrected contour of the cleft lip nose. Plast Reconstr Surg 1990; 85:182-6.
7. Maull DJ, Grayson BH, Brecht L, Cutting C. Long term effects of nasoalveolar molding. annual meeting of the American Cleft Palate Craniofacial Association. 1999. https://pubmed.ncbi.nlm.nih.gov/10499400/
8. Ross RB, MacNamera MC. Effect of presurgical infant orthopedics on facial esthetics in complete bilateral cleft lip and palate. Cleft Palate Craniofac J 1994; 31:68-73.
9. Hotz M, Gnoinski W. Comprehensive care of cleft lip and palate children at Zürich University: a preliminary report. Am J Orthod 1976; 70:481-504.
10. Yarholar LM, Shen C, Wangsrimongkol B, et al. The Nasoalveolar Molding Cleft Protocol: Long-Term Treatment Outcomes from Birth to Facial Maturity. Plast Reconstr Surg 2021; 147:787-94.
11. Maliha SG, Kantar RS, Gonchar MN, et al. The Effects of Nasoalveolar Molding on Nasal Proportions at the Time of Nasal Maturity. Cleft Palate Craniofac J 2021; 58:284-9.
12. Matsuo K, Hirose T, Tomono T, et al. Nonsurgical correction of congenital auricular deformities in the early neonate: a preliminary report. Plast Reconstr Surg 1984; 73:38-50.
13. Grayson BH, Maull D. Nasoalveolar molding for infants born with clefts of the lip, alveolus and palate. Cleft Lip and Palate, Springer, 2006. p. 451-8.
14. Ovsenik M, Primožič J. How to push the limits in the transverse dimension? Facial asymmetry, palatal volume and tongue posture in children with unilateral posterior cross bite: a three-dimensional evaluation of early treatment. Orthod Fr 2014; 85:139-49.

15. Cobourne MT. The complex genetics of cleft lip and palate. Eur J Orthod 2004; 26:7-16.

16. Yılmaz HN, Özbilen EÖ, Üstün T. The Prevalence of Cleft Lip and Palate Patients: A Single-Center Experience for 17 Years. Turk J Orthod 2019; 32:139-44.

17. Impellizzeri A, Giannantoni I, Polimeni A, Barbato E, Galluccio G. Epidemiological characteristic of Orofacial clefts and its associated congenital anomalies: retrospective study. BMC Oral Health 2019; 19:290.

18. Bianchi F, Calzolari E, Ciulli L, et al. Environment and genetics in the etiology of cleft lip and cleft palate with reference to the role of folic acid. Epidemiol Prev 2000; 24:21-7.

19. McNeil C. Orthodontic procedures in the treatment of congenital cleft palate. Dent Rec (London) 1950; 70:126-32.

20. Adeyemi AT, Bankole OO. Attitude of cleft care specialists in Africa towards pre-surgical orthopaedics. East Afr Med J 2012; 89:414-20.

21. Santiago PE, Grayson BH, Cutting CB, Gianoutsos MP, Brecht LE, Kwon SM. Reduced need for alveolar bone grafting by presurgical orthopedics and primary gingivoperiosteoplasty. Cleft Palate Craniofac J 1998; 35:77-80.

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Original Article

Prediction of Transient or Permanent Congenital Hypothyroidism

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ABSTRACT

Aim: Congenital hypothyroidism (CH) is one of the most common endocrinological problems in the neonatal period. CH, which occurs in 1:3,000-4,000 births, is a preventable cause of mental retardation. In the literature, the most common cause of CH is dysgenesis of the thyroid gland, followed by thyroid dyshormonogenesis. We aimed to determine the prevalence of permanent (P-CH) and transient (T-CH) CH in cases followed up with a diagnosis of CH and to identify a prediction method for persistency.

Materials and Methods: We retrospectively analyzed the medical records of 105 children with CH. TSH levels in a screening program, TSH and fT4 levels of the first venous sample, 10-15th day of treatment, monthly in the first 6 months, 2-3 monthly until 18th months, and 6-monthly until 3 years of age were recorded. L-T4 doses (per microgram per body weight) in each visit were also recorded.

Results: From the 105 children (58 males, 47 females) enrolled in this study, 38 (36.2 %) were referred from the National Newborn Screening Program. Treatment was discontinued during the 3rd year follow-up period in 44 (41.9 %) of the cases with normal thyroid gland morphology. L-thyroxine (L-T4) therapy was discontinued at a median age of 1.9+-1.08 years.TSH levels at the time of diagnosis were higher in the P-CH group, but this difference was not statistically significant (p=0.165).

At the sixth month, first and second years of follow-up, L-T4 doses were significantly higher in the P-CH than in the T-CH group (p<0.001, p<0.001, p<0.001 respectively). TSH levels were also higher in the P-CH group than in the T-CH group (p=0.123, p=0.038, p=0.049 respectively). Consistent with these results, measured fT4 levels were found to be lower in the P-CH group compared to the T-CH group (p=0.431, p=0.361, p=0.028 respectively).

Conclusion: L-T4 doses at 6, 12 and 24 months may predict transient hypothyroidism in patients with normal thyroid gland morphology before 36 months.

Keywords: Congenital hypothyroidism, dyshormonogenesis, screening, thyroid dysgenesis, permanent hypothyroidism, transient hypothyroidism

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Introduction

Congenital hypothyroidism (CH) is one of the most common endocrinological problems in the neonatal period. CH, which occurs in 1:3,000 to 4,000 live births, is a preventable cause of mental retardation. In a study from Turkey, its prevalence was 1/2,525 (1,2). CH is two times more common in girls than in boys and is classified into 2 types: permanent CH (P-CH) and transient CH (T-CH). P-CH requires life-long levo-thyroxine (L-T4) treatment whereas T-CH shows continuous, normal thyroid function after discontinuation of LT4 treatment. Although the distinction between P-CH and T-CH is clinically one of the most important concerns for the parents of affected children, differentiating between the 2 types in the neonatal period is difficult, and LT4 treatment should be prioritized to avoid mental retardation (3). The majority of P-CH cases were thyroid dysgenesis; followed by ectopic thyroid gland and aplasia/hypoplasia (4). Only 15% of P-CH cases were thyroid dyshormonogenesis (5). T- CH includes; iodine deficiency, excessive iodine exposure, thyroid stimulating hormone (TSH) receptor blocking antibodies transmitted from mother to fetus, and maternal usage of antithyroid drugs (2).

CH is one of the most important causes of preventable mental retardation and constitutes a serious public health problem. Many developed countries have largely eliminated intellectual disability caused by CH owing to newborn screening programs (NSPs) (1). In Turkey, the National NSP (NNSP) for CH (dried blood spot at 48-72 hours of life) was started on December 26, 2006 by the Turkish Directorate of Public Health. According to the NNSP, an infant is considered to have passed the screening test when the blood spot TSH is <5.5 mIU/L. Values between 5.5 mU/L and 20 mIU/L, are reported for a second evaluation. All cases with a capillary TSH concentration above 5.5 mIU/L in repeat blood samples or above 20 mIU/L in the first sample are referred to the appropriate center for evaluation by venous thyroid function testing, including free thyroxine (fT4) and TSH.

In the present study, we retrospectively analyzed CH cases from the neonatal period up to three years of age in order to determine the prevalence of permanent and transient CH.

Materials and Methods

Study Population and Design

This retrospective design study included patients referred from the NNSP and patients diagnosed with CH at Ege University Pediatric Endocrinology Clinic between January 1st, 2014 and December 31th, 2017. CH was diagnosed if TSH was >10 µIU/mL within the first month of life, with low/normal fT4 levels. Patients who were diagnosed in other hospitals, who had premature delivery history, whose first thyroid function tests were unknown, whose treatment was started in other hospitals or who were not followed up for three years for various reasons were excluded from this analysis. Cases with central hypothyroidism were not included in the study.

Demographic measures, auxological measurements, date of birth, admission age, postnatal age, gender, gestational age in weeks and maternal thyroid disease history were extracted from the systematically collected medical records. Other concomitant congenital diseases were recorded. All weight and height standard deviation (SD) score calculations were made by an automatic calculator (3).

TSH levels in a screening program, TSH and fT4 levels of the first venous sample, 10-15th day of treatment, monthly in the first 6 months, 2-3 monthly until 18th months, and 6-monthly until 3 years of age were recorded. L-T4 doses (per microgram per body weight) in each visit were also recorded. Four and six weeks after the treatment was discontinued, TFT and fT4 were re-evaluated. All serum fT4 and TSH concentrations were measured at least 4 hours after the last L-thyroxine administration.

Thyroid ultrasonography (USG) was performed in all patients. Thyroid glands with a volume less than 0.64 mL (10th percentile) were considered to be hypoplastic for the neonatal period, and those with a volume greater than 1.15 mL (95th percentile) were considered to be hyperplasic (4). Thyroid scintigraphy was performed in those patients whose thyroid gland could not be visualized by USG. According to thyroid imaging results; thyroid glands were classified as agenesis, hemiagenesis, ectopia, hypoplasia or normal.

Cases with normal thyroid appearance were accepted as thyroid dyshormonogenesis, and other cases were accepted as thyroid dysgenesis. In those patients with normal thyroid gland; discontinuation of treatment was tried at any time until the age of 3, and then having TSH <10 mIU/mL and normal fT4 level for at least 6 months were classified as transient hypothyroidism. Patients with thyroid dysgenesis and/or continued treatment at the end of the third year were classified as permanent hypothyroidism.

Those children who gave assent and whose parents gave signed consent were enrolled in the study. The study was approved by the Ege University Medical Ethics Committee with approval number: 20-12T/24.

Laboratory Methods

Serum TSH and fT4 levels were measured by electrochemiluminescence immunoassay using Elecsys 2010 modular analytics E170 (Roche Diagnostics, Indianapolis, IN, USA). For cases between 6 days and 3 months; the normal range of TSH is 0.72-11.0 µU/mL, and for fT4, it is 0.9-2.2 ng/dL. For older cases; TSH level were considered normal if between 0.27-4.2 µIU/mL, and fT4 level was considered normal if between 1.1-2.1 ng/dL.

Statistical Analysis

Analysis was carried out using SPSS for windows 25.0, descriptive statistics are reported using mean ± SD for normally distributed variables, and median for skewed data. Groups were compared by independent samples t-test for normally distributed variables and the Mann-Whitney U test for skewed data. Trends across time were analyzed using linear polynomial contrasts (ANOVA). A p-value <0.05 was considered statistically significant, no adjustment was made for multiplicity of statistical tests.

Results

Out of 192 (101 females, 91 males) patients, 105 patients who met the study criteria were enrolled. Out of these 105 patients, 58 (55.2%) were male, and 47 (44.8%), were female. A history of maternal autoimmune thyroid disease was positive in 34 (32.4%) patients. Mean gestational age was 38.82±1.42 weeks, and mean birth weight was 3,167±551 gr. The mean age at diagnosis was 22.3±21.9 days. The mean serum TSH level was 85.08±65.60 (2.64-501) µIU/mL, and the mean fT4 level was 0.96±0.35 (0.14-1.67) ng/dL in all patients at admission. Mean screening capillary TSH was 66.30±48.50 µIU/mL, first venous TSH was 90.87±82.48 (7.4-498) µIU/mL and first venous fT4 level was 0.87±0.34 (0.23-1.67) ng/dL in those patients who were referred from the NNSP (n=38; 36.2 %). In the remaining 67 (63.8%) patients, venous TSH levels, obtained for various reasons, were high.

Thyroid USG was performed in all patients. Based on the findings of thyroid imaging, the morphology of the thyroid glands was classified as follows: 1 (0.9%) hemiagenesis, 3 (2.8%) hypoplasia and 94 (89.5%) of normal morphology (Table I). In 7 (6.6%) cases, the thyroid gland was not visualized in the normal location and thyroid scintigraphy was performed. Four of these patients had sublingual ectopic thyroid gland and three of them had agenesis on thyroid scintigraphy.

Treatment was discontinued during the 3-year follow-up period in 44 (41.9%) cases with normal thyroid gland morphology. L-T4 therapy was discontinued at a median age of 1.9±1.08 years. The mean serum TSH level was 3.04±1.17 µIU/mL, and the mean fT4 level was 1.37±0.30 ng/dL at the time of discontinuation. The last dose of L-T4 treatment used was 1.24±0.45 mcg/kg/day.

At the time of diagnosis, fT4 levels were significantly higher in the T-CH group than in the P-CH group, including thyroid dysgenesis (p=0.037). TSH levels at the time of diagnosis were higher in the P-CH group than in the T-CH group, but this difference was not statistically significant (p=0.165). No significant difference was found between the auxological measurement of T-CH and P-CH patients. The laboratory and auxological measurements of the patients with permanent and transient CH at the time of diagnosed are summarized in Table II. In the P-CH group; TSH values measured in the early period (1st, 2nd and 3rd months) were lower and fT4 values were higher. However, this difference was not statistically significant (Table III).

Table I. Thyroid imaging (ultrasound)

	Appearance (n)	Rate (%)
Normal thyroid glang morphology	94	89.5
Hypoplastic gland	3	2.8
Hemiagenesis of the gland	1	0.9
Not visualized in the normal location (ectopy/agenesis)	7	6.6

Table II. Baseline characteristics of infants with permanent and transient congenital hypothyroidism

Parameter	Permanent CH (n=61)	Transient CH (n=44)	p-value
TSH levels (N: 0.27-4.2 mIU/mL)	97.11±76.40	63.22±50.84	0.165
fT4 levels (N: 1.1-2.1 ng/dL)	0.90±0.35	1.04±0.33	**0.03**
L-T4 dose at onset (mcg/kg/day)	8.68±3.54	8.01±3.22	0.322
Weight SDS	-0.45±1.31	-0.57±1.19	0.631
Height SDS	-0.46±1.29	-0.46±0.81	0.983

CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score

At the sixth month follow-up, first year follow-up and second year follow-up, L-T4 doses were significantly higher, TSH levels were significantly higher, and serum fT4 levels were significantly lower in in the P-CH group than the T-CH group (Table IV). The LT4 dosage cut-off by receiver operating characteristic (ROC) curve analysis was 1.96 [with sensitivity at 73% and specificity at 82%, area under the curve (AUC)=0.82], 1.56 (with sensitivity at 73%, specificity at 73%, AUC=0.76), and 1.24 µg/kg/day [with sensitivity at 85%, specificity at 73%, AUC=0.84) at ages 1, 2, and 3 years, respectively. The ROC curve is shown in Figure 1.

In subgroup analysis, those cases with thyroid dysgenesis were excluded and the remaining cases were examined in 2 groups as either permanent or transient dyshormonogenesis. There was no significant difference in the TSH, fT4 levels and L-T4 doses at the time of diagnosis between these groups (p=0.424, p=0.069 and p=0.589 respectively) (Table V). At the six-month, one-year and two-year follow-up, L-T4 doses were higher in the permanent dyshormonogenesis group than in the transient dyshormonogenesis group (p=0.020, p=0.015, p=0.143 respectively) (Table VI).

Two cases (1.9%) were Down syndrome and both of these cases had dyshormonogenesis. Fifteen (14.2%) cases had a history of concomitant congenital disease. The most common congenital disease was congenital heart disease (46.6%) (Table VII). Two of the patients (13.3%) with concomitant congenital disease had thyroid dysgenesis, while the others had dyshormonogenesis.

Table III. First, 2nd and 3th month laboratory data of permanent and transient CH cases

Parameter	Permanent CH (n=61)	Transient CH (n=44)	p-value
1st month TSH levels (N: 0.27-4.2 mIU/mL)	3.75±2.77	2.00±1.63	0.529
1st month fT4 levels (N: 1.1-2.1 ng/dL)	1.70±0.51	1.66±0.45	0.731
2nd month TSH Levels (N: 0.27-4.2 mIU/mL)	2.51±1.51	1.35±1.07	0.140
2nd month fT4 levels (N: 1.1-2.1 ng/dL)	1.56±0.35	1.51±0.29	0.544
3th month TSH levels (N: 0.27-4.2 mIU/mL)	3.67±2.71	1.83±1.57	0.194
3th month fT4 levels (N: 1.1-2.1 ng/dL)	1.44±0.30	1.48±0.24	0.561

CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone, fT4: Free thyroxine

Discussion

Our cross-sectional study is one of the most comprehensive retrospective analyzes performed on a national basis to evaluate the data of those cases with either transient or permanent hypothyroidism. Several authors have proposed numerous distinguishing factors between P-CH and T-CH; however, markers for the early detection of T-CH have yet to be validated (5-9).

In studies of CH, P-CH is more frequent than T-CH. In Hashemipour et al.'s (10) study, the prevalence of P-CH was 59.8%, while Scavone et al. (11) reported it to be 65.5%. In a study conducted in Turkey in which 189 cases were analyzed, the prevalence of P-CH was 53.2% (10), while in another study, it was 54 (5). Yanmaz et al. (12) showed a P-CH rate of 41.5%, and they thought that this low frequency may be due to the high consanguineous marriage rate in the study population region. In our study, the rate of permanent hypothyroidism was 58%, and this was similar to other studies in the literature.

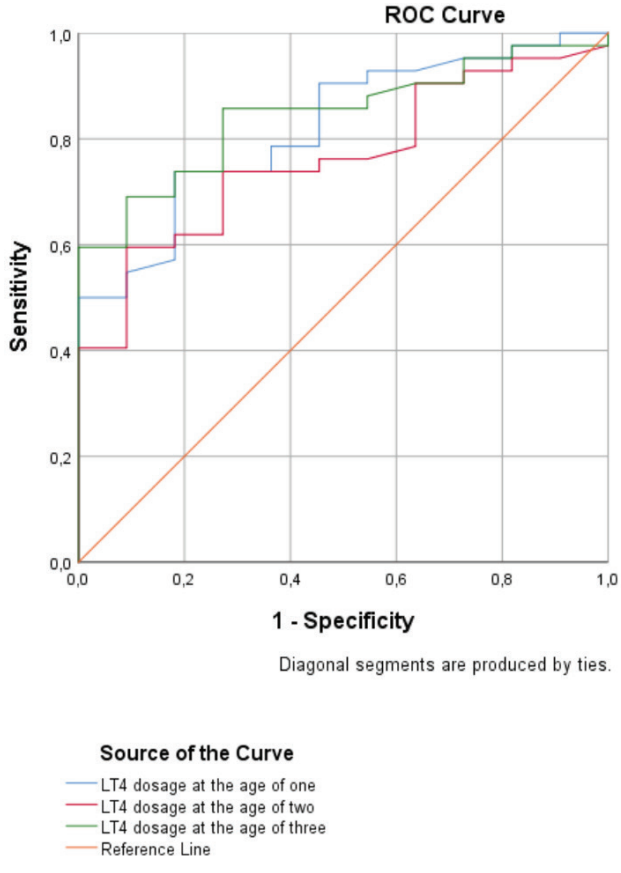

Figure 1. ROC curve of LT4 dosages
ROC: Receiver operator characteristic

Traditionally, it is known that 85% of CH is dysgenesis and 15% is dyshormonogenesis. In our study, thyroid dysgenesis was 18% of the permanent hypothyroidism, much lower than expected. Similar to our study, Kara et al. (13) reported this rate to be 61%, and Bezen et al. (14) reported it to be 56.5%. In similar studies in the literature, this rate was reported to be 50-85% (2,5,7,11). However, in a study by Donbaloğlu et al. (15), the rate of thyroid dysgenesis was 33.3%. In a multi-center study conducted in China, 829 cases detected in CH screening were analyzed retrospectively; thyroid imaging was performed in 664 (80.1%) and thyroid dysgenesis was found in 194 (29.2%) cases (16).

In a study from Japan, 99 cases were analyzed for TSH level and L-T4 dose at the time of diagnosis. These parameters were higher in the P-CH group (17). In our study group, in accordance with this data in the literature, the fT4 level at the time of diagnosis was

Table IV. Follow-up and treatment data of the cases with permanent and transient congenital hypothyroidism

Parameter	Permanent CH (n=61)	Transient CH (n=44)	p-value
6th month TSH levels (N: 0.27-4.2 mIU/mL)	5.91±3.62	1.97±0.97	0.123
6th month fT4 levels (N: 1.1-2.1 ng/dL)	1.52±0.70	1.64±0.76	0.431
6th month L-T4 dose (mcg/kg/day)	2.74±1.02	1.98±0.94	**0.000**
6th month weight SDS	-0.21±1.25	-0.01±0.94	0.430
6th month height SDS	-0.23±1.28	-0.04±0.94	0.346
12th month TSH Levels (N: 0.27-4.2 mIU/mL)	4.24±4.02	2.29±1.09	**0.038**
12th month fT4 levels (N: 1.1-2.1 ng/dL)	1.35±0.24	1.40±0.23	0.361
12th month L-T4 dose (mcg/kg/day)	2.42±0.97	1.72±0.45	**0.000**
12th month weight SDS	-0.23±1.17	-0.23±0.83	0.774
12th month height SDS	-0.18±1.13	-0.12±1.02	0.794
24th month TSH Levels (N: 0.27-4.2 mIU/mL)	4.29±4.27	2.71±1.26	0.490
24th month fT4 levels (N: 1.1-2.1 ng/dL)	1.41±0.21	1.30±0.21	**0.028**
24th month L-T4 dose (mcg/kg/day)	2.24±1.28	1.50±0.39	**0.009**
24th month weight SDS	-0.22±1.25	-0.09±1.26	0.289
24th month height SDS	-0.52±1.20	-0.31±0.87	0.446

CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score
Significant p-values are shown in bold

Table V. Baseline characteristics of infants with permanent and transient dyshormonogenesis cases

Parameter	Permanent dyshormonogenesis cases (n=50)	Transient dyshormonogenesis cases (n=44)	p-value
TSH levels (N: 0.27-4.2 mIU/mL)	82.8±63.8	63.8±51.3	0.424
fT4 levels (N: 1.1-2.1 ng/dL)	0.92±0.35	1.04±0.33	0.069
L-T4 dose at onset (mcg/kg/day)	8.42±3.53	8.04±3.26	0.589
Weight SDS	-0.43±1.35	-0.62±1.17	0.472
Height SDS	-0.4±1.30	-0.45±0.82	0.676

TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score

Table VI. Follow-up and treatment data of the cases with permanent and transient dyshormonogenesis cases

	Permanent dyshormonogenesis cases (n=50)	**Transient dyshormonogenesis cases (n=44)**	**p-value**
Parameter	2.97±2.68	1.99±0.97	0.391
6th month TSH levels (N: 0.27-4.2 mIU/mL)	1.54±0.77	1.65±0.76	0.506
6th month fT4 levels (N: 1.1-2.1 ng/dL)	2.70±1.05	2.00±0.95	**0.002**
6th month L-T4 dose (mcg/kg/day)	**1.18±0.24**	**0.97±0.01**	0.559
6th month weight SDS	-0.15±1.18	-0.01±0.94	0.447
6th month height SDS	3.98±3.84	2.37±1.02	0.417
12th month TSH levels (N: 0.27-4.2 mIU/mL)	1.32±0.20	1.40±0.23	0.112
12th month fT4 levels (N: 1.1-2.1 ng/dL)	2.29±0.88	1.74±0.45	**0.015**
12th month L-T4 dose (mcg/kg/day)	**1.20±0.35**	**0.84±0.23**	0.586
12th month weight SDS	-0.25±1.20	-0.17±0.99	0.751
12th month height SDS	4.47±4.39	2.77±1.23	0.660
24th month TSH levels (N: 0.27-4.2 mIU/mL)	1.42±0.22	1.31±0.21	**0.042**
24th month fT4 levels (N: 1.1-2.1 ng/dL)	2.01±1.01	1.47±0.36	0.143
24th month L-T4 dose (mcg/kg/day)	**1.17±0.19**	**1.28±0.10**	0.313
24th month weight SDS	-0.48±1.07	-0.33±0.88	0.559

TSH: Thyroid stimulating hormone, fT4: Free thyroxine, L-T4: Levo-thyroxine, SDS: Standard deviation score
Significant p-values are shown in bold

Table VII. Congenital anomalies accompanying congenital hypothyroidism

	Number	**Rate (%)**
Tetralogy of Fallot	2	13.3
Pulmonary stenosis	2	13.3
Aortic coarctation	1	6.6
Atrioventricular septal defect	1	6.6
Double outlet right ventricle	1	6.6
Cleft palate	1	6.6
Tracheoesophageal fistula	2	13.3
Duodenal atresia	1	6.6
Anal atresia	1	6.6
Horseshoe kidney	1	6.6
Posterior urethral valve	1	6.6
Meningomyelocele	1	6.6

significantly lower in the P-CH group compared to the T-CH group. However, the TSH levels and L-T4 doses were not statistically significant higher in the P-CH group as was seen in several other studies (6,18). Similarly, Tamam et al. (19) reported that TSH levels were significantly higher and fT4 levels were significantly lower at the time of diagnosis in the P-CH group than in the T- CH group. In another study, fT4 levels were lower in patients with P- CH in accordance with the etiology of the patients (12). In a study from Brazil, it was shown that initial TSH levels cannot be determinative in making a distinction between the transient and permanent disease types (20).

Itonaga et al. (17) reported that the dose of L-T4 used in the first and second years of follow-up was higher in the P-CH group. Furthermore, they showed that CH patients with an LT4 dosage >3.26 µg/kg/day at age 1 year, >2.29 µg/kg/day at age 2 years and >2.32 µg/kg/day at age 3 years were likely to have P-CH (17). In a study in Turkey, drug doses in the sixth month, first and second year were significantly higher in the P-CH group (12). In our study,

similar to the literature, LT4 doses at the sixth month, first and second year were significantly higher in the P-CH group. The cut-off values we obtained were similar to other studies (6,17). However, although those patients in the P-CH group used higher doses of medication, their first and second year TSH levels were higher than the T-CH group. This finding is not expected under appropriate treatment and we speculate that there may have been problems with treatment compliance.

Study Limitations

Our study has some limitations such as its retrospective design, no free T3 levels, thyroglobulin and urine iodine levels and the lack of complete data regarding maternal drug intake and the use of iodine during delivery.

Conclusion

Our cross-sectional retrospective study is one of the comprehensive analysis performed on a national basis to evaluate the data of cases with transient or permanent hypothyroidism. We are conscious that these results will not modify the current standard of practice but we believe that our data, supported by other studies, may allow for earlier discrimination between T-CH and P-CH. In conclusion, the results of this study show that fT4 levels at diagnosis and the L-thyroxine dose at the sixth month, first and second year can be used to distinguish between T-CH and P-CH.

Ethics

Ethics Committee Approval: The study was approved by the Ege University Medical Ethics Committee with approval number: 20-12T/24.

Informed Consent: Those children who gave assent and whose parents gave signed consent were enrolled in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.E., Design: F.E., S.Ö., Data Collection or Processing: H.G.B., A.A., E.E., Analysis or Interpretation: H.G.B., A.A., E.E., Z.V., Literature Search: S.Ö., D.G., Project Administration: Ş.D., Writing: F.E., H.G.B., A.A., E.E., D.G.

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References

1. Mass Screening Committee; Japanese Society for Pediatric Endocrinology; Japanese Society for Mass Screening, Nagasaki K, Minamitani K, et al. Guidelines for mass screening of congenital hypothyroidism (2014 revision). Clin Pediatr Endocrinol 2015; 24:107-33.
2. LaFranchi SH. Approach to the diagnosis and treatment of neonatal hypothyroidism. J Clin Endocrinol Metab 2011; 96:2959-67.
3. Demir K, Konakçı E, Özkaya G, et al. New features for child metrics: Further growth references and blood pressure calculations. J Clin Res Pediatr Endocrinol 2020; 12:125-9.
4. Köksal N, Aktürk B, Sağlam H, Yazıcı Z, Çetinkaya M. Reference values for neonatal thyroid volumes in a moderately iodine-deficient area. J Endocrinol Invest 2008; 31:642-6.
5. Ünüvar T, Demir K, Abacı A, Büyükgebiz A, Böber E. The role of initial clinical and laboratory findings in infants with hyperthyrotropinemia to predict transient or permanent hypothyroidism. J Clin Res Pediatr Endocrinol 2013; 5:170-3.
6. Messina MF, Aversa T, Salzano G, et al. Early discrimination between transient and permanent congenital hypothyroidism in children with eutopic gland. Horm Res Paediatr 2015; 84:159-64.
7. Srinivasan R, Harigopal S, Turner S, Cheetham T. Permanent and transient congenital hypothyroidism in preterm infants. Acta Paediatr 2012; 101:179-82.
8. Kravarusic J. Diabetes Technology Use in Adult swith Type 1 and Type 2 Diabetes. Endocrinol Metab Clin North Am 2020; 49:37-55.
9. Chung HR, Shin CH, Yang SW, et al. High incidence of thyroid dysfunction in preterm infants. J Korean Med Sci 2009; 24:627-31.
10. Hashemipour M, Hovsepian S, Kelishadi R, et al. Permanent and transient congenital hypothyroidism in Isfahan-Iran. J Med Screen 2009; 16:11-6.
11. Scavone M, Carboni E, Stefanelli E, et al. Prediction of Transient or Permanent Congenital Hypothyroidism from Initial Thyroid Stimulating Hormone Levels. Indian Pediatr 2018; 55:1059-61.
12. Yanmaz SY, Ünal E, Taş FF, Yıldırım R, Haspolat YK. Characteristics of Patients with Congenital Hypothyroidism. J Curr Pediatr 2019; 17:412-23.
13. Kara C, Günindi F, Can Yılmaz G, Aydın M. Transient congenital hypothyroidism in Turkey: An analysis on frequency and natural course. J Clin Res Pediatr Endocrinol 2016; 8:170-9.
14. Bezen D, Dilek E, Torun N, Tütüncüler F. Etiological evaluation of primary congenital hypothyroidism cases. Turk Pediatr Ars 2017; 52:85-91.
15. Donbaloğlu Z, Savaş-Erdeve Ş, Çetinkaya S, Aycan Z. Cases referred from the turkish national screening program: Frequency of congenital hypothyroidism and etiological distribution. J Clin Res Pediatr Endocrinol 2019; 11:240-6.
16. Chen J, Lin S, Zeng G, et al. Epidemiologic characteristics and risk factors for congenital hypothyroidism from 2009 to 2018 in Xiamen, China. Endocr Pract 2020; 26:585-94.
17. Itonaga T, Higuchi S, Shimura K, et al. Levothyroxine Dosage as Predictor of Permanent and Transient Congenital Hypothyroidism: A Multicenter Retrospective Study in Japan. Horm Res Paediatr 2019; 92:45-51.

18. Rabbiosi S, Vigone MC, Cortinovis F, et al. Congenital hypothyroidism with eutopic thyroid gland: Analysis of clinical and biochemical features at diagnosis and after re-evaluation. J Clin Endocrinol Metab 2013; 98:1395-402.

19. Tamam M, Adalet I, Bakir B, et al. Diagnostic spectrum of congenital hypothyroidism in Turkish children. Pediatr Int 2009; 51:464-8.

20. Pezzuti IL, Lima PP, Dias VM. Congenital hypothyroidism: the clinical profile of affected newborns identified by the Newborn Screening Program of the State of Minas Gerais, Brazil. J Pediatr (Rio J) 2009; 85:72-9.

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Original Article

The Effect of Massage on Salivary Secretory Iga Level in Preterm Infants

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ABSTRACT

Aim: Secretory Immunoglobulin A (sIgA) is one of the most important components of the immune system and has a prominent role in preventing infections that are transmitted through the gastrointestinal tract and respiratory mucosa. The primary objective of this study was to evaluate the effect of massage on the salivary sIgA level in pre-term infants and the secondary objective was to assess the effect of massage on neonatal weight gain.

Materials and Methods: This study was performed on 150 preterm infants weighing between 1,500 gm and 2,000 gm who were hospitalized in 3 main medical centers of Khorramabad city, Iran between March 2018 and March 2019. The 3 major selected centers were Asalian, Shahid Madani and Shahid Rahimi Hospitals. All infants were randomly allocated to either the intervention (n=75) or the control (n=75) group. Due to our criteria, 18 patients were excluded from this study. In total, 132 infants were included in this study. The initial samples of sIgA were obtained from the saliva of the neonates in both groups on the second day after birth and when acute symptoms of respiratory distress syndrome had resolved. The second samples were collected on the 14th day after birth. During this period, neonates of the intervention group were massaged properly using the Field technique for 15 minutes, three times a day by a trained Neonatal Intensive Care Unit nurse for 12 consecutive days. It should be noted that due to the effect of breast milk on the neonates' sIgA levels, we selected all subjects from those who were not fed with breast milk for some reason, but were fed with formula instead.

Results: According to our findings, a significant difference was observed between the mean weight of the infants between the second and 14th days after birth in both the intervention and control groups ($p<0.001$). However, in comparison, there was no significant difference between the mean weight changes of the infants in both groups ($p=0.845$). Moreover, there was a significant difference between the mean sIgA level changes between the second and 14th days after birth in both groups ($p<0.001$), but these changes were more significant in the intervention group compared to the control group ($p<0.001$).

Conclusion: These results showed that massage therapy in neonates can increase the level of sIgA which plays an important part in the infant's immune system. However, this had no positive effect on the weight gain process. It is recommended that massage therapy be used as a safe auxiliary therapeutic procedure for preterm infants and that mothers can learn and perform this technique as a simple way to boost the immune system of their infants.

Keywords: Massage, salivary secretory IgA, preterm infants, immune system, preterm, weight gain

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Introduction

Massage therapy is an interesting topic in neonatal medicine and many studies have been conducted over the last decade. New studies support the efficacy of massage therapy as a complementary therapeutic method in neonatal medicine (1). Touching and stroking infants during massage stimulate nerve pathways and speed up myelination of the brain and nervous system through increased hypothalamic activity followed by increased somatotropin levels. In animal studies, the lack of skin and tactile stimuli reduces the growth of all organs, and when the animals return to normal tactile stimulation, this defect is eliminated, which highlights the beneficial effects of massage on growth hormone levels (2). Massage inside the infant's mouth increases the levels of gastrointestinal hormones such as insulin and gastrin, which highlights the fact that skin stimulation and massage in the same way will increase similar hormones. Studies on neonatal insulin and glucose levels have shown that massage in preterm infants will increase insulin and IGF-1 levels (1). In the field of pain management in children, it has been mentioned that massage by parents during sleep is useful for reducing chronic and myofascial pain (3). It is believed that, like breastfeeding by the mother, massage by the father will facilitate proper bonding between the father and infant. The mother as a massager reduces the level of stress hormones in the mother's body and significantly reduces the rate of postpartum depression and anxiety (1,4).

Neonatal Intensive Care Units (NICUs) are full of stress and massage therapy can lessen the level of stress hormones in preterm infants, as well as improve the developmental status of low-birthweight neonates (5-7). Immunoglobulins (Ig) are components of the humoral immune system that are produced in response to internal and external antigens. Each antibody molecule has an overall symmetrical structure consisting of four polypeptide chains, two identical light chains and two identical heavy chains. Antibody molecules are classified into different classes, subclasses, types and subtypes based on differences in the structures of the heavy and light chain constant regions. There are five main classes of Igs: IgG, IgM, IgA, IgD, and IgE-some of which include a number of distinct subclasses (8).

The placenta selectively blocks various substances to prevent transmission from the mother to the fetus. Of all the antibodies, only IgG can cross the placental barrier. IgA and IgM are blocked from crossing the placenta and so their levels in infancy confirm their production by the infant itself (9,10).

IgA comprises monomeric and polymeric IgA of two subtypes, IgA_1 and IgA_2. In adults, IgA_1 is the main subtype in serum but, in the mucosa, IgA_2 production is higher than IgA_1 (11). Serum IgA is mainly monomeric while secretory IgA is dimeric and is joined by the J chain and the secretory part. IgA is often secreted by the secretory cells of the breast as a dimer. IgA is the main antibody found in many body secretions, including tears, saliva, respiratory and intestinal secretions, mucous and milk (12). IgA is the most important Ig in breast milk and it protects the mucosal surfaces against foreign pathogens until the infant progressively is able to make its own IgA, which sometimes takes weeks to months after birth. It can also protect infants from diseases which are transmitted via the mucosa of the gastrointestinal tract and respiratory system (9,10,13).

In infants, due to the underdeveloped humoral and cellular immune systems, the risk of infection is significantly increased compared to other age groups. Therefore, in infants, limited infections are potentially more likely to become systemic and severe infections (14). Akimoto et al. (15) showed that 12 months of exercise could significantly increase both the concentration and secretion rate of secretory IgA (sIgA) in elderly subjects. The concentration of salivary IgA was significantly increased in subjects who received four relaxation methods including massage therapy, compared with a touch control group (16). One analysis found that receiving massages is an effective method to recover from temporary immunosuppression state induced by heavy exercise and to enhance levels of sIgA (17).

In the current study, we aimed to investigate the effect of neonatal massage on increasing the level of sIgA in the saliva of preterm infants who were admitted to Asalian, Shahid Madani and Shahid Rahimi Hospitals in Khorramabad city, Iran between March 2018 and March 2019.

Materials and Methods

This randomized clinical trial was conducted on 150 preterm infants who were admitted to NICUs in the three main hospitals in Khorramabad city, Iran between March 2018 and March 2019. Initially, the sample size was calculated to be 63 for each group. However, to ensure the adequacy of the participants, 75 infants were allocated to each group. Infants were selected from formula-fed infants because of the possible effect of breastfeeding on sIgA levels. The participants were randomly divided into intervention and control groups. The inclusion criteria were as follows: preterm infants with gestational age <37 weeks, weighing

between 1,500 and 2,000 gm, formula-fed, an absence of congenital infections, no congenital anomalies, an having no prohibition of massage (e.g. skin lesions, hematoma or dislocation of limbs).

Infants were excluded from this study if any of the following criteria applied: evidence in favor of infection (for example, positive blood culture or positive CSF culture), a requirement for mechanical ventilation, a history of seizure or an occurrence of seizure during the study, a history of immunodeficiency among first-degree relatives, a requirement for blood transfusion, transferal of the infant to another hospital for any reason, the presence of any congenital anomalies, a history of maternal illness during the pregnancy period prior to delivery such as hepatitis B or syphilis (based on screening tests), a requirement for surgery in the course of the study, discharge from the hospital, dissatisfaction of the parents with respect to continuing the study and receiving some medications for instance, antibiotics and intravenous Ig.

Written consent was obtained from the parents before enrollment in the study. Hundred-fifty infants were randomly divided into 2 groups: The control group (n=75) and the intervention group (n=75). Of these, 18 cases were excluded (7 infants from the intervention and 11 infants from the control group) and 132 infants remained until the completion of the study (68 infants in the intervention and 64 infants in the control group). The major reason of exclusion was the lack of sufficient saliva (3 infants in the intervention and 5 infants in the control group). Other reasons for exclusion were as follows: The parent's unwillingness to continue the study (3 infants from the intervention and 4 infants from the control group) and 3 infants died during the study (one infant in the intervention and 2 infants in the control group).

In the intervention group, 41 (60.3%) and 27 (39.7%) of the cases were male and female, respectively. In the control group, 31 (48.4%) and 33 (51.6%) of the subjects were male and female, respectively. In terms of gender, both groups were similar (p=0.22).

Only the researchers were aware of infant's groups (intervention or control) and the laboratory was blind to which group they were in. The neonates in both groups were administered standard ward care during the course of this study. Based on standards for NICUs, the room temperature was between 2-26 °C.

We performed the massage based on the Field technique. Massaging was gentle using the ventral surface of both hands with gentle pressure and it was performed by a trained NICU nurse who played no other role in the study and she was also blind to the hypothesis of the study. Before starting the massage, her hands were washed and warmed. Sunflower oil was used as a lubricant. The infants were placed in a quiet environment under a radiant warmer. The infants of the intervention group received massages for 15 minutes, three times per day, for 12 consecutive days. Each massage session consists of three phases of 5 minutes. The infants received their massages one hour after being fed. During the first and third phase of the massage therapy, the neonate was placed in a prone position, and was massaged for five one-minute periods (five seconds per stroking motion) over each region in the following sequence: A) 12 stroking movements from the top of the head to the neck downwards and then reversed; B) 12 stroking movements from the neck to the shoulders and then reversed; C) 12 stroking movements from the upper back down to the waist and then reversed; D) 12 stroking movements from the thighs down to the ankles and the reversed; E) 12 stroking movements from the shoulder to the hand and then reversed on both arms. In the second phase, the infant was put in a supine position and six flexion/extension moves were performed on the limbs in the following order: each arm, each leg and finally both legs together. Each flexion/extension movement lasted approximately 10 seconds. The control group did not receive massage therapy during the study.

In both groups, the initial and second saliva samples were obtained using a sterile infant mucus extractor from the mouth of the neonates. The initial and second samples were collected on the second and 14th day after birth, respectively. The salivary sIgA level was measured using an IgA saliva ELISA kit (DiaMetra, Perugia, Italy) according to the manufacturer's protocol.

In both groups, the weight of the neonates was also measured on the second and 14th day after birth. This study did not interfere with the treatment of the infants.

All phases of this study and consent forms were approved by the Ethics Committee of Lorestan University of Medical Sciences (LUMS.REC.1396.232) and the registration ID of this study in Iranian Registry of Clinical Trials is IRCT20171225038056N1.

Statistical Analysis

Data were expressed as means ± standard deviation. After determining the measures of central tendencies and measures of dispersion, independent t-test and paired t-test were used to analyze the data. All results were

analyzed using IBM SPSS for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant for all analyses.

Results

According to the findings, the mean weight of the infants in the control group was 1,706.95±146.07 gm and 2,051.64±157.41 gm on the second and 14th day after birth, respectively. There was also a significant difference between the mean weight of the infants in the control group on the second and 14th day after birth (p<0.001) (Figure 1). The mean weight of the infants in the intervention group was 1,684.41±136.4 gm on the second day and 2,032.42±145.49 gm on the 14th day after birth. There was a significant difference between the mean weight of the infants in the intervention group on the second and 14th day after birth (p<0.001) (Figure 1).

According to the results, the mean weight changes showed no significant difference between the intervention and control groups on the second or 14th day after birth (p=0.845) (Figure 2).

The mean sIgA levels in the control group on the second and 14th day were 8.25±3.76 (µg/dL) and 9.68±3.67 (µg/dL), respectively, and there was also a significant difference between the mean sIgA level on the second and 14th day (p<0.001) (Figure 3). Moreover, the mean sIgA levels in the intervention group on the second and 14th day after birth were 9.71±4.52 (µg/dL) and 17.8±6.4 (µg/dL), respectively, and we found a significant difference between the mean sIgA levels before and after massage therapy (p<0.001) (Figure 3).

The results of our study demonstrated that the mean sIgA level changed between the intervention and control groups on the second and 14th day after birth and there was a significant difference between the two groups (p<0.001) (Figure 4).

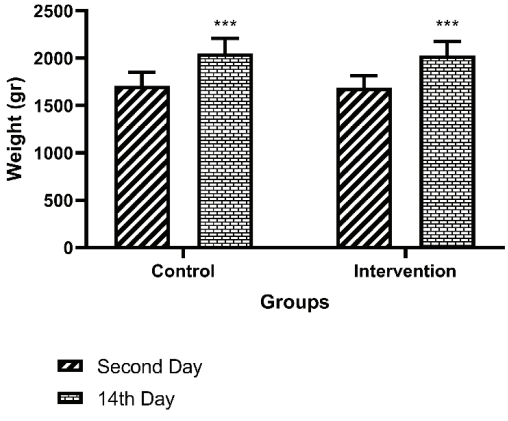

Figure 1. Comparison of mean weight changes between second and 14th day after birth in the intervention and control groups

Discussion

IgA is one of the most important Igs in the human body and it protects infants against those diseases that are transmitted via the mucosa of the gastrointestinal tract and respiratory system (13). Massage therapy is a new subject in neonatal medicine and new studies support the efficacy of massage as a safe and complementary therapeutic method in the field of neonates (1).

In the present study, for the first time, the effect of massage therapy on salivary sIgA levels in preterm infants was investigated. Our findings in this research provide

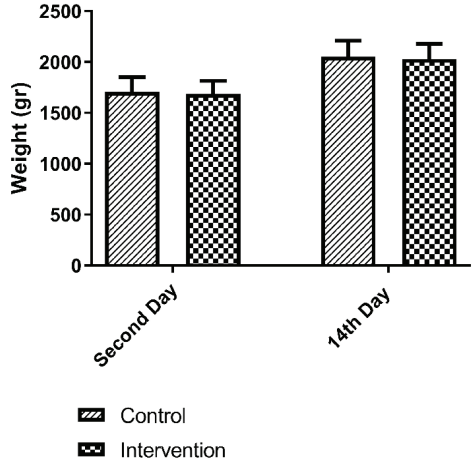

Figure 2. Comparison of mean weight changes between the intervention and control groups on the second and 14th day after birth

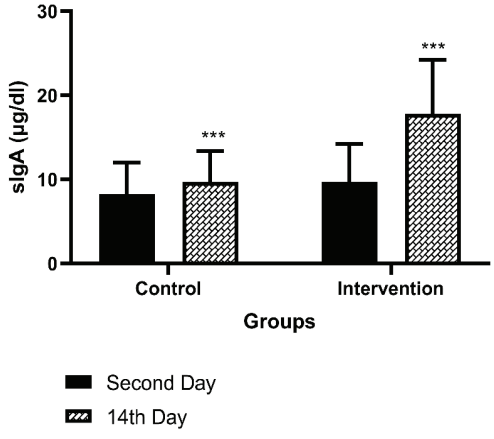

Figure 3. Comparison of mean sIgA level changes between the intervention and control groups on the second and 14th day after birth
sIgA: Secretory immunoglobulin A

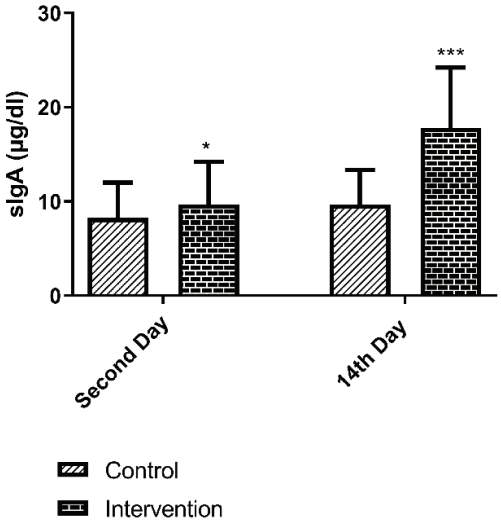

Figure 4. Comparison of mean sIgA level changes between the intervention and control groups on the second and 14th day after birth
sIgA: Secretory immunoglobulin A

evidence indicating that the sIgA levels was significantly higher on the 14th day in the intervention group than in the control group, but we could not observe an increase regarding the mean weight parameter.

Some previous studies have addressed the effects of massage on improving bone density (6,18), neurodevelopmental status in preterm infants (19,20), bilirubin levels of infants with jaundice (21,22), sleep quality in infants with low birth weight (23) and reducing the length of hospital stays (24).

Our study showed that weight gain was not significantly different between those infants who received massages and those who did not. This result was contrary to previous studies (7,25-29).

A study performed by Scafidi et al. (29) on preterm infants demonstrated that tactile/kinesthetic stimulation can improve weight gain and sleep behavior in low-birth-weight infants. In another study, they also showed that massage can accelerate the process of discharging low-birth-weight infants from the hospital by 6 to 10 days (30). Research conducted on infants aged between 32 and 37 weeks found that massage has a significant effect on improving mental-behavior status (20). Another study evaluated the effect of massage on salivary cortisol levels in preterm infants and showed that massage therapy can reduce the level of cortisol as a stress indicator in saliva (31). The results of another study demonstrated that the Field technique massage and gentle human touch can also decrease urine cortisol levels in preterm infants (5).

Ang et al. (32) investigated the effect of massage therapy on the immune system of preterm infants and they found that this method could be associated with higher NK cell cytotoxicity.

We believe that more subjects should be included in future studies and further studies are needed on this new topic in neonatology. Finally, it is recommended that massage therapy be performed by parents or trained nurses as a complementary therapeutic method for infants.

Conclusion

According to the results of our study, the sIgA levels in preterm infants who received massage for 12 consecutive days was significantly higher compared to a control group who did not receive any intervention. Furthermore, at the end of the study, there was no significant difference in weight gain between the intervention and control groups. Massage therapy can be used as a safe complementary practice for infants and it can also promote bonding between the mother and infant. Our observations provide new information about the effect of massage therapy on boosting the mucosal immune system in preterm infants. However, further studies can be carried out to investigate the use of massage therapy on more samples over a longer period of time in order to clarify the true effects of such complementary methods on the immune system and on the outcomes of neonatal infections.

Ethics

Ethics Committee Approval: All phases of the study and consent forms were approved by the Ethics Committee of Lorestan University of Medical Sciences (LUMS.REC.1396.232) and the registration ID of this study in Iranian Registry of Clinical Trials is IRCT20171225038056N1.

Informed Consent: A written consent was obtained from parents before enrollment in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.F., Design: Ar.K., Data Collection or Processing: Ar.K., Analysis or Interpretation: R.M., A.K., Literature Search: M.F., Writing: Ar.K., R.M., A.K.

Conflict of Interest: The authors declare that they have no conflict of interest.

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References

1. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant, Vol 2, 10 ed2014. p. 327-50.
2. Gardner SL, Carter BS, Enzman-Hines M, Hernandez JA. Merenstein & Gardner's Handbook of Neonatal Intensive Care, 7 ed2010. p. 245-62.
3. Kliegman RM, Stanton B, St. Geme JW, Schor NF. Nelson Textbook of Pediatrics, Vol 1, 20 ed2015. p. 442.
4. Tricia Lacy Gomella MDC, Fabien G. Eyal. Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs, 7 ed2013. p. 217-8.
5. Asadollahi M, Jabraeili M, Mahallei M, Asgari Jafarabadi M, Ebrahimi S. Effects of Gentle Human Touch and Field Massage on Urine Cortisol Level in Premature Infants: A Randomized, Controlled Clinical Trial. J Caring Sci 2016; 5:187-94.
6. Stalnaker KA, Poskey GA. Osteopenia of Prematurity: Does Physical Activity Improve Bone Mineralization in Preterm Infants? Neonatal Netw 2016; 35:95-104.
7. Vickers A, Ohlsson A, Lacy JB, Horsley A. Massage for promoting growth and development of preterm and/or low birth-weight infants. Cochrane Database Syst Rev 2004;2004:Cd000390.
8. Schroeder Jr HW, Cavacini L. Structure and function of immunoglobulins. The Journal of allergy and clinical immunology 2010; 125:S41-S52.
9. Quigley J. The role of oral immunoglobulins in systemic and intestinal immunity of neonatal calves. Ames, IA, Iowa State University 2004.
10. Ravivarma KR, Babar ST, Master J, Bapat JP, Baxi AJ. Immunoglobulins in newborns: differential study of premature and full term infants. J Postgrad Med 1979; 25:97-101.
11. Brandtzaeg P, Farstad IN, Johansen FE, Morton HC, Norderhaug IN, Yamanaka T. The B-cell system of human mucosae and exocrine glands. Immunol Rev 1999; 171:45-87.
12. Goldman AS, Chheda S, Keeney SE, Schmalstieg FC. Immunology of Human Milk and Host Immunity. Fetal and Neonatal Physiology 2011; 1690-701.
13. Pineda-Martínez S, Hernández-Islas JL, Escobedo-Torres MP, et al. Immunoglobulin Concentrations in Plasma and Saliva During the Neonatal Period. Pediatr Neonatol 2016; 57:213-8.
14. Mhairi G. MacDonald MMKS, Martha D. Mullett. Avery's Neonatology: Pathophysiology and Management of the Newborn2015. p. 506-7.
15. Akimoto T, Kumai Y, Akama T, et al. Effects of 12 months of exercise training on salivary secretory IgA levels in elderly subjects. Br J Sports Med 2003; 37:76-9.
16. Green RG, Green ML. Relaxation increases salivary immunoglobulin A. Psychological Reports 1987; 61:623-9.
17. Arroyo-Morales M, Olea N, Ruíz C, et al. Massage after exercise--responses of immunologic and endocrine markers: a randomized single-blind placebo-controlled study. J Strength Cond Res 2009; 23:638-44.
18. Haley S, Beachy J, Ivaska KK, Slater H, Smith S, Moyer-Mileur LJ. Tactile/kinesthetic stimulation (TKS) increases tibial speed of sound and urinary osteocalcin (U-MidOC and unOC) in premature infants (29-32weeks PMA). Bone 2012; 51:661-6.
19. Lai MM, D'Acunto G, Guzzetta A, et al. PREMM: preterm early massage by the mother: protocol of a randomised controlled trial of massage therapy in very preterm infants. BMC Pediatrics 2016; 16:146.
20. Rajaram R, Vizhi DM, Kumar V. Effects of early neonatal massage with therapeutic positioning in preterm and low birth weight babies on neurobehavioral and neurodevelopmental status. Int J Pharm Bio Sci 2017; 8.
21. Dalili H, Sheikhi S, Shariat M, Haghnazarian E. Effects of baby massage on neonatal jaundice in healthy Iranian infants: A pilot study. Infant Behav Dev 2016; 42:22-6.
22. Lin CH, Yang HC, Cheng CS, Yen CE. Effects of infant massage on jaundiced neonates undergoing phototherapy. Ital J Pediatr 2015; 41:94.
23. Kelmanson IA, Adulas EI. Massage therapy and sleep behaviour in infants born with low birth weight. Complement Ther Clin Pract 2006; 12:200-5.
24. Mendes EW, Procianoy RS. Massage therapy reduces hospital stay and occurrence of late-onset sepsis in very preterm neonates. J Perinatol 2008; 28:815-20.
25. Diego MA, Field T, Hernandez-Reif M, Deeds O, Ascencio A, Begert G. Preterm infant massage elicits consistent increases in vagal activity and gastric motility that are associated with greater weight gain. Acta Paediatr 2007; 96:1588-91.
26. Field T, Diego MA, Hernandez-Reif M, Deeds O, Figuereido B. Moderate versus light pressure massage therapy leads to greater weight gain in preterm infants. Infant Behav Dev 2006; 29:574-8.
27. Jabraeile M, Rasooly AS, Farshi MR, Malakouti J. Effect of olive oil massage on weight gain in preterm infants: A randomized controlled clinical trial. Niger Med J 2016; 57:160-3.
28. Rad Z, Haghshenas M, Javadian Y, Hajiahmadi M, Kazemian F. The effect of massage on weight gain in very low birth weight neonates. J Clin Neonatol 2016; 5:96-9.
29. Scafidi FA, Field TM, Schanberg SM, et al. Effects of tactile/kinesthetic stimulation on the clinical course and sleep/wake behavior of preterm neonates. Infant Behavior and Development 1986; 9:91-105.
30. Scafidi FA, Field TM, Schanberg SM, et al. Massage stimulates growth in preterm infants: A replication. Infant Behavior and Development 1990; 13:167-88.
31. Asmarani R, Irwanto I, Suryawan A, Irmawati M, Utomo M. Effect of Massage on Salivary Cortisol Level in Preterm Neonates. Iranian Journal of Neonatology IJN 2020; 11:12-6.
32. Ang JY, Lua JL, Mathur A, et al. A randomized placebo-controlled trial of massage therapy on the immune system of preterm infants. Pediatrics 2012; 130:e1549-58.

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Original Article

The Role of Fetal MRI-based Texture Analysis in Differentiating Congenital Pulmonary Airway Malformation and Pulmonary Sequestration

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ABSTRACT

Aim: The purpose of our study was to evaluate the diagnostic performance of fetal magnetic resonance imaging (MRI)-based texture analysis (TA) to differentiate the two most common lung malformations, congenital pulmonary airway malformation (CPAM) and pulmonary sequestration (PS).

Materials and Methods: This retrospective single-center study included 24 patients with CPAM and 8 patients with PS who had a fetal MRI examination between January 2015 and December 2020. T2-weighted coronal images were used for TA. One reader designated the malformation borders and drew a region-of-interest for TA. The differences in values of the texture features between the groups were assessed and receiver operating characteristic curves were calculated for each statistically significant feature. P-value<0.05 was considered statistically significant.

Results: Forty-eight texture features were calculated for each malformation. Twenty features on T2-weighted images were significantly different between the CPAMSs and PSs. Among these, short-run high gray-level emphasis and long-run emphasis, which are gray-level run-length matrix features parameters, had the largest area under the curves: 0.956 (sensitivity 87%, specificity 95%) and 0.943 (sensitivity 87%, specificity 85%), respectively.

Conclusion: Our results suggest that fetal MRI-based TA may be used to distinguish CPAMs from PSs in fetuses with uncertain pulmonary findings prior to birth.

Keywords: Fetal, magnetic resonance imaging, computer-assisted image processing, lung malformation

Introduction

Congenital lung malformations (CLMs) are being noticed prior to birth more frequently nowadays by means of innovations in fetal ultrasonography (US) and magnetic resonance imaging (MRI) (1). The frequency of CLMs has been suggested to be 1 in 2,000 to 2,500 live births in studies conducted recently (2,3). Despite the fact that radiologists and perinatologists are generally able to make a specific diagnosis antenatally by fetal US, similar images in different abnormalities can complicate the diagnostic process. Thus, fetal MRI first came into use as a supplementary

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examination and then became one of the routine imaging methods for the evaluation of CLMs in most centers (4-6). Nevertheless, it can still be impossible to differentiate the two most commonly encountered malformations, congenital pulmonary airway malformation (CPAM) and pulmonary sequestration (PS), by means of fetal MRI (7).

Texture analysis (TA) is a mathematical program that produces extensive numerical information from radiologic images within a region-of-interest (ROI) (8). In recent years, the role of TA in differentiating similar-looking tumors in various radiological examinations or predicting outcomes in different clinical conditions has been evaluated and has demonstrated promising results (9-12). However, there is inadequate data regarding fetal MRI-based TA in the literature. To our knowledge, to date, no prior studies have been conducted to examine the role of TA in distinguishing CLMs in the antenatal period.

Based on positive results regarding texture studies, we speculated that different malformations might be distinguished antenatally despite having similar images in fetal MRI. Hence, the purpose of our study was to assess the diagnostic performance of fetal MRI-based TA to differentiate between CPAM and PS.

Materials and Methods

Patient Selection

Ethical approval for this study was obtained from the University of Health Sciences Turkey, Tepecik Training and Research Hospital, Clinical Researches Ethics Committee (approval number: 2021/03-12, date: 24.03.2021). Informed consent was waived due to the retrospective nature of the study. The radiology and perinatology archives of a single tertiary center were scanned retrospectively to determine fetuses who were evaluated due to CLMs and had a fetal MRI examination between January 2015 and December 2020. Those patients who were diagnosed as CPAM or PS based on postnatal computed tomography (CT) findings were included in this study. Four patients with severe motion artifacts were excluded because of poor imaging quality. Finally, a total of 32 patients (24 CPAM and 8 PS) were included in this study.

MRI Protocol

Fetal MRI examinations were performed using a 1.5-T MRI system (Siemens Aera, Germany). Maternal sedation was not required in any of the scannings. While the mother was in the supine position, a torso phased array coil was placed on the pelvis, especially focusing on the fetus. T2-weighted Half-Fourier acquisition single-shot turbo-spin-echo (HASTE) sequences in axial, sagittal, and coronal planes were acquired separately for the head and the body of the fetus. True fast imaging with steady-state free precession, Dixon T1-weighted, and echo-planar sequences were included in the protocol in certain conditions to obtain more information about the abnormality. Overlapping or interspacing was not preferred in the HASTE sequences of the fetal body. The HASTE sequence was acquired with the following parameters: time to repetition/time to echo, 1,100/122 ms; slice thickness, 4-5 mm; field of view (FOV), 300-400 mm; matrix, 256×256; flip angle, 180; number of excitations, 1.

MRI Interpretation and TA

MRI images were examined by two readers (one pediatric radiologist with 4 years of experience and a 9-year experienced radiologist) in consensus. The site of the lesion (right or left) and the maximum diameter of the lesion were recorded.

TA was performed using the freely available software LIFEx (Version 5.1, www.lifexsoft.org) (13). Two radiologists who also evaluated the MRI examinations performed the TA measurements in consensus. Coronal T2-weighted HASTE sequences in Digital Imaging and Communications in Medicine format were obtained and entered into the LifeX program for the ROI delineation. The ROI drawings were performed manually by including the whole lesion on the image for which the largest lesion diameter was observed (Figure 1), as demonstrated previously in the literature (14,15). The number of gray levels was adjusted to 7 bits

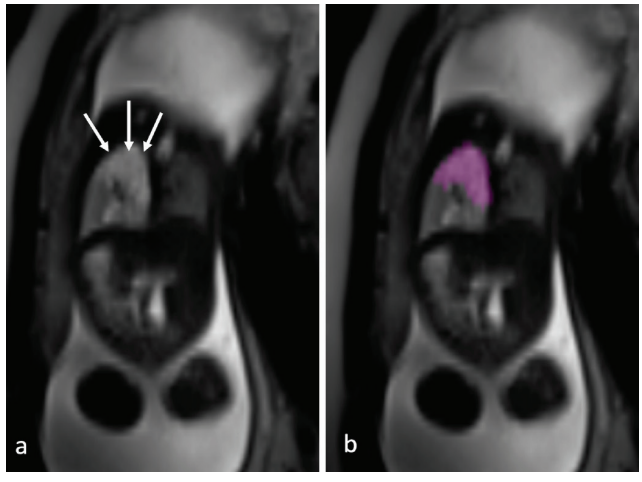

Figure 1. (a) A hyperintense lesion (arrows) is seen in the left lung in coronal T2-weighted fetal MRI. (b) ROI was drawn for the texture analysis

MRI: Magnetic resonance imaging, ROI: Region-of-interest

(128) to ensure uniformity. An automatic measurement was performed between mean ± 3 standard deviations (SDs) of the ROI content to specify intensity rescaling numbers. The minimum and maximum limits were accepted as the mean value of ROI - 3 SD and + 3 SD, respectively. Numbers above or below mean ± 3 SDs at the beginning were adjusted to mean ± 3 SDs. Furthermore, the voxel widths in the X-Y-Z directions were normalized as X=0.5 mm, Y=0.5 mm, and Z=2.5 mm, after counting their mean ± 3 SDs. Finally, forty-eight TA features including six first-order (histogram) statistics, thirty-two second-order statistics, seven conventional, and three shape features were extracted for each patient.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means and SD and categorical variables as frequency counts and percentages. The distribution of the variables was examined by Kolmogorov Smirnov and Shapiro-Wilk tests. Chi-square test or Fisher's exact test was used to compare categorical variables between the two patient groups (CPAM and PS). The comparison of continuous variables was performed by the Mann-Whitney U test or independent t-test. Receiver operating characteristic (ROC) curve analyses were constructed for each statistically significant feature to assess the performance of TA for making a diagnosis. P-values less than 0.05 were considered statistically significant.

Results

Patient Characteristics and MRI Features

Thirty-two patients (24 CPAM and 8 PS) were included in this study. The mean gestational age at the time of fetal MRI examination was 24.3±3.3 (20-33) weeks. The mean maternal age was 28.2±5.2 (20-39) years. None of the demographic features showed a statistical difference between the two groups (Table I). Thirteen (40.6%) of the malformations were located in the left hemithorax. The mean maximum diameter of the malformations was 22.91±6.4 mm. PSs were all located in the left hemithorax. The left-sided location of the PS group was statistically significant (p=0.007). In the postnatal period, CT examination was performed on all patients in order to detect a systemic feeding vessel.

Texture Analysis

Forty-eight texture features were calculated for each malformation on coronal T2-weighted HASTE images. Twenty features including 5 gray-level co-occurrence matrix (GLCM) features, 7 gray-level run-length matrix (GLRLM) features, 1 neighborhood gray-level difference matrix (NGLDM) feature, 6 gray-level zone length matrix (GLZLM) features, and 1 shape feature were significantly different between the CPAMSs and PSs (Table II).

Among the GLCM features, homogeneity, entropy-log10, and entropy-log2 values were higher in the PS group while energy and dissimilarity values were found to be lower in those patients with PS. Of the GLRLM parameters, long-run emphasis (LRE), long-run high gray-level emphasis (LRHGE), gray-level non-uniformity (GLNU), and run length non-uniformity (RLNU) values were greater while short-run emphasis (SRE), short-run high gray-level emphasis (SRHGE), and run percentage values were lower in the PS group compared to the CPAMs. The NGLDM_ contrast feature demonstrated lower values in the PS group. In those patients with PS, long-zone emphasis (LZE) and GLNU, which are two of the GLZLM parameters, showed higher values. On the other hand, short-zone emphasis (SZE), short-zone high gray-level emphasis (SZHGE), long-zone high gray-level emphasis (LZHGE), and zone percentage (ZP) were the other parameters of GLZLM which were seen to be lower in the PS group. Lastly, one of the shape features, namely compacity, was higher in the PS group.

The ROC curve analysis results with optimal cut-off values to differentiate CPAM and PS according to TA values

Table I. Demographic data and MRI features

	CPAM (n=24)	PS (n=8)	p-value
Gestational week at fetal MRI	23.96±3.1	25.63±4.0	0.117
Maternal age	28.79±5.2	26.75±5.3	0.360
Birth weight (kg)	3312±254	3245±375	0.265
Location (left/right)	11/13	8/0	**0.007**
Maximum diameter (mm)	23.79±6.5	20.25±5.7	0.191

CPAM: Congenital pulmonary airway malformation, PS: Pulmonary sequestration, MRI: Magnetic resonance imaging

Table II. Comparison of the texture analysis features between the two groups

Texture features	CPAM (n=24)	PS (n=8)	p-value
Histogram			
Skewness	-0.1984±0.3905	-0.3160±0.5233	0.572
Kurtosis	2.9420±0.5405	2.9287±0.7976	0.632
Excess kurtosis	-0.0575±0.5404	-0.0710±0.7972	0.632
Entropy-log10	1.7808±0.0959	1.8512±0.0603	0.067*
Entropy-log2	5.9150±0.3201	6.1475±0.2047	0.064*
Energy	0.0197±0.0042	0.0167±0.0033	0.068
GLCM			
Homogeneity	0.1159±0.0207	0.1590±0.0232	**<0.001**
Energy	0.0093±0.0077	0.0029±0.0029	**0.013***
Contrast	651.3333±240.4242	438.1250±247.5897	0.051
Correlation	0.2230±0.2532	0.4752±0.2721	0.064
Entropy-log10	2.2700±0.4608	2.7450±0.3836	**0.018**
Entropy-log2	7.5395±1.5345	9.1237±1.2829	**0.015**
Dissimilarity	20.0250±4.2173	15.3900±4.5875	**0.029**
GLRLM			
SRE	0.9907±0.0037	0.9821±0.0094	**0.003**
LRE	1.0400±0.0156	1.1612±0.1693	**<0.001**
LGRE	0.0031±0.0042	0.0050±0.0074	0.862
HGRE	4614.1666±7.1728	4610.0000±11.9522	0.497
SRLGE	0.0030±0.0040	0.0049±0.0071	0.761
SRHGE	4572.9166±15.7367	4521.2500±42.2365	**<0.001**
LRLGE	0.0034±0.0047	0.0061±0.0097	0.896
LRHGE	4879.1666±428.2818	5092.5000±359.9503	**<0.001**
GLNU	5.7508±4.9567	18.1075±27.6785	**0.013**
RLNU	336.5291±350.7447	1212.6250±2044.9866	**0.015**
RP	0.9872±0.0049	0.9748±0.0135	**0.006**
NGLDM			
Coarseness	0.0239±0.0126	0.0148±0.0105	0.107
Contrast	2.7074±1.7891	1.2028±0.5543	**0.012***
Busyness	0.0142±0.0058	0.0422±0.0785	0.459*
GLZLM			
SZE	0.8919±0.0307	0.8268±0.0886	**0.011**
LZE	1.6783±0.3355	3.9300±3.7660	**0.002**
LGZE	0.0028±0.0036	0.0036±0.0045	0.794
HGZE	4599.5833±81.3729	4611.2500±121.9411	0.948*
SZLGE	0.0023±0.0029	0.0024±0.0028	0.433
SZHGE	4103.7500±181.7023	3743.7500±356.5684	**0.001**
LZLGE	0.0076±0.0143	0.0238±0.0526	0.486
LZHGE	7732.9166±1520.55	3738.7500±1614.46	**0.002**
GLNU	4.5292±3.6623	10.1137±11.9746	**0.021**
ZLNU	210.8833±196.3578	377.1250±344.4616	0.058
ZP	0.8520±0.0481	0.7265±0.1278	**0.002**
Conventional indices			
Q1	396.9250±254.1990	363.6250±212.7150	0.896
Q2	428.1416±270.5008	410.5000±250.9222	0.896
Q3	460.1958±288.5882	445.8750±274.9875	0.948*
Min	281.5666±181.9861	258.7500±160.2121	0.896
Mean	427.0791±270.3255	405.0000±244.3627	0.896
Std	455.0972±116.3722	405.2644±198.1508	0.843
Max	544.8791±351.3055	519.6250±316.8875	1.000

Table II. Continued

Texture features	CPAM (n=24)	PS (n=8)	p-value
Shape features			
Volume (mL)	3.7567±3.8214	5.4962±3.8065	0.177
Volume (voxels)	676.1666±139.2360	559.5000±233.5899	0.744
Compacity	0.7638±0.3357	1.0386±0.5099	**0.041**

*Independent t-test. Other p-values were calculated by using Mann-Whitney U test. Bold values indicate statistically significant.
CPAM: Congenital pulmonary airway malformation, PS: Pulmonary sequestration, GLCM: Gray-level co-occurrence matrix, GLRLM: Gray-level run-length matrix, SRE: Short-run emphasis, LRE: Long-run emphasis, LGRE: Low gray-level run emphasis, HGRE: High gray-level run emphasis, SRLGE: Short-run low gray-level emphasis, SRHGE: Short-run high gray-level emphasis, LRLGE: Long-run low gray-level emphasis, LRHGE: Long-run high gray-level emphasis, GLNU: Gray-level non-uniformity, RLNU: Run length non-uniformity, RP: Run percentage, NGLDM: Neighborhood gray-level difference matrix, GLZLM: Gray-level zone length matrix, SZE: Short-zone emphasis, LZE: Long-zone emphasis, LGZE: Low gray-level zone emphasis, HGZE: High gray-level zone emphasis, SZLGE: Short-zone low gray-level emphasis, SZHGE: Short-zone high gray-level emphasis, LZLGE: Long-zone low gray-level emphasis, LZHGE: Long-zone high gray-level emphasis, ZLNU: Zone length non-uniformity, ZP: Zone percentage, Q1: The first quartile, Q2: The second quartile, Q3: The third quartile, Min: Minimum, Std: Standard, Max: Maximum

Table III. The diagnostic performances of the texture analysis features with the cutoff values for pulmonary sequestration on coronal T2-weighted imaging

Texture feature	Area under the curve	95% Confidence interval	Cut-off value	Sensitivity (%)	Specificity (%)	p-value
GLCM_Homogeneity	0.940	0.856-1.000	>0.141	87	83	< 0.001
GLCM_Entropy-log10	0.781	0.609-0.954	>2.590	75	75	0.019
GLCM_Entropy-log2	0.784	0.613-0.955	>8.600	75	75	0.018
GLRLM_LRE	0.943	0.861-1.000	>1.055	87	85	< 0.001
GLRLM_LRHGE	0.789	0.628-0.950	>4835.0	87	67	0.016
GLRLM_GLNU	0.797	0.639-0.955	>8.980	87	67	0.013
GLRLM_RLNU	0.792	0.633-0.951	>244.0	87	63	0.015
GLZLM_LZE	0.865	0.709-1.000	>2.065	75	85	0.002
GLZLM_GLNU	0.776	0.614-0.938	>4.235	87	75	0.021
Shape_Compacity	0.745	0.515-0.974	>0.839	75	67	0.041
GLCM_Energy	0.789	0.621-0.957	<0.002	75	75	0.016
GLCM_Dissimilarity	0.760	0.540-0.981	<18.75	75	70	0.030
GLRLM_SRE	0.852	0.686-1.000	<0.986	75	88	0.003
GLRLM_SRHGE	0.956	0.887-1.000	<4555.0	87	95	< 0.001
GLRLM_RP	0.828	0.626-1.000	<0.980	75	85	0.006
NGLDM_Contrast	0.802	0.632-0.972	<1.465	75	67	0.012
GLZLM_SZE	0.805	0.562-1.000	<0.859	75	85	0.011
GLZLM_SZHGE	0.880	0.745-1.000	<3975.0	75	80	0.001
GLZLM_LZHGE	0.530	0.576-0.946	<4525.0	50	65	0.002
GLZLM_ZP	0.865	0.704-1.000	<0.814	75	80	0.002

GLCM: Gray-level co-occurrence matrix, GLRLM: Gray-level run-length matrix, LRE: Long-run emphasis, LRHGE: Long-run high gray-level emphasis, GLNU: Gray-level non-uniformity, RLNU: Run length non-uniformity, GLZLM: Gray-level zone length matrix, LZE: Long-zone emphasis, SRE: Short-run emphasis, SRHGE: Short-run high gray-level emphasis, RP: Run percentage, NGLDM: Neighborhood gray-level difference matrix, SZE: Short-zone emphasis, SZHGE: Short-zone high gray-level emphasis, LZHGE: Long-zone high gray-level emphasis, ZP: Zone percentage

are displayed in Table III. Two GLRLM parameters, SRHGE and LRE, showed the largest area under the curve results: 0.956 (95% confidence interval (CI), 0.887-1) and 0.943 [95% CI 0.861-1], respectively (Figure 2). A GLRLM_SRHGE value of <4555.0 had the finest diagnostic results with a sensitivity of 87% and a specificity of 95% for diagnosing PS. The optimal cut-off TA value for the GLRLM_LRE was >1.055, with a sensitivity of 87% and a specificity of 85%.

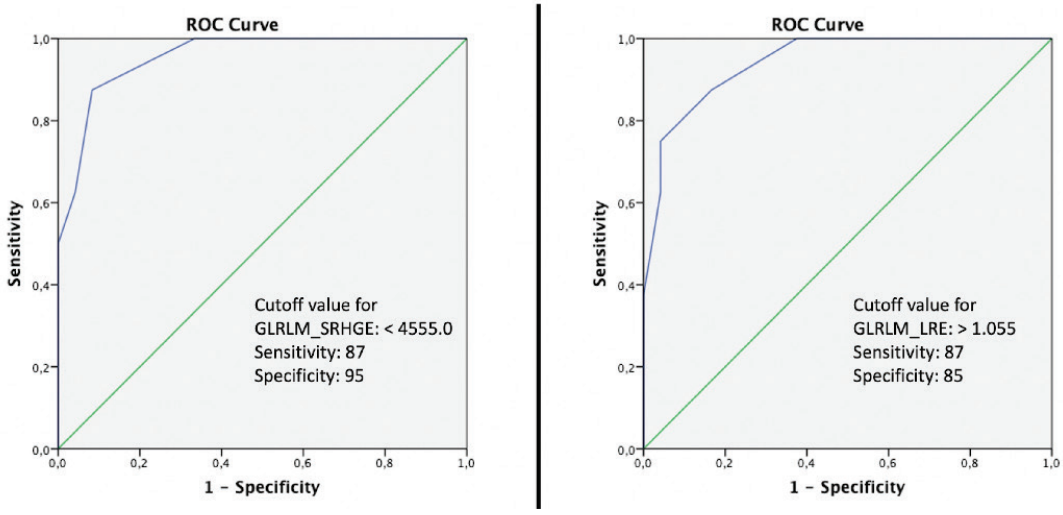

Figure 2. Receiver operating characteristics curves of the GLRLM_SRHGE and the GLRLM_LRE for differentiating pulmonary sequestration
ROC: Receiver operating characteristic, GLRLM: Gray-level run-length matrix, SRHGE: Short-run high gray-level emphasis, LRE: Long-run emphasis

Discussion

In this study, we assessed the performance of TA values to differentiate between fetuses with CPAM and PS on fetal MRI examinations. As far as we know, this study is the first in the literature to analyze the texture parameters between CLMs. Our study showed that fetal MRI-based TA may help to distinguish between CPAM and PS antenatally. Several TA parameters demonstrated a significant difference between those patients with CPAM and those with PS, in addition to the favorable area under the curve results from 0.745 to 0.956 in our study. A GLRLM_SRHGE value of <4555.0 and a GLRLM_LRE value of >1.055 were found to be the most significant parameters to make an accurate diagnosis with a sensitivity of 87% in both and a specificity of 95% and 85%, respectively.

TA allows for the extraction of quantitative features from the medical images by means of dedicated software (16). The principle of TA is based on the knowledge that pixels in an image contain quantitative information, which may reveal the underlying pathophysiology of a texture (17). TA features are divided into subgroups as first-order features (histogram), second-order features, shape features, and conventional indices. First-order features, also defined as histogram analysis, contain the distribution of voxel values inside an ROI (18). Second-order features describe the statistical associations between pixels (18). The GLCM shows pixel pairs in a figure towards a particular route while the GLRLM calculates the size of pixels (17). The NGLDM reflects the difference in gray-level values between a particular pixel and its neighbors (19). The GLZLM calculates the size of uniform pixels for each grey level (15). The shape features represent the geometric factors like volume, sphericity, and compacity within an ROI.

The data obtained from TA and their meanings do not reflect any visual finding on the radiological images. In this study, we did not find any differences in the first-order and conventional features and this may indicate that CPAM and PS have a comparable distribution of gray-level intensities in fetal MRI images. The shape features also did not show any significance except for compacity, which was one of the least significant features among all significant variables. However, a number of second-order features demonstrated statistical significance in our study. To summarize the parameters of interest; SRE, SRHGE, SZE, SZHGE, LZHGE, and ZP values were lower in the PS group while LRE, LRHGE, and LZE values were higher. According to these findings, we can interpret that high gray-levels are less frequent in PSs. This may be explained by the knowledge that CPAMs have cystic components (7) and this microstructural texture results in higher gray-levels in the T2-weighted MRI image. The GLRLM_SRHGE and the GLRLM_LRE values showed the highest significance in this study, supporting our theory.

The opportunity of evaluating relations between quantitative data and imaging features has brought a new point of view to various clinical conditions. However, to the best of our knowledge, TA has not been evaluated in fetal MRI images. Therefore, we did not have the chance to compare our results with the literature. Making an accurate and trustworthy diagnosis is very important in CLMs as it

may change the management, for instance, resection or observation in asymptomatic patients (20,21). Although fetal US and MRI can determine an accurate diagnosis mostly, it has also been reported that both US and MRI were unable to diagnose CLMs in approximately 25% of cases (22). It was also indicated that although fetal MRI was superior to US for correctly determining the PS, the sensitivity rate was 70%. For these reasons, we evaluated the performance of TA in addition to fetal MRI, to figure out if it might help to determine the right diagnosis in the two most common CLMs, namely, CPAM and PS. Our diagnostic performance rates with fetal MRI-based TA were found to be higher than the study conducted by Mon et al. (22), in which they demonstrated the diagnostic accuracy of fetal US and MRI in CLMs.

Study Limitations

There were some limitations in this study. The retrospective nature of the study and the small number of subjects were the major limitations. Secondly, TA was performed on two-dimensional slices instead of volumetric measurement. Although three-dimensional analysis represents more extensive information, two-dimensional analysis has also been proven to provide adequate results (23). Thirdly, it is a known fact that TA values may be affected by different imaging protocols. Even though all fetal MRI examinations were performed by one scanner and had the same acquisition parameters, the FOV varied between 300-400 mm depending on the size of the fetuses. We normalized the voxel sizes and standardized the pixel discrimination to reduce this limitation (24). Finally, although TA values were measured automatically, two observers manually delineated the margins and drew the ROIs.

Conclusion

Fetal MRI-based TA provided comprehensive information regarding the two most common CLMs. Various texture parameters, particularly the GLRLM features, revealed important data to differentiate between CPAM and PS with high rates of sensitivity and specificity. By means of further trials with a larger population, TA might be used as a valuable modality to predict diagnosis in patients with CLMs prior to birth.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Turkey, Tepecik Training and Research Hospital, Clinical Researches Ethics Committee (approval number: 2021/03-12, date: 24.03.2021).

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: D.Ö., Ö.Ö., Design: F.C.S., Data Collection or Processing: O.S., F.C.S, B.K.A., Analysis or Interpretation: F.C.S., O.S., Literature Search: O.S., B.K.A., Ö.Ö., Writing: O.S.

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References

1. Goldstein RB. A practical approach to fetal chest masses. Ultrasound Q 2006; 22:177-94.
2. Burge D, Wheeler R. Increasing incidence of detection of congenital lung lesions. Pediatr Pulmonol 2010; 45:104.
3. Lima JS, Camargos PA, Aguiar RA, Campos AS, Aguiar MJ. Pre and perinatal aspects of congenital cystic adenomatoid malformation of the lung. J Matern Fetal Neonatal Med 2014; 27:228-32.
4. Levine D, Barnewolt CE, Mehta TS, Trop I, Estroff J, Wong G. Fetal thoracic abnormalities: MR imaging. Radiology 2003; 228:379-88.
5. Liu YP, Chen CP, Shih SL, Chen YF, Yang FS, Chen SC. Fetal cystic lung lesions: evaluation with magnetic resonance imaging. Pediatr Pulmonol 2010; 45:592-600.
6. Santos XM, Papanna R, Johnson A, et al. The use of combined ultrasound and magnetic resonance imaging in the detection of fetal anomalies. Prenat Diagn 2010; 30:402-7.
7. Biyyam DR, Chapman T, Ferguson MR, Deutsch G, Dighe MK. Congenital lung abnormalities: embryologic features, prenatal diagnosis, and postnatal radiologic-pathologic correlation. Radiographics 2010; 30:1721-38.
8. Kassner A, Thornhill RE. Texture analysis: a review of neurologic MR imaging applications. AJNR Am J Neuroradiol 2010; 31:809-16.
9. Sarioglu O, Sarioglu FC, Akdogan AI, et al. MRI-based texture analysis to differentiate the most common parotid tumours. Clin Radiol 2020; 75:877.
10. Sarioglu FC, Sarioglu O, Guleryuz H, Ozer E, Ince D, Olgun HN. MRI-based texture analysis for differentiating pediatric craniofacial rhabdomyosarcoma from infantile hemangioma. Eur Radiol 2020; 30:5227-36.
11. Sandrasegaran K, Lin Y, Asare-Sawiri M, Taiyini T, Tann M. CT texture analysis of pancreatic cancer. Eur Radiol 2019; 29:1067-73.
12. Sarioglu O, Sarioglu FC, Capar AE, Sokmez DFB, Topkaya P, Belet U. The role of CT texture analysis in predicting the

clinical outcomes of acute ischemic stroke patients undergoing mechanical thrombectomy. Eur Radiol 2021; 31:6105-15.

13. Nioche C, Orlhac F, Boughdad S, et al. LIFEx: A Freeware for Radiomic Feature Calculation in Multimodality Imaging to Accelerate Advances in the Characterization of Tumor Heterogeneity. Cancer Res 2018; 78:4786-9.
14. Cannella R, Rangaswamy B, Minervini MI, Borhani AA, Tsung A, Furlan A. Value of Texture Analysis on Gadoxetic Acid-Enhanced MRI for Differentiating Hepatocellular Adenoma From Focal Nodular Hyperplasia. AJR Am J Roentgenol 2019; 212:538-46.
15. Li Z, Mao Y, Huang W, et al. Texture-based classification of different single liver lesion based on SPAIR T2W MRI images. BMC Med Imaging 2017; 17:42.
16. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology 2016; 278:563-77.
17. Rizzo S, Botta F, Raimondi S, et al. Radiomics: the facts and the challenges of image analysis. Eur Radiol Exp 2018; 2:36.
18. Koçak B, Durmaz EŞ, Ateş E, Kılıçkesmez Ö. Radiomics with artificial intelligence: a practical guide for beginners. Diagn Interv Radiol 2019; 25:485-95.
19. Stoecker WV, Chiang CS, Moss RH. Texture in skin images: comparison of three methods to determine smoothness. Comput Med Imaging Graph 1992; 16:179-90.
20. Aziz D, Langer JC, Tuuha SE, Ryan G, Ein SH, Kim PC. Perinatally diagnosed asymptomatic congenital cystic adenomatoid malformation: to resect or not? J Pediatr Surg 2004; 39:329-34.
21. Ng C, Stanwell J, Burge DM, Stanton MP. Conservative management of antenatally diagnosed cystic lung malformations. Arch Dis Child 2014; 99:432-7.
22. Mon RA, Johnson KN, Ladino-Torres M, et al. Diagnostic accuracy of imaging studies in congenital lung malformations. Arch Dis Child Fetal Neonatal Ed 2019; 104:372-7.
23. Ng F, Kozarski R, Ganeshan B, Goh V. Assessment of tumor heterogeneity by CT texture analysis: can the largest cross-sectional area be used as an alternative to whole tumor analysis? Eur J Radiol 2013; 82:342-8.
24. Collewet G, Strzelecki M, Mariette F. Influence of MRI acquisition protocols and image intensity normalization methods on texture classification. Magn Reson Imaging 2004; 22:81-91.

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Original Article

Thiopurine-S-Methyltransferase Gene Polymorphism and Drug-related Toxicity in Children Treated for Acute Leukemia and Non-Hodgkin's Lymphoma

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ABSTRACT

Aim: Thiopurine S-methyltransferase (TPMT) is an essential enzyme in the metabolism of thiopurine drugs, and its activity may change due to different polymorphisms in the *TPMT* gene. The *TPMT* gene has different genetic polymorphisms in different ethnic groups. This study aimed to determine the frequency of TPMT polymorphisms in children with acute leukemia/non-Hodgkin lymphoma (AL/NHL) and healthy children and to evaluate their association with severe toxicities in the study population.

Materials and Methods: Sixty-seven pediatric AL/NHL patients and 84 healthy children were evaluated. Genotyping for the TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, TPMT*4, TPMT*5, TPMT*6, and TPMT*7 alleles were performed by the real-time polymerase chain reaction technique. The number of grade 3 or higher hematologic and hepatic toxicities were recorded from the patient charts.

Results: In the AL/NHL patients, we found that the patients had generally wild-type TPMT*1 allele in 80.6%, whereas TPMT*2 (238G>C) was seen in 1.5%, TPMT*3A (c.460G>A and c.719A>G) in 0%, and TPMT*3B polymorphisms (460G>A) in 17.9%. We found wild-type TPMT*1 allele in 98.8% and TPMT*3B polymorphisms (460G>A) in 1.2% of the healthy volunteers. Grade ≥3 myelosuppression developed in 22/54 patients with the wild type allele, and it developed in 5/12 patients with TPMT*3B allele. Six (8.9%) patients had grade ≥3 aspartate aminotransferase elevations, 17 (25%) patients had grade ≥3 alanine transaminase elevations (1-5 times), and 42 patients had (62.6%) grade ≥3 total bilirubin elevations.

Conclusion: TPMT*3B polymorphism was the most common allele detected in our study group. This allele frequency is very high in comparison to other studies from our country and it was over-represented in comparison to the healthy volunteers. We did not find any relationship between severe hematologic/hepatic toxicities and *TPMT* gene polymorphisms.

Keywords: Thiopurine S-methyltransferase, leukemia, lymphoma, polymorphism, toxicity, childhood

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Introduction

Thiopurine drugs, such as 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG), are cytotoxic agents used to treat acute leukemia and non-Hodgkin's lymphoma (NHL). Oral 6-MP is a mainstay of the maintenance therapy of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphomas (LLs). Oral 6-TG is another thiopurine drug used in the maintenance treatment of acute myeloid leukemia (AML). One of the most frequent adverse effects of thiopurine drugs is myelosuppression, which is usually reversed by decreasing the dosage of the drug.

Thiopurine S-Methyltransferase (TPMT) is a cytosolic enzyme that converts thiopurine drugs into inactive metabolites via methylation reactions and it provides protection against 6-MP/6-TG drug toxicity (1). Usually, 90% of patients have normal TPMT activity. However, in 10% of patients, TPMT enzyme activity may be different due to different *TPMT* gene polymorphisms. Patients who carry homozygous *TPMT* gene polymorphisms with two non-functional *TPMT* genes (0.3%) have no TPMT enzyme activity and may experience life-threatening myelosuppression when taking thiopurine drugs (1,2). Patients with heterozygous mutations with one non-functional allele have intermediate enzyme activity and have a higher risk for toxicity than normal patients, but 40-70% can tolerate these drugs. Due to these life-threatening toxicities, the Clinical Pharmacogenetics Implementation Consortium (2013) and the US Food and Drug Administration (2015) recommended testing for *TPMT* gene polymorphism before starting mercaptopurine treatment and adjusting dosages according to gene status (2).

The *TPMT* gene is located on chromosome 6p22.3, and more than 23 single nucleotide polymorphisms have been reported (3). TPMT 1 (wild-type) allele codes the normal active enzyme. The most common alleles responsible for deficiency are TPMT 2 (c.238G>C), TPMT 3A (c.460G>A and c.719A>G), and TPMT 3C (c.719G>A). These account for 80-95% of deficient cases. TPMT 3A and 3B polymorphisms may result in an apparent lack of TPMT enzyme activity. On the other hand, TPMT 2 and TPMT 3C polymorphisms do not affect enzyme activity, but they result in a prominent decrease in TPMT protein levels (4,5). Therefore, patients with ALL, AML, and LL may have different sensitivities to thiopurines as a result of these genetic polymorphisms in the *TPMT* gene.

TPMT has different genetic polymorphisms in different ethnic groups. Therefore, we aimed to determine the frequency and type of TPMT polymorphisms in our study population and assess its relationship with the hematologic and hepatic toxicities of 6-MP and 6-TG.

Materials and Methods

Subjects

This study included patients with leukemia, lymphoma, and healthy subjects as a control group. The healthy subjects were collected from those patients who were seen for any reason other than malignancy in the general pediatrics outpatient service. The local ethics committee approved this study, and informed consent was obtained from the parents.

Treatment protocols were ALL-Berlin-Franfurt-Münster-90 (BFM), ALL-BFM-95, and Türkiye ALL-2000 for ALL in consecutive years, while AML-BFM-93 was used for AML, and NHL-BFM-90 and 95 were used for LL. In the maintenance treatment of ALL and LL, 6-MP was given at a dosage of 50 mg/m^2/day and oral methotrexate was given weekly (total treatment duration two years for ALL). In the AML maintenance treatment, 6-TG was given at a dosage of 40 mg/m^2/day for one year.

In the maintenance protocols, patients were given 100% of the estimated drug dosage if white blood cell (WBC) counts were between 2,000-3,000/mm^3 and 50% of the dosage if WBC counts were between 1,000-2,000/mm^3. The drug is withdrawn in cases where WBC is less than 1,000/mm^3. Similarly, the drug is withdrawn in cases where hepatotoxicity is ≥3 grade. The number of grade ≥3 hematologic (Hemoglobin, WBC, platelet counts) and hepatic toxicities [serum alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin levels] were obtained from the patient charts by the investigators.

We used the Common Toxicity Criteria version 5 recommended by the National Cancer Institute for hematological and hepatic toxicity. The grades explain the severity of toxicity; Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Death (6).

The patients were followed up at the outpatient service bi-weekly. The highest value measured in each month was considered to be the toxicity value.

DNA Isolation and TPMT Genotyping

Genomic DNA was extracted from all subjects' peripheral blood leukocytes using the high pure polymerase chain reaction (PCR) template preparation kit (Roche Applied Science, Mannheim, Germany) and stored at -20 °C until use. Genotyping for the TPMT*2, TPMT*3A,

TPMT*3B, TPMT*3C, TPMT*4, TPMT*5, TPMT*6 and TPMT*7 alleles was performed according to the modified protocol of Tai et al. (4) by means of real-time PCR using the Light Cycler® v.2.0 instrument (Roche Applied Science, Mannheim, Germany). For this purpose, specific primers and hybridization probes (TIB MOLBIOL, Berlin, Germany) for the analyzed alleles were used combined with the Light Cycler DNA Master Hybridization Probes Kit (Roche Applied Science, Mannheim, Germany). Polymorphic alleles were identified by the specific melting temperature (Tm) of the resulting amplicons.

Statistical Analysis

Data were analyzed using SPSS software (version 21.0). The means of the groups were analyzed using non-parametric tests. Correlation of the TPMT polymorphisms with different parameters was performed using the chi-square or Fisher's exact tests, and a p-value of <0.05 was considered statistically significant.

Results

The study group consisted of 67 patients (43 male, 24 female), and the mean age was 8.1 years (1-18 years). The diagnosis was ALL in 42, AML in 5, and LL in 20 patients. The control group consisted of 84 healthy children (34 male and 50 female) with a mean age of 9.5 years (1-18 years). Patient characteristics are given in Table I.

Table I. Characteristic features of the patients

	Patients (n)	Control group (n)
Age, years	8.1 (1-18)	9.5 (1-18)
Gender		
Male Female	43 24	34 50
Disease		
ALL AML NHL	42 5 20	- - -

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, NHL: Non-Hodgkin lymphoma

In the genotyping, we found that the patients in the study group had generally wild-type TPMT (*1) allele at a prevalence of 80.6%, TPMT*2 (G238C) at a prelence of 1.5 % and TPMT*3B polymorphisms (G460A) at a prevalence of 17.9% (Table II). The polymorphisms detected were heterozygous mutations, and no homozygous mutations were detected. Other polymorphisms including TPMT*3A, TPMT*3C (A719G), TPMT*3D, TPMT*4 (G-A), TPMT*5 (T146C), TPMT*6 (A539T) and TPMT*7 (T681G) were not detected.

In the control group, wild-type TPMT (*1) was 98.8% and TPMT*3B was 1.2%. Other polymorphisms were not detected. The leukemia-lymphoma patients were found to have less wild-type TPMT but more TPMT*3B polymorphism (p=0.0001 and 0.0001) (Table II).

As for hematologic toxicity, only one patient (1.5%) developed grade ≥3 anemia (2 times) during maintenance treatment, and this patient had a wild-type TPMT allele. However, 28 patients (41.8%) developed grade ≥3 leukopenia. Of these patients, 22 of them had wild-type TPMT allele, 5 of them had TPMT*3B polymorphism, and one of them had TPMT*2 polymorphism. None of the patients developed grade ≥3 thrombocytopenia (Table III).

As for severe hepatic toxicity, six (8.9%) patients had grade ≥3 AST elevations, while 17 (25%) patients had grade ≥3 ALT elevations (1-5 times), and 42 patients (62.6%) had grade ≥3 total bilirubin elevations (1-23 times) (Table III).

We did not find any relationship between the numbers of severe (grade ≥3) hematologic/hepatic toxicities and *TPMT* gene polymorphisms in the statistical analysis.

Discussion

Thiopurine drugs, such as 6-MP and 6-TG are a mainstay of the maintenance therapy of acute leukemia and LLs. TPMT enzyme catalyzes the methylation and inactivation of thiopurine drugs. The enzyme activity is influenced by polymorphisms in the *TPMT* gene and TPMT has different genetic polymorphisms in different ethnic groups. It is important to know TPMT polymorphisms in the population

Table II. TPMT polymorphism distribution of the patients

TPMT allele	SNP position	Genotype distrubition n=67 (patient)	Genotype distrubition n=86 (control)
TPMT 1	Wild	54 (80.6)	85 (98.8)
TPMT 2	238 G>C	1 (1.5)	0
TPMT 3B	460 G>A	12 (17.9)	1 (1.2)

TPMT: Thiopurine S-methyltransferase, SNP: Single-nucleotide polymorphism

Table III. Grade≥3 hematologic/hepatic toxicities in patients according to TPMT polymorphism (n=67)

	ALT (n)	AST (n)	T. Bil	Anemia (n)	Leukopenia (n)	Trombocytopenia (n)
TPMT 1	11	5	31	1	22	0
TPMT 2	0	0	1	0	1	0
TPMT 3B	6	1	10	0	5	0

TPMT: Thiopurine S-methyltransferase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

to evaluate the safety of these drugs. Therefore, we aimed to determine the frequency and type of TPMT polymorphisms in Turkish children. The most common polymorphism was TPMT*3B allele in healthy Turkish children (1.2%). Other polymorphisms (TPMT*2, TPMT*3B, TPMT*3A, TPMT*3C, TPMT*3D, TPMT*4, TPMT*5, TPMT*6, TPMT*7) were not determined. There is a limited data about the TPMT polymorphisms in healthy Turkish children. Sayitoğlu et al. (7) analyzed TPMT genotypes in healthy Turkish individuals and detected the prevalence of the TPMT*2 to be 2%, TPMT*3B to be 0%, and TPMT*3C to be 1.4%. However, this is different from our results. We did not detect TPMT*2 and TPMT*3C allels.

In the leukemia-lymphoma group, we found that leukemic children had wild type TPMT allele (TPMT*1) in 80.6%, TPMT*3B in 17.9%, and TPMT*2 in 1.5%. Unlike other studies, TPMT*3B allele frequency was very high in our patients. TPMT*3B is a rare allele that is usually absent in many populations. Tumer et al. (8) studied 106 Turkish children with ALL and detected TPMT*2 in 0%, TPMT*3B in 0.9%, and TPMT*3C in 0.9%. Similarly, Akın et al. (9) studied 169 children with leukemia and detected TPMT*2 in 0%, TPMT*3A in 1.7%, TPMT*3B in 1.7%, and TPMT*3C in 2.4%. We did not detect TPMT*3C and TPMT*3A in our population. This difference may be related to our study population. Our population was recruited from Western Anatolia. However, other studies were recruited from the Marmara region of Central Anatolia. Only a few studies have reported TPMT*3B polymorphism as high in the literature. Moreno-Guerrero et al. (10) studied Mexican children with different cancer types and reported TPMT*3B polymorphism at a rate of 7.5%. However, another study from Mexico reported TPMT*3B to be 0.1% in leukemia patients (11). According to these results, we thought there might be regional differences within the same country. In Europe, TPMT-3B was only reported in the Spanish population to be 1.5%, and other studies from our country at a prevalence of 0.9-1.7% (7-9,12). Among Asian countries, an Iranian study reported TPMT*3B allele to be 1.6% in the healthy population (13).

The increased TPMT*3B allele frequency in the patient group compared to healthy children is striking in our study group. This result raises the question of whether these polymorphisms might affect leukemia susceptibility. We know that folate metabolism plays an important role in DNA synthesis and methylation. Deviations in the folate metabolism resulting from polymorphisms in genes encoding folate-dependent enzymes may affect susceptibility to leukemia. One of the most extensive series from Mexico studied 849 patients (428 ALL, 421 non-ALL), and they found TPMT polymorphism frequency to be higher in ALL patients but did not find it statistically significant (11). Previous studies from the Mexican population also reported TPMT polymorphisms are not a risk factor for ALL (14,15).

In our study, TPMT*3C allele was not detected. However, TPMT*3C is the most frequent allele in Asian and African populations (16). Leukemic children from Singapore were reported to have TPMT*3C allele at a rate of 3% in the Chinese population, 2.3% in Malaysians, whereas children from Thailand have TPMT*3C at a rate of 11% (17,18).

TPMT*3A is the most common allele in the Caucasian and American populations but was not detected in our study. Lennard et al. (19) evaluated 1,320 children with ALL in England and detected TPMT*3A at a rate of 4.5%, and TPMT*3B at a rate of 0%. For the Serbian population, TPMT*3A allele frequency was reported as 3.2% while TPMT*2 was 0.2%, and TPMT*3B was 0.5% (20).

TPMT*2 is another less common allele. This allele has been detected 0-0.1% in Asian populations and 0.1-0.85% in European populations (11,13). On the other hand, two larger sample-sized studies in Iran reported this allele at a rate of 2.16-3.93% (13,21). In our study, TPMT*2 frequency was 1.5%.

As for drug toxicity, theoretically, it can be assumed that children with heterozygous or homozygous polymorphisms might experience more hematologic or hepatic toxicities of 6-MP and 6-TG as a result of decreased enzyme activity, decreased thiopurine clearance from plasma, and accumulation of the drug in the body. There are many studies regarding thiopurine dosage and its relevance with TPMT alleles, but this research is very limited in the pediatric age group.

Relling et al. (22) showed that 6-MP dose reductions due to toxicity, rates of thrombocytopenia, neutropenia, and hospitalization due to infection were highest among those patients homozygous for mutant TPMT, intermediate among heterozygous mutations, and lowest among wild-type patients. Interestingly, they showed hepatotoxicity tends to be more frequent in wild-type patients. We speculate that methylated metabolites probably contribute to hepatotoxicity. El-Rashedy et al. (23) had similar results when they reported TPMT mutant patients to have a high risk of hematological toxicity, but there was no statistically significant increase in hepatotoxicity. However, we did not find any relationship between the hematologic/hepatic toxicity and *TPMT* gene polymorphisms. Similar to our findings, Ayesh et al. (24) evaluated 56 ALL patients in the Palestinian territories. Out of 14 myelosuppression cases, only one patient had TPMT polymorphism and this reported myelosuppression could not be explained only by the existence of polymorphism. Farfan et al. (25) studied 103 Chilean ALL children and detected polymorphisms of TPMT*3A in 7%, and TPMT*3C in 1%. However, they did not find any relationship between toxicity and wild-type or mutant alleles (25). These results suggest the effect of other genetic factors or other polymorphisms in the development of toxicity.

In the last decade, several studies have shown that there are many genes involved in thiopurine metabolism and drug intolerance, such as BCC4, ABCC5, IMPDH1, ITPA, SLC28A3, XDH and NUDT15 (26). Especially, NUDT15 and ITPA are the most important of these. NUDT15 is an enzyme involved in the metabolism of thiopurine drugs and has shown a strong association with thiopurine intolerance. Yang et al. (27) reported that NUDT15 polymorphism causes susceptibility to thiopurine-induced myelosuppression. However, Moradveisi et al. (28) reported that TPMT and NUDT15 polymorphisms are quite rare and, therefore, the ITPA polymorphism is important. They found that the ITPA polymorphism was more common in their study group and that there was a significant relationship between the ITPA polymorphism and the dosing intensity of 6-MP (28). Interestingly, a study from our country showed that TPMT and ITPA variants were rare in our population, but SLC01B1 polymorphisms were common, and these variants were associated with thiopurine intolerance (29).

Conclusion

In conclusion, *TPMT* gene polymorphisms are important because of life-threatening complications during 6-MP and 6-TG therapies. TPMT*3B polymorphism, which is described as being rare in the published data, was the most common allele detected in our AL/NHL patient group. Our study showed different results from previous studies in Turkey. We did not find a possible relationship between polymorphisms and severe hematologic or hepatic toxicities.

Ethics

Ethics Committee Approval: The Local Ethics Committee of Ege University Faculty of Medicine approved this study (approval number: 05-4/5, date: 28.04.2021).

Informed Consent: Informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept and Design: E.A., B.K., Ç.A., Z.K., M.K., Data Collection or Processing: B.K., Ç.A., Analysis Interpretation: E.A., Literature Search: M.K., Writing: E.A., M.K.

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References

1. Azimi F, Jafariyan M, Khatami S, Mortazavi Y, Azad M. Assessment of thiopurine-based drugs according to thiopurine-S-methyltransferase genotype in patients with acute lymphoblastic leukemia. Iran J Ped Hematol Oncol 2014; 4:32-8.
2. Dean L, Kane M. Mercaptopurine Therapy and TPMT and NUDT15 Genotype. In: Pratt VM, Scott SA, Pirmohamed M, et al (eds). Medical Genetics Summaries: Bethesda, National Center for Biotechnology Information (US), 2012.
3. Szumlanski C, Otterness D, Her C, et al. Thiopurine methyltransferase pharmacogenetics: human gene cloning and characterization of a common polymorphism. DNA Cell Biol 1996; 15:17-30.
4. Tai HL, Krynetski EY, Schuetz EG, Yanishevski Y, Evans WE. Enhanced proteolysis of thiopurine S-methyltransferase (TPMT) en-coded by mutant alleles in humans (TPMT*3A, TPMT*2): mechanisms for the genetic polymorphism of TPMT activity. Proc Natl Acad Sci USA 1997; 10:94:6444-9.
5. Wang L, Nguyen TV, McLaughlin RW, Sikkink LA, Ramirez-Alvarado M, Weinshilboum RM. Human thiopurine S-methyltransferase pharmacogenetics: variant allozyme misfolding and aggresome formation. Proc Natl Acad Sci U S A 2005; 28:102:9394-9.
6. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf Published: November 27, 2017.
7. Sayitoğlu MA, Yıldız İ, Hatırnaz Ö, Özbek U. Common Cytochrome p4503A (CYP3A4 and CYP3A5) and Thiopurine S-methyl trans-ferase (TPMT) polymorphisms in Turkish population. Turk J Med Sci 2006; 36:11-5.

8. Tumer TB, Ulusoy G, Adali O, Sahin G, Gozdasoglu S, Arinç E. The low frequency of defective TPMT alleles in Turkish population: a study on pediatric patients with acute lymphoblastic leukemia. Am J Hematol 2007; 82:906-10.

9. Akın DF, Aşlar-Öner D, Kürekçi E, Akar N. Frequency of thiopurine S-methyltransferase gene variations in Turkish children with acute leukemia. Turk J Pediatr 2018; 60:147-52.

10. Moreno-Guerrero SS, Ramírez-Pacheco A, Dorantes-Acosta EM, Medina-Sanson A. Analysis of genetic polymorphisms of thiopurine S-methyltransferase (TPMT) in Mexican pediatric patients with cancer. Rev Invest Clin 2013; 65:156-64.

11. Jiménez-Morales S, Ramírez-Florencio M, Mejía-Aranguré JM, et al. Analysis of thiopurine S-methyltransferase deficient alleles in acute lymphoblastic leukemia patients in Mexican patients. Arch Med Res 2016; 47:615-22.

12. Corominas H, Domènech M, del Río E, Gich I, Domingo P, Baiget M. Frequency of thiopurine S-methyltransferase alleles in different ethnic groups living in Spain. Med Clin (Barc) 2006; 126:410-2.

13. Bahari A, Hashemi M, Bari Z, Moazeni-Roodi A, Kaykhaei MA, Narouie B. Frequency of thiopurine S-methyltransferase (TPMT) alleles in southeast Iranian population. Nucleosides Nucleotides Nucleic Acids 2010; 29:237-44.

14. Gutiérrez-Álvarez O, Lares-Asseff I, Galaviz-Hernández C, et al. Involvement of MTHFR and TPMT genes in susceptibility to child-hood acute lymphoblastic leukemia (ALL) in Mexicans. Drug Metab Pers Ther 2016; 31:41-6.

15. Taja-Chayeb L, Vidal-Millán S, Gutiérrez O, Ostrosky-Wegman P, Dueñas-González A, Candelaria M. Thiopurine S-methyltransferase gene (TMPT) polymorphisms in a Mexican population of healthy individuals and leukemic patients. Med Oncol 2008; 25:56-62.

16. Hamdy SI, Hiratsuka M, Narahara K, et al. Genotype and allele frequencies of TPMT, NAT2, GST, SULT1A1 and MDR-1 in the Egyptian population. Br J Clin Pharmacol 2003; 55:560-9.

17. Kham SK, Tan PL, Tay AH, Heng CK, Yeoh AE, Quah TC. Thiopurine methyltransferase polymorphisms in a multiracial asian population and children with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2002; 24:353-9.

18. Hongeng S, Sasanakul W, Chuansumrit A, Pakakasama S, Chattananon A, Hathirat P. Frequency of thiopurine S-methyltransferase genetic variation in Thai children with acute leukemia. Med Pediatr Oncol 2000; 35:410-4.

19. Lennard L, Cartwright CS, Wade R, Richards SM, Vora A. Thiopurine methyltransferase genotype-phenotype discordance and thiopu-rine active metabolite formation in childhood acute lymphoblastic leukemia. Br J Clin Pharmacol 2013; 76:125-36.

20. Dokmanovic L, Urosevic J, Janic D, et al. Analysis of thiopurine S-methyltransferase polymorphism in the population of Serbia and Montenegro and mercaptopurine therapy tolerance in childhood acute lymphoblastic leukemia. Ther Drug Monit 2006; 28:800-6.

21. Azad M, Kaviani S, Soleimani M, Noruzinia M, Hajfathali A. Common Polymorphism's Analysis of Thiopurine S-Methyltransferase (TPMT) in Iranian Population. Yakhteh Medical Journal 2009; 11:311-6.

22. Relling MV, Hancock ML, Rivera GK, et al. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine S-methyltransferase gene locus. J Natl Cancer Inst 1999; 91:2001-8.

23. El-Rashedy FH, Ragab SM, Dawood AA, Temraz SA. Clinical implication of thiopurine methyltransferase polymorphism in children with acute lymphoblastic leukemia: a preliminary Egyptian study. Indian J Med Paediatr Oncol 2015; 36:265-70.

24. Ayesh BM, Harb WM, Abed AA. Thiopurine methyltransferase genotyping in Palestinian childhood acute lymphoblastic leukemia patients. BMC Hematol 2013; 13:3.

25. Farfan MJ, Salas C, Canales C, et al. Prevalence of TPMT and ITPA gene polymorphisms and effect on mercaptopurine dosage in Chilean children with acute lymphoblastic leukemia. BMC Cancer 2014; 14:299.

26. Zgheib NK, Akika R, Mahfouz R, et al. NUDT15 and TPMT genetic polymorphisms are related to 6-mercaptopurine intolerance in children treated for acute lymphoblastic leukemia at the Children's Cancer Center of Lebanon. Pediatr Blood Cancer 2017; 64:146-50.

27. Yang JJ, Landier W, Yang W, et al. Inherited NUDT15 variant is a genetic determinant of mercaptopurine intolerance in children with acute lymphoblastic leukemia. J Clin Oncol 2015; 33:1235-42.

28. Moradveisi B, Muwakkit S, Zamani F, Ghaderi E, Mohammadi E, Zgheib NK. ITPA, TPMT, and NUDT15 Genetic Polymorphisms Predict 6-Mercaptopurine Toxicity in Middle Eastern Children With Acute Lymphoblastic Leukemia. Front Pharmacol 2019; 10:916.

29. Eldem İ, Yavuz D, Cumaoğullari Ö, et al. SLCO1B1 Polymorphisms are Associated With Drug Intolerance in Childhood Leukemia Maintenance Therapy. J Pediatr Hematol Oncol 2018; 40:289-94.

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Original Article

Comparison of Two Different Methods in Reducing Pain and Fear due to Dressing Change in 7-10 Years Old Children

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ABSTRACT

Aim: This randomized controlled study aims to analyze the effects virtual reality (VR) and carton distraction techniques pain due to dressing change and fair levels in children that underwent abdominal surgery.

Materials and Methods: The study was conducted on 96 children between 7 and 10 years of age, who visited pediatric surgery department of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between 1 November 2018 and 30 November 2019. Personal information form on children and parents, Wong-Baker faces pain rating scale and children's fear scale were used for data collection. Due to dressing change, no intervention was made to the children in the first group whereas children in the second and third groups watched video with VR headset and cartoon from tablet, respectively. Pain severity and fear levels were self-assessed. Descriptive statistics, correlation analysis, Wilcoxon signed-rank, Kruskal-Wallis, Mann-Whitney U, Pearson's chi-square and Fisher-Freeman-Halton exact tests were used for data analysis. Statistical significance was set at $p<0.05$.

Results: Mean age of children was 8.58±1.13 and 56.3% (n=54) were male. Pain and fear scores due to dressing change were lower for the VR and carton distraction groups. Statistically significant difference between the control and the distraction groups stemmed from the VR distraction group ($p<0.05$).

Conclusion: This study found that allowing children to watch video with VR headset due to dressing change is an effective way to distract attention and decrease pain and fear levels.

Keywords: Child, cartoon distraction, dressing change, fear and pain, pediatric nurse randomized controlled trial, virtual reality

Introduction

Perception of pain is influenced by a combination of various emotional and behavioral factors, including age, gender, social environment, culture, education and experiences (1,2). Dressing changes after the surgery, injection, bloodletting and similar healthcare interventions are the primary sources of fear experienced by hospitalized children. Pain that stems from these procedural interventions are defined as procedural pain (3,4). Parents are mostly concerned with dressing change after abdominal surgery since it causes pain and fear among their children (3,5). Fear and anxiety are considered as two important factors that cause procedural pain due to dressing change. On addition, negative pain experiences during procedural interventions may have life-long effects on children (6).

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Avoiding pain, sorrow and suffering during healthcare delivery is an important professional responsibility of nurses (7). The clinical guideline of American Pain Society (APS) recommends the use of different pharmacological and non-pharmacological modalities for the treatment of postoperative pain in children (8). Similarly, the American Society of Pain Management Nursing (ASPMN) recommends non-pharmacological modalities in order to reduce analgesic medication use and improve the quality of life by eliminating pain. APS also recommends the use of cognitive-behavioral modalities for pain management in children (8).

Distracting is a frequently used technique of pain management (6,9,10). Lee et al. (11) found that watching animated cartoons was a cheap and very effective way to alleviate preoperative anxiety of children aged 3 to 7 years. Lange et al. (12) reported that virtual reality (VR) distraction reduced behavioral pain and anxiety of children who received painful intervention. The systematic review of Luo et al. (13) recommended combining VR distraction and analgesics for procedural pain management.

During invasive interventions, pediatric nurses use distraction techniques in order to reduce pain. These methods have positive effects on not only the children and their parents but also the nurses who provide healthcare. We did not find any studies in the literature that compared the effects of watching videos with a VR headset with watching a cartoon from a tablet computer on pain reduction in children while undergoing dressing change after abdominal surgery. This experimental study aimed to compare the effects of VR and cartoons as a distraction while undergoing dressing change on the pain and fear levels of children between 7 and 10 years of age who had undergone appendectomy or other minor abdominal surgery.

Research Hypotheses

1. Hypothesis (H0): Distracting methods such as watching cartoons or VR do not affect the pain and fear while undergoing a dressing change in children.

2. Hypothesis (H1): Children who use VR glasses (Group B) for pain distraction will have less pain and fear while undergoing a dressing change than children watching cartoons (Group C).

3. Hypothesis (H1): Children watching cartoons (Group C) will have less pain and fear while undergoing a dressing change than children in the control group (Group A).

Materials and Methods

This randomized-controlled experimental study was conducted on children aged 7 to 10 years, who visited the pediatric surgery department of a training and research hospital and underwent abdominal surgery between 1st November 2018 and 30th November 2019. The study aimed to compare the effects of VR and cartoon distraction on pain and fear levels while undergoing a dressing change in children who had undergone appendectomy or other minor abdominal surgeries. The sample size was calculated according to the data of a similar study (5) in which we set the G*Power (3.1.0) of the test (1-β) as 0.80 and the significance level α as 0.05. Each of the three groups required 32 individuals and the study was completed with a total number of 96 participants. The participants were stratified according to age and gender variables and randomized into control and intervention groups. Research randomizer software (https://www.randomizer.org/) was used for the homogenous allocation of the participants. Before entering the data on sample size, sets 1, 2 and 3 were used as titles to indicate the control, VR distraction and cartoon distraction groups. The order of the participants in the sample was randomly determined by the software. The children were allocated to the set 1, 2 and 3 groups according to their date of hospitalization (Figure 1).

Inclusion Criteria:

- At least two days passed since the operation,
- Age ranging from 7-10 years,
- Voluntary participation by parents and child,
- Having undergone appendectomy or other small abdominal surgery,
- Parents and child who speak and understand Turkish.

Exclusion Criteria:

- Having received pain killers or sedative medication in last 6 hours.
- History of epilepsy, migraine or vestibular disease,
- Physical or mental health problems that prevent communication.

Data Collection Tools

The personal information form on children and parents (PIFCP), Wong-Baker faces pain rating scale (WBFPS) and the children's fear scale (CFS) were used for data collection. The PIFCP was prepared by the researchers by using the relevant literature. The form included 11 close-ended questions on the sociodemographic characteristics of the children and their parents, the medical history of the children, and the factors that may influence pain and fear levels of the children, including previous surgeries, prior experience of

dressing changes, the length of hospital stay and chronic diseases.

WBFPS shows six faces and asks children between 3 and 18 years of age to self-assess their level of pain. The first face on the far left indicates "no hurt" and represents a pain score of 0 whereas the sixth face on the far right indicates "hurts worst" and represents a score of 10. The Cronbach's alpha test (r=86) was used for reliability (14). WBFPS was assessed using self-report and reports from the parents, the researcher and the nurse who changed the dressing in this study.

CFS was developed by McMurtry in 2011. The Turkish validity and reliability of the scale was assessed by Gerçeker et al. (15) in 2018. The scale shows five faces and asks the children between 5 and 10 years of age to self-assess their level of fear. The first face on the far left indicates "not

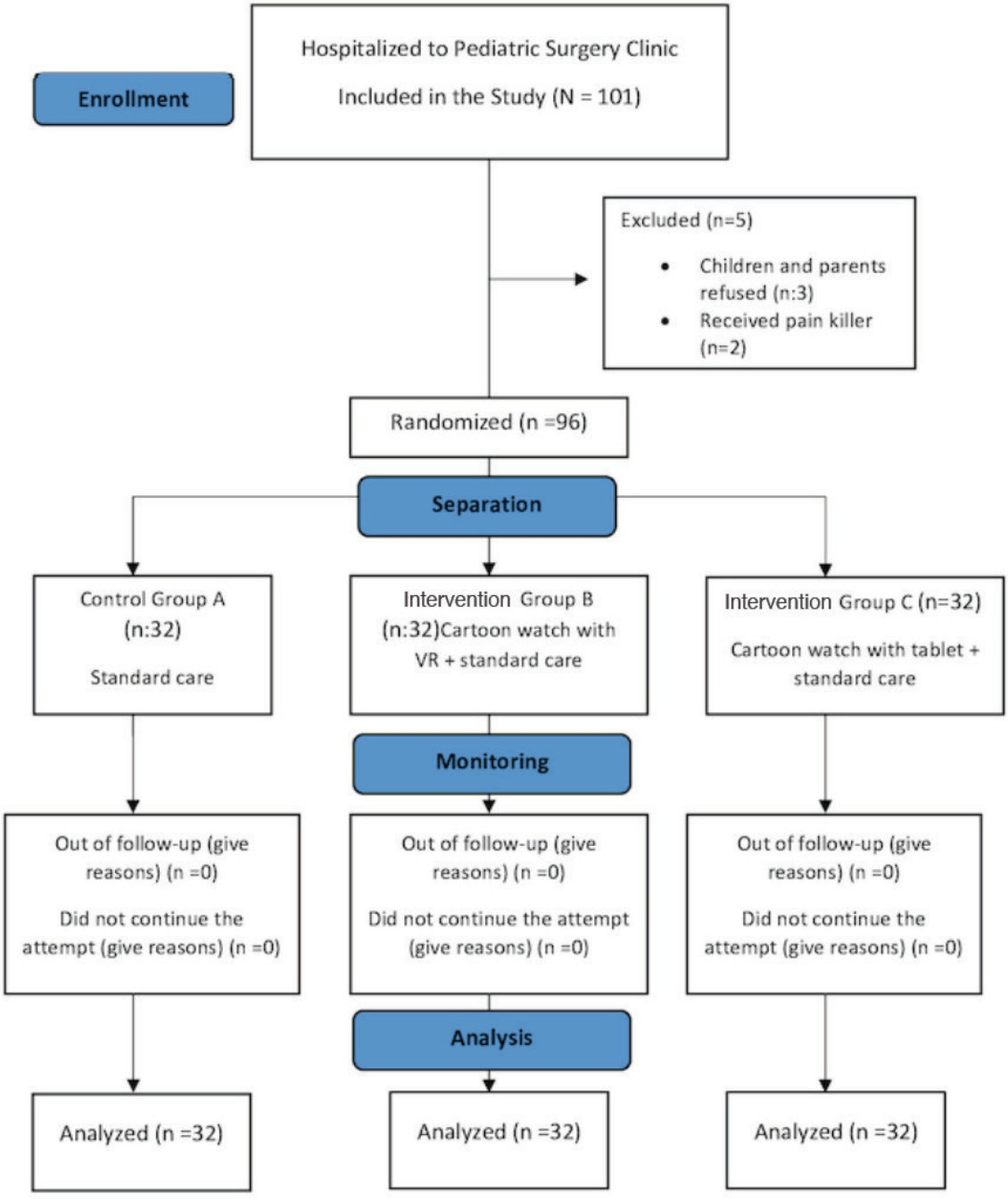

Figure 1. Consort flow diagram

scared at all" and represents a fear score of 0 whereas the fifth face on the far right indicates "the most scared possible" and represents a fear score of 4 (15).

We used a white 3D PREO myVRbox VR headset. The VR headset transforms a display from a mobile phone, computer or other technological device with LED, LCD or Plasma screens to a more realistic image by creating visual illusion (http://acikarsiv.beun.edu.tr/xmlui/bitstream/handle/20.500.12628/9401/G%c3%b6ksu%2c%20Fatma.pdf?sequence=1&isAllowed=y). The VR headset was supplied by the researcher and disinfected after each use. Additionally, an Apple A1823 iPad tablet was used by the children to watch a cartoon. The tablet was supplied by the researcher and disinfected after each use (Figure 2, 3).

Data Collection Procedures

Study data was collected over a period of one year (1st November 2018/30th November 2019). Before starting the research, we obtained institutional and ethics committee permission and permission and permission from the authors to use the scales. We also obtained verbal and written informed consent of the participant children and their parents.

Figure 2. VR glasses used in data collection
VR: Virtual reality

Figure 3. Cartoon showing children on tablet while collecting data

Dressing change in all groups was performed by the same pediatric nurse, who had been working in the department of pediatric surgery for three years. It took place in the dressing room of the pediatric surgery department, where the parents and the researchers were present.

The first phase of the research started with the determination of the samples that matched the inclusion criteria (96 children). Next, the aim and scope of the research were explained to the children and their parents by the researcher. In the second stage, 96 children were allocated to the control and the intervention groups, with 32 participants in each group.

Control Group A (n=32)

Group A was the control group that received their dressing change without any intervention. The dressing room was located in the clinic. The children were with their parents during the dressing change. Before the dressing, the researcher recorded the demographic characteristics via the Personal Information Form. The children and their parents were informed about WBFPS and CFS and pain and fear levels were evaluated through the expression of the child. The dressing took 8-10 minutes. After the dressing change, pain and fear levels were assessed by the researcher.

Implementation Phase

Children in Group B watched a video with VR headset while undergoing a dressing change (n=32). Firstly, the researcher prepared the mobile VR support system for use. Secondly, the parent and child were brought to the dressing room. Then, their demographic characteristics were recorded to the PIFCP. Before the evaluation of pain and fear levels, the VR glasses were shown to the children and they were allowed to examine them. After this, the mobile phone was attached to the VR glasses. Then, the VR glasses were placed on the child's eyes and were placed in a comfortable position. The VR headset was switched on three minutes before the dressing change and it was on until the dressing change ended. For group B, 3D-VR VIDEOS 234 SBS VR Video 2k Google cardboard was used. The dressing change was completed in about 8-10 minutes. After the dressing change, pain and fear levels were assessed by the researcher. Finally, the VR glasses and the mobile phone were disinfected.

Children in Group C watched cartoons on a tablet (n=32). All steps of group B were also applied for group C (e.g: Demographic characteristics were recorded and an assessment for pain and fear was carried out). The "Keloğlan: Food Competition" cartoon was used for Group C. For group C, a different cartoon had to be chosen than for Group B because the cartoon was not adapted to VR glasses. The tablet was given to the children three minutes before the dressing change and they were allowed to lie down in a comfortable position. Then, the tablet was switched on by the researcher and the dressing was changed by the nurse. The process took about 8-10 minutes. After the dressing change, the children were asked to show the faces that reflected their fear and pain levels during the intervention on CFS and WBFPS. The researchers marked the faces shown by the participants.

Statistical Analysis

The collected data were analyzed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software. Statistical significance for all analysis was set at 0.05. Mean, standard deviation, median, frequency, percentage and minimum-maximum values were used as descriptive analysis. The Wilcoxon sign-rank test was used for the comparison of quantitative data without normal distribution and the Kruskal-Wallis test was performed for inter-group comparison. Dunn's test was used for paired comparison and Bonferroni correction was used for p-values. Spearman's Rho correlation analysis was used to evaluate the relationship between variables. Pearson's chi-square test and Fisher-Freeman-Halton exact test were used for the comparison of qualitative data.

Ethical Considerations

We obtained permission from Acıbadem University and Acıbadem Health Institutions Medical Research Ethics Committee (ATADEK: 2018-11/11, dated: 26.07.2018) and institutional permission from University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (no: 82998542-771-21701, dated: 16.11.2018). Health professionals working at the department of pediatric surgery of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital were informed about the research. The children and their parents were informed about the aim and the scope of the research. Verbal and written informed consent of the parents and verbal informed consent of the children were obtained. The participants and their parents were informed that they could withdraw at any time without any reason.

Results

Participant characteristics: The mean age of the participants was 8.58±1.13 years, 56.3% (n=54) were male whereas the remaining 43.7% (n=42) were female. It was observed that majority of the children (n=85) had been operated on their right abdomen. Most of the children's (n=59) pain level measurements were evaluated in post-op 3-5 days (Table I). There was no statistically significant difference between the three groups in terms of their descriptive characteristics, such as age, gender, surgical history, experience and time of dressing change, dressing site or chronic diseases ($p>0.05$) (Table I).

Pain scores and comparison of the groups: The mean WBFPS scores of the control, VR and cartoon distraction groups while undergoing dressing change were 3.56±1.74, 0.44±0.98 and 1.63±1.56, respectively. The difference between the groups was statistically significant ($p=0.001$; $p<0.01$) (Table II). Paired comparison to reveal the source of the difference showed that the mean WBFPS scores of the cartoon and VR distraction groups were lower than the control group and the mean WBFPS score of the VR distraction group was lower than cartoon distraction group (Table II, III, Figure 4). The 2nd and 3rd Hypotheses were confirmed by these findings.

Fear scores and comparison of the groups: The mean CFS scores for the control, VR and cartoon distraction groups while undergoing dressing change were 2.50±0.67, 0.50±0.92 and 1.09±0.93, respectively. The difference between the groups was statistically significant ($p=0.001$; $p<0.01$) (Table III). Paired comparison to reveal the source of the difference showed that the mean CFS scores of the

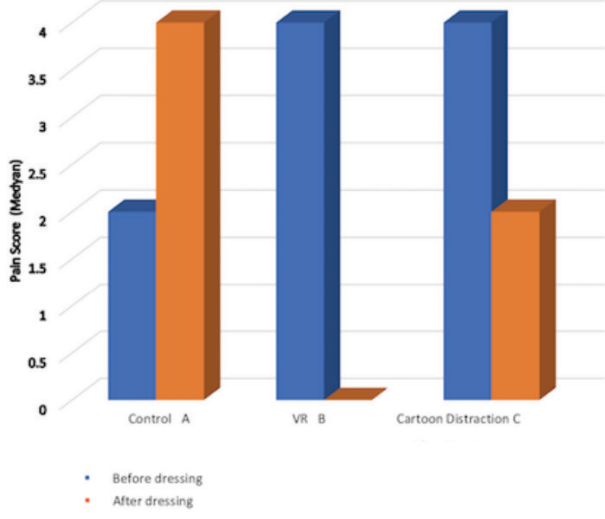

Figure 4. Pain score before and after

cartoon and VR distraction groups were lower than the control group and the mean CFS score of the VR distraction group was lower than cartoon distraction group. These findings confirmed hypotheses 2 and 3 (Table III).

Discussion

This study examined the effects of two different distraction methods on the pain and fear levels of children. This study aimed to compare the effects of VR and cartoons as a distraction to pain and fear while undergoing a dressing change of children between 7 and 10 years of age who had undergone abdominal surgery. The VR distraction was more effective than the cartoon distraction for reducing pain and fear while undergoing a dressing change.

Existing studies show that children suffer from pain and fear due to procedures. Procedural pain may have adverse effects on children and may increase in later interventions if it is not prevented or properly managed (16,17). This, in turn, may result in an unwillingness to receive procedures and even a delay in treatment (3,18). For this reason, all health professionals agree on the point that effective methods should be used to reduce pain and fear

Table I. Characteristics of children (n=96)

	Control group A (n=32)		**VR group B (n=32)**		**Cartoon distraction group C (n=32)**		**Analysis**
Characteristics of children							
	n	**%**	**n**	**%**	**n**	**%**	
Age							
7 years 11 months	5	15.7	10	31.2	7	21.9	p=0.711
8 years 11 months	10	31.2	7	21.9	6	18.8	
9 years 11 months	8	25.0	8	25.0	8	25.0	
10 years	9	28.1	7	21.9	11	34.3	
Gender							
Female	13	40.6	16	50.0	13	40.6	p=0.683
Male	19	59.4	16	50.0	19	59.4	
Surgery history							
No	25	78.1	26	81.3	27	84.4	p=0.815
Yes	7	21.9	6	18.7	5	15.6	
Dressing change history							
No	31	97	29	90.6	30	93.8	p=0.869
Yes	1	3.1	3	9.4	2	6.2	
Dressing change day							
0-2. day	2	6.2	0	0.0	2	6.2	p=0.630
3-5. day	22	68.8	18	56.3	19	59.4	
6-8. day	6	18.8	11	34.3	7	21.9	
9-11. day	2	6.2	3	9.4	3	9.4	
12-14. day	0	0.0	0	0.0	1	3.1	
Dressing place							
Right abdomen	28	87.5	27	84.4	30	93.8	p=0.611
Left abdomen	4	12.5	5	15.6	2	6.2	
Chronic illness							
No	31	96.9	29	90.6	30	93.8	p=0.869
Yes	1	3.1	3	9.4	2	6.2	

VR: Virtual reality

due to procedures. The ASPMN states that nurses should intervene in order to provide the best pain management before, during and after procedures based on the needs of the patients, the setting and the situation (18). Within this context, distraction is a widely used technique of pain management in pediatric clinics. Various techniques independently employed by nurses have decreased the pain and fear of children (3,19).

Pediatric nurses, who have been with pediatric patients for longer than other team members, can apply non-pharmacological methods to reduce pain and fear more correctly and independently. Distraction methods that can be applied to age groups of children by nurses are VR glasses, video/television streaming, playing computer game, cold/hot applications, giving toys and breathing exercises (20). VR is a relatively new technique to provide distraction and it might be more effective than other traditional methods (21).

In the systematic review and meta-analysis study conducted by Eijlers et al. (21), it was reported that the VR method reduces pain and anxiety in children. It was also reported that "the VR interventions for pain and anxiety were potentially more efficacious for younger than for older children" (21).

Pain and fear scores of the children in this study, who watched a video with a VR headset were lower than those children who watched a cartoon from a tablet or did not watch anything, and the difference between the groups was statistically significant (p<0.01) (Table II). Mott et al. (22) found that augmented VR systems alleviated the pain levels of children undergoing a burns dressing change between the ages of 3.5 and 14 years. Das et al. (23) analyzed the effects of playing a VR game on procedural pain of children with acute burn injuries between the ages of 5 and 18 years and found that those children who received pharmacological analgesia had higher pain scores than the children who received pharmacological analgesia with a VR game. The randomized-controlled trial of Hua et al. (10) on the effects of VR distraction on pain relief while undergoing a dressing change in children aged from 4 to 16 years with chronic wounds found that VR distraction lowered pain and fear scores and reduced the length of time needed for the dressing change. The pilot study of Gershon et al. (24) found that VR distraction reduced pain and anxiety in children with cancer, aged from 7 to 19 years, whose treatment protocols required access to subcutaneous venous port device. Khadra et al. (25) conducted a pilot study to evaluate the impact of VR distraction on procedural pain management in children

Table II. Comparison of pain score pre-dressing and post-dressing

		Groups			
		Control group A	**VR group B**	**Cartoon distraction group C**	**p-value**
Pre-dressing	Min-max (median) Mean+SD	0-8 (2) 1.8±1.83	2-6 (4) 3.44±1.37	0-10 (4) 3.37±1.86	x^2: 19,325 [c]**0.001****
Post-dressing	Min-max (median) Mean+SD	0-8 (4) 3.56±1.74	0-4 (0) 0.44±0.98	0-6 (2) 1.63±1.56	x^2: 46,139 [c]**0.001****
	Difference **p**	1.69±1.45 [d]**0.001****	-3.00±1.14 [d]**0.001****	1.75±1.59 [d]**0.001****	x^2: 62,933 [c]**0.001****

[c]: Kruskal-Wallis test, [d]: Wilcoxon signed ranks test, SD: Standard deviation, VR: Virtual reality
**p<0.01

Table III. Comparison of pain score pre-dressing and post-dressing

		Groups			Test value
		Control group A	**VR group B**	**Cartoon distraction group C**	**p-value**
Pre-dressing	Min-max (median) Mean+SD	0-3 (2) 1.75±0.88	0-4 (2) 2.47±1.05	0-4 (2) 1.91±0.99	x^2: 8,658 [c]**0.001****
Post-dressing	Min-max (median) Mean+SD	1-4 (3) 2.50±0.67	0-4 (0) 0.50±0.92	0-3 (1) 1.09±0.93	x^2: 49,234 [c]**0.001****
	Difference **p**	0.75±0.67 [d]**0.001****	-1.97±1.18 [d]**0.001****	-0.81±1.15 [d]**0.001****	x^2: 56,372 [c]**0.001****

[c]: Kruskal-Wallis test, [d]: Wilcoxon signed ranks test, SD: Standard deviation, VR: Virtual reality
**p<0.01

aged from 2 months to 10 years with burn injuries requiring a hydrotherapy session and found that projector-based VR was a feasible and acceptable intervention for the management of procedural pain. Asl Aminabadi et al. (26) studied the impact of VR distraction on pain and anxiety levels during dental treatment in 120 children aged from 4 to 6 years and found that VR eyeglasses decreased pain perception and state anxiety. In this sense, our findings are in line with the literature. Therefore, we may conclude that the VR headset is an effective method to distract the attention of children and reduce their pain and anxiety while undergoing a dressing change.

The findings of various studies support the preposition that cartoon distraction is an effective and practical method to reduce pain due to medical procedures (3,27,28). In our study, the cartoon distraction group obtained lower pain and fear scores than the control group and the difference between the groups was statistically significant ($p<0.01$) (Table II and III). Similar to our findings, Cohen et al. (27) found that watching a cartoon during immunizations was an effective and practical intervention to reduce the pain and anxiety of 92 children between the ages of 4 and 6 years. Downey and Zun (28) conducted a study on 100 children between 3 and 18 years of age who visited an emergency department due to acute pain from any cause. They found that starting to watch a cartoon five minutes before a painful intervention was an effective method to reduce perceived pain (28). The quasi-experimental study of James et al. (29) on 50 children between 3 and 6 years of age found that an animated cartoon was an effective distraction strategy to reduce pain. Devi et al. (30) reported that perceived pain decreased after the intervention of an animated cartoon video as a distraction strategy among preschoolers. Lobo and Umarani (31) conducted a quasi-experimental study on 60 children of 3-6 years of age and found that cartoon distraction reduced venipuncture pain. Similarly, Yoo et al. (32) found that animation distraction using a laptop computer reduced perceived pain during venipuncture in 40 children between 3 and 7 years of age. Kuo et al. (33) allocated 276 children aged 3 to 7 years into control, picture book and animated cartoon groups and found that cartoon distraction was a more effective method to reduce behavioral stress for children aged 4 to 5 years. Wang et al. (34) randomized 300 children aged 8 to 9 years into cartoon distraction, psychological intervention and control groups and found that the pain score of the cartoon distraction group was lower than the psychological intervention group.

Lee et al. (11) compared the effects of viewing an animated cartoon with playing with a favorite toy on preoperative anxiety in 130 children between 3 and 7 years of age and found that allowing children to watch animated cartoons was a very effective method to alleviate preoperative anxiety. Gupta et al. (35) randomized 70 children of 7 years of age into the groups of children who were held by a family member during venipuncture and child who were held by family member in conjunction with an animation distraction during venipuncture and they found that children who received an animation distraction intervention had lower levels of pain. Hussein (36) allocated 75 school age children into control, active distraction (i.e. playing a video game) and passive distraction (i.e. watching a cartoon) groups and they found that the pain scores of the active distraction group was lower than the other groups. The findings of Hussein (36) contradicts our findings. This difference may be related with the active interaction of the children with the video game in the study of Hussein (36), which may be a better distraction technique than a passive cartoon distraction. Similarly, Inan and Inal (37) randomized 180 children of 6 to 10 years of age into control, video game, cartoon and parent distraction groups and found that playing video games was the most effective method to reduce pain perception in children during venipuncture. The findings of Inan and Inal (37) are also different from our findings and this difference may be related with the possibility that video game as an active distraction technique may be more effective than a passive cartoon distraction technique.

In this study, children who watched a video with a VR headset were the active distraction group whereas those children who watched a cartoon on a tablet were the passive distraction group. The literature suggests that both distraction techniques are effective to reduce pain and fear among children during dressing change. The VR distraction group obtained significantly lower pain and anxiety scores than the cartoon distraction and the control groups (21). This finding is in line with the literature, which suggests that active distraction methods are more effective than passive distraction methods as a means of reducing anxiety and pain. However, no studies in the literature had compared the effectiveness of VR and cartoon distraction. This study's findings imply that VR glasses allow children to actively interact with the video so that it was more effective than the passive cartoon distraction technique as a means of reducing fear and pain.

Although there are many studies that use VR technology to reduce pain and anxiety in pediatric patients (21), in clinics, it is not widely practiced by nurses or other healthcare professionals. For the widespread uses of the VR method in the clinic, it may be necessary to use more interactive VR glasses where children can also participate instead of only watching. It is also believed that standards should be established for evidence to be used in clinics.

Study Limitations

The sample of this study is limited to those patients from the department of pediatric surgery in University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital. For this reason, the research findings may only be generalized to the patients who have similar characteristics to our sample.

Conclusion

This randomized-controlled study, which aimed to assess the effects of VR and cartoon distraction techniques on pain and anxiety in children while undergoing a dressing change, found that the VR distraction method was more effective than the cartoon distraction method as a means of reducing fear and pain in children aged 7 to 10 years of age who had undergone abdominal surgery.

Within this context;

• Using a VR headset and allowing children to watch a cartoon should be extended as distraction techniques to reduce pain and fear of children while undergoing a dressing change.

• Procedural pain management guidelines prepared for the pediatric patients should include VR and cartoon distraction techniques.

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Ethics

Ethics Committee Approval: We obtained permission from Acıbadem University and Acıbadem Health Institutions Medical Research Ethics Committee (ATADEK: 2018-11/11, dated: 26.07.2018).

Informed Consent: Verbal and written informed consent of the parents and verbal informed consent of the children were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.Ö., B.U., Design: F.Ö., B.U., Data Collection or Processing: F.Ö., B.U., Analysis or Interpretation: F.Ö., B.U., Writing: F.Ö., B.U.

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References

1. Aygin D, Var G. Pain Management İn Trauma Patients And Nursing Approaches. Sakarya Medical Journal 2012; 2:61-70.
2. Aktaş H, Ünal E, Gülhan NF. Approach to Pain in Burn Patients. Hacettepe University Faculty Of Health Sciences Journal 2016; 3:46-57.
3. İnal S, Canbulat N. Using of Distraction Methods on Procedural Pain Management of Pediatric Patients. J Curr Pediatr 2015; 2:372-8.
4. World Union of Wound Healing Societies. Principles of best practice: Minimising pain at wound dressing-related procedures. A consensus document. London, MEP Ltd, 2004.
5. Canbulat N, İnal S, Sönmezer H. Efficacy of distraction methods on procedural pain and anxiety by applying distraction cards and kaleidoscope in children. Asian Nurs Res (Korean Sc Nurs Sci) 2014; 8:23-8.
6. He HG, Jahja R, Sinnappan R, et al. Singaporean nurses' provision of guidance to parents on non-pharmacological postoperative pain-relief methods: An educational intervention study. Nurs Health Sci 2011; 13:344-51.
7. Freitas DMO, Spadoni VS. Is virtual reality useful for pain management in patients who undergo medical procedures? Einstein (São Paulo) 2019; 17:4837.
8. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17:131-57.
9. Özveren H, Uçar H. The Knowledge of Student Nurses on Some Non-Pharmacological Methods Used in the Pain Control. Hacettepe University Faculty of Health Sciences Nursing Journal 2009; 16:59-72.
10. Hua Y, Qiu R, Yao WY, Zhang Q, Chen XL. The effect of virtual reality distraction on pain relief during dressing changes in children with chronic wounds on lower limbs. Pain Manag Nurs 2015; 16:685-91.
11. Lee J, Lee J, Lim H, et al. Cartoon distraction alleviates anxiety in children during induction of anesthesia. Anesth Analg 2012; 115:1168-73.
12. Lange B, Williams M, Fulton I. Virtual reality distraction during pediatric medical procedures. Pediatric Pain Letter 2006; 8:6-10.
13. Luo H, Cao C, Zhong J, Chen J, Cen Y. Adjunctive virtual reality for procedural pain management of burn patients during dressing change or physical therapy: A systematic review and meta-

analysis of randomized controlled trials. Wound Repair Regen 2019; 27:90-101.

14. Savino F, Vagliano L, Ceratto S, Viviani F, Miniero R, Ricceri F. Pain assessment in children undergoing venipuncture: The Wong-Baker faces scale versus skin conductance fluctuations. Peer J 2013; 1:37.
15. Gerçeker GÖ, Ayar D, Özdemir Z, Bektaş M. Gaining of Children's State Anxiety and Children's Fear Scale to Turkish Language. E-Journal of Dokuz Eylül University Nursing Faculty. 2018; 11:9-13.
16. Ducharme J. Acute pain and pain control: State of the art. Ann Emerg Med 2000; 35:592-603.
17. Weisman SJ, Bernstein B, Schechter NL. Consequences of inadequate analgesia during painful procedures in children. Arch Pediatr Adolesc Med 1998; 152:147-9.
18. Czarnecki ML, Turner HN, Collins PM, Doellman D, Wrona S, Reynolds J. Procedural pain management: A position statement with clinical practice recommendations. Pain Manag Nurs 2011; 12:95-111.
19. Cura Üzen Ş, Oğul T, Kurt FY. Complementary and alternative medicine practices used for relieving pain in pediatric age groups. Zeynep Kamil Med J 2018; 49:126-9.
20. Kara R, Bal Yılmaz H. Examining the Methods Used to Reduce the Interventional Pain by Nurses in Pediatric Clinics. Journal of Education and Research in Nursing 2020; 17:104-11. DOI: 10.5222/HEAD.2020.13334
21. Eijlers R, Utens EMWJ, Staals LM, et al. Systematic Review and Meta-analysis of Virtual Reality in Pediatrics: Effects on Pain and Anxiety. Anesth Analg 2019; 129:1344-53.
22. Mott J, Bucolo S, Cuttle L, et al. The efficacy of an augmented virtual reality system to alleviate pain in children undergoing burns dressing changes: A randomised controlled trial. Burns 2008; 34:803-8.
23. Das DA, Grimmer KA, Sparnon AL, McRae SE, Thomas BH. The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: A randomized controlled trial [ISRCTN87413556]. BMC Pediatr 2005; 5:1.
24. Gershon J, Zimand E, Pickering M, Rothbaum BO, Hodges L. A pilot and feasibility study of virtual reality as a distraction for children with cancer. J Am Acad Child Adolesc Psychiatry 2004; 43:1243-9.
25. Khadra C, Ballard A, Déry J, et al. Projector-based virtual reality dome environment for procedural pain and anxiety in young children with burn injuries: A pilot study. J Pain Res 2018; 14:343-53.
26. Asl Aminabadi N, Erfanparast L, Sohrabi A, Ghertasi Oskouei S, Naghili A. The impact of virtual reality distraction on pain and anxiety during dental treatment in 4-6 year-old children: A randomized controlled clinical trial. J Dent Res Dent Clin Dent Prospects 2012; 6:117-24.
27. Cohen LL, Blount RL, Panopoulos G. Nurse coaching and cartoon distraction: An efective and practical intervention to reduce child, parent, and nurse distress during immunizations. J Pediatr Psychol 1997; 22:355-70
28. Downey LV, Zun LS. The impact of watching cartoons for distraction during painful procedures in the emergency department. Pediatr Emerg Care 2012; 28:1033-5.
29. James J, Ghai S, Rao K, Sharma N. Effectiveness of "Animated Cartoons" as a distraction strategy on behavioural response to pain perception among children undergoing venipuncture. Nursing and Midwifery Research Journal 2012; 8:198-207.
30. Devi P, Shinde J, Patil NB. Effectiveness of animated cartoon video as a distraction strategy on pain perception during and after venipuncture among preschoolers. International Journal of Psychiatric Nursing 2017; 3:26-31.
31. Lobo MR, Umarani J. Cartoon distraction reduces venipuncture pain among preschoolers–a quasi experimental study. International Journal of Scientific Research 2013; 2:454-6.
32. Yoo H, Kim S, Hur HK, Kim HS. The effects of an animation distraction intervention on pain response of preschool children during venipuncture. Appl Nurs Res 2011; 24:94-100.
33. Kuo HC, Pan HH, Creedy DK, Tsao Y. Distraction-based interventions for children undergoing venipuncture procedures: A randomized controlled study. Clin Nurs Res 2018; 27:467-82.
34. Wang ZX, Sun LH, Chen AP. The efficacy of non-pharmacological methods of pain management in school-age children receiving venepuncture in a paediatric department: A randomized controlled trial of audiovisual distraction and routine psychological intervention. Swiss Med Wkly 2008; 138:579-84.
35. Gupta HV, Gupta VV, Kaur A, et al. Comparison between the analgesic effect of two techniques on the level of pain perception during venipuncture in children up to 7 years of age: A quasi-experimental study. J Clin Diagn Res 2014; 8:1-4.
36. Hussein HA. Effect of active and passive distraction on decreasing pain associated with painful medical procedures among school aged children. World Journal of Nursing Sciences 2015; 1:13-23.
37. Inan G, Inal S. The impact of 3 different distraction techniques on the pain and anxiety levels of children during venipuncture. Clin J Pain 2019; 35:140-7.

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Original Article

Vaccination Status of Children Hospitalized for Measles: Parental Vaccination Refusal and Related Factors

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ABSTRACT

Aim: This study investigated the vaccination status of those children who received inpatient treatment due to measles and explored the beliefs and practices of their parents related to the refusal of childhood vaccines.

Materials and Methods: This study was a descriptive research performed at a training and research hospital in eastern Turkey. The study data were collected from the parents of children with measles who were receiving inpatient treatment. In this study, the introductory information form and the State-Trait Anxiety Inventory were used.

Results: The results revealed that 61.8% of those children with measles had not been vaccinated against measles. Factors that played a role in the parents' vaccine refusal included family elders' unwillingness, negative media reports, the side effects of vaccines, and negative attitudes towards health care workers. Parents with poor socio-economic status, low educational status, and extended family types were found to have significantly higher rates of vaccine refusal. The parents had an average state anxiety score of 60.15±5.73 and an average trait anxiety score of 50.21±3.33.

Conclusion: Many factors were found to influence the causes of parents not having their children vaccinated. Community-based training is needed to address the parents' misconceptions, concerns, and lack of knowledge about vaccinations. Renewing policies on vaccinations, establishing standards, and imposing legal sanctions can be effective in reducing vaccine refusal rates.

Keywords: Child, measles, parent, vaccine hesitancy, vaccination refusal

Introduction

Vaccines are considered to be the most effective health intervention in terms of cost and reliability in preventing infectious diseases worldwide (1-3). Decreases in mortality and morbidity of many infectious diseases are seen with vaccination programmes (4,5). The March 2018 report of the World Health Organization (WHO) stated that immunization prevents 2-3 million deaths per year globally (6).

Measles is a highly contagious viral infection with potentially serious complications (7,8). Although it has a safe and effective vaccine, it remains a major cause of death among young children worldwide. According to WHO data, more than 140,000 people died of measles in 2018 (9). In 2019, 2,785 cases of measles were reported in Turkey, 197,683 in the African Region, and 429,650 worldwide (10).

The WHO emphasizes the necessity of vaccination against measles for all vulnerable children and adults. It is

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also reported that standardization is required to ensure that two doses of the measles vaccine are included in the national vaccination schedule of all countries (11). The measles, mumps, and rubella vaccine (MMR) is administered to all children in Turkey in the 12th month and in the first grade of primary education by health organizations within the scope of the expanded programme on immunization (3).

Despite the potential benefits of vaccines, the rates of parental hesitation about childhood vaccines have increased, and vaccine refusal has become increasingly common (4). Increasing cases of vaccine hesitancy and vaccine refusal lead to decreases in vaccination rates, causing an increase in the frequency of infectious diseases (5,6). The re-emergence of vaccine-preventable outbreaks in many countries, including measles and pertussis, is cited as evidence of this situation (6). Measles outbreaks have also been reported in Europe due to low vaccination rates (8).

Parental vaccine hesitancy and refusal are two of the reasons for low vaccination rates in both developed and developing countries (1). The main reason reported for rejecting or interrupting vaccination is concern about the safety of one or more vaccines (12-14). This anxiety is often experienced towards the MMR vaccine. In particular, concerns have been raised over the past two decades that the MMR vaccine causes autism spectrum disorders due to their mercury content (15). This concern has led to a decrease in vaccination rates in Europe and the United States and an increase in the number of many vaccine-preventable diseases (1,12). However, the reasons for parental vaccine hesitancy and refusal include information gaps, parental distrust of vaccines and the health system, negative propaganda spreading on social media (2), and the belief that vaccines overburden the immune system (15). Cases of vaccine refusal and individual vaccine exemption for non-medical and personal reasons manifest as major public health issues in the form of outbreaks, imposing considerable economic and social burdens on countries (6,8,16). Only a few studies have examined the factors affecting parental attitudes and practices in vaccine hesitancy and refusal, which have become increasingly common in recent years, severely affecting public health. This study investigated the vaccination status of those children admitted due to measles and explored their parents' beliefs and practices on vaccine hesitancy and refusal.

Materials and Methods

Study Design and Participants

This descriptive research was conducted between November 2019 and March 2020 at a training and research hospital in eastern Turkey, in a province with a mixed population structure engaged primarily in seasonal agricultural labour, with high fertility rates and high poverty levels.

The inclusion criteria for this study were as follows: parents whose child; (1) (3-6 years old) was diagnosed with measles and hospitalized for treatment; (2) who could understand and speak Turkish or Kurdish; and (3) who volunteered to participate in the study. Parents whose child had a history of a diagnosed metabolic disease or psychiatric disorders were excluded from this research.

All parents meeting the inclusion criteria within the specified dates were included without sample selection. The researchers visited the inpatient ward three days a week (Monday, Wednesday, and Friday) to collect study data from the parents. The study was completed by collecting data from 89 parents.

Data Collection

The introductory information form and the State-Trait Anxiety Inventory (STAI) were used for data collection. The data were collected by the researchers using a face-to-face interview technique lasting 20 minutes on average.

The introductory information form was prepared by the researchers in line with the literature (2,12-14,17). The questionnaire consisted of 28 items to evaluate the sociodemographic characteristics of the children and their parents, as well as the disease characteristics (e.g., the duration of hospitalization, the duration of the rash, and the path of transmission) and vaccination practices.

STAI: This is a self-report scale developed by Spielberger. It consists of two sub-scales (with 20 items each) that separately assess the level of state and trait anxiety. The total score of each sub-scale varies from 20 to 80. Higher scores indicate higher levels of anxiety (18-20). This scale has been proven to be valid and reliable for the Turkish adult population by Öner and LeCompte (21). In this study, the Cronbach's alpha was 0.83 for the State Anxiety Inventory and 0.88 for the Trait Anxiety Inventory.

Pilot Application

After the data collection form was developed by the researchers, it was submitted to three faculty members, two from Paediatrics Nursing and one from Public Health Nursing-for their expert opinion. A pilot study involving 10 parents was carried out after the questionnaire was revised according to the expert opinions. In the pilot study, the questions on the data collection form were evaluated in

terms of clarity, understandability, and deficiencies, and incomprehensible statements in the questionnaire were revised. In this way, evidence was sought for the content and face reliability and validity of the questionnaire. Then, the questionnaire was finalized and readied for the actual application. The data from the pilot study were not used due to changes and corrections to the questionnaire.

Ethical Approval

The necessary ethical permission from the İnönü University Health Sciences Non-Interventional Clinical Research Ethics Committee was obtained (ethical approval number: 445-4). The study purpose was explained to all parents who met the research inclusion criteria, and the data collection form was given. Parents were informed about the study, and those who agreed to participate voluntarily and signed the written informed consent were included in the study. After the data collection was completed, training on childhood vaccinations was provided by the researcher to address the parents' lack of knowledge under the "ethics principle of beneficence".

Statistical Analysis

SPSS Version 22.00 for Windows (IBM Corp., Armonk, United States of America) was used for statistical analysis. From the descriptive statistics, mean, standard deviation, percentage distribution, and frequency distribution were used. The Shapiro-Wilk test was implemented to determine whether the sample data were normally distributed. The chi-square test and independent samples t-test were used to compare data between those parents who had and those who did not have their child vaccinated. The data were evaluated at a 95% confidence interval, and $p<0.05$ was set as the significance level. The Cronbach's alpha reliability coefficients were calculated for the two inventories.

Results

Table I summarizes some of the sociodemographic characteristics of the children and their parents. In this study, 61.8% of the children were female (n=55), and the average age was 4.75±0.93 years (n=89, one child per parent). In addition, 51 of the 89 children (57.3%) lived in an extended family type, and 50.6% of the families had poor socio-economic status. Among the parents, 40.4% of the mothers were housewives, 43.8% were working as agricultural labourers, and 77.6% of the fathers were factory workers. In addition, an average of 9.66±4.98 children lived together in one household.

Table I. Distribution of some socio-demographic characteristics of the children and parents

Variables	**Mean ± SD**	**Min.- Max.**
Child's age (years)	4.75±0.93	3-6
Mother's age	31.28±8.30	20-49
Father's age	35.75±5.94	25-48
Number of children	6.00±3.32	2-13
	n	**%**
Child's gender		
Female	55	61.8
Male	34	38.2
Child's educational status		
Not going to school	50	56.2
Pre-school	39	43.8
Chronic disease in child		
Yes	18	20.2
No	71	79.8
Mother's education level		
Illiterate	52	58.4
Primary education	17	19.1
High school	12	13.5
University	8	9
Father's education level		
Illiterate	53	59.6
Primary education	15	16.8
High school	4	4.5
University	17	19.1
Family socio-economic status		
Good	18	20.2
Middle	26	29.2
Bad	45	50.6
Total	**89**	**100**

SD: Standard deviation, Min.: Minimum, Max.: Maximum

The distribution of the reasons for measles vaccine refusal is presented in Table II and Figure 1. Of the children included in this study, 61.8% [95% confidence interval (CI): 28.4-46.1] did not get the measles vaccine. The reasons for this included family elders' unwillingness (60.7%; 95% CI: 52.8-70.5), negative media reports (57.3%; 95% CI: 49.4-67.1), fear of vaccine side effects (51.7%; 95% CI: 42.7-61.8), a lack of home visits by midwives/nurses (42.7%; 95% CI: 34.0-51.7), the belief that children die because of the vaccine (27%; 95% CI:

17.2-37.9), a lack of reminders by midwives/nurses for the vaccine (23.6%; 95% CI: 16.9-36.4), and negative attitudes towards health care professionals (14.6%; 95% CI: 7.1-26.0) (Table II, Figure 1).

Of the parents, 52.8% (95% CI: 43.8-64.5) reported that their child had not had any other childhood vaccinations that are included on the national vaccination calendar. The reasons for the refusal of all vaccines included unwillingness of family elders (52.8%; 95% CI: 43.8-64.5), negative media reports (50.6%; 95% CI: 41.6-62.9), a lack of home visits by midwifes/nurses (46.1%; 95% CI: 37.4-56.2), vaccine side effects (42.7%; 95% CI: 31.8-52.8), the belief that children die because of vaccination (27.0%; 95% CI: 19.1-39.0), and negative attitudes towards health care professionals (27.0%; 95% CI: 19.4-37.1).

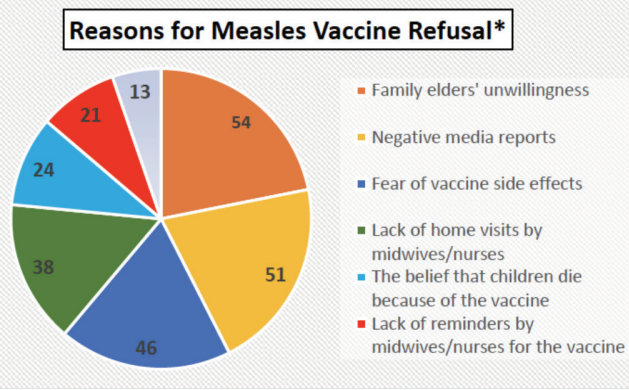

Figure 1. Reasons for measles vaccine refusal among parents
**Some parents have reported more than one reasons*

Table II. Reasons for measles vaccine refusal among parents

	n	%	95% CI values
Measles vaccine status			
Made	34	38.2	28.4-46.1
Refused	55	61.8	53.9-71.6
Reason for vaccine refusal*			
Family elders' unwillingness	54	60.7	52.8-70.5
Negative media reports	51	57.3	49.4-67.1
Fear of vaccine side effects	46	51.7	42.7-61.8
Lack of home visits by midwives/nurses	38	42.7	34.0-51.7
The belief that children die because of the vaccine	24	27.0	17.2-37.9
Lack of reminders by midwives/nurses for the vaccine	21	23.6	16.9-36.4
Negative attitudes of health care professionals	13	14.6	7.1-26.0

*Some parents have reported more than one reasons.
CI: Confidence interval

Parents reported that their children had been infected with measles in the street/neighbourhood (80.9%), park (49.4%), hospital (37.1%), or at school (21.3%). The duration of hospitalization of the children was 3.92±1.34 days (range, 1-7); 50.6% had a rash on their skin, which continued for 1.39±1.46 days. Among the parents, 79.8% had a fear of measles, 29.2% reported performing "etching", a traditional method of healing the child (burning with hot iron bars on the skin to treat various diseases), 59.6% reported that their other children also had an infectious disease, and 58.4% reported the presence of refugees in their neighbourhood; also, 52.8% reported that they would not vaccinate their children in the future.

The parents had an average state anxiety score of 60.15±5.73 (95% CI: 58.53-61.30) and an average trait anxiety score of 50.21±3.33 (95% CI: 49.58-50.87) (Table III).

Table IV compares some characteristics between those parents who had and those who did not have their child vaccinated against measles. The study data indicated that a significantly higher number of girls were not vaccinated than boys. Also, 10.5% of parents living in a nuclear family did not vaccinate their child, and not all parents of the extended family type had vaccinated their children. The education level of the parents, occupation of the mother, socio-economic level of the family, age of the child and the paternal age were the factors affecting the vaccination of the children against measles. The duration of the rash in children who did not get the measles vaccine was significantly higher than those who got the vaccine ($p<0.05$). The mean anxiety scores were significantly higher in those parents who did not get their child the MMR vaccine than in those who did (95% CI: 58.94-61.36, p=0.017 for trait anxiety; and 95% CI: 49.51-50.91, p=0.001 for state anxiety) (Table IV).

Table III. Parents' State-Trait Anxiety Inventory Scores

	Mean ± SD	Min.- Max.	95% CI values
State anxiety inventory	60.15±5.73	44-66	58.53-61.30
Trait anxiety inventory	50.21±3.33	40-54	49.58-50.87

SD: Standard deviation, Min.: Minimum, Max.: Maximum; CI: Confidence interval

Table IV. A comparison of some characteristics of parents who had and did not have vaccine their child against measles

Variables	Measles vaccine made n (%)	Measles vaccine refused n (%)	χ^2/F and p-value
Child's gender			
Female	10 (18.2)	45 (81.8)	χ^2=22,274*
Male	24 (70.6)	10 (29.4)	p=0.000
Family type			
Nucleus	34 (89.5)	4 (10.5)	χ^2=70,099*
Extended	0 (0)	51 (100)	p=0.000
Mother's profession			
Housewive	20 (55.6)	16 (44.4)	χ^2=51,348*
Agricultural labourers	0 (0)	39 (100)	p=0.000
Factory workers	14 (100)	0 (0)	
Mother's education level			
Illiterate	0 (0)	52 (100)	χ^2=77,642*
Primary education	15 (88.2)	2 (11.8)	p=0.000
High school	11 (91.7)	1 (8.3)	
University	8 (100)	0 (0)	
Father's education level			
Illiterate	3 (5.7)	50 (94.3)	χ^2=78,763*
Primary education	11 (73.3)	4 (26.7)	p=0.000
High school	3 (75.0)	1 (25.0)	
University	17 (100)	0 (0)	
Family socio-economic status			
Good	18 (100)	0 (0)	χ^2=62,933*
Middle	16 (61.5)	10 (38.5)	p=0.000
Bad	0 (0)	45 (100)	
Child's age (years)	4.41±0.89	4.96±0.90	F=0.628** p=0.006
Mother's age	30.52±6.84	31.76±9.11	F=11,759** p=0.470
Father's age	32.64±5.06	37.67±5.67	F=0.241** p=0.000
Rash duration	0.14±0.60	2.16±1.30	F=29,071** p=0.000
Parental state anxiety score	58.32±7.27	61.29±4.21	F=5,947** p=0.017
Parental trait anxiety score	48.73±3.11	51.12±3.15	F=12,180** p=0.001

*Chi-square test was used.
**Independent sample t-test was used

Discussion

Although vaccines are the most successful and reliable public health intervention in history, a significant increase in parents' negative attitudes towards childhood vaccines has been noted (4,15,17). This study explored the practices and attitudes of parents of children with measles in an eastern province of Turkey regarding childhood vaccination, especially the measles vaccine, and the factors affecting vaccination.

Different rates of vaccine hesitancy and refusal have been reported in the literature. In this study, 61.8% of children had not received the measles vaccine because of their parents' refusal. However, this percentage is the non-vaccination rate among those children with measles and does not reflect the overall community. Depending on the country- and time-specific hesitancy, there are differences in the rates of hesitant parents among countries (12). For the measles-rubella vaccination campaign, Krishnamoorthy et al. (13) found that almost a fifth (14.1%) of parents expressed hesitation in vaccinating their children. In a cross-sectional study conducted by Giambi et al. (12) involving parents of 16 to 36-month-old children in Italy, the vaccine hesitancy rate was 16%. Furthermore, vaccine hesitancy and refusal are more common among some faith-based groups or ethnic minorities (15). Although the present study was a regional single-centre study, the finding of the high vaccine refusal rates is remarkable. This suggests that regional differences in vaccine refusal should be considered, and regions with a high refusal rate should be evaluated separately.

Many factors play a role in parents developing a negative attitude towards childhood vaccines (12-15,22,23). A previous Turkish study found reasons such as the belief that vaccines are dangerous or useless, a distrust of vaccines, a belief in natural immunity, a belief that the child will not get sick and are not in the risk group, a religious belief, and a belief that vaccines will cause autism and infertility (14). Some parents have a negative attitude towards all vaccines, whereas others have hesitation towards only certain vaccines, especially measles. In our study, the predominant reason (60.7%) as to why parents do not get their children vaccinated against measles was that "parents do not want children to be vaccinated". The excessive influence of family elders on parents was due to the patriarchal social structure in the study cohort, with half of the families being of an extended family type. Notably, none of the parents of the extended family type had their children vaccinated against measles. This finding demonstrates the impact of family elders on vaccine refusal.

Negative media reports were found to significantly affect (57.3%) the refusal of the measles vaccine. Negative news and propaganda on social media have been effective in increasing vaccine refusal rates (2,13). The most popular of these negative reports establishes a link between the measles vaccine and autism (14,15). Jama et al. (15) reported that mothers stated that some children stop talking after the measles vaccine; based on this, they believe that the measles vaccine causes autism. Hviid et al. (24) evaluated the relationship between the MMR vaccine and autism in 657,461 children and found strong evidence that this vaccine does not increase the risk of autism. Despite studies showing that the measles vaccine is not associated with autism, the perceived relationship between the measles vaccine and autism remains a common concern influencing vaccine hesitancy and refusal (1,2,12,14).

In our study, 51.7% of the parents did not vaccinate their child because of the side effects of the vaccine. However, the side effects seen after the vaccine are usually local and mild (7,17). During a national catch-up measles vaccination program, 152,648 children in the 7-14 age group were vaccinated, and 30% of them reported side effects. More than half of the reported side effects were local and mild (7). These results show that parents do not have accurate knowledge of the side effects and that unfounded beliefs negatively affect the vaccination rates.

Another factor in parents' negative attitudes towards vaccination was their "negative attitudes towards health care professionals". Sabahelzain et al. (1) reported that complex factors such as religious causes, geographic barriers, old vaccine experiences (pain, fever), and the role of health workers contributed to vaccine refusal. The fact that health care professionals play an essential role in vaccine hesitancy and refusal supports our research findings (2,12,13).

Other reasons for vaccine hesitancy and refusal include information gaps, vaccine safety, parental distrust of the health system, and the impact of social networks (2). In our research, 52.8% of parents reported that their child did not receive any other childhood vaccine. We determined that the reasons why parents do not vaccinate their children were in line with the reasons why they do not get the measles vaccine.

We found that vaccination rates among children were significantly lower in those parents with a low education level (Table IV). This finding is similar throughout Turkey. The rates of vaccination of children against measles decrease with decreasing levels of maternal education (25). A study of

461 participants in India found that rates of vaccine hesitancy increased as parental education levels decreased and factors such as maternal age, maternal education level, and the profession of the parents were other sociodemographic characteristics affecting vaccine hesitancy (13). However, there are studies that indicate otherwise. One study investigating parental knowledge, attitudes, and practices about vaccination reported higher rates of vaccinated children of those parents with lower educational levels and of younger parents (4). These results show that numerous variables affect vaccine hesitancy and refusal.

In the present study, family type and socio-economic status were found to influence the parents' decision to get their child vaccinated, and all the parents with an extended family type and poor socio-economic status had failed to get their children vaccinated against measles (Table IV). Similarly, a study investigating the causes of vaccine hesitancy and refusal of parents found that those parents who rejected the vaccine had a lower socio-economic level (14). The Turkish Demographic and Health Survey also found that the children of parents with low income and those living in rural areas had lower rates of vaccination (25). In addition to the poor socio-economic level of the parents in the present study, the proportion of farmworkers was also found to be high. Families working as seasonal agricultural workers go to other cities temporarily for 4-7 months each year, live in tents, and thus have difficulty accessing health services during this process. This may contribute to the lower vaccination rates in the children of parents who work as seasonal farmer labourers.

A noteworthy result of this study is that a large proportion of parents (52.8%) stated that they would not vaccinate their children in the future. In 2019, the WHO declared vaccine hesitancy as one of the top 10 threats to global health (13). Our research also found that a large proportion of children suffering from measles were not vaccinated. This is the negative public health implication of vaccine refusal for vaccine-preventable diseases. Some studies consider the refusal of childhood vaccines to be child neglect (14,26). A study that assessed the ethics of not getting children vaccinated against measles stated that the vaccination should not be a parental choice; it should be considered a social obligation, and society is obliged to provide vaccination if the parents fail to get their children vaccinated (26).

Our data also revealed that the state anxiety levels of the parents were high (60.15±5.73), and that there was a significant difference between the state and trait anxiety score averages among those parents who had and those who did not have their children vaccinated ($p<0.05$). This condition, which indicates that parents have experienced anxiety, should not be associated with vaccine refusal because a large proportion of parents stated that they will not vaccinate their children in the future. Thus, the high levels of parental anxiety can be explained by reasons such as hospitalization, being away from work, staying at home with other children, or an interruption of their activities of daily living.

Study Limitations

This study has several limitations. First, the fact that the research only included those parents of hospitalized children diagnosed with measles is a significant limitation of this research. Second, the single-centred nature of the research conducted on participants with particular sociodemographic characteristics reduces the generalizability of the research findings. The region has a culturally mixed characteristic, with a high refugee population and a very broad perspective of socio-economics and education. Therefore, the research findings do not represent all of Turkey.

Conclusions

In this study, many factors such as family elders, media reports, vaccine side effects, and attitudes to health care workers played a role in the parents' refusal to get their child vaccinated against measles. Community-based training should be carried out to address the misconceptions, concerns, and lack of knowledge about this vaccination. Both parents and family elders must be included in this process of raising awareness of vaccines.

Health care professionals play a critical role in informing families about vaccinations. Therefore, health care professionals, who are the most reliable and vital source of information for parents, must undergo a training process and repeat this training periodically. Sharing the best evidence with the community through health care professionals can prevent the spread of misinformation.

Renewing the policies on vaccinations, establishing standards, and imposing legal sanctions can be effective in reducing vaccine refusal rates. Some standards can be established; such as proof of vaccination so that children can attend a public school or a day care facility. Future studies should involve parents of different ethnic and socio-demographic characteristics and other vaccines included in the vaccine calendar to further explore parental vaccine hesitancy and refusal.

Ethics

Ethics Committee Approval: Necessary ethical permissions was obtained from the İnönü University Health Sciences, Non-Interventional Clinical Research Ethics Committee (approval number: 445-4).

Informed Consent: Informed written consent from parents was received through the children.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept and Design: M.Z., E.H.Y., M.E.D., Data Collection and Processing: M.Z., M.E.D., Analysis and Interpretation: E.H.Y., M.Z., Literature Search: M.Z., E.H.Y., M.E.D., Writing: M.Z., E.H.Y., M.E.D.

Conflict of Interest: The authors declared no conflict of interest.

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References

1. Sabahelzain MM, Moukhyer M, Dubé E, Hardan A, van den Borne B, Bosma H. Towards a further understanding of measles vaccine hesitancy in Khartoum state, Sudan: A qualitative study. PLoS One 2019; 14:e0213882.
2. Jama A, Lindstrand A, Ali M, Butler R, Kulane A. Nurses' perceptions of MMR vaccine hesitancy in an area with low vaccination coverage. Pediatr Heal Med Ther 2019; 10:177-82.
3. Gülcü S, Arslan S. Vaccine application on children: A current review. Journal of Duzce University Health Sciences Institute 2018; 8:34-43.
4. Facciolà A, Visalli G, Orlando A, et al. Vaccine hesitancy: an overview on parents' opinions about vaccination and possible reasons of vaccine refusal. J Public health Res 2019; 8:13-8.
5. Gür E. Vaccine hesitancy - vaccine refusal. Turk Pediatr Ars 2019; 54:1-2.
6. Düzgün MV, Dalgıç Aİ. Can vaccine rejection, an increasing danger to public health, be prevented? J Curr Pediatr 2019; 17: 424-34.
7. Tosun S, Olut AI, Tansug N. Adverse effects of single-component measles vaccine in school children. Vaccine 2017; 35:7309-11.
8. Lo Vecchio A, Cambriglia MD, Fedele MC, et al. Determinants of low measles vaccination coverage in children living in an endemic area. Eur J Pediatr 2019; 178:243-51.
9. World Health Organization (2019) Measles. 2019 https://www.who.int/immunization/diseases/measles/en/ (accessed 2 February 2020).
10. World Health Organization (2020) Measles and Rubella Surveillance Data. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/ (accessed 18 February 2020).
11. World Health Organization. (2017) Measles vaccines: WHO position paper April 2017. http://www.who.int/wer. (accessed 12 February 2020).
12. Giambi C, Fabiani M, D'Ancona F, et al. Parental vaccine hesitancy in Italy - results from a national survey. Vaccine 2018; 36:779-87.
13. Krishnamoorthy Y, Kannusamy S, Sarveswaran G, Majella MG, Sarkar S, Narayanan V. Factors related to vaccine hesitancy during the implementation of measles-rubella campaign 2017 in rural Puducherry - A mixed-method study. J Fam Med Prim Care 2019; 8:3962-70.
14. Topçu S, Almış H, Başkan S, Turgut M, Orhon FŞ, Ulukol B. Evaluation of childhood vaccine refusal and hesitancy intentions in Turkey. Indian J Pediatr 2019; 86:38-43.
15. Jama A, Ali M, Lindstrand A, Butler R, Kulane A. Perspectives on the measles, mumps and rubella vaccination among Somali mothers in Stockholm. Int J Environ Res Public Health 2018; 15:2428.
16. Lo NC, Hotez PJ. Public health and economic consequences of vaccine hesitancy for measles in the United States. JAMA Pediatr 2017; 171:887-92.
17. Callender D. Vaccine hesitancy: More than a movement. Hum Vaccin Immunother 2016; 12:2464-8.
18. Yayan EH, Zengin M, Düken ME, Suna Dağ Y. Reducing children's pain and parents' anxiety in the postoperative period: A therapeutic model in Turkish sample. J Pediatr Nurs 2020; 51: 33-8.
19. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992; 31:301-6.
20. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Arthritis Care Res (Hoboken) 2011; 63(Suppl 11):467-72.
21. Öner N, LeCompte A. Durumluk Sürekli Kaygı Envanteri El Kitabı. İstanbul, Bogaziçi Üniversitesi yayınları, 1983.
22. Napolitano F, D'Alessandro A, Angelillo IF. Investigating Italian parents' vaccine hesitancy: a cross-sectional survey. Hum Vaccin Immunother 2018; 14:1558-65.
23. Dubé E, Gagnon D, MacDonald N, Bocquier A, Peretti-Watel P, Verger P. Underlying factors impacting vaccine hesitancy in high income countries: a review of qualitative studies. Expert Rev Vaccines 2018; 17:989-1004.
24. Hviid A, Hansen JV, Frisch M, Melbye M. Measles, mumps, rubella vaccination and autism a nationwide cohort study. Ann Intern Med 2019; 170:513-20.
25. Hacettepe University Institute of Population Studies. (2019). Turkey Demographic and Health Survey 2018.http://www.hips.hacettepe.edu.tr/tnsa2018/rapor/TNSA2018_ana_Rapor.pdf. (accessed 18 February 2020).
26. Bester JC. Not a matter of parental choice but of social justice obligation: Children are owed measles vaccination. Bioethics 2018; 32:611-9.

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Original Article

Frequency and Associated Factors of Home Injuries in Pre-school Children over 3 Years of Age

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ABSTRACT

Aim: The home injury risk of children is high because of a lack of awareness to danger, a sensitivity to environmental risks and curiosity about finding and learning new things. The main aims of this study were to determine the frequency of home injuries in children over 3 years of age; to examine the relationship between the frequency of home injuries and the characteristics of the home and the safety measures taken.

Materials and Methods: The study data were collected through a questionnaire on socio-demographic characteristics, safety of the home and the "Scale for Identification by Mothers of the Safety Measures Taken to Prevent Home Injuries in Children between 0-6 Ages".

Results: In this study, it was determined that 26.4% of children had had a home injury at least once in their life, and 7.3% of the children had had a home injury during the previous year. The most common home injury was falling and the most frequently injured area was the upper and/or lower extremity. It was determined that the injuries occurred most frequently in the lounge, in summer, on Tuesdays, and in the afternoon.

Conclusion: Supervision of children is very important in terms of preventing possible injuries. It should not be forgotten that home injuries are preventable. Parents should be educated with regards to home injuries.

Keywords: Home injuries, injuries, frequency, playschool, play age child

Introduction

An accident is an unplanned, unexpected, sudden occurrence of injury, damage, or loss of person/property that can be avoided (1). According to the World Health Organization, an accident is defined as "an unexpected event that leads to physical and mental impairment that occurs suddenly" (2). An injury that happens in a house or in the surrounding area is called a home injury. In other words, home injuries are injuries that occur in the living room, kitchen, bedroom, balcony, garden, garages, etc. Home injuries are considered to be an important public health problem as they can lead to injury, disability and death (3). Children have a high risk of home injuries due to a lack of awareness of hazards, sensitivity to environmental risks, and a curiosity about finding and learning. Especially in the pre-school period, children who are at home are more susceptible to home injuries. Injuries affect the health of the child by acting physically, psychologically and socially, causing disorder, illness, disability and even death. Although there is no definite number for home injuries in Turkey, according to research, it has been determined that 18-25% of all injuries are caused by home injuries. In our country, the ratio of home injuries in children between 0-6 years old was reported to be 38% (4) and it was found that 50-80%

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of falling events in the same age group resulted in death (5). Injuries which are the result of misbehaviour or negligence are preventable by precautionary measures.

The purpose of this study was to determine the frequency of home injuries seen in children over 3 years of age who were attending kindergartens attached to the Directorate of National Education located in a provincial centre and to investigate the home-related characteristics of these injuries and any relationships between parental safety measures and home injuries.

Materials and Methods

This cross-sectional study was conducted at a provincial centre in the Mediterranean Region. The study sample included children over 3 years of age who were attending all kindergartens attached to the Directorate of National Education in the province centre (n=1,399). It was planned to reach the entire universe without sampling but only 1,240 children were included due to reasons such as absenteeism, not knowing Turkish, not accepting the questionnaire, etc. (88.6%). Data were collected by means of a questionnaire on the socio-demographic characteristics of children and the safety of the house in terms of home injuries, "The Scale for 0-6 age group of children in order to detect Security Measures Against Homicide" and by face-to-face interviews with their mothers. Çınar and Görak (6) developed a scale in order to recognize the measures to be taken by the mothers of children between the ages of 0-6 years for the protection of their children against home injuries. This scale is Likert-type 5 and includes a total of 40 items among which 34 were positive and 6 were negative. In this scale, answers are given in the form of always, often, sometimes, rarely or never. Among the responses to positive statements; always was assessed as 5 points, often as 4 points, sometimes as 3 points, rarely as 2 points and never as 1 point. Among the responses to negative statements; always was assessed as 5 points, often as 4 points, sometimes as 3 points, rarely as 2 points and never as 1 point. Scores were calculated by adding the points from each item of the scale. The lowest score that can be obtained from the scale is 40, and the highest score is 200. A high score indicates that the mothers displayed positive behaviour in taking security measures against home injuries. The Cronbach's alpha coefficient was reported to be 0.82, and was calculated to be 0.87 in this study.

All accidents, injuries and characteristics were classified using the International Classification of Diseases-10 diagnostic code system (7).

A 20-item checklist which identifies security measures to be taken at home was prepared and the number of security measures implemented/identified at home was determined. The minimum number of security measures that can be taken is 0, and the highest number of security measures is 20.

The dependent variable of research was the condition of child who had had a home injury in the past year; and independent variables were; age, gender, having a chronic illness, the presence of a person in need of special care at home, income status, mother's age, mother's educational status, mother's occupation, father's age, father's educational status, father's occupation, type of house, type of home heating system and the security measure scale points. Data were evaluated using descriptive statistics, t-test and chi-square analysis via the SPSS version 15.0 package program.

In univariate analysis, variables that were significantly related to home-related injuries (having chronic illness, low income, number of home-based measures) and the safety measure diagnostic score (not significant) were included in the logistic regression model. The analysis was performed by the backward-LR method. The model fit was assessed by the Hosmer-Lemeshow test and as the test result was $p>0.05$ ($p=0.672$), it was determined that the model had a high predictive value.

Required permissions for the study was obtained from the Ethics Committee of the Süleyman Demirel University Faculty of Medicine (Decision no: 200).

Results

In our study group, 50.4% were male, the average age was 55.8±9.0 months (Table I). 92.1% of the children's families were nuclear families and 8.2% of children's families had low income. The mean age of the children's parents was 33.1±5.0 years (mothers) and 36.3±5.4 years (fathers). 51.0% of the parents and 60.0% of the fathers had graduated from university. 40.7% of the parents and 1.7% of the fathers were not working. 81.5% of the houses in which the children live were apartments (Table II). 26.4% of the children had had a home injury at some point in their life and 7.3% of them had a home injury within the previous year. Within the previous year, the two most common types of home injuries resulted from falling from rest/armchair/furniture/tree (25.3%) or collision with objects (19.2%). The most commonly injured area of the body was the upper and/or lower extremity (53.5%). The most common cause of injury was household items/blunt

Table I. The descriptive characteristics of the research group and their distribution according to home injury status

Characteristics	Total[a]	Home injury occurance		p-value
		Positive	Negative	
Age of children [Mean (±SD)]	55.8 (±9.0)	54.7 (±10.3)	55.9 (±8.9)	**0.003**
Gender [n (%)]				
Male	615 (49.6)	48 (7.8)	567 (92.2)	0.462
Female	625 (50.4)	42 (6.7)	583 (93.3)	
Number of siblings [Mean (±SD)]	0.9 (±0.8)	1.0 (±0.8)	0.9 (±0.7)	0.502
In which order [n (%)]				
First-single	833	43 (6.8)	590 (93.2)	0.429
Middle	73	8 (11.0)	65 (89.0)	
Last	534	39 (7.3)	495 (92.7)	
Chronic disease [n (%)]				
Yes	64 (5.2)	10 (15.6)	54 (84.4)	**0.021**
No	1176 (94.8)	80 (6.8)	1096 (93.2)	
Total [n (%)]	**1240 (100.0)**	**90 (7.3)**	**1150 (92.7)**	

SD: Standard deviation
[a]The percentages given in the total column are column percentage; others are row percentage

Table II. The characteristics of the research group about family and house and their distribution according to home injury status

Characteristics	Total[a]	Home injury occurance		p-value
		Positive	Negative	
Family type [n (%)]				
Nucleus	1142 (92.1)	84 (7.4)	1058 (92.6)	0.215
Extended family	66 (5.3)	2 (3.0)	64 (97.0)	
Single parent	32 (2.6)	4 (12.5)	28 (87.5)	
Number of people living at home [Mean (±SD)]	3.9 (±0.9)	4.0 (±0.9)	3.9 (±0.8)	0.612
People who needs special care at home				
Yes	21 (1.7)	1 (4.8)	20 (95.2)	0.657
No	1219 (98.3)	89 (7.3)	1130 (92.7)	
Income level of the family				
Poor	17 (1.4)	1 (5.9)	16 (94.1)	0.826
Middle and upper	1223 (98.6)	89 (7.3)	1134 (92.7)	
The income-expense balance of the family				
Income equal to expense or income more than expanse	1138 (91.8)	75 (6.6)	1063 (93.4)	**0.002**
Income less than expense	102 (8.2)	15 (14.7)	87 (85.3)	
Mother's age [Mean (±SD)]	33.1 (±5.0)	32.8 (±4.6)	33.1 (±5.0)	0.580
Educational status of mother [n (%)]				
High school and lower	608 (49.0)	49 (8.1)	559 (91.9)	0.286
University and higher	632 (51.0)	41 (6.6)	591 (93.4)	

Table II. Continued

Characteristics	Total[a]	Home injury occurance		p-value
		Positive	Negative	
The working condition of the mother [n (%)]				
Not working	505 (40.7)	42 (8.3)	463 (91.7)	0.234
Working	735 (59.3)	48 (6.5)	687 (93.5)	
Father's age [Mean (±SD)]	36.3 (±5.4)	36.3 (±4.5)	36.3 (±5.4)	0.952
Educational status of father [n (%)]				
High school and lower	496 (34.0)	39 (7.9)	457 (92.1)	0.503
University and higher	744 (66.0)	51 (6.9)	693 (93.1)	
The working condition of the father [n (%)]				
Not working	16 (1.7)	1 (6.2)	15 (93.8)	0.882
Working	1219 (98.3)	88 (7.2)	1131 (92.8)	
Type of house [n (%)]				
Apartment	1010 (81.5)	73 (7.2)	937 (92.8)	0.931
Single house	230 (18.5)	17 (7.4)	213 (92.6)	
Type of house heating [n (%)]				
Heater	1139 (91.9)	81 (7.1)	1058 (92.9)	0.504
Stove	101 (8.1)	9 (8.9)	92 (91.1)	
Number of security measures taken at home [Mean (±SD)]	15.9 (±2.6)	15.2 (±2.6)	16.0 (±2.6)	**0.018**
Security measure diagnostic score [Mean (±SD)]	174.5 (±15.2)	171.4 (±16.7)	174.8 (±15.1)	**0.040**
Total [n (%)]	**1240 (100.0)**	**90 (7.3)**	**1150 (92.7)**	

SD: Standard deviation
[a]The percentages given in the Total column are column percentage; others are row percentage

objects (68.7%). 63.6% of the children were treated in a health facility after their injury and 3.0% had permanent damage (Table III). The injuries mostly happened in the living room (25.3%). The injuries most frequently occurred in June-July-August (38.4%), on Tuesdays (19.2%) and in the afternoon (47.5%) (Table IV). The mean score of the security measures of the mothers was determined to be 174.5±15.2 (minimum: 98/maximum: 200). The safety measures score was lower in those mothers whose children who had had an injury (p=0.040). It was determined that fewer safety precautions were taken in the homes of those children who had had an injury (p=0.018) (Table II). Household injuries were more frequent among children with chronic illnesses and those living in families with lower incomes (p=0.021 and p=0.002) (Table I and II). There was no difference in the frequency of household injuries according to variables such as age of the child, number of siblings, number of children, number of people living at home, or the age of the parents or their education (Table I and II).

The variables and analysis results that were significant in this model when the variables that were significantly related in univariate analyses (having chronic disease, low income, home prevention measure, and security measure diagnosis score) were taken into the logistic regression model are shown in Table V. It was seen that a chronic illness in the child [odds ratio (OR)=2.68] and a low income in the family (OR=2.73) were found to increase the incidence of home injuries. On the other hand, a high security assessment diagnostic score of the mothers (OR=0.98) was found to reduce the incidence of home injuries.

Discussion

In this study, the frequency of home injuries in children over 3 years of age attending a kindergarten was determined and factors relating to these home injuries were examined. 26.4% of the children were found to have had a home injury during a period of their lives, and 7.3% were found to have had a home injury within the previous 1 year. Similarly, in a thesis study conducted by Boztaş (8) with children aged

between 0-48 months, the incidence of injuries as a result of home injuries during their lives was reported to be 24.5%. In a study conducted in a children's clinic of a university hospital, 30.2% of children in the 0-6 age group were found to have had at least one home injury (9). It is possible that some families would not remember an injury after a certain period of time. At the same time, some families might try to conceal some of their home injuries. Considering these facts, it can be thought that the frequency of home injuries in children is higher than reported (10). This is an important public health problem because of the high incidence of home injuries in children and their consequences such as permanent injury or even death. One of the most important

Table III. Characteristics of injuries due to home injuries in the last year in the research group

Characteristics	**n (%)**
Type of injury	
Falling from bed/sofa/furniture/tree	25 (25.3)
Collision with objects	19 (19.2)
Falling due to slipping/falling from the stairs	17 (17.2)
Compression, catching, crushing, pressing between objects	10 (10.1)
Contact with hot liquids/household appliances/ materials	8 (8.1)
Contact with animals/biting	6 (6.0)
Contact with sharp object	5 (5.0)
Other**	9 (9.1)
Injured region	
Upper and/or lower extremity	53 (53.5)
Head -neck-eye-ear-face	40 (40.5)
Body-thorax-back	3 (3.0)
General (poisoning-drowning)	3 (3.0)
Injury-causing object	
Household goods/blunt objects	68 (68.7)
Hot objects (stove, hot water, fire)	7 (7.1)
Animals	6 (6.0)
Cutting/drilling tools	6 (6.0)
Electric/electric tools	2 (2.0)
Other	10 (10.2)
Intervention in health facility after injury	
Yes	63 (63.6)
No	36 (36.4)
Result after the injury	
Full recovery	95 (96.0)
Permanent damage	3 (3.0)
Temporary damage	1 (1.0)
Total	**99 (100.0)**

*In the past year, a total of 99 injuries happened including 82 children involved in one injury, 7 children involved in an injury for two times and 1 children for 3 times.
**Contact with electrical devices/electric shock 2 times; ingestion of foreign bodies in to body cavities/skin 3 times foreign body evacuation/threats to breathing 2 times; medicine etc. biological substance poisoning 2 times

Table IV. In the research group, space and time characteristics of the home injuries in the last year

Characteristics	**n (%)**
The place where the injury happened	
Lounge	25 (25.4)
Living room	14 (14.1)
Children room	14 (14.1)
Kitchen	14 (14.1)
Garden	8 (8.1)
Master bedroom	7 (7.1)
Entree	7 (7.1)
Apartment vacancy, stairs, elevator	5 (5.0)
Balcony, roof	3 (3.0)
Bathroom	1 (1.0)
Toilet	1 (1.0)
The month of the injury	
December-January-February	19 (19.2)
March-April-May	24 (24.2)
June-July-August	38 (38.4)
September-October-November	18 (18.2)
The day of the injury	
Tuesday	19 (19.2)
Monday	18 (18.2)
Friday	16 (16.2)
Wednesday	15 (15.2)
Saturday	12 (12.1)
Sunday	12 (12.1)
Thursday	7 (7.0)
Time period of the injury	
Afternoon	47 (47.5)
Evening	27 (27.3)
Morning	23 (23.2)
Night	2 (2.0)
Total	**99 (100.0)**

Table V. Logistic Regression Analysis Results

Variable *	OR (95% confidence interval)	p-value
Presence of Chronic Disease in Child	2.68 (1.30-5.51)	**0.007**
Lower income of family	2.73 (1.49-4.99)	**0.001**
Security Prevention Diagnostic Score	0.98 (0.97-0.99)	**0.029**
Hoshmer-Lemeshow Test		0.672

OR: Odds ratio (Estimated Relative Risk)
* In the Logistic regression analysis Backward-LR method; "Number of Security Measures to be taken at Home" is excluded from the model.

reasons for the frequent occurrence of home injuries is that these injuries are unpredictable. Many of these injuries happen in situations where risky behaviour is not foreseen by families (11). Another reason is that children have to live in an environment which was designated for adults (12). Designing children's environments according to the needs of children and taking precautions against injuries will significantly reduce the risk of home injuries.

In this study, it was determined that the two most common home injury types were falling and collision with objects respectively within the previous year. In a thesis study conducted by Gündüz and Aytekin (13), it was found that the most common causes of home injuries were falling (55.0%) and collision with objects (15.2%). In a study by Özmen et al. (14), it was found that falling was the most common type of home injury. This may be due to the fact that this age group is not yet aware of the danger, their muscular coordination has not yet reached a sufficient level, they have increased mobility and there is a lack of supervision by their parents.

In this study, it was determined that the most commonly injured area in children was the upper and/or lower extremity. As the most common home study accident is falling, extremity injuries can be seen more frequently. This result is compatible with other studies in the literature. In a survey conducted by Kılıç et al. (15), it was found that the most frequently injured body areas were hands, arms and fingers (55%), and legs and feet (27%) were second. In a study conducted by Sütoluk et al. (16), it was reported that the most common injury type was the upper extremity injuries.

In this study, it was determined that children had injuries the most frequently in the living room. In most of the studies in the literature, the most common location of accidents at home was identified as the living room (9,13,17). This can be thought to be due to the fact that families spend most of their time in the living room, and that children use this part of the house as a playground.

In this study, home injuries were found to occur most frequently in summer. It is reported in the literature that injuries related to home injuries occur more frequently in spring and summer (18). This may be due to increased movement of children because of increased air temperatures and associated increased movements.

In this survey, it was found that home injuries most frequently occur on Tuesday. A study by Şahiner et al. (19) found that home injuries are most common on Monday. It is thought that injuries happen more often as a result of the parents being more tired after the first working day of the week and thus supervising their children less.

In this study, it was determined that home injuries were seen more frequently in the afternoon. This may be due to the fact that this part of the day is play-time for children. This result is similar to other studies in the literature. Boztaş's study (8) reported that home injuries occur most frequently between 12.00 and 19.00 hours. In a thesis study conducted by Yıldırım (20), it was found that children aged between 1-4 years had home injuries most frequently in the afternoon.

In this study, it was determined that the presence of a chronic disease in the child in multiple analyses was one of the determinants in the increasing incidence of home injuries. Children with health problems can be considered to have a higher risk of injury because they are more sensitive. Boztaş's study (8) found that children who had health problems experienced twice as many home injuries in a two-week period when compared to children who did not have any health problems. In this study, it was determined that, in multiple analyses, a lower family income is a determinant in the increase in the frequency of home injuries. In other studies in the literature, it was stated that the children of families with low socio-economic levels have more home injuries (10,21,22). This may be due to the fact that families with low economic levels have poor housing. The priorities of spending may differ due to the inadequate economic situations of these families. As a result, the necessary arrangements may not have been made to prevent injuries at home.

In this study, it was determined that in multivariate analyses, high scores on the safety measures of the mothers were determinants in reducing the incidence of home injuries. In other studies in the literature, it was reported that children who had had home injuries had a lower score

in the diagnosis of security measures by their mothers (10,13). This age group of children are not conscious of protecting themselves against injury. For this reason, it is very important for the mothers to create safe environments for their children and to remove any dangerous objects or keep their children away from dangerous situations.

In this study, it was found that although there was not a decisive factor in the multivariate analysis of the lower security measures taken at home by some families, fewer safety measures had been taken in the homes of children who had had a home injury in univariate analyses. An unsafe home environment plays an important role in the occurrence of home injuries. Home injuries are preventable events when injuries are predicted by identifying risk factors at home. A study by Balibey et al. (23) reported a significant positive correlation between the home unsafety score and home injuries per child.

Study Limitations

In this study, due to the memory factor, it is possible that parents might not have remembered or not fully remember home injuries which had happened to their children. The findings from this study are specific to the city where the study was conducted and differences may be seen with other cities or across the country. This cross-sectional study has limitations. As the cause and the result were evaluated at the same time, it is difficult to say that the factor lead to the result.

Conclusion

It is important for healthy societies to be protected against risks and for individuals to be in a healthy environment throughout their childhood. Injuries are an important problem which affects all of the people in a society and these preventable events can occur frequently during childhood, having negative health effects by causing physical and psychological problems.

In this study, it was found that one in four children had had a home injury at one time in their lives, the most common home injury type being falling, and the most frequently injured area was the upper and/or lower extremity. It was determined that injuries occurred most commonly in the living room, during the summer months, on Tuesdays and in the afternoon. Those with chronic illnesses, those with lower family income, and those with lower scores on the identification of security measures by their mothers were found to have more frequent domestic injuries.

Children in this age group are very inquisitive. Parental supervision of their children is very important as a means of prevention from possible injuries. It should not be forgotten that home injuries are not a matter of bad luck and they can be avoided if measures are taken. In order to determine the precautions to be taken, parents should make observations in the house and in the garden by going down to the eye level of the child. As a result, possible hazards can be determined and eliminated. Children should be informed about the conditions they should be careful about and the actions that should not be done, and they should be informed about the results of their negative behaviour. Particularly, awareness studies should be carried out for mothers and other child carers regarding home injuries.

Ethics

Ethics Committee Approval: Required permissions for the study was obtained from the Ethics Committee of the Süleyman Demirel University Faculty of Medicine (Decision no: 200).

Informed Consent: Informed consent was obtained from the participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Design: E.U., S.Y., M.V.Y., A.Ç., Y.T., Data Collection or Processing: E.U., S.Y., M.V.Y., A.Ç., Y.T., Analysis or Interpretation: E.U., S.Y., M.V.Y., A.Ç., Y.T., Writing: E.U., S.Y., M.V.Y., A.Ç., Y.T.

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References

1. Özcebe H. Kazalar ve İlk Yardım. İçinde: Güler Ç, Akın L (ed). Ankara, Halk Sağlığı Temel Bilgiler Hacettepe Üniversitesi Yayınları, 2006.
2. World Health Organization [WHO]. (2005). Preventing Children Accidents and Improving Home Safety In The European Region. Identifying Means To Make Dwellings Safer. Report of a WHO expert meeting, Bonn May 30-31 2005. Retrieved 05/01/2021, from http://www.euro.who.int/__data/assets/pdf_file/0008/98666/Bonn_accident_rep.pdf
3. Bertan M, Çakır B. Halk Sağlığı Yönünden Kazalar. İçinde: Bertan M, Güler Ç (ed). Halk Sağlığı Temel Bilgiler Kitabı. Ankara, Güneş Kitabevi Yayınları, 1997.
4. Erkal S, Şafak Ş. Tuzluçayır Sağlık Ocağı Bölgesinde Yaşayan Ailelerde Ev Kazası Görülme Durumu ve Konutların Ev Kazası Riski Açısından İncelenmesi. Sağlık ve Toplum 2003; 96-100.

5. Çınar ND. 0-6 Yaş Grubu Çocukların Ev Kazalarından Korunmasında Ailenin Rolü. Klinik Çocuk Forumu 2004; 62-6.

6. Çınar NS, Görak G. Validity and reliability study of the development of the scale to identification safety measures for mothers' home accidents in 0-6 years old children. Çocuk Forumu Dergisi 2003; 6:22-7.

7. World Health Organization [WHO]. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Version for 2010 Retrieved 05/01/2021, from http://apps.who.int/classifications/icd10/browse/2010/en#/XIX

8. Boztaş G. Identification of Children 0-48 Months of Home Injuries Affecting Results of mothers and their views on the behavior of the resulting injury Factor. Thesis, Hacettepe University Faculty of Medicine, Department of Public Health, Ankara, 2008.

9. Şekerci E, İnal S. Investigation of Home Accidents Knowledge and Practices of Mothers of 0-6 Age Group Inpatient Children. HSP 2016; 3:160-72.

10. Karatepe TU, Akış N. The Frequency of Having Home Accident Among 0-6 Aged Children and Related Factors. Journal of Uludag University School of Medicine 2013; 39:165-8.

11. Öntürk ZK, Balcı S. Childhood injuries: Creating safe home environment. Cumhuriyet Nurs J 2015; 4:41-7.

12. WHO. Child and Adolescent Injury Prevention: A WHO Plan of Action 2006-2015. Geneva, 2006. Retrieved 05/01/2021, from http://apps.who.int/iris/bitstream/10665/43267/1/9241593385_eng.pdf

13. Gündüz G, Aytekin A. Attitudes of Mothers Towards Protecting Their Children From Home Accidents and the Affecting Factors. Behcet Uz Cocuk Hast Derg 2015; 5:184-92.

14. Özmen D, Ergin D, Şen N, Çetinkaya AÇ. Tr: 0-6 Yaş Grubu Çocuğu Olan Annelerin Ev Kazalarına Yönelik Güvenlik Önlemlerinin Tanılanması. Eng: To identify safety measures of mothers of children aged between 0 and 6 years against home accidents. Aile ve Toplum 2007; 3:13-20.

15. Kılıç B, Demiral Y, Özdemir Ç, et al. Incidence of Home Injuries in a Slum Settlement District in İzmir. Toplum Hekimliği Bülteni 2006; 25:27-32.

16. Sütoluk Z, Savaş N, Demirhindi H, Özdener N, Akbaba M. Etiological and Demographic Characteristics of Domestic Accidents at the Adult Emergency Department of Faculty of Medicine, Cukurova University. Toplum Hekimliği Bülteni 2007; 26:29-33.

17. Alasya E. The Incidence of Home Accidents Among Children Aged 1-6 Years and the Practices of Mothers Related With Home Accidents. Near East University, Institute of Health Science Nursing Program, Master's Thesis, Lefkoşa, 2012.

18. Baysal SU, Yıldırım F, Bulut A. Çocuk Güvenliği Yaralanmalardan ve Zehirlenmelerden Korunma Güvenlik Kontrol Listesi. İstanbul, İstanbul Tıp Fakültesi Basımevi, 2005.

19. Şahiner P, Özkan Ö, Hamzaoğlu O. The incidence and risk factors of the home accidents in the households with low socioeconomic level in Kocaeli. TAF Prev Med Bull 2011; 10:257-68.

20. Yıldırım N. The determination of risks factors for home accidents among children in the one to four years old period and the effectiveness of nursing interventions based on social learning theory on decreasing these risk factors. (Doctorate Thesis), Hacettepe University, Institute of Health Sciences, Program of Public Health Nursing, Ankara, 2010.

21. Kendrick D, Young B, Mason-Jones AJ, et al. Home Safety Education and Provision of Safety Equipment For İnjury Prevention. Cochrane Database Syst Rev 2007; CD005014.

22. Schwebel DC, Gaines J. Pediatric Unintentional İnjury: Behavioral Risk Factors and İmplications for Prevention. J Dev Behav Pediatr 2007; 28:245-54.

23. Balibey M, Polat S, Ertem İ, Beyazova U, Şahin F. Factors causing home accidents in childhood. STED 2011; 20:89-97.

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Case Report

A Case Report Based on Watson's Theory of Human Caring Model: Child with Corrosive Esophageal Injury and the Child's Parents

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ABSTRACT

Corrosive esophageal injuries are mostly traumatic in childhood. In this case report, the child suffering from nutritional problems due to corrosive esophageal injury and her parents are discussed according to Watson's Theory of Human Caring Model. It is also intended to set an example for using a model in nursing care in the field of pediatric surgery. Since love and compassion are at the center of this model, it was applied comfortably in the department of pediatric surgery. Because in the department of pediatric surgery, love, compassion, and understanding are shown as well as supporting the child and parents to be operated on. In the case, nursing care was applied over the three basic concepts of the model. The child, mother and father were supported and observed with the caritas processes that started in the preoperative period and continued after the surgery. As a result of the care given and the authentic relationship established according to this model, the satisfaction of the child and her parents increased.

Keywords: Child, corrosive esophageal injury, family, nursing care, Watson's Theory of Human Caring Model

Introduction

Corrosive esophageal injuries are a major health problem worldwide, especially in middle-income countries. The main purpose in the treatment of these injuries is the survival of the child, the prevention of perforation and esophageal stenosis, the preservation of oral nutrition and the continuity of quality of life (1,2). Therefore, nurses should get to the core of children's needs by using nursing models in the care of children with these injuries. They should also establish an authentic and understandable relationship with the patient's parents (3).

Watson's Theory of Human Caring Model, which is one of the nursing models that help nurses to provide this care, defines the basis of nursing care as science and art (3-5). Since love and compassion are at the center of this model, it requires knowing the strengths and weaknesses of individuals and their reactions to events (5-10). In order to achieve all this, this model with three basic concepts

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is needed, namely, a transpersonal caring relationship, a caring moment, and caritas processes.

In this case, the problems and care of a 6-year-old girl and her parents who were hospitalized for gastric transposition surgery due to corrosive esophageal injury were evaluated according to Watson's Theory of Human Care Model.

Case Report

This case report was made in accordance with the CARE Guidelines Checklist.

Case Information and Clinical Findings

The patient was a girl and she had accidentally drunk drain-cleaner at the age of five. Immediately after the accident, the girl's parents took her to a hospital. She was treated for 45 days in the hospital. Due to respiratory distress, the patient was connected to a mechanical ventilator. In the following days, when she could not be taken off the mechanical ventilator, a tracheostomy was performed. She could not be fed orally because of the stenosis in the long segment of the esophagus. Therefore, enteral feeding started from the gastrostomy. She was dilated nine times in the hospital, but these dilatations failed. Thereupon, her parents applied to the pediatric surgery of a university hospital in another city.

At the age of six, the patient underwent gastric transposition surgery. She was in the intensive care unit for six days after the operation and was monitored for three days with a mechanical ventilator. After being taken off the mechanical ventilator, she suffered from coughing and secretion. An attempt was made to initiate enteral feeding via a jejunostomy followed by oral intake in intensive care. When the child's general condition stabilized, she was brought to the service and was kept under surveillance for 14 days.

Timeline

This model was started from the moment the child first came to the clinic and continued until her discharge from hospital (Figure 1).

Diagnostic Assessment

In the perioperative process, chest radiography, laboratory tests (hemogram, biochemistry, coagulation) and blood product preparation were performed.

Therapeutic Intervention

Nursing care was applied to the child and parents via the three basic concepts of this model: transpersonal care relationship, caring moment, and caritas processes.

Transpersonal Caring Relationship

The transpersonal caring relationship is the first basis for going to deep care known as the caring moment, with love and respect for all humanity (4). Looking at the family's past perceptions, her parents stated that the child was in a peaceful and happy family. It was seen that the child and her parents were tired and exhausted. The parents stated that the girl was nervous and had psychological problems due to the recurrent surgeries. The mother was tired of coming to the hospital all the time and the father was anxious. The parents were asked, "Can you inform us about your goals and expectations after leaving here?" for interaction. As a part of the transpersonal caring relationship, before the gastric transposition surgery, the parents and the child were supported via the efforts of the nurse, physician, and dietitian.

Caring Moment

The caring moment is the moment when two people with their own history come together and create a meaningful, authentic, and spiritual connection between them (4). The first maintenance moment started a bit unfavorably as

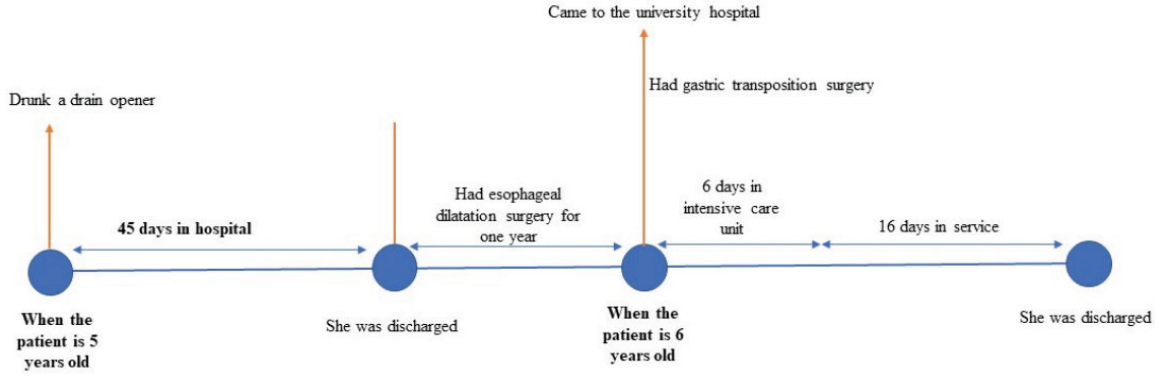

Figure 1. Timeline of the case according to Watson's Theory of Human Caring Model

the child was contacted in order to apply an intravenous catheter. In the later moments of care, arrangements were made regarding nutrition, which is the most basic requirement in the perioperative period.

Caritas Processes

The caritas process is the essence of nursing and is a guide for nurses. These processes lead to the emergence of the healing and caring aspect of nursing. The caritas processes consist of 10 caritas factors (4). In this context, the evaluation of the child and her parents is given in Table I.

Patient Follow-up and Outcomes

In this case, there was a high level of anxiety in the child and the parents, as well as a sense of helplessness and guilt in the parents. The girl and her parents were supported by the perioperative caritas processes. The girl and her parents were observed in line with the nursing interventions. The result of this observation was evaluated both objectively (weight monitoring, respiratory sounds, and self-care requirements) and subjectively (parents' feedback). The parents and the child's self-confidence increased, they became happier and calmer individuals. While communicating with the nurse, they were more comfortable and were able to go into deeper issues. Before being discharged, the child wanted to be photographed with the nurse.

Discussion

This section is discussed over the three basic concepts of this model. These are the interpersonal caring relationship, the caring moment and the caritas processes.

This model has been used in the care of chronic diseases such as hypertension, chronic heart failure, and cancer which require long-term treatment in nursing (6-10). In this case report, this model was used for a child who had come 22 times into the pediatric surgery unit.

Transpersonal Caring Relationship

The transpersonal caring relationship involves the scientific, professional, ethical, aesthetic, creative and personalized giving and taking behaviors and reactions between nurses and patients. In this model, a holistic approach is used in the interpersonal care relationship (5). Based on this model, Aktaş et al. (8) were able to express the hidden feelings and thoughts with the interaction established in a case diagnosed with schizophrenia (9). In a study conducted on this subject in a pediatric intensive care unit, it was found that a unique relationship with pediatric patients was able to be established using this model (10). In this case, the nurse tried to establish a natural, sincere and authentic relationship with the child and the parents. The nurse asked the child and their parents to express themselves, share their experiences and express their expectations in order to evaluate this area. Thus, an attempt was made to establish a relationship of trust between the nurse, patient and parents.

Caring Moment

The caring moment in this model is the process of understanding each other between the caregiver and the care-recipient (4). Erbay et al. (7) highlighted a sincere, understanding and patient approach to those patients who experience hypertensive attacks by using this model in nursing care. In this way, the participation of the individual in nursing care practices was ensured (7). In this case, although the first care moment was negative, it turned into a positive situation when the nurse learned the expectations, beliefs and feelings of the child and her parents in the following days. Communication between the nurse and the child began to increase. This situation started to increase the satisfaction of the mother and father of the child.

Caritas Processes

The caritas process is the last step towards problem solving in this model. This improvement process consists of ten steps. Caring behaviors are used in this process. These are touch, sensitivity, active listening, eye contact, comfort, honesty, respect, trust, openness, and accessibility. In a case report, care behaviors such as touch, sensitivity, active listening, eye contact, comfort, honesty, respect, trust, and openness are accessible (4). Ten individualized care approaches were applied to ten individualized healing processes in the case of uterine atony according to this model. With the care given, it was observed that the mother's trust increased, her worries decreased and she took a more active role in the care of her baby (9). In this case report, the child and their parents were supported with a perioperative caritas processes. The child and her parents were observed in line with the results of nursing interventions.

The care given according to the Watson's Theory of Human Caring Model offers a different approach from the care given according to the medical model. This model reflects the essence of nursing. This model focuses on healing individuals with the concept of love and compassion. The care provided by Watson's caritas processes ensures that individuals are treated in a holistic way, and so it increases the satisfaction and safety of the individual.

Table I. Nursing care applied to child and parents according to Watson's Theory of Human Care Model (Caritas Factors and Caritas Processes) (4)

Caritas factors	Caritas processes
Formation of a humanistic-altruistic system of values (Embrace)	The child and her parents were approached with love, sincerity, understanding and patience. The nurse introduced herself. She then called girl by name. The opportunity to watch cartoons and play games was given in the perioperative period. Eye contact was made with the child to overcome the child's fear of nurses. Her mother and father were respected. She has been told that the growth curve of the girl is the same as her peers in order to reduce your parents' anxiety. Her parents were respected. Despite all the experiences, the importance of accepting the child and family as they are was explained.
Instillation of faith-hope (Inspire)	The child and her parents were encouraged to ask questions about her disease to express her fears and thoughts, and were supported that he could achieve positive results if they cooperated with the treatment team. The girl was given the opportunity to play games with other children. Positive and reassuring communication was established with the child to express their concerns and fears. The girl stated that he wanted to go to the restaurant with her family to eat meatballs and potatoes after the operation. Both parents stated that they wanted the child to be fed like their peers and to stop repetitive surgeries. She was honored for the fears, desires and hopes of the child and family. For inspiration, they were introduced to the other child with the same illness and their family.
Cultivation of sensitivity to one's self and to others (Trust)	Her parents were told that they had to accept themselves spiritually, and then the current situation of the child. All the issues expressed by parents regarding the child's situation were approached sensitively and without prejudice. Play and cartoon, which is the child's interest, were used as a means of relaxation for the child. The results of the care given were treated with sensitivity.
Development of a helping-trusting, human caring relationship (Nurture)	The girl was afraid and angry that she could not heal and undergo recurrent surgeries. When she cried, she was not prevented from crying for relaxation. In a helpful and reassuring manner, parents' guilt was discussed. The trust of the nurse and the readiness of the nurse to help the patient and her family strengthened the relationship with the nurse. Support was provided for independence and individual freedom, not dependency on family and child.
Promotion and acceptance of the expression of positive and negative feelings (Forgive)	The negative emotions experienced by girl and her parents due to non-healing and recurrent surgeries were listened. Parents' dream of being like their child's peers was discussed. It actively listens and ensures that energy passes through without being consumed by the feelings of others. The patient and her parents rested, emphasizing that the energies of parents and child should not be consumed by negative emotions. The importance of staying as "a family" despite the constant hospitalization was emphasized.
Systematic use of a creative problem-solving caring process (Deepen)	Perioperative self-care needs of the child (nutrition, dressing, hair combing) were explained to her family. Preoperative and juicy foods were explained. Postoperative feeding in the upright position, eating less or less frequently were emphasized. Equipment attached to the child was removed when he needed to dress and undress. To solve secretion problem, the child was given a semi-fowler position and cold steam. The patient was taught breathing and coughing exercises. Mobilization of the child in the service and intensive care unit was provided. For the comfort of the child, she wanted to watch TV cartoons. The intensive care unit was taken with the child's parents when appropriate. In the ward, time was arranged for the child to go to the game room for comfort. In the ward, support was provided for the patient to perform self-care needs. Continuity of those taught in intensive care was continued in the ward. It stated that the information taught to the child and her parents increases the trust of parents and the child and their anxiety decreases in both service and intensive care.
Promotion of transpersonal teaching-learning (Balance)	Girl and her parents were informed about the importance of oral feeding after gastric transposition. Information was given on excessive fat and spicy foods, and that foods that are too hard to digest should not be eaten, and that the bite was chewed well. It was emphasized that she should not eat at least two hours before going to bed at night. Her mother was told how to cook at home. Advice was given on how the child could alternatively give her favorite foods (making unseasoned baked potatoes instead of French fries etc.). I was told that the food at night should not be eaten. To prevent reflux, she was informed about how to lie in the semi-fowler position and how to give this position. In the learning-teaching process, they were helped to accept the information and readiness of learning and to accept others as they are and where they are.
Provision for a supportive, protective, and/or corrective mental, physical, societal, and spiritual environment (Co-create)	In the pediatric surgery service, the nursing room is in the middle of the ward and is an audible and mobile place where treatment is prepared, patient acceptance, and visits. Therefore, the patient's room was identified as a quieter room away from the nurse's room. The bed linen of the patient's room was changed daily in the morning, and bathing was provided twice a week. The child's room was left clean after invasive and non-invasive procedures. During her stay in the intensive care unit, the child's self-care needs were met each morning and her linen was changed.
Assistance with gratification of human needs (Minister)	The child was helped with what she could do in her own care (issues such as oral care, oral aspiration). The equipment used in the care of the child (use of cold steam and aspiration device etc.) was explained to the girl. Favorite foods were added to the child's diet (such as banana, potato, meatballs). She was told to eat these foods without skipping meals and in small bites. An observation was made whether the child and her family made all these attempts.
Allowance for existential-phenomenological-spiritual forces (Open)	The beliefs and hopes of the girl and the family were tried to be strengthened. The morale of the child and her parents was raised through the implementation of all process steps and trainings. Regardless of life, her parents were spoken about that what is essential in all situations is love and goodness. Despite all these difficult processes, it was talked to the child and their parents that every moment of life was full of goodness and love. The feelings and opinions of the child and her parents on this subject were also discussed. Here, the importance of love of family members for each other were emphasized.

*This table was created by the authors to show the nursing interventions made in accordance with the caritas factors in the Watson's Theory of Human Care Model

The positive change, satisfaction and increase in harmony observed in both the child and the family as a result of the authentic relationship established in this case report show the effectiveness of the Watson's Theory of Human Caring Model. In addition, an example of providing holistic care in accordance with this model in pediatric surgery services is also shown. It is thought that this model will help nurses to determine the care needs of those children and their parents with corrosive esophageal injuries and to apply nursing interventions correctly. At the same time, maintaining this model-based care in all pediatric cases will help both the child and the parents to meet all their physical, psychological, emotional and spiritual needs and to provide nursing care in a holistic way. In-service training and courses should be organized to increase the awareness of nurses working in pediatrics and pediatric surgery services about nursing care based on Watson's Theory of Human Caring Model.

Patient Perspective

The patient and her parents were happily discharged. Her parents were happy that their daughter was in a good condition. The girl was happy that she could be fed orally. Communication with the nurses became more cordial for the child.

Ethics

Informed Consent: The approval concerning publication of case's treatment and follow-up period was obtained from patient's parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept and Design: N.G.Ö.Ö., F.V., Analysis and Interpretation: N.G.Ö.Ö., F.V., Literature Search: N.G.Ö.Ö., Writing: N.G.Ö.Ö., F.V., K.Y.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. De Lusong MAA, Timbol ABG, Tuazon DJS. Management of esophageal caustic injury. World J Gastrointest Pharmacol Ther 2017; 8:90-8.
2. Alser O, Hamouri S, Novotny NM. Esophageal caustic injuries in pediatrics: A sobering global health issue. Asian Cardiovasc Thorac Ann 2019; 27:431-5.
3. Pajnkihar M, McKenna HP, Štiglic G, Vrbnjak D. Fit for practice: Analysis and evaluation of Watson's Theory of Human Caring. Nurs Sci Q 2017; 30:243-52.
4. Watson J. Jean Watson's Theory of Human Caring. In: Smith MC, Parker ME. (eds). Nursing Theories and Nursing Practice 5th ed. Philadelphia, F.A. Davis Company, 2015; 321-39.
5. Gönen Şentürk S, Küçükgüçlü Ö, Watson J. Caring for caregivers of individuals with dementia: From the perspective of Watson's Theory of Human Caring. Journal of Hacettepe University Faculty of Nursing 2017; 4:62-72.
6. Costello M. Watson's Caritas Processes ® as a framework for spiritual end of life care for oncology patients. International Journal of Caring Sciences, 2018; 11:639-44.
7. Erbay Ö, Yıldırım Y, Fadıloğlu Ç, Şenuzun Aykar F. Use of Watson's Theory of Human Caring in Nursing Care of Patients with Hypertensive Attack: Case Report. Turk J Cardiovasc Nurs 2018; 9:82-8.
8. Aktaş Y, Arabacı LB, Dülgerler Ş. Nursing care according to the Watson's Human Care Model in a patient diagnosed with schizophrenia: A case report. İzmir Katip Çelbi Üniversitesi Sağlık Bilimleri Fakültesi Dergisi 2020; 5:51-7.
9. Demirhan İ, Tuncay Yılmaz S, Şahin S, Kaplan S. Nursing process in uterine atony cases according to Watson's Theory of Human Caring. Gümüşhane University Journal of Health Sciences 2019; 8:510-7.
10. Elbahnasawy HT, Lawend J, Mohammed EK. Application of Watson Caring Theory for nurses in pediatric critical care unit. IOSR Journal of Nursing and Health Science 2016; 5:56-67.

Erratum

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The change made in the article titled "Risk Factors of Hyponatremia in Children with Lower Respiratory Tract Infection (LRTI)" in the research articles section published in JPR 2021;8(4) are as follows.

Page 479

Published;

[1]All India Institute of Medical Sciences, Department of Pediatrics and Neonatology, New Delhi, India

Reported Correction;

[1]All India institute of Medical Sciences, Department of Pediatrics and Neonatology, Bhubaneswar, India

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Erratum

In the article with "Clinical, Laboratory and Molecular Approach to Ten Children with Congenital Neutropenia" citation information which was published in the third issue of first volume of Journal of Pediatric Research, authors noticed that the text of TUBITAK Project support acknowledgment regarding the study was inadvertently forgotten. Authors apologize to the readers for the mistake.

The change made in the article titled "Clinical, Laboratory and Molecular Approach to Ten Children with Congenital Neutropenia" in the research articles section published in JPR 2016;3(1) are as follows.

Page 11;

Published;

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Reported Correction;

Finansal Destek: Bu çalışma, Avrupa Nadir Hastalıklar Araştırma Projeleri (E-RARE) ile birlikte TÜBİTAK (Türkiye Bilimsel ve Teknolojik Araştırma Kurumu) tarafından maddi olarak desteklenmiştir (no.112S022). Vermiş oldukları desteklerden dolayı çok teşekkür ederiz.