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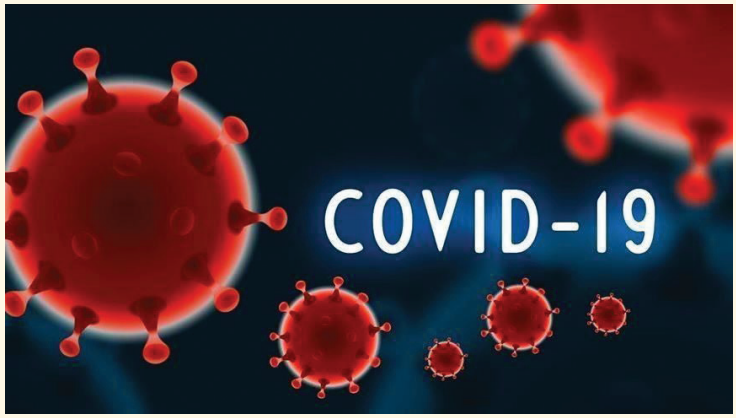

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Özgür Çoğulu
Ege University, Faculty of Medicine, Department of Pediatrics, İzmir, Turkey
E-posta: ozgur.cogulu@ege.edu.tr
ORCID ID: orcid.org/0000-0002-9037-5599

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Address for Correspondence

Özgür Çoğulu
Ege University Faculty of Medicine, Department of Pediatrics, Bornova, 35100 İzmir, Turkey
Phone: +90 232 390 10 05 - 390 10 31
Fax: +90 232 390 13 57
E-mail: ozgur.cogulu@ege.edu.tr

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Editor: Özgür Çoğulu
Ege University Faculty of Medicine, Department of Pediatrics, Bornova, 35100 İzmir, Turkey
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Molla Gürani Mah. Kaçamak Sok. No: 21/1
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Preparation of research articles, systematic reviews and meta-analyses must comply with study design guidelines:

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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/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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To ensure controllability of the research findings, the study design, study sample, and the methodological approaches and applications should be explained and their sources should be presented.

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discussion sections. The whole text must not exceed 1500 words. Reviews are texts in which a current subject is examined independently, with reference to scientific literature. The whole text must not exceed 18 A4 paper sheets. Letters to the Editor must be manuscripts, which do not exceed 1000 words, with reference to scientific literature, and those written in response to issued literature or those, which include development in the field of pediatrics. These manuscripts do not contain an abstract. The number of references is limited to 5.

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Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English evaluation) towards the study should appear at the end of the article.

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Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in English, an unstructured summary not exceeding 50 words, and key words. The main text should consist of introduction, case report, discussion and references. The entire text should not exceed 1500 words (A4, formatted as specified above). A maximum of 10 references shall be used in case reports.

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Review articles can address any aspect of clinical or laboratory pediatry. Review articles must provide critical analyses of contemporary evidence and provide directions for future research. **The journal only accepts and publishes invited reviews.** Before sending a review, discussion with the editor is recommended.

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CORRESPONDENCE

Prof. Dr. Özgür Çoğulu

The Journal of Pediatric Research

Ege University Faculty of Medicine, Department of Pediatrics, Bornova, 35100 İzmir, Turkey

Phone: +90 232 390 10 05 - 390 10 31

Fax: +90 232 390 13 57

E-mail: ozgur.cogulu@ege.edu.tr

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Contents

Original Articles

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Editorial

Dear Readers,

We are so proud and happy to welcome you to the second issue of "The Journal of Pediatric Research" in 2020. Nowadays, the coronavirus covid-19 outbreak that has influenced the whole world has changed the course of life. The importance of investments in scientific research was once again revealed. With the efforts of healthcare professionals and scientists, the world will survive these troubled days. In this respect, it will continue to publish very valuable scientific researches in our journal without slowing down.

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In this issue, we present you with 14 research articles from different disciplines. This issue, with its articles published, covers several scientific areas in pediatrics such as neonatology, pediatric endocrinology, pediatric hematology, pediatric emergency medicine, pediatric immunology, and pediatric nursing. This broad range makes our journal special. The impact factor of "The Journal of Pediatric Research" is growing and it gives us hope to enter greater scientific areas and new international indexes.

I would like to acknowledge the members of our editorial board reviewers, authors and Galenos Publishing House for preparing the first issue of 2020. We look forward to your scientific contributions in our future issues.

Sincerely yours,

Tahir Atik, M.D., PhD, Assoc. Prof.
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Original Article

Vitamin B12 Serum Levels of Six to Nine-month-old Infants According to Feeding Practices

Hüseyin Dağ[1], Melike Özberk Koç[2], Okan Dikker[3], Hasan Dursun[1]

[1]University of Health Sciences Turkey, İstanbul Okmeydanı Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey
[2]Bakırköy Children's Health and Diseases Clinic, Department of Pediatricians, İstanbul, Turkey
[3]University of Health Sciences Turkey, İstanbul Okmeydanı Training and Research Hospital, Clinic of Medical Biochemistry, İstanbul, Turkey

ABSTRACT

Aim: Vitamin B12 is naturally obtained from animal-derived foods and is important for the development and wellbeing of babies. Vitamin B12 deficiency is a general health concern in developing countries. This study aimed to investigate the effects of different feeding practices on vitamin B12 levels and hemogram parameters in infants aged 6-9 months.

Materials and Methods: A total of 120 infants (61 boys, 59 girls) aged 6-9 months were retrospectively evaluated. These babies were assigned to three groups according to feeding practices: 1) only breast milk, 2) breast milk and formula, and 3) only formula in addition to complementary foods. Laboratory data (vitamin B12, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, and absolute neutrophil count) of the patients were retrospectively compared.

Results: The mean and median age of the patients was 6.6±1.1 months. The vitamin B12 levels in babies that only received formula were statistically significantly higher than those in babies taking only breast milk or taking both breast milk and formula ($p<0.05$). Furthermore, vitamin B12 levels were significantly lower in babies receiving only breast milk than in those receiving both formula and breast milk ($p<0.001$).

Conclusion: This study showed that vitamin B12 levels were lower in babies that only received breast milk compared to those in babies receiving formula. The babies that were receiving formula only had the highest levels of vitamin B12. This study determined that breast milk alone was not sufficient to maintain normal levels of vitamin B12 in 6 to 9-month-old babies in the region. Therefore, both mothers and babies should be provided with the necessary support in terms of vitamin B12 levels, and prophylaxis should be discussed from the viewpoint of preventive healthcare services.

Keywords: Child, breast milk, formula, vitamin B12

Introduction

The most significant role of vitamin B12 is its function in DNA synthesis, which is required for cell division and proliferation. Vitamin B12 is water-soluble and synthesized mainly by microorganisms. Humans cannot synthesize vitamin B12. Vitamin B12 is obtained from cobalamin in foods, and especially in animal-derived foods. Dietary deficiency of this vitamin is rare for those who have normal eating habits, as the amount of vitamin B12 is sufficient in most animal-obtained foods. However, vitamin B12 inadequacy is seen in those with a low dietary intake of vitamin B12 (1).

Vitamin B12 is a significant factor for the process of child development. Vitamin B12 deficiency can cause neurological disorders and hematologic changes, in addition

Address for Correspondence
Hüseyin Dağ MD, University of Health Sciences, İstanbul Okmeydanı Training and Research Hospital, Clinic of Pediatrics, İstanbul, Turkey
Phone: +90 553 393 34 98 E-mail: huseyindag2003@gmail.com ORCID: orcid.org/0000-0001-7596-7687
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to developmental delays and regressions (1). Vitamin B12 fortified foods and supplements, in addition to animal-derived foods, can be consumed in cases of deficiency (2). Vitamin B12 inadequacy is prevalent in those on strict vegetarian or vegan regimes as well as in individuals who live in developing countries (3-6).

Breast milk is the main source of micronutrients needed by a newborn (7), and babies who are only fed with breast milk receive nearly 0.25 µg vitamin B12 from a healthy mother within the first 6 months (4). The vitamin B12 level of babies is associated with the vitamin B12 level of their mothers (8). Previous studies have shown that babies receiving breast milk alone had notably lower serum vitamin B12 rates in comparison to those babies receiving formula (9,10).

Delayed diagnosis and treatment during childhood, in spite of the low cost of this treatment, may entail irreversible neurological damage, in addition to severe anemia. Therefore, patients presenting to an outpatient clinic should be examined for vitamin B12 inadequacy. Anemia within the first 2 years of life can occur due to a vitamin B12 deficiency in breastmilk, especially in developing countries, and manifests with neurodevelopmental delay (11,12).

This research aimed at investigating the effectiveness of varied feeding practices on vitamin B12 serum levels and hemogram parameters in 6 to 9-month-old infants.

Materials and Methods

The Clinical Trials Ethics Committee of Okmeydanı Training and Research Hospital approved this study as per the approval number:1079, date: December 18th, 2018. Consent forms were filled out by all participants. The study groups consisted of 120 babies aged 6-9 months, consisting of 61 males and 59 females who did not have any medical problems and were brought to the pediatric outpatient clinics of Okmeydanı Training and Research Hospital between January 2018 and November 2018 for routine checkup and immunization follow-up. Data on feeding history and multivitamin use were obtained for all infants. Babies who were premature, had a low birth weight, had any metabolic or chronic disease, or were hospitalized for any disease were excluded from this study. Patients who had incomplete files, or those who did not have data concerning B12 levels or complete blood count data, or those with an indeterminable feeding history were not included in this study.

The infants were divided into three groups according to their feeding practices: 1) only breast milk, 2) breast milk and formula, and 3) only formula in addition to complementary foods. In this study, 77 babies received only breast milk, 19 babies received both breast milk and formula, and 24 babies received formula only. In addition, all babies were receiving complementary foods according to the statements of their families. However, objective data on the amount of complementary foods given to the baby could not be obtained. Laboratory datum [vitamin B12, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), white blood cell count (WBC), and absolute neutrophil count (ANC)] of the patients were retrospectively evaluated between the groups. Vitamin B12 levels were assayed using the chemiluminescent immunoassay with a Roche Cobas Integra 400 Plus analyzer. Values lower than 250 pg/mL were considered low. Hemogram parameters were assayed with a Mindray BC-6800 hemogram device.

Statistical Analysis

Data were analyzed using the SPSS 20.0 for Windows package software (IBM). Continuous variable data with a normal distribution are given as mean ± standard deviation, and data with a non-normal distribution are given as median and range. Data with a normal distribution was analyzed using a histogram and Kolmogorov-Smirnov test. The statistical differences between non-normal data were analyzed using the Mann-Whitney U test, while the differences between more than two groups were analyzed using the Kruskal-Wallis test. The statistical differences between two categorical datasets were analyzed using the chi-square test. Categorical data are stated numerically with percentage. $P<0.05$ was acknowledged as statistically meaningful.

Results

The mean and median age of the patients was 6.6±1.1 months; 50.8% (n=61) of the patients were male and 49.1% (n=59) of the patients were female. Vitamin B12 levels in those infants that only received formula were statistically notably higher than those in infants receiving only breast milk or both breast milk and formula ($p<0.05$). Vitamin B12 levels were significantly lower in infants receiving only breast milk than in those receiving formula in addition to breast milk ($p<0.05$). There was no statistically notable difference between the groups in terms of Hb, Hct, MCV, WBC, and ANC levels (Table 1).

Vitamin B12 deficiency was mainly seen in babies receiving only breast milk. None of the babies receiving only formula had vitamin B12 deficiency (Table 2).

The mean baby weight, gender, type of birth (normal birth or cesarean section) and gestational weeks of the three groups were found to be statistically similar (Table 3).

Discussion

Vitamin B12 deficiency is a health worry generally encountered in developing countries (5). Vitamin B12 is critical for development during the fetal, neonatal, and infancy periods.

Therefore, vitamin B12 deficiency can cause numerous diseases, especially developmental and neurological disorders (13,14). It is important for a mother to consume foods that are rich in vitamin B12 throughout the lactation period (15). It is recommended to breastfeed babies for more than 6 months, and breast milk is a natural source of vitamin B12 for the baby. However, some studies have shown that restrictive vegetarian and vegan diets resulted in lower levels of vitamin B12 in the mother and therefore led to vitamin B12 deficiency in babies (4,15-18). Vitamin B12 deficiency is not uncommon in babies receiving only breast milk (4,17-21). Studies have shown that babies who were fed formula had increased vitamin B12 levels compared to those that were breast fed (9,10).

In this study, the effects of varied feeding implementations on vitamin B12 levels in the bloodstream of babies who were brought to our hospital were investigated. Similar to other studies, this current study revealed that vitamin B12 levels were lower in infants receiving only breast milk compared to those receiving formula in addition to breast milk as well as those receiving only formula. It was also observed that those babies who were only receiving formula had much higher levels of vitamin B12. According to these results, it was apparent that vitamin B12 levels differed according to feeding practices. It is therefore important to consume formulas fortified with vitamin B12 to prevent vitamin B12 deficiency.

Vitamin B12 insufficiency in mothers is the leading reason of vitamin B12 deficiency in babies during infancy. When babies are only fed breast milk, they can have severe vitamin B12 deficiency if their mothers also have vitamin B12 deficiency. (22,23). In a study conducted in Istanbul and Izmit, Ackurt reported that 48% of women in the early pregnancy period (13-17 weeks), 80% of women in the late pregnancy period (28-32 weeks), and 60% of women in the postpartum period had vitamin B12 deficiency. In addition, the delayed or non-introduction of complementary feeding or feeding babies with cow's milk as the primary food source contributed to vitamin B12 insufficiency in infants (24). In

Table I. Biochemical data of the groups according to feeding practices

Parameters	Babies receiving breast milk only (n=77) (mean ± SD)	Babies receiving breast milk + formula (n=19) (mean ± SD)	Babies receiving formula only (n=24) (mean ± SD)	p
Vitamin B12 (pg/mL)	228.8±155.5	359.5±192.9	618.5±248.2	0.002
Hb (g/dL)	11.5±1.0	11.6±0.8	11.9±1.0	0.404
Hct (%)	33.8±3.2	33.0±2.5	34.1±3.0	0.295
MCV (fL)	90.6±106.5	73.4 ± 3.3	74.9±4.3	0.380
WBC (mm³)	9.549±2.544	10.248±2.568	8.655±1.541	0.194
ANC (mm³)	2.224±1.465	1.762±714	1.989±714	0.400

*, Kruskal-Wallis test, ANC: Absolute neutrophil count, MCV: Mean corpuscular volume, RBC: Red blood cell, WBC: White blood cell, SD: Standard deviation, Hb: Hemoglobin, Hct: Hematocrit

Table II. Evaluation of vitamin B12 levels according to the reference interval in different feeding practices

	Babies receiving only breast milk (n=77)	Babies receiving breast milk and formula (n=19)	Babies receiving only formula (n=24)
Vitamin B12 below the reference interval	37 (48.1%)	3 (15.8%)	0-0
Vitamin B12 within the reference interval	40 (51.9%)	16 (84.2%)	24 (100%)

Table III. Demographic features of babies

	Babies receiving breast milk (n=77)	Babies receiving breast milk + formula (n=19)	Babies receiving formula only (n=24)	p
Baby weight (gram)	3,520.2 ±199.5	3.466±121.2	3.320±124.2	0=0.124
Baby gender (male/female)	35/42	10/9	13/11	0=0.130
Delivery method (normal birth/cesarean section)	45/32	13/6	17/7	0=0.109
Gestational week (week)	39.1±0.4	39.3±0.8	38.9±0.7	0=0.095

another study conducted in Sivas, Demirel et al. (25) stated that the incidence of vitamin B12 insufficiency during the third trimester was 66.7% in healthy pregnant women.

In a study by Koç et al. (26), 39.8% of babies who were healthy according to their families had a vitamin B12 deficiency, and 75% of the mothers of those babies with vitamin B12 deficiency also had vitamin B12 insufficiency. Monagle et al. (27) found infantile megaloblastic anemia in 19 children under the age of 1 in their clinic, and reported that vitamin B12 insufficiency in 6 (30%) children was secondary to the vitamin B12 insufficiency in their mothers, and that these 6 children were only receiving breast milk. In another study, Minet et al. (28) demonstrated that healthy infants who were receiving breast milk had lower vitamin B12 levels than those who were receiving formula.

This current study's findings are similar to the results of previous studies. It has been determined that, despite complementary feeding, breast milk alone was not adequate to sustain normal levels of vitamin B12 in 6 to 9-month-old infants in this region. Vitamin B12 levels, which can lead to negative outcomes in cases of deficiency, should be measured in infants (22,28). Vitamin B12 levels should also be assessed in mothers, and those with low levels of vitamin B12 should be provided with vitamin supplement in order to increase the vitamin B12 level in their breast milk. Accordingly, a vitamin B12 test and complete blood count should be performed when an infant is brought to an outpatient clinic. In this study, 3 babies had a vitamin B12 deficiency even though they were receiving formula in addition to breast milk. Consequently, formula intake cannot completely rule out vitamin B12 deficiency, since infants taking formula in addition to breast milk also had a vitamin B12 deficiency.

When clinical signs suggest vitamin B12 deficiency in a child, fasting plasma homocysteine levels should be investigated even if serum vitamin B12 level and MCV results are normal. It has been reported that testing only for vitamin B12 levels could lead to a misdiagnosis in 10-26% of patients. Accuracy can be increased to 99.8% when methyl malonic acid and homocysteine tests are carried out (29). Accurate diagnosis is of the utmost importance in these patients in order to administer vitamin B12 in addition to treatment to the infants receiving breast milk. Homocysteine levels were not measured in this study as none of the patients had neurodevelopmental disorders, according to their records. Moreover, we suggest that standard algorithms concerning an approach to vitamin B12 deficiency in children can be created as the number of studies on this field increases.

Previous studies have shown that vitamin B12 insufficiency can be caused by strict vegetarian diets or pernicious anemia for 90% of infants (27,30). On the other hand, determinants such as poverty or low socioeconomic status, incorrect feeding habits, and an increased use of vitamin B12 due to a high number of pregnancies also have an impact on the high percentage of vitamin B12 deficiency in babies and their mothers in underdeveloped and developing countries (31,32). It is also apparent that the risk of developing vitamin B12 deficiency increases with lower economic status and a higher number of pregnancies. In the current study, none of the babies receiving formula had a vitamin B12 deficiency. Therefore, infants should receive a sufficient amount of complementary foods rich in vitamin B12. Accordingly, it is important to consider and provide early treatment for vitamin B12 deficiency in breastfeeding mothers and their infants with a low intake of animal-derived foods, especially in regions with low socioeconomic status, in addition to a vegetarian diet.

Of the hematologic findings for vitamin B12 deficiency, increased MCV characteristically develops before anemia, and the clinical signs are observed at a later time. This study found that there was no statistically major variation between the groups with respect to MCV levels in healthy infants who had different feeding practices. However, the MCV levels in infants that only received breast milk were increased compared to those in the other groups.

It was observed that vitamin B12 levels were lower in infants taking only breast milk than in those taking formula, and that babies who were only taking formula had the highest levels of vitamin B12. This research confirmed that breast milk alone was not adequate to maintain normal levels of vitamin B12 in 6 to 9-month-old infants in the region. Accordingly, vitamin B12 levels should be checked during pregnancy and in case of deficiency, a suitable replacement therapy should be provided for pregnant women in a manner to encompass the postpartum period in order to protect the baby from the dramatic outcomes of vitamin B12 insufficiency. Vitamin B12 levels must be tested in addition to a complete blood count in routine screening of children. Formula should be recommended for babies found to have vitamin B12 deficiency to supplement insufficient breast milk from their mothers. Replacements should be administered if there is a vitamin B12 deficiency despite sufficient breast milk. In addition, routine B12 prophylaxis and dosages in infants should be discussed as a part of preventive medicine practices in developing countries.

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Ethics

Ethics Committee Approval: The Clinical Trials Ethics Committee of Okmeydanı Training and Research Hospital approved this study as per the approval number: 1079, date: December 18th, 2018.

Informed Consent: Consent forms were filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.D., M.Ö.K., Design: M.Ö.K., O.D., H.D., Data Collection or Processing: H.D., Analysis or Interpretation: O.D., Ha.D., Literature Search: Ha.D., Writing: H.D.

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Original Article

Thyroid Function in Obese Children and Adolescents and its Relationships with Metabolic Parameters

Özlem Korkmaz

Başkent University Faculty of Medicine, Dr Turgut Noyan Training and Research Center, Department of Pediatric Endocrinology, Adana, Turkey

ABSTRACT

Aim: The purpose of this study was to evaluate levels of free thyroxin (T4) and thyroid-stimulating hormone (TSH) in obese children and adolescents, and to identify potential correlations between glucose and lipid metabolism parameters.

Materials and Methods: One hundred obese patients aged 8-18 years were retrospectively evaluated in the pediatric endocrinology outpatient clinic. All participants' anthropometric measurements, free T4 and TSH concentrations, glucose levels and lipid profiles were recorded.

Results: The mean age of the participants was 11.43±2.64 years. TSH levels exhibited significant positive correlation with fasting blood glucose and cholesterol levels. Multiple regression analysis showed that a one-unit increase in blood glucose and cholesterol raised TSH levels by 0.047 units and 0.012 units, respectively.

Conclusion: The relationship between thyroid function and other metabolic risk factors in obese children is still unclear. Our findings are important in terms of showing that obesity may exert a central effect on thyroid function, before the emergence of any effects on insulin levels and anthropometric characteristics. A greater understanding of the association between thyroid function and obesity will be useful to the development of strategies aimed at preventing or treating childhood obesity.

Keywords: Childhood obesity, thyroid hormone, glucose levels, lipid profile

Introduction

Childhood obesity has become a major global health problem (1). As the prevalence of obesity increases, so does that of numerous comorbidities associated with obesity, including abnormalities in the endocrine, cardiovascular, gastrointestinal, pulmonary, orthopedic and neurologic systems, as well as important psychological and social problems. Some comorbidities, such as type 2 Diabetes Mellitus and steatohepatitis are extremely common in obese children, while thyroid dysfunctions are also frequently observed (2,3). There has recently been increased interest in the association between thyroid dysfunction and obesity (4-6). The mechanisms underlying the thyroid hormone changes in obesity are unclear. However, several mechanisms have been proposed in the literature describing the different forms of thyroid dysfunction in obese individuals. These include subclinical hypothyroidism due to iodine deficiency, autoimmune thyroiditis and thyroid-stimulating hormone (TSH) receptor gene mutation, functional disorders in the hypothalamus-pituitary-thyroid axis, thyroid hormone resistance, mitochondrial dysfunction, and production

Address for Correspondence
Özlem Korkmaz MD, Başkent University Faculty of Medicine, Dr Turgut Noyan Training and Research Center, Department of Pediatric Endocrinology, Adana, Turkey
Phone: +90 505 450 49 15 E-mail: ozlem-korkmazz@hotmail.com ORCID: orcid.org/0000-0001-9093-6205
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of Leptin-mediated pro-Thyrotropin-releasing hormone (TRH) (7,8). Thyroid hormones are known to affect the regulation of energy homeostasis, fat oxidation, and lipid and carbohydrate metabolism. Increased TSH levels are therefore regarded as indicative of the changing energy balance in obesity (9,10).

TSH level elevation has been associated with high triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) levels, insulin resistance, and a risk of coronary disease in obese children (11,12). However, it is unclear whether obesity and TSH levels have an 'adaptive association', whether the metabolic rate increases in order to reduce weight gain, whether an increase occurs in subclinical hypothyroidism or thyroid resistance, and therefore, whether obesity contributes to the dysfunctions in glucose and/or lipid metabolism, or is instead a by-product of increased weight.

Few studies to date have focused on the relationship between obesity and thyroid function in Turkish children and adolescents (13-16). Furthermore, the relationship between thyroid function and other metabolic risk factors in obese children is unclear. This research was intended to evaluate levels of free thyroxin (T4) and TSH in obese children and adolescents, and to identify potential correlations between glucose and lipid metabolism markers.

Materials and Methods

One hundred obese patients aged 8-18 years were retrospectively evaluated in the pediatric endocrinology outpatient clinic between 01 September, 2018, and 20 December, 2018.

Ethical approval was obtained from Başkent University Faculty of Medicine Ethical Committee (approval number: KA19/27). The current study was conducted according to the principles set out in the Helsinki Declaration and Good Clinical Practice guidelines. Informed consent was obtained.

Subjects with chronic medication requirements, who declined to take part, with underlying chronic disease, or diagnosed with syndromic obesity were excluded from the study.

Anthropometric data, including weight, weight Standard Deviation score (SDS), height, height SDS, Body Mass index (BMI) and BMI SDS, were recorded for all subjects. All anthropometric data were converted to SDSs using Turkish standard data (17). Subjects with BMI SDS>2 were regarded as obese.

Blood samples were collected from all patients in order to measure thyroid hormones (TSH, fT4), lipid profile, and glucose and insulin. All blood specimens were collected in the morning between 08:00 and 10:00 after 10-hour fasting. Insulin measurement was performed using the chemiluminescence method on an Advia Siemens Centaur XP device (Ireland). Fasting blood glucose was measured using the spectrophotometric method on an Advia Siemens 1800 (Japan) device. Homeostatic Model Assessment - Insulin Resistance (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mmol/L) x fasting insulin (mUI/L) / 22.5 (18). TSH (reference range: 0.27-4.2 µIU/mL) and fT4 (reference range: 11-26 pmol/L) concentrations were measured via chemiluminescence methods with an Abbott Architect i4000 (USA) device. TC (mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL), LDL-C (mg/dL) and TG (mg/dL) concentrations were measured using photometric methods on an Abbott Architect c8000 (USA) device.

Statistical Analysis

Statistical analysis was performed on SPSS version 21 (SPSS Inc., Chicago, IL). The Shapiro-Wilk test was used to examine normality. Pearson and Spearmen correlation coefficients were calculated (in accordance with normality of distribution) to determine relationships between variables. Multiple linear regression analysis with stepwise selection was used for more reliable assessment of the relationships between TSH and fT4, and gender, age, anthropometric measurements, carbohydrate and lipid parameters related to obesity. P values less than 0.05 were regarded as statistically significant.

Results

One hundred (57 girls, 43 boys) obese children and adolescents were included in the study. The mean age of the subjects was 11.43±2.64 years. Descriptive statistics of our variables are given in Table I.

Analysis between fT4 and TSH values and other parameters measured in the study revealed no significant correlations for fT4, whereas fasting glucose (r=0.265; p=0.008), (Figure 1) and cholesterol (r=0.220; p=0.028) (Figure 2) levels were significantly and positively correlated with TSH values (Table II).

Multiple linear regression analysis was performed with fT4 as a dependent variable, but none of our independent variables demonstrated any significant results. However, fasting glucose and cholesterol emerged as significant independent variables when TSH was defined as the dependent variable. The multiple linear regression model was TSH=0.047 * fasting glucose +0.012 * cholesterol

Table I. Main anthropometric, biochemical and hormonal parameters in obese patients	
	Mean ± SD
Age (years)	11.43±2.64
Weight (kg)	65.37±16.47
Weight SDS	2.76±0.70
Height (cm)	149.21±13
Height SDS	0.69±1.20
BMI SDS	2.60±0.40
fT4 (pmol/L)	14.45±1.97
TSH (µIU/mL)	3.60±1.79
Glucose (mg/dL)	88.27±6.69
Insulin (mUI/L)	15.02±6.95
HOMA-IR	3.29±1.63
Total cholesterol (mg/dL)	167.77±31.47
HDL-cholesterol (mg/dL)	47.96±9.48
LDL-cholesterol (mg/dL)	101.54±26.92
Triglyceride (mg/dL)	121.72±47.33
BMI: Body Mass index, SDS: Standard Deviation score, fT4: Free thyroxin, TSH: Thyroid-stimulating hormone, HOMA-IR: Homeostatic Model Assessment - Insulin Resistance, kg: kilogram, cm: centimeter	

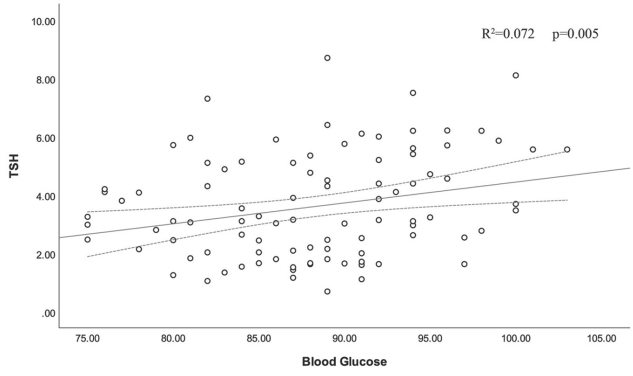

Figure 1. Scatter plot of thyroid-stimulating hormone and blood glucose

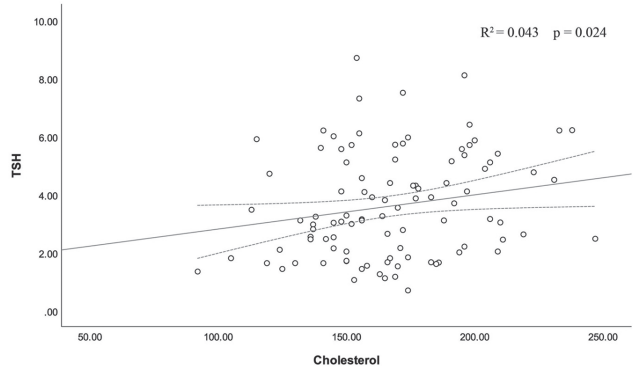

Figure 2. Scatter plot of thyroid-stimulating hormone and cholesterol

- 5.008 (p=0.002), showing that a one-unit increase in fasting glucose raises increases TSH by 0.047 units, while a one-unit increase in cholesterol values raises TSH by 0.012 units (Table III).

Discussion

TSH levels in the current study were positively correlated with blood glucose and TC levels in a group of otherwise healthy obese pediatric patients. Multiple regression analysis revealed that TSH levels were directly affected by fasting glucose and cholesterol levels. However, fT4 levels were not associated with any of the parameters measured. Although we did not investigate causal relationships, the fact that TSH levels were associated with glucose and cholesterol levels while fT4 levels were not, may indicate that obesity has an initial effect on central thyroid function, which may lead to the development of metabolic pathologies.

The effects of thyroid hormones on energy balance and adipose tissue have been the subject of considerable research in recent years. Several recent cross-sectional studies have reported associations between thyroid hormones and obesity (4,5,19-23). Levels of cyclic adenosine monophosphate (AMP), a second messenger for many hormones including TSH and TRH, are closely associated with energy balance and the production/use of adenosine triphosphate (ATP). The correlation between TSH and blood glucose levels may indicate a complex relationship in terms of energy production and thyroid levels. Although TSH elevation may represent a simple response to increased glucose, aimed at regulating metabolism to compensate for and utilize the ATP-producing glucose in tissues, there may also be a more complex explanation. In the context of insulin resistance in obese patients, ATP depletion may develop in cells, leading to a decrease in the production of the second messenger c-AMP by adenylate cyclase. Liver cells are one of the main targets of thyroid hormones, and the action of these hormones in hepatocytes would be affected by depletion of cyclic AMP. The clinical result of this would be hepatocyte unresponsiveness to thyroid hormones, and an increase in TSH levels could be required to compensate for this decrease. These may represent the first steps in a progressive series of events culminating in TSH resistance (24,25). Other studies of obese children show that only a minority suffer from autoimmune thyroiditis, while most demonstrate moderately increased TSH levels without thyroid disease (10,26). Similarly, Dekelbab et al. (27) reported a higher prevalence of mild elevation of TSH values, in the absence of autoimmune thyroid disease, in a group of obese children compared to normal weight

Table II. Relationships between various parameters and the levels of free thyroxin and thyroid-stimulating hormone

		Age	Weight	Weight SDS	Height	Height SDS	BMI SDS	Glucose
fT4	**R**	-0.036	-0.148	-0.088	-0.112	-0.015	-0.141	0.003
	p	0.719	0.143	0.382	0.267	0.883	0.160	0.978
TSH	**R**	0.146	0.143	0.113	0.092	-0.057	0.112	0.265
	p	0.147	0.156	0.263	0.361	0.576	0.269	0.008*
		Insulin	**HOMA-IR**	**Cholesterol**	**HDL**	**LDL**	**Triglyceride**	
fT4	**R**	-0.119	-0.126	0.008	-0.063	0.096	-0.115	-
	p	0.237	0.212	0.934	0.533	0.343	0.253	-
TSH	**R**	0.141	0.195	0.220	0.015	0.183	0.165	-
	p	0.163	0.051	0.028*	0.885	0.069	0.100	-

* ; Statistically significant correlation, fT4: Free thyroxin, TSH: Thyroid-stimulating hormone, BMI: Body Mass index, SDS: Standard Deviation score, HOMA-IR: Homeostatic Model Assessment - Insulin Resistance

Table III. Multiple linear regression analysis results with TSH as a dependent variable

	β	Std. Error	t	p	95.0% CI for β	
					Lower	Upper
(Constant)	-5.008	2.469	-2.028	0.045	-9.909	-0.107
Fasting glucose	0.074	0.026	2.898	0.005	0.023	0.125
Cholesterol	0.012	0.005	2.29	0.024	0.002	0.023

TSH = 0.047 * Fasting Glucose + 0.012 * Cholesterol - 5.008, n=100, R2=0.119, F=6.561, p=0.002

control groups. Stichel et al. (28) determined a significant increase in childhood obesity TSH and T3 levels, although in most cases these increases cannot be explained by thyroid autoimmunity or iodine deficiency. Further controlled studies are therefore required to explain our findings, which are far from conclusive, given that many other factors (such as iodine deficiency, and thyroid autoimmunity) capable of altering thyroid levels were not evaluated in our study.

Some studies have reported slightly greater elevation in TSH levels in obese individuals compared to normal weight subjects, and have detected a positive association between TSH levels and BMI and weight change (10,29). Reinehr and Andler (30) observed a moderate increase in peripheral thyroid hormones (T3,T4) and TSH levels in obese children. TSH elevation exhibited no significant correlation with BMI (or any other anthropometric measurement) in the present study. However, TSH was significantly correlated with cholesterol levels. Multiple regression analysis results also indicated that a one-unit increase in cholesterol values corresponded to a 0.012-unit increase in TSH levels. Although various studies have investigated the relation of thyroid function and lipid profiles in obese and overweight pediatric patients, the results have been inconsistent (31). Grandone et al. (20) reported no correlation between TSH levels and HDL-C and TGs. However, consistent with our findings, Aeberli et al. (12) reported that TSH levels in obese pediatric patients exhibited a significant positive correlation with TC cholesterol and LDL-C.

We determined a significant positive correlation between TSH and fasting glucose levels, which was also apparent at multiple regression analysis, a one-unit increase in fasting glucose being found to cause an increase of 0.047 units in TSH. However, analysis of relationships between HOMA-IR and insulin levels with fT4 and TSH revealed no significant correlations. Although experimental studies have shown that thyroid hormones may impact insulin sensitivity by influencing the expression or activation of uncoupling protein, β adrenergic receptor and peroxisome proliferator-activated receptor-γ (32), our findings may suggest that TSH levels (and therefore thyroid function) are affected much earlier than insulin. If so, then it is plausible to suggest that early TSH changes are in fact a contributor to the insulin resistance seen in obese patients. Future studies would benefit from long-term follow-up of thyroid and insulin levels in children with obesity in order to elucidate which causes the other, or to determine whether a causal relationship exists between these two crucial parameters of human metabolism.

Both hyperthyroidism and hypothyroidism are capable of resulting in impaired glucose tolerance in hepatic, muscle, and adipose tissues (33). Although a number of different studies have investigated the relation between thyroid function and insulin resistance in children and adults, the reported findings regarding the link between insulin resistance and hypothyroidism or hyperthyroidism are inconsistent (34). Maratou et al. (35) reported similar levels of insulin resistance in cases of hypothyroidism and of subclinical hyperthyroidism. However, associations between hypothyroidism and insulin resistance subsequently progressing to Metabolic syndrome in adults have been reported by a number of authors (36,37).

The limitations of our study include the absence of a control group; however, our aim was to assess the relationships of measured parameters in obese children and adolescents. Our analyses are not therefore necessarily affected by the lack of a control group. Nevertheless, a control group would have provided an opportunity to observe the differences in the relationships among parameters (or lack thereof) between obese and non-obese subjects, and this must be regarded as a limitation. Second, this is a retrospective single-center study with all the restrictions associated with such studies. Finally, we were unable to analyze various other factors that may have affected thyroid levels, such as iodine deficiency, and autoimmune thyroiditis.

Conclusion

The purpose of this study was to determine fT4 and TSH concentrations in obese children and adolescents and to investigate potential correlations between such parameters as anthropometric measurements, glucose levels and lipid profile. Fasting blood glucose and cholesterol were positively correlated with TSH, while none of the parameters investigated were associated with fT4 levels. We believe that our findings will make a significant contribution to the existing literature by showing that obesity may exert a central effect on thyroid function, before the emergence of any effects on insulin levels and anthropometric characteristics. Since the physiopathology of thyroid function changes in childhood obesity and the effects of thyroid function on lipid and carbohydrate metabolism are still controversial, further studies are required for an improved understanding of the association between thyroid function and obesity.

Ethics

Ethics Committee Approval: The author assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Başkent University) and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees of Başkent University (approval number: KA-19/27).

Informed Consent: Informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

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Original Article

Retrospective Evaluation of Childhood Cutaneous Mastocytosis Cases

Burcu Akıncı, Hamiyet Hekimci Özdemir, Nihal Özdemir Karadaş, Akkız Şahin Yaşar, Zuhal Önder Siviş, Yeşim Aydınok, Kaan Kavaklı, Can Balkan, Deniz Yılmaz Karapınar

Ege University Hospital, Clinic of Pediatric Hematology and Oncology, İzmir, Turkey

ABSTRACT

Aim: Mastocytosis is a rare disease characterized by clonal mast cell proliferation in one or more organs. It can lead to different clinical manifestations and has no definitive treatment. In this study, we aimed to evaluate the clinical and laboratory characteristics of our patients diagnosed with mastocytosis in our clinic.

Materials and Methods: Thirteen patients that were followed up with the diagnosis of mastocytosis at the Pediatric Hematology Clinic, in the Ege University Faculty of Medicine between November 1999 and April 2016 were retrospectively analyzed.

Results: Seven of patients were female (53.8%) and six were male (42.6%). The mean age at diagnosis was 20 (3-68) months. At the time of diagnosis, complete blood count and peripheral smear were found to be compatible with the anemia of iron deficiency in three patients. Other parameters were normal. Mean tryptase level was detected as 5.9 (3.6-16.6) ng/mL, and only one tryptase level was found as slightly increased. The median level of total IgE was 91.1 (4.47-362) IU/mL. Mast cell proliferation was not detected in bone marrow aspiration and biopsy material of any patients. All of the cases were evaluated as cutaneous type mastocytosis.

Conclusion: The possibility of mastocytosis in systemic form in childhood is very rare and bone marrow examination may be necessary in selected cases.

Keywords: Mastocytosis, cutaneous, tryptase, child

Introduction

Mastocytosis is a very rare disease that can lead to different clinical presentations depending on the tissues where clonal mast cells accumulate. The clinical spectrum of the disease may vary from relatively benign forms with isolated skin involvement to highly aggressive severe forms in which widespread systemic involvement results in poor prognosis. Over the years, significant progress has been made in the management of mastocytosis seen in the adulthood; however, childhood mastocytosis has remained a rarely researched topic due to the rareness of interventional procedures (1-4).

Mast cells, which originate from CD34 + hematopoietic cells, are considered as an important component of the immune system. They are present in all vascularized tissues, primarily the skin and mucous membranes. The growth, differentiation and proliferation of mast cells are controlled by c-kit (CD117), a tyrosine kinase receptor, and its ligand, stem cell factor. These factors are also involved in the pathogenesis of mastocytosis (5,6).

Address for Correspondence
Burcu Akıncı, Ege University Hospital, Clinic of Pediatric Hematology and Oncology, İzmir, Turkey
Phone: +90 505 829 61 16 E-mail: bdeveci@windowslive.com ORCID: orcid.org/0000-0001-6026-4786
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According to the criteria published by the World Health Organization in 2016, adult type mastocytosis was divided into three groups as cutaneous mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma. Cutaneous type mastocytosis is localized to the skin and is examined under three subgroups which are maculopapular mastocytosis (urticaria pigmentosa), diffuse CM and soliter mastocytoma. SM is characterized by mast cell accumulation in internal organs such as bone marrow, spleen, lymph nodes, and the gastrointestinal tract. SM is divided into subtypes such as indolent SM, smoldering SM, SM with an associated hematologic neoplasm, aggressive SM and mast cell leukemia (7,8).

SM is defined by major and minor criteria. Major criteria is the multifocal dense infiltrate of mast cells in the bone marrow or in other extracutaneous organ(s) (>15 mast cells per aggregate). Minor SM criteria are: (a) 25% of mast cells show an abnormal morphology in bone marrow smears, or are spindle-shaped cells in biopsies of extracutaneous organ(s); (b) a KIT mutation at codon 816 in extracutaneous organ(s) or bone marrow; (c) Expression of CD2 and/or CD25 in bone marrow or extracutaneous organ(s); (d) serum tryptase >20 ng mL−1. If at least one major and one minor or at least three minor criteria are fulfilled, the diagnosis of SM is given (1,3,8). Diagnostic criteria of SM are presented in Table I. Although mastocytosis is rarely seen in systemic forms in childhood CM localized to the skin is much more frequent), it has been reported that some of these cases do not enter into remission after adolescence and the severity of the disease may increase (1-4). In this study, we aimed to evaluate the clinical and laboratory findings of cases with a mastocytosis diagnosis in our clinic.

Materials and Methods

Thirteen patients diagnosed with mastocytosis in the Pediatric Hematology Clinic of Ege University Medical Faculty from November 1999 to April 2016 were included in this study. Ethical approval was obtained (Acıbadem University ATADEK, 2019-19/11). Patients were accepted into the study after having given written informed consent from parents. All diagnoses were confirmed via histopathological investigation of skin biopsy samples. Evaluations were performed by retrospective evaluation of patient files. The patients' clinical findings, complete blood count results, biochemical parameters, tryptase levels, total Ig E levels, and the results of abdominal ultrasonography and bone marrow examinations were recorded.

Table I. Diagnostic criteria for systemic mastocytosis

Major 1. Multifocal dense infiltrates of mast cells (tryptase positive) in bone marrow and/or other extracutaneous tissues (aggregates of more than 15 mast cells).
Minor 1. More than 25% of the mast cells in bone marrow smears or tissue biopsy sections are spindle shaped or display atypical morphology. 2. Detection of a c-kit point mutation in codon 816 in blood, bone marrow, or other lesional tissue. 3. Evidence of CD2 and/or CD25 on mast cells in bone marrow, blood, or extracutaneous tissue. 4. Serum tryptase more than 20 ng/mL

Statical Analysis

All demographic and clinical wariables were summarized using count and percentage n (%) for categorical variables and means plus or minus standard deviations for continuous variables.

Results

Our patient group was comprised of 7 girls and 6 boys. The mean age at diagnosis was 20 (3-68) months. Patients' medical records showed that all applications to the department were due to skin rash. None of the patients had a family history of this disease. There were no pathological findings except mastocytosis-specific rashes on physical examination of the patients. The rashes were mostly located on the trunk. They were also seen in extremities and face. At the time of diagnosis, complete blood count and peripheral smear were found to be compatible with the iron deficiency anemia in three patients. Other parameters were normal. Mean absolute eosinophil count was 421.4/µL (70-980/µL). Liver and kidney function tests and other biochemical values were within their respective reference ranges. Abdominal ultrasonography was performed in 12 patients. In one patient, liver calcification was detected incidentally and the patient was diagnosed with hydatid cyst afterwards. The other patients had normal ultrasonography findings. Total tryptase levels had been measured in all but one of our patients. Mean tryptase level was 5.9 (3.6-16.6) ng/mL. In only one of our patients, the level of tryptase was found to be slightly increased (16.6 ng/mL); however, on subsequent measurements (3 times), they were found to diminished. Total IgE levels were determined in 8 of our patients and the median level was 91.1 (minimum 4.47-maximum 362) IU/mL. Two patients were observed to have high total IgE values (126 and 362 IU/mL) in regard to age-adjusted reference intervals. The laboratory characteristics of patients are presented in Table II. Bone marrow aspiration

Table II. Laboratory characteristics of patients			
Patient number	**Tryptase Level (kUA/L)**	**IgE (IU/mL)**	**Eosinophil ratio**
1	4.08	-	2.08
2	-	362.00	2.3
3	3.6	9.96	0.33
4	4.3	58.90	4.2
5	4.84	-	1.79
6	8.64	-	0.9
7	4.6	72.70	1
8	7.4	126.00	4
9	3.6	4.47	1.4
10	4.41	-	7.1
11	16.6	-	6.1
12	3.33	133.00	4.1
13	5.4	91.1	2.4

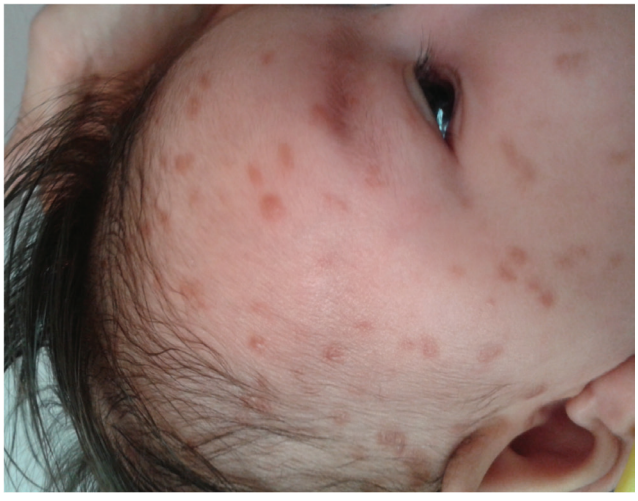

Figure 1. Maculopapuler rash on patient's face

and biopsy were performed on 9 of the 13 patients, none of them indicated an increase of mast cells. All cases were evaluated as cutaneous type mastocytosis. In general, the patients were followed up without any treatment. Oral antihistaminic drugs and local clobetazol proprionate were applied to them during periods of increased pruritis. Patients did not receive any other systemic treatment. In follow-up, there was no increase in the lesions of the patients.

Discussion

Mastocytosis is a rare disease. While epidemiological studies are insufficient, both in our country and the world, its prevalence is estimated to be 1 in 10,000. Moreover, it has also been reported that approximately 1 in 1,000 to 8,000

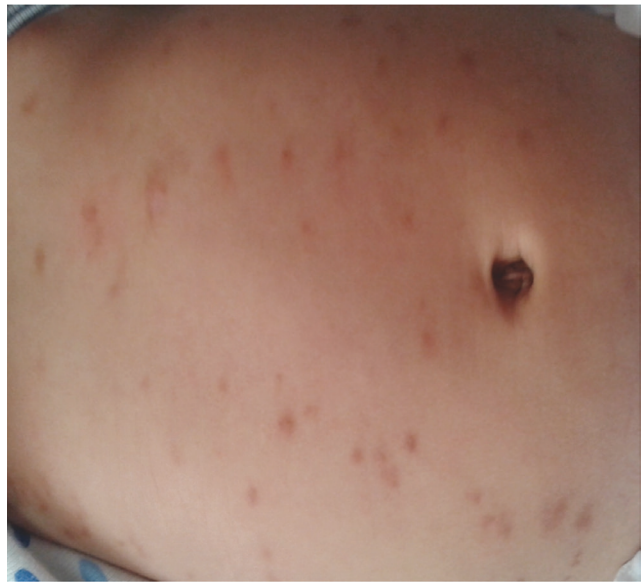

Figure 2. Rash on a patient's trunk

patients who apply to dermatology clinics are diagnosed with mastocytosis (9-11). Mastocytosis can be seen both in childhood and adulthood. In 55% of cases, the findings and symptoms of the disease appear within the first two years of life, 10% of patients manifest symptoms between 2-15 years, and the remaining 35% of the patients show initial findings after 15 years of age. According to a publication from our country, 73% of mastocytosis cases were reported in children, while 26.7% were reported in adults (12,13). In our cases, the average age of diagnosis was 20 months and the female/male ratio was 1.1/1. Related literature is conflicting, while some report that mastocytosis is more frequent in females, others indicate that it is more common among males (14-17).

Mastocytosis is now classified with myeloproliferative neoplasms. Increased local concentrations of soluble mast cell growth factor in lesions of CM are believed to stimulate mast cell and melanocyte proliferation. Activating mutations of the proto-oncogene c-kit have been identified. Although pediatric mastocytosis can spontaneously regress, it is a clonal disease most commonly associated with D816V and other activating c-kit mutations. The induction of melanocytes explains the hyperpigmentation that is commonly associated with cutaneous mast cell lesions. The stimulation of pruritus is associated with production of IL-31. IL-6 levels have been shown to be elevated and correlated with the disease severity, indicating IL-6 is involved in the pathogenesis of mastocytosis (5,6,8).

CM is divided to three categories namely maculopapüler form, diffuse CM and solitary mastocytoma (18). CM

typically manifests as maculopapular or plaque-like rashes seen on the trunk and extremities in the majority of cases, and particularly on the sides of the head and face in children. Figures 1 and 2 show skin rashes in our cases. In both forms of the disease, itching, redness, tachycardia, syncope, gastrointestinal symptoms such as nausea, vomiting, abdominal pain can develop as a result of secretion of mediators such as histamine, heparin and tryptase from the accumulated mast cells. The risk of anaphylaxis is increased in cases with mastocytosis, which is more common in those with SM. In the literature, anaphylactic risk is reported to be 22-50% in adults and 6-10% in children. It should be kept in mind that anaphylaxis can often be triggered by fever, infections, and even, albeit rarely, by various foods and medicines during childhood. In its systemic form, symptoms are associated with the affected organs. Hepatomegaly, elevations in liver function tests, acid and portal hypertension may occur due to liver involvement; splenomegaly and hypersplenism may occur in cases with spleen involvement; pancytopenia may develop due to bone marrow involvement; gastrointestinal tract involvement may manifest with hypoalbuminemia and weight loss. More rarely, osteoporosis and pathologic fractures can be seen secondary to skeletal involvement (1,2,19). None of our patients showed any evidence of such findings.

As previously mentioned, SM is defined by major and minor criteria. Major criterion is the multifocal dense infiltrate of mast cells in the bone marrow or in other extracutaneous organ(s). Minor SM criteria are defined as: 25% of mast cells in bone marrow smears, or are spindle-shaped cells in biopsies of extracutaneous organ(s); a KIT mutation at codon 816 in extracutaneous organ(s) or bone marrow; expression of CD2 and/or CD25 in bone marrow or extracutaneous organ(s); or serum tryptase >20 ng mL−1. We need one major and one minor or at least three minor criteria to diagnose SM (1,3,8). In childhood, it is difficult to determine the exact number of cases with systemic involvement, due to the rareness of the systemic form among children and the fact that bone marrow biopsy is performed in selected cases (3,4). There is no universal consensus on which tests should be performed and how often they should be repeated when mastocytosis is diagnosed in childhood. Contrary to adult mastocytosis, complete blood count, biochemical parameters and peripheral smear findings are normal, as was the case in our study (4). Serum tryptase levels are shown as the most reliable parameter for predicting mast cell activation, and therefore, the severity and prevalence of mastocytosis. Serum tryptase levels are expected to be high especially in patients with very common skin involvement or systemic findings (20,21). Since it is one of the cornerstones of SM, without doing bone marrow aspiration and biopsy, diagnosis of some systemic cases may be overlooked. In a large study consisting of 173 patients, the authors found only two cases of systemic involvement in children with diffuse CM (22). In our study, serum tryptase level was at the upper limit of normal in only one patient and follow up measurements were normal. It is known that eosinophils and mast cells coexist in many clonal and nonclonal diseases. Both cells are derived from CD34 + hematopoietic cells and have the ability to regulate their tissue microenvironment. A number of previous studies have shown that eosinophilia can be detected in SM and can indicate an aggressive disease (23,24). Clinical consequence of eosinophilia in SM might largely depend on the subtype of disease and the underlying molecular mechanisms. In one recent study, the total eosinophil ratio was normal. It is also known that IgE levels and IgE-mediated anaphylaxis risk may be increased in patients with mastocytosis (25,26). IgE levels were measured in 8 of our cases, and values were elevated in 2 patients. However, anaphylaxis did not develop in any of our cases.

Our findings show that, even if bone marrow aspiration and biopsy are performed, it is difficult to confirm the diagnosis in patients without conclusive findings for mastocytosis (blood count and smear, increased tryptase, hepatosplenomegaly). Since tryptase activity is an important marker of disease activity, and considering the fact that it was shown to increase beyond the reference range only once in one patient, it may be appropriate to measure tryptase at certain intervals in suspected patients.

Ethics

Ethics Committee Approval: The study was approved by Acıbadem University Ethics Committee/ATADEK (approvel number:2019-19/11).

Informed Consent: Informed written parental consent was obtained before enrolling children into the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.A., N.Ö.K., A.Ş.Y., Z.Ö.S., Concept: B.A., Design: B.A., K.K., C.B., D.Y.K., Data Collection or Processing: B.A., H.H.Ö., N.Ö.K., A.Ş.Y., Z.Ö.S., Analysis or Interpretation: B.A., Y.A., Literature Search: B.A., Writing: B.A., D.Y.K.

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Original Article

Patient Safety Related Implementations of Nurses Working in the Neonatal Intensive Care Unit and Related Factors

Elanur Kaleci[1], Fatma Taş Arslan[2]

[1]Necmettin Erbakan University Faculty of Nursing, Department of Pediatric Nursing, Konya, Turkey
[2]Selçuk University Faculty of Nursing, Department of Pediatric Nursing, Konya, Turkey

ABSTRACT

Aim: This study was carried out in order to determine patient safety related implementations of nurses working in neonatal intensive care.

Materials and Methods: This descriptive study was carried out in Neonatal Intensive Care Units (NICU) in six hospitals in Konya city center between April and May 2012. Ninety-six nurses working in intensive care units participated in this survey. Newborn Patient Safety Survey Form was used in this study. The analysis of the data was done by number, percentage, Kruskall-Wallis, Man-Whitney U and Independent t tests.

Results: It was seen that nurses scored most in interventions regarding falling among the fields of patient safety implementations (92.42±6.36). A meaningful difference was found between NICU nurses' state of education and patient safety intervention regarding the medication score average ($p<0.05$) and also nurses' working years and patient safety intervention regarding identity implementations score average ($p<0.05$).

Conclusion: It was determined that nurses implemented interventions regarding falling most among patient safety implementations. It was seen that patient safety implementations of nurses were related to their state of education, working years, the number of patients cared for daily, and also receiving patient safety training.

Keywords: Nurses, patient safety, intensive care units, neonatal

Introduction

Patient safety is all of the precautions taken by the health institutions and personnel of these institutions in order to pre-determine, report and correct errors and prevent injury caused by health care services (1,2). The aim of patient safety is to provide safety by creating an environment which will affect patients, patients' relatives and hospital personnel psychologically and physically. Patient safety is a basic need and an unmistakable right of individuals (2).

Neonatal intensive care units (NICU) are special, multidisciplinary units constructed to provide care for patients who need special care and whose health condition is critical (3,4,5,6,7,8). The fact that the newborn in NICU is vulnerable to external factors increases the risk of medical error. Medical errors occur in premature babies especially in the ones born before the 30th week of pregnancy and those lighter than 1.500 grams (57% in 24 to 27-week-babies whereas only 3% in full-term babies) (9).

Neonatal nurses are important in providing and continuing patient safety and for their efficiency in carrying out activities during the patient's stay in hospital. Nurses are intertwined with patient safety in every field of care.

Address for Correspondence
Elanur Kaleci MD, Necmettin Erbakan University Faculty of Nursing, Department of Pediatric Nursing, Konya, Turkey
Phone: +90 539 547 08 70 E-mail: elanur42@gmail.com ORCID: orcid.org/0000-0002-9326-8756
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Informing on medical error, decreasing or removing the risk of medical error, supporting patient safety and reporting unwanted events are among the duties of nurses. Nurses who work in units such as NICU which require sensitivity about patient safety should take an active role and be careful (10).

Recently some implementations regarding prevention and control of infections, color code implementations, safety reporting systems, training health personnel in patient and personnel safety and setting up committees in order to carry out the necessary activities to provide patient and employee safety have been performed in our country (11). However, in the literature, a limited number of studies regarding patient safety of nurses working in pediatric clinics have been reported in our country (12,13). Also, no studies about patient safety in NICU are to be found in our country. It is necessary to carry out studies to raise nurses' awareness of patient safety and to determine the inadequacies in patient safety in NICU and nursing implementations. These studies will contribute to determine nursing implementations related to patient safety and to remove inadequacies in safety implementations for patients who receive care. Furthermore, it is thought that they will contribute to increase the importance given to patient safety as well as to take precautions to provide and improve patient safety. In this context, this study was carried out to find out about nursing implementations of NICU nurses regarding patient safety and related factors.

Research questions:

- What is the intervention score of nurses working in NICU regarding patient safety implementations?

- What are the factors related to nursing intervention scores of patient safety implementations?

Materials and Methods

This study was carried out in NICUs of six hospitals in Konya city center in 2012 descriptively. In this research, 101 nurses were included in the sample without any participation criteria as the number of nurses in the population was limited. However, 96 nurses were included in the study because of personal reasons such as maternity leave or sick notes meaning that 95% of the population was reached.

In this research, a "Neonatal Patient Safety Questionnaire Form" consisting of two parts was prepared and used by the researchers in light of the existing literature (8,14,15,16,17,18). The first part of the questionnaire was composed of 16 questions about the nurses' socio-demographic and professional characteristics and their views on patient safety. The second part was composed of 92 questions determining interventions of neonatal nurses regarding patient safety implementations. These questions were sent to 8 experts studying in the field of neonatal health care and their views were obtained. Kendall's W analysis was done in order to assess the compatibility of the experts' views. It was found that there was no statistical difference between the scores of 8 experts (Kendall's W=0.00, p=0.67) and that the experts' views were compatible with one another.

The questions that determined nursing interventions regarding patient safety in the second part were grouped under 7 headings: interventions regarding medication (20 questions), interventions regarding identity implementations (9 questions), interventions regarding care implementations (20 questions), interventions regarding hospital infections (16 questions), interventions regarding equipment use (11 questions), interventions regarding falling (6 questions) and interventions regarding communication (10 questions). The nurses were asked to reply to the questions related to interventions regarding patient safety implementations as "I implement", "I sometimes implement" and "I do not implement". For example, they were asked to choose from the options "I implement", "I sometimes implement" or "I do not implement" for the question "I tie the diaper folded below the umbilical cord." A scoring system was used to interpret interventions regarding patient safety practices in an easy way. Nurses' answers were scored as follows: "I implement" (3 points), "I sometimes implement" (2 points) and "I do not implement" (1 point). The scores obtained from the patient safety fields (field score) and from all items (total score) were calculated. Because the number of questions in the patient safety fields in our study were not the same, the data was converted to 0-100 score interval and each heading was formulized by being scored. The score calculation was as follows: [((Total score of the individual/ number of questions)-1)x50]. For example, the score of an individual whose total raw score from interventions regarding patient safety medication practices was 60 was calculated as follows: [((60/20)-1)x50=100].

The data was collected within two months by using a face-to-face interview method. The statistical analysis of the data was done by using number, percentage, Kruskall-Wallis, Man-Whitney U and Independent t tests. Permission to conduct the research was obtained from the ethics committee of Selcuk University, Faculty of Medicine Hospital. Verbal consent of the nurses working in NICU and written permissions from the related hospitals to conduct the research were obtained.

Findings

Descriptive Characteristics

It was found that the age averages of the NICU nurses who participated in the study was 27.87±5.35, that 41.7% of them were in the age group 24 to 29 and that 26.1% of them had one child. It was also determined that 55.2% of the nurses were university graduates, that the average working years was 6.73±5.55 and that the number of years working in NICU was 4.02±4.34 years. 58.3% of the NICU nurses worked mixed shifts and cared for 6.58±2.41 patients on average (Table 1). 40.6% of the nurses stated that they spend most of their working hours on nursing care, 13.5% stated that they spend most of their working hours on medical paperwork, 12.5% of them stated that they spend most of their working hours on diagnosis and therapy processions and 33.3% stated that they spend their working hours on all of these mentioned above.

Information Regarding Patient Safety

99% of the NICU nurses stated that they were aware of patient safety and 51.6% stated that they have sufficient information on patient safety. 74% of the nurses stated that they have received training on patient safety, 62.5% stated that they have training on patient safety in the NICU they worked at and 81.2% stated that patient safety was of great importance (Table 2).

Nurses' Intervention Scores Regarding Patient Safety Implementations

Nurses' intervention scores regarding patient safety implementations in NICU (medication, identity, hospital infections, equipment use, falling, and communication) were determined in the research. Nurses' intervention scores regarding patient safety implementations were as follows: intervention score regarding medication implementations was 92.42±6.36, intervention score regarding identity implementations was 63.14±30.30, intervention score regarding care implementations was 91.69±8.59, intervention score regarding hospital infections implementations was 95.41±6.80, intervention score regarding equipment use was 87.83±13.68, intervention score regarding falling was 95.75±7.35, intervention score regarding communication was 92.19±11.74 and the total score was 89.56±7.39. It was seen that the nurses scored highest in interventions regarding falling (92.42±6.36) and scored lowest in interventions regarding identity implementations (63.14±30.30).

Nurses' Intervention Scores Regarding Patient Safety Implementations and Related Factors

It was found that there was a meaningful difference in score averages of nursing intervention regarding medication implementations according to their level of education (Kendall's W=9.767, p=0.008). In further analysis (Bonferroni-corrected Mann Whitney U test), it was revealed that score averages of university graduate nurses were meaningfully lower than high school graduate

Table I. Sociodemographic and professional characteristics of Neonatal Intensive Care Units nurse

Variable	n	%
Age groups (mean age: 27.87±5.35)		
18-23	20	20.8
24-29	40	41.7
30 or over	36	37.5
Number of children		
none	50	52.1
1 child	25	26.0
2 or over	21	21.9
Educational status		
High school	17	17.7
Associate degree	26	27.1
University degree	53	55.2
Number of years working in nursing (mean: 6.73±5.55)		
Less than one year	5	5.2
1-5 years	43	44.8
6-10 years	25	26.0
more than 10 years	23	24.0
Number of years working with newborns (mean: 4.02±4.34)		
Less than one year	12	12.5
1-5 years	59	61.5
6-10 years	15	15.6
more than 10 years	10	10.4
Type of shifts		
Daytime	19	19.8
Night	21	21.9
Night and daytime mixed	56	58.3
The average daily number of patients receiving care (mean = 6.58±2.41)		
3-6	51	53.1
7 or over	45	46.9

Table II. Neonatal Intensive Care Units nurses' opinions about patient safety		
Opinions	**n**	**%**
Do you have information on the concept of patient safety?		
Yes	95	99.0
No	1	1.0
If you answered yes to the above questions		
I think it is sufficient	49	51.6
I have a limited knowledge	41	43.1
I think it is insufficient information	5	5.3
Did you receive training on patient safety?		
Yes	71	74.0
No	25	26.0
Is the unit where you work giving patient safety training?		
Yes	60	62.5
No	36	37.5
Do you think patient safety matters?		
Very important	78	81.2
Important	18	18.8

nurses (Mann Whitney U=812,500, p=0.004). Also, there was a meaningful difference in nursing intervention score average regarding identity implementations in terms of working years (Kendall's W=9.259, p=0.026). In further analysis (Bonferroni-corrected Mann Whitney U test), it was found that score averages of those nurses who had been working less than one year were meaningfully higher than those nurses who had worked 1 to 5 years (MW-U=28,500, p=0.005).

Also, it was determined in this study that nursing intervention score averages of those nurses who cared for 7 or more patients regarding identity implementations, equipment use and total patient safety score averages were meaningfully lower (respectively; t=2.678, p=0.009, t=3.197, p=0.002, t=2.257, p=0.026). It was also revealed that nursing intervention score averages regarding identity implementations of the nurses who received patient safety training were meaningfully higher compared to those nurses who did not receive training (t=2.178, p=0.032) (Table 3).

Discussion

This study aimed to determine the patient safety related implementations of nurses working in NICU and related factors. It was found that more than half of the NICU nurses provided care to 3-6 patients and less than half of them provided care to 7 or more patients. According to the circular issued by the Ministry of Health on the 3rd of April 2008 03/04/2008, no.11395 (2008/25) one nurse in every shift in a Level 1 Intensive Care Unit is required whereas at least one nurse for 4 beds in every shift is required in a Level 2 Intensive Care Unit. Also, it was stated in the circular that in Level 3 Intensive Care Units, at least one nurse for three beds is required in each shift. It was seen in our study that the numbers of nurses per patient were low compared to the circular issued by the Ministry of Health. The fact that the number of nurses per patient is low creates problems such as fatigue, distraction, being unable to concentrate, and communication problems, heavy workload and burnout syndrome (19,20). About half of the nurses participating in the study stated that they have spent most of their working hours on nursing care practices. In other studies, it was found that rather than focusing on patient care, nurses spent most of their time on supplying medication-equipment, answering the phone, writing out the suggested prescriptions or checking out entrance and exit times of employees. Moreover, they spent almost 1/3 of their working time on indirect care practices (18,21). In a study conducted by Turkmen and Uslu (17), it was stated that nurses spent 13.6% of their time which was allocated for the patient on indirect care implementations such as receiving and checking out doctor requests and that they spent 35.7% of their working hours on filling out forms. An inadequate number of nurses may result in allocating less time to patients, increased medical errors and reduced care duration and patient safety.

Information Related to Patient Safety

In this study, the nurses stated that they were aware of patient safety, received training on patient safety and patient care was of great importance. In another study, 95.2% of nurses stated that patient safety is very important (22). In another study conducted by Pronovost et al. (7) in Britain, it was found that nurses' safety perception scores were higher than the doctors' safety perception scores. In a study done by Cirpi et al. (13), 96.9% of the nurses stated that patient safety implementations were necessary, 93.3% of them stated that they were aware of patient safety implementations, and 92.3% of them stated that they volunteered to be assigned in patient safety implementations. From this aspect, our research findings bear similarities to the literature. It was seen in our study that nurses were aware of patient safety and valued the patient safety concept. Nurses play a key role in improving quality in health care. Establishing and improving patient safety could only be possible if the personnel

Table III. Neonatal intensive care units nurses for patient safety initiatives towards application ratings and comparison of related factors

Variable	n	Medication practice	Identity practice	Care practice	Hospital infections	Equipment use	Falling down	Communication	Total score
Educational status									
High school -a	17	96.32±4.43	69.61±30.18	95.15±6.22	97.79±4.39	92.51±6.21	96.57±5.94	96.18±6.00	93.25±4.15
Associate degree -b	26	93.17±4.82	64.96±26.38	89.81±8.45	96.03±5.20	88.46±12.48	94.55±9.11	93.08±10.00	89.69±6.74
License	53	90.80±6.98	60.17±32.22	91.51±9.10	94.34±7.90	86.02±15.64	96.07±6.86	90.47±13.56	88.31±8.16
KW (SD: 2)	-	9.767	1.141	4.980	3.111	1.053	0.435	1.847	5.131
p	**-**	**0.008**	0.565	0.083	0.211	0.591	0.804	0.397	0.077
Difference	**-**	**a>b**	-	-	-	-	-	-	-
Working in the profession for years									
Less than one year -a	5	95.00±6.37	94.44±9.62	87.50±13.23	96.25±6.77	90.00±19.92	96.67±4.56	85.00±23.18	91.96±11.21
1-5 years -b	43	91.98±6.67	56.33±29.98	91.80±8.15	94.69±7.70	84.04±15.02	95.16±8.77	92.56±11.92	88.25±7.67
6-10 years	25	92.10±6.44	70.22±28.14	93.60±7.64	96.00±5.67	92.36±7.03	96.00±6.42	92.20±11.55	91.26±6.42
more than 10 years	23	93.04±5.89	61.35±31.53	90.33±9.27	95.92±6.42	89.53±14.01	96.38±6.06	93.04±8.22	89.65±6.91
KW (SD: 3)	-	1.304	9.259	2.539	0.478	6.611	0.047	0.635	4.048
p	-	0.728	**0.026**	0.468	0.924	0.085	0.997	0.888	0.256
Difference	-	-	**a>b**	-	-	-	-	-	-
Newborn working years									
Less than one year	12	93.96±7.27	78.24±31.02	94.38±10.12	97.40±4.58	88.26±17.60	95.83±7.54	91.25±16.53	92.26±9.22
1-5 years	59	92.58±6.69	62.05±30.52	91.78±7.97	94.65±7.43	86.67±12.80	95.62±7.94	92.54±11.68	89.27±7.44
6-10 years	15	90.83±4.60	53.70±22.09	89.83±11.20	97.71±3.44	92.42±10.12	96.11±5.33	92.00±9.41	88.84±6.22
more than 10 years	10	92.00±5.75	65.56±35.89	90.75±5.66	94.06±8.26	87.27±18.41	95.83±7.08	91.50±10.01	89.13±6.72
KW (SD: 3)	-	3.166	4.496	3.927	2.246	3.924	0.234	0.697	4.518
p	-	0.367	0.213	0.269	0.523	0.270	0.972	0.874	0.211
Shape shifts									
Daytime	19	93.68±4.89	54.68±27.67	91.32±7.61	94.41±6.21	89.71±12.29	95.61±6.44	92.37±8.39	88.99±4.75
Night	21	91.43±6.15	69.84±32.09	91.79±9.05	94.05±8.14	89.18±10.99	95.24±8.96	90.71±16.30	89.75±8.71
Night and daytime mixed	56	92.37±6.89	63.49±30.32	91.79±8.86	96.26±6.43	86.69±15.06	95.98±7.11	92.68±10.83	89.68±7.70
KW (SD: 2)	-	0.999	2.861	0.307	2.716	0.402	0.253	0.433	1.492
p	-	0.607	0.239	0.858	0.257	0.818	0.881	0.805	0.474
The average daily number of patients receiving care									
3-6	51	92.45±6.25	72.00±27.87	93.38±8.50	96.08±6.43	90.73±12.50	96.57±7.30	92.94±10.87	91.40±6.95
7 or over	45	92.39±6.55	53.09±30.09	89.78±8.37	94.65±7.19	84.55±14.35	94.81±7.39	91.33±12.72	87.48±7.40
t (SD: 94)	-	0.047	3.197	2.088	1.025	2.257	1.168	0.668	2.678
p	-	0.962	0.002	0.039	0.308	0.026	0.246	0.506	0.009
Patient safety training receive status									
Yes	75	92.82±6.34	67.06±28.07	91.16±8.83	95.25±7.28	89.44±11.67	95.66±7.43	91.90±12.20	90.04±7.44
No	21	91.30±6.42	52.00±34.09	93.20±7.82	95.88±5.32	83.27±17.74	96.00±7.26	93.00±10.51	88.20±7.24
t (SD: 94)	-	1.026	2.178	1.021	0.396	1.966	0.199	0.401	1.074
p	-	0.308	0.032	0.310	0.693	0.052	0.842	0.690	0.285

KW: Kendall's W, SD: Standard deviation

comprehended the importance of the issue. In this context, training the health personnel in a hospital may develop an understanding regarding patient safety.

Intervention Scores of Nurses Regarding Patient Safety Implementations

In this research, nurses scored highest in implementations regarding falling followed by hospital infections, medication, communication, care, and equipment use respectively and scored lowest in identity practices. These implementations might affect neonatal care, morbidity and mortality. In the literature, it was stated that medication errors are most common among the issues affecting patient safety (5,23,24). This might be related to the abundant number of studies on medication implementations. The fact that identity implementation scores were lowest show that these are not implemented precisely. Identifying the patient and performing related nursing interventions in NICU and other clinics is vital. With this in mind, creating procedures regarding identity implementations, training and inspecting these implementations are needed.

Factors Related to Intervention Scores Regarding Patient Safety Implementations

It was found in this study that score averages of high school graduate nurses were higher than the score averages of university graduate nurses in terms of medication implementations. This is thought to have resulted from the fact that the sample group was small. It was also found in this research that score averages in terms of identity implications of nurses who had worked less than one year were higher than those nurses who had worked between 1 and 5 years. This result might show that nurses who had worked less than one year were novice nurses and were careful not to make any mistakes. It was found that in patient safety intervention score averages of identity implementations and equipment use by the number of patients who were provided daily care and in total patient safety scores, the score averages of those nurses who provided care for 7 or more patients were lower than those nurses who provided care for between 3 and 6 patients. These results show that the number of patients per nurse affects patient safety in NICU. As the number of patients per nurse increases, the risk of therapy and care errors increase. It is accepted that patients are safest when one nurse is assigned to one or two patients in intensive care units (25).

In this research, it was determined that nurses who received training scored higher than those nurses who did not by receiving training in patient safety in terms of identity implementations. Nursing interventions regarding identity implementations are implemented the least, but it is thought that providing training in all patient safety fields would increase the level of information. It was also concluded that providing these trainings at regular intervals would improve patient safety and increase care standards.

Limitations of Research

The limitation of this study is that it only sampled nurses working in hospitals with NICU in Konya province.

Conclusion

Patient safety in neonatal units is one of the basic factors in nursing care. Providing care for human beings without causing any harm is the foundation of the nursing profession. Nurses who work in units such as NICU where sensitivity is required in patient safety have to play a lot of roles in this issue.

In this research, it was seen that nurses were aware of patient safety and performed related implementations. The nurses scored highest in interventions regarding falling and scored lowest in interventions regarding identity implementations. It was also revealed that the nurses' patient safety implementations were related to their level of education, years of working, the number of patients who were provided with care daily, and receiving training on patient safety.

It is suggested that nurses, who play a key role in providing patient safety, should improve patient safety implementations. With this aim in mind, NICU- unique guidelines should be prepared in patient safety fields (medication, identity, providing care, hospital infections, equipment use, falling and communication). In activities such as in-service training, congresses, seminars, conferences or symposiums etc. patient safety should be included more extensively and these programs should be repeated at regular intervals. The number of nurses and patients to be provided with daily care should accord with the standards and their continuity should be ensured to increase success in patient safety implementations. In order to prevent medical errors, patient safety culture should be created in hospitals and an active error notification system should be set up. Committees related to patient safety should be established in health institutions and they should work actively.

Ethics

Ethics Committee Approval: The study was approved by the Selçuk University Faculty of Medicine Ethics Committee (Approval number: 2012/04, 24.04.2012).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., F.T.A., Design: E.K., F.T.A., Data Collection or Processing: E.K., Analysis or Interpretation: E.K., F.T.A., Literature Search: E.K., Writing: E.K., F.T.A.

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Original Article

Single Versus Multiple Doses of Surfactant Treatment in Preterm Infants

Betül Siyah Bilgin, Özge Altun Köroğlu, Demet Terek, Mehmet Yalaz, Mete Akisu, Nilgün Kültürsay

Ege University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İzmir, Turkey

ABSTRACT

Aim: Exogenous surfactant may be needed not only for Respiratory Distress syndrome (RDS) treatment; but also, in the management of other pulmonary diseases of infants. In this study, we aimed to investigate the impact of single versus multiple doses of surfactant therapy in pulmonary problems of preterm infants.

Materials and Methods: In this study, preterm infants who needed surfactant treatment were retrospectively evaluated. Surfactant therapy for RDS were given as 200 mg/kg poractant or 100 mg/kg beractant and repeated with 100 mg/kg doses when needed later. Poractant or beractant (100 mg/kg) were given in the treatment of other pulmonary diseases.

Results: Totally 64 preterm patients were recruited into this study. Patients in group 1 (43.8%) received a single dose of surfactant; whereas group 2 patients (56.2%) had more than one dose. Mean gestational age and birth weight of infants in group 2 were significantly lower than group 1 ($p<0.05$). Intrauterine growth restriction (IUGR) was more common in group 2 ($p=0.041$). Multiple doses of surfactant were needed for severe RDS, atelectasis, pulmonary hemorrhage and pneumonia. Duration of mechanical ventilation and hospitalization were longer in group 2 ($p<0.05$). Mortality rates were higher in group 2 ($p=0.011$).

Conclusion: Preterm infants with earlier gestational age and lower birth weight; particularly with IUGR may need multiple doses of surfactant due to more severe respiratory problems regardless of antenatal steroid or maternal chorioamnionitis status. Duration of mechanical ventilation, hospitalization and also neonatal mortality remained higher due to disease severity in preterms who needed multiple doses of surfactant.

Keywords: Preterm, respiratory distress syndrome, atelectasis, pulmonary hemorrhage, pneumonia

Introduction

In 1959, Avery et al. (1) showed that a deficiency of surface-active material (surfactant) may be significant in the pathogenesis of hyaline membrane disease in preterm infants. Exogenous surfactant was first used in Respiratory Distress syndrome (RDS) treatment by Fujiwara et al. (2) in 1980. Exogenous Surfactant increases the lung compliance and functional residual capacity at expiration, provides homogenous gas distribution at inspiration and increases oxygenation and survival in RDS patients (3).

Exogenous surfactant is now also used in many clinical situations, other than RDS, which cause endogen surfactant

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Address for Correspondence
Betül Siyah Bilgin, Ege University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İzmir, Turkey
Phone: +90 232 390 12 82 E-mail: betulsiyah@yahoo.com ORCID: orcid.org/0000-0003-3807-4809
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dysfunction or inactivation such as pulmonary hemorrhage, pneumonia, Meconium Aspiration syndrome, acute lung injury, bronchopulmonary dysplasia (BPD) or congenital diaphragmatic hernia (4). Single or multiple doses of surfactant may be needed not only for RDS treatment; but also for other indications in the management of sick newborns. The impact of multiple doses of surfactant on morbidity and mortality is not clearly known. When single or multiple doses of surfactant replacement in RDS are compared, pneumothorax and death rates are found to be lower in the latter (5). In this study, we aimed to investigate the impact of single versus multiple doses of surfactant therapy in sick preterm infants.

Material and Methods

Study Design

In this study, preterm infants (≤36 6/7 weeks), born between July 2011- June 2012, who needed surfactant due to neonatal pulmonary problems in Ege University Neonatal Intensive Care Unit were retrospectively evaluated. This study was approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 11-12.2/4). Informed consent of the parents of the study subjects were obtained.

Clinical Data

Antenatal risk factors such as multiple gestation, antenatal corticosteroids, maternal age, premature rupture of membranes, chorioamnionitis and neonatal characteristics such as gestational age (according to last menstrual period), birthweight, intrauterine growth [based on the growth curve of Lubchenco et al. (6)], gender, mode of delivery, apgar scores and clinical progress were recorded. Definition of intrauterine growth restriction (IUGR) was based on a series of prenatal weight evaluations showing a decrease in weight percentiles.

Diagnostic criteria for the diagnosis of lung diseases were as follows:

Respiratory distress syndrome: Existence of clinical findings of respiratory distress (tachypnea, grunting, cyanosis, retractions), need for oxygen and/or positive pressure ventilation and typical X-ray findings (reticulogranular pattern, decreased aeration, air bronchograms, ground glass) and an absence of suspicious or proven findings of infection (7).

Atelectasis: Based on X-ray findings.

Pulmonary hemorrhage: Bloody aspirate from endotracheal tube with at least one of the following: micro lobular infiltrates in chest X-Ray, increase in mechanical ventilation support, more than 0.3 increase in the fraction of inspired oxygen from basal level or an acute decrease of hematocrit (>10%) (8).

Congenital pneumonia: Clinical findings of respiratory distress, need for oxygen and/or mechanical ventilation support, extrapulmonary clinical signs of sepsis starting from birth and typical chest X-ray findings with suspicious or proven infection (maternal chorioamnionitis, maternal urinary tract infections, increased or decreased leukocyte count or serum C-reactive protein increase and positive blood or endotracheal aspirate cultures) on the first day of life (7).

Bronchopulmonary dysplasia: The severity of disease was determined according to the need for oxygen support at postnatal 28th day and the need for oxygen/positive pressure ventilation at term (9).

Surfactant treatment was administered as described in the European Consensus Guidelines and the American Academy of Pediatrics (10). Surfactant preparations were chosen according to the clinical teams' decisions as beractant or poractant. Prophylactic or rescue surfactant therapy for RDS was given as 200 mg/kg poractant or 100 mg/kg beractant and later repeated with 100 mg/kg doses. 100 mg/kg poractant or beractant were given for other pulmonary diseases. For patients who developed atelectasis, pulmonary lavage was carried out with 50 mg/kg surfactant diluted to four-fold saline (5 mg phospholipid/mL). Treatment was administered slowly in aliquots of 2.5 mL (11).

Prophylactic surfactant therapy was performed for all infants who were born at less than 26 weeks of gestation, with the INSURE (Intubate-SURfactant-Extubate to CPAP) technique and to preterm infants with gestational age <30 weeks who needed intubation in the delivery room within 15 minutes of birth (10). Preterm infants who did not have prophylactic surfactant in the delivery room were given rescue surfactant therapy within the first six hours if their FiO_2 value was >0.40 and arterial-to-alveolar oxygen tension ratio was (a/A PO_2) <0.2. Response to surfactant replacement therapy was evaluated by arterial blood gas analysis (at 2nd and 6th hours of surfactant replacement therapy) and chest X-ray (at 6th hour of surfactant replacement therapy). Surfactant replacement therapy was repeated at a maximum of three doses, if the findings of RDS persisted after six hours from initial surfactant treatment (10). In the treatment of other pulmonary diseases, surfactant replacement was considered when FiO_2

was >0.40 and arterial-to-alveolar oxygen tension ratio (a/A PO_2) was <0.2.

At the retrospective follow-up; patients were assigned into two groups according to their surfactant replacement status: Group 1 consisted of patients who received a single dose of surfactant; and group 2 consisted of patients who received multiple doses of surfactant. Presence of pneumothorax, intraventricular hemorrhage, patent ductus arteriosus and chronic lung disease, duration of mechanical ventilation and hospitalization, the need for postnatal steroids and mortality were recorded. With regard to surfactant replacement treatments; indications, timing and total number of applications were followed up in addition to blood gas analyses and a/A PO_2 ratios.

Statistical Analysis

SPSS 17.0 software was used for statistical analyses. For comparison of groups; chi-square test was used for categorical data and Mann-Whitney U test was used as a nonparametric test. P values <0.05 were considered statistically significant.

Results

For the whole study group of 64 infants, the mean gestational age was 28.37±3.00 (23-36) weeks; mean birth weight was 1.238±609 (580-2.950) grams, mean number of surfactant therapy applications was 2.29±1.59 (1-6).

The demographic characteristics of the study group are given in Table 1. The indications of surfactant treatment and the rate of single versus multiple doses are given in Table 2.

Twenty-eight patients (43.8%) (Group 1) received a single dose of surfactant; whereas the remaining 36 (56.2%) (Group 2) patients needed multiple doses. The mean gestational age and birth weight of those infants in group 2 were significantly lower than group 1 (p values <0.05). IUGR was more common in group 2 (p=0.041); however other clinical characteristics such as gender, multiple gestation, antenatal corticosteroids, premature rupture of membranes or chorioamnionitis did not differ between the groups (Table 1).

Multiple doses of surfactant were needed for severe RDS, atelectasis pulmonary hemorrhage, and pneumonia (Table 2). Surfactant lavage treatment was performed for nine preterm infants in the treatment of atelectasis and radiological recovery was observed in seven (77.7%) of them. The duration of mechanical ventilation and hospitalization were longer in group 2 (all p values <0.05). Mortality rates were higher group 2 (p=0.011) (Table 3).

Discussion

Exogenous surfactant is used in the treatment of many clinical conditions other than RDS such as pneumonia, Meconium Aspiration syndrome, newborn pneumonia, genetic deficiency of surfactant, acute lung damage, resistant pulmonary hypertension, BPD or congenital diaphragmatic hernia in the neonatal period (4). These diseases usually show endogenous surfactant dysfunction or inactivation or structural deficiency. Plasma proteins, erythrocyte, meconium, cytokine and other inflammatory products, proteases or reactive oxygen species may disrupt surfactant synthesis and structure.

A single dose of surfactant was given to 28 patients and multiple doses were given to 36 patients for the treatment of RDS in our study. Patients who needed multiple surfactant doses had lower birthweight and

Table I. Demographic characteristics of study population

	All patients (n=64)	Group 1 (Single dose) (n=28)	Group 2 (Multiple doses) (n=36)	p
Gestational age, weeks[a]	28.4±3.0	29.2±3.1	27.7±2.7	0.048
Birth weight, gram[a]	1.238±609	1.439±650	1.082±532	0.019
Male gender	39 (60.9%)	16 (57.1%)	23 (63.9%)	0.615
Cesarean	46 (71.9%)	21 (75%)	25 (69.4%)	0.781
IUGR	15 (23.4%)	3 (10.7%)	12 (33.3%)	0.041
Apgar 1st min[a]	3.8±2.1	4.4±2.2	3.4±1.9	0.074
Multiple birth	17 (26.6%)	7 (25.0%)	10 (27.8%)	1.00
ANCS	46 (71.9%)	22 (78.6%)	24 (66.7%)	0.403
PROM	12 (18.8%)	6 (21.4%)	6 (16.7%)	0.750
Chorioamnionitis	3 (4.7%)	0	3 (8.3%)	0.250

[a]: Mean ± standard deviation (range), ANCS: Antenatal corticosteroids, IUGR: Intrauterine growth restriction, PROM: Premature rupture of membranes

earlier gestational age. In the limited number of previous studies, application of multiple doses was found to be more effective on oxygenation with a tendency to decrease mortality rates as well as pneumothorax risk (RR 0.51; 95% CI 0.30-0.88) (5,12). Multiple doses of surfactant were reported to be needed more commonly in more extreme preterm infants, infants with very low birthweight and in cases with maternal chorioamnionitis (13). The European Consensus Guidelines on the management of RDS recommends that if RDS findings continue (such as oxygen and mechanic ventilation need) secondary or sometimes tertiary surfactant applications should be used (14). In our study, multiple doses of surfactant were given to those infants with severe RDS due to lung immaturity.

In this study, preterm infants with IUGR required a significantly higher number of doses of surfactant therapy. Results of studies on IUGR's impact on RDS severity vary greatly (15-19). In one study conducted by Peacock et al. (15) respiratory system morbidities of small for gestational age (SGA) and appropriate for gestational age (AGA) infants who were born under 1.000 grams were compared and no difference in surfactant quantity was found. Similarly, Bartels et al. (16) found the RDS percentage in AGA and SGA groups to be equal. However, Spinillo et al. (17) reported a significantly increased risk of RDS in preterm infants with IUGR. Chronic lung disease is reported to be more common in the SGA group compared to AGA preterms (18). Preterm IUGR infants have a higher pulmonary morbidity risk and therefore they may need more doses surfactant treatment than the AGA infants within the same age range (19).

Pulmonary hemorrhage may be another indication for multiple doses of surfactant treatment. Prematurity, IUGR, patent ductus arteriosus, respiratory problems, mechanical ventilation and surfactant treatment are risk factors for pulmonary hemorrhage (20). Hemoglobin, erythrocyte, membrane lipids and serum proteins disrupt the function of surfactant, hence, surface tension increases and secondary RDS develops (21). There is no randomized study showing the impact of surfactant's administration in pulmonary hemorrhage treatment. Most of the studies on this issue are based on observations. It has been shown that exogenous surfactant application improves oxygenation in the supportive treatment of pulmonary hemorrhage in the short term, however, no long-term benefit has been found. Pandit et al. (22) showed an improvement in oxygenation indexes after surfactant administration when they evaluated cases of pulmonary hemorrhage retrospectively. Analyzing the associated factors of surfactant dysfunction of 27 babies who had pulmonary hemorrhage and edema, Amizuka et al. (23) reported that exogenous surfactant application may overcome surfactant inhibition, and this may be an adjuvant treatment that solves respiratory problems. Aziz and Ohlsson (24) did not come to a conclusion about this treatment in their meta-analyses published in 2008.

Table II. Indications for surfactant replacement therapy

	All patients (n=64)	**Group 1 (Single dose) (n=28)**	**Group 2 (Multiple doses) (n=36[a])**
RDS	62	27	35
Atelectasis	9	0	9
Pulmonary hemorrhage	8	0	8
Pneumonia	4	1	3
Total	83	28	55

[a]: Patients who received surfactant therapy due to atelectasis and pulmonary hemorrhage were all previously given surfactant therapy for RDS. Two patients who had multiple doses of surfactant therapy due to pneumonia had also received surfactant therapy for RDS previously, RDS: Respiratory distress syndrome

Table III. Clinical outcome of study groups

	All patients (n=64)	**Group 1 (Single dose) (n=28)**	**Group 2 (Multiple doses) (n=36)**	**p**
NEC	27 (42.2%)	7 (25%)	20 (55.6%)	0.028
ICH	14 (21.8%)	4 (14.3%)	10 (27.8%)	0.322
ROP	19 (29.7%)	5 (17.9%)	14 (38.9%)	0.121
BPD	21 (32.8%)	4 (14.3%)	17 (47.2%)	0.007
Duration of mechanical ventilation, days[a]	27.74 (44.47)	10.75 (13.20)	42.02 (55.85)	0.002
Duration of hospitalization, days[a]	55.91 (39.19)	43.04 (30.74)	75.60 (41.87)	0.004
Mortality	18 (28.1%)	3 (10.7%)	15 (41.7%)	0.011

[a]Mean±SD (range). NEC: Necrotizing enterocolitis, ICH: Intracranial hemorrhage, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia

Plasma proteins and cytokines in the neonatal pneumonia exudate may also inactivate surfactant. Surfactant treatment in B group streptococcus pneumonia has reduced the reproduction of bacteria and improved lung functions in animal experiments (25). Improvement was reported in the gas exchange with surfactant treatment in group B Streptococcus pneumonia in The Collaborative European Multicenter Study Group study. However, response to surfactant treatment is slower than RDS treatment and needs more repetitive doses (26). In the study conducted by Alkan et al. (27), surfactant treatment except for RDS, was mostly given to patients who were diagnosed with pneumonia in the newborn period with the longest survival time. The quantity of dose was not given in this study and the average gestational week was 35.6 weeks (27). Gortner et al. (28) gave surfactant to 15 extremely low birth weigh cases with congenital pneumonia. Although the fraction of inspired oxygen (fiO_2) need decreased initially, it rose to its former state within 12 hours. A maximum of four doses were given. One surfactant dose was given to six cases and multiple surfactant doses (up to 4) were administered to nine cases (28). In our study, four cases with congenital pneumonia were given surfactant. One patient needed one dose; while three others were given multiple doses of surfactant. Therefore, we think that preterm infants with congenital pneumonia may need multiple dose surfactant treatment due to surfactant inactivation. Future controlled studies are required to research the impacts of surfactant treatment of congenital pneumonia.

In this study, diluted surfactant lavage was performed for the nine mechanically ventilated preterm patients with atelectasis in their chest X-ray and low a/A PO_2 values. Those infants had already been given surfactant treatment for RDS or other pulmonary problems. After surfactant lavage radiologic, clinical improvement was observed in seven patients (77%). Atelectasis may develop in preterm infants under mechanical ventilation due to primary or secondary surfactant deficiency, an increase in inflammatory mediators or a decrease in mucociliary clearance. Surfactant lavage treatment may be considered for infants who develop atelectasis during mechanical ventilation. The objective of surfactant lavage is to remove the inflammatory mediators, to clear away the mucous material with lavage and to replace the inactivated surfactant. Krause et al. (29) reported a 65% improvement in atelectasis by giving diluted surfactant with bronchoalveolar lavage followed by dornase alfa to four infants diagnosed with atelectasis after respiratory syncytial virus pneumonia.

The limitations of our study are as follows: being single centered, the small number of patients included in the study and the changes in surfactant application policies over time in RDS treatment due to the nature of this retrospective study.

The frequency of ROP (retinopathy of prematurity) and ICH (Intracranial hemorrhage), in terms of the morbidities seen in preterm infants, was not different among the groups who received single-dose or multiple-dose surfactant treatment; but NEC (Necrotizing enterocolitis) and BPD were more frequent in the multiple-dose surfactant treatment group. Multiple doses of surfactant decrease the NEC and mortality rate in RDS treatment (5). In our study, NEC and mortality rates were found to be higher in preterm patients who needed multiple doses of surfactant treatment. However, infants who were given multiple doses of surfactant had lower birthweight, earlier gestational age, longer time spent in mechanical ventilation, longer hospitalization and higher BPD and mortality rates than infants who needed only one surfactant dose.

Conclusion

Multiple doses of surfactant were needed in the treatment of RDS, atelectasis pulmonary hemorrhage and pneumonia in preterm patients with a low gestational age and birthweight; and also for those being IUGR regardless of antenatal steroid or chorioamnionitis status. The duration of ventilation, hospitalization and rates of BPD and neonatal mortality were higher due to disease severity in patients who needed multiple doses of surfactant.

Ethics

Ethics Committee Approval: This approval was received from Ege University Faculty of Medicine Clinical Research Ethics Committee (approval no: 11-12.2/4, date: 12.01.2012).

Informed Consent: Informed consent of the parents of the study subjects were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.S.B, D.T., Concept: N.K., M.Y., Design: N.K., M.A., Data Collection or Processing: B.S.B, D.T., Analysis or Interpretation: Ö.A.K., Literature search: B.S.B., Ö.A.K., Writing: B.S.B., Ö.A.K.

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Original Article

Identification of Substance Abuse Among Children in a Pediatric Emergency Department

Nükhet Aladağ Çiftdemir, Tuba Eren, Yasemin Karal

Trakya University Faculty of Medicine, Department of Pediatrics, Edirne, Turkey

ABSTRACT

Aim: Illicit substance use is a worldwide important public health problem with increasing substance abuse rates and decreasing starting age. In this study, our aim was to determine the complaints of the patients in pediatric emergency department (PED) admission in order to increase awareness about substance abuse.

Materials and Methods: The data of this cross-sectional study was gathered from those patients admitted to a PED with complaints of substance abuse and patients without a history of substance abuse, but with a positive urine drug test. A screening urine test was used for the qualitative determination of drug substances. If positive, a quantitative liquid chromatography integrated mass/mass spectrometry test was ordered for confirmation.

Results: A total of 17 patients presented to the emergency department. The most frequent symptoms were unstable cognitive conditions and tachycardia. Laboratory analyses showed high creatine kinase-MB. Synthetic cannabinoids were the most frequently detected substance in urine screening and confirmation tests. Twenty-nine percent of patients were hospitalized and no mortality was observed.

Conclusion: The use of illegal substances has increased in teenagers. Emergency department doctors must be informed and trained regarding substance abuse since patients frequently presented to the emergency department with cognitive malfunctions. Also, it should be remembered that patients may present with symptoms concerning various organ systems.

Keywords: Pediatric emergency, substance use, synthetic cannabinoids

Introduction

Illicit substance abuse is a major public health problem leading to biological, psychological and social disorders when addiction occurs over a longer period of time (1). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) collects, analyzes and disseminates scientific information on drug-related issues and provides an evidence-based picture of the drug phenomenon. The use of illicit substances among the general population in Turkey appears to be rare according to the 2017 EMCDDA report. In 2011, cannabis was the most common illicit drug used, followed by amphetamines and MDMA/ecstasy. The highest rate of illicit substance abuse was in young males (15-34 years old). Worldwide use of synthetic cannabinoids (SCs) have increased in recent years leading to an increase in unexpected complications and symptoms (2). Many clinicians are unaware of the prevalence and severity of physical and psychoactive symptoms, and the potentially serious consequences related to the use of SCs (3).

There has been an alarming increase in substance abuse and more importantly the age that people start to abuse substances has decreased in Turkey (4). Increased abuse of

Address for Correspondence
Nükhet Aladağ Çiftdemir, Trakya University Faculty of Medicine, Department of Pediatrics, Edirne, Turkey
Phone: +90 533 311 38 00 E-mail: nukhetaladag@yahoo.com ORCID: orcid.org/0000-0002-0365-2181
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substances will lead to an increase in hospital admissions. Based on our recent publication (5), we suspect there are more undiagnosed cases of substance abuse. To address this concern, we performed a urine drug test on suspected patients at a pediatric emergency department (PED).

Materials and Methods

The data gathered from the patients admitted with complaints of substance abuse and patients who had substances detected in their urine using screening tests despite having no history of substance use in PED between April 2015 and August 2016 were analyzed. In that time period, a total of 21,062 patients were admitted to the PED, 2,432 (11.54%) of them were between 13 and 18 years of age.

Screening were performed on patients with substance use, and on patients with complaints of unexplained unstable cognitive conditions, chest pain and palpitation. Forty three patients underwent a urine screening test. There were positive results in 24 patients. Within these 24 patients, 5 were excluded from the study due to a negative confirmation test after a positive urine screening and no history of substance use. Furthermore, 2 patients without confirmation tests were also excluded. This study contains the results of 16 patients with a positive confirmation test results and one patient with Withdrawal syndrome.

The Rapid DOA Panel test (Figure 1) is an immunochromatography based one step in vitro test. This test was used for substance screening in the urine samples of 24 patients in the PED. This test qualitatively determines the presence of drug substances in human urine. To confirm the findings of the screening test, a quantitative liquid chromatography integrated mass/mass spectrometry test was used (Figure 2). The confirmation test was performed in Trakya University Technology Research and Development Application and Research Center laboratory on the same day using fresh urine. The confirmation test results were obtained within hours. Cases were analyzed in terms of age, gender, admission time, primary complaints in admission, clinical findings, laboratory findings, method of substance use, additional substance use, length of hospital stay, period of monitorization and mortality rates. Intoxication severity was assessed using (1) the Poison Severity score (PSS) according to the following grades: none (grade 0), minor (grade 1), moderate (grade 2), severe (grade 3) and fatal (grade 4) and (2) the Glasgow Coma scales (GCS). Oral informed consent was obtained from the patients and/or their parents. Also, the results were shared with the patients and their parents. The study was approved by the Trakya University Faculty of Medicine, Scientific Research Ethics Committee (approval no: 2018/366, decision no: 17/21, date: 15.10.2018).

Figure 1. Rapid drugs of abuse panel test

Statistical Analysis

Research data were ahalyzed by SPSS 23.0 statistical package program. Descriptive statistics were presented as mean (± SD), median (minimum, maximum), frequency distribution and percentage.

Results

The general aspects of the patients are listed in Table I. Only 2 patients in our study were female (female/male: 2/15). The age range was between 1 and 17 years. Most of the patients were adolescents who were between 13-17 years of age (n=14), one patient was 1-year-old and two patients were 9-years-old. Four patients had a history of Bonzai (common name for SCs in Turkey) abuse, one patient had a history of simultaneous Bonzai and cannabis abuse,

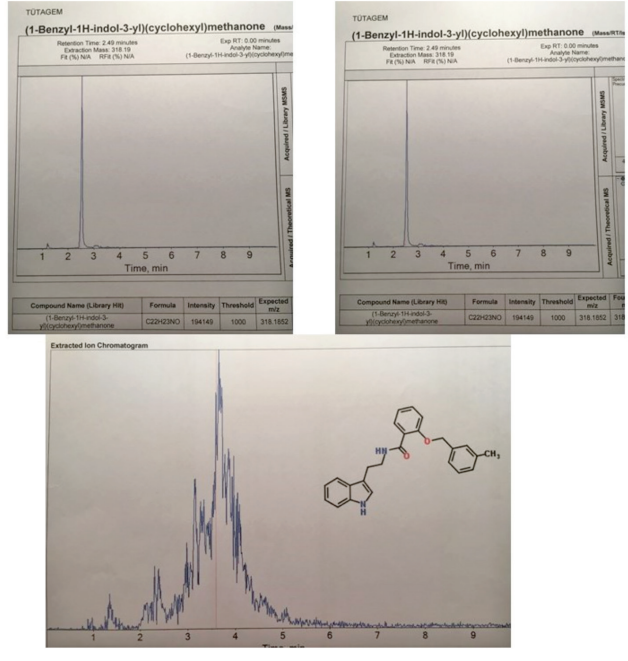

Figure 2. Quantitative liquid chromatography integrated mass/mass spectrometry test

Table I. General aspects of the patients

Case no	Age/ Gender	Complaint on admission	Accompanying findings	Heart rate per minute	Blood pressure (mmHg)	Glasgow Coma scale	Abnormal laboratory findings	Method of substance abuse	Hospitalization/ observation duration (hours)	Substance
1	14/Male	Headache, pins and needles sensation on left arm, change in consciousness	Mydriasis, confusion, headache, drowsiness	98	100/65	14	LDH: 325 U/L CK: 489 U/L CK-MB: 45 U/L Troponin-I: 0.038 µg/L	Unknown	No/18 hours	SC
2	16/ Female	Unable to talk, gibberish	Confusion, drowsiness, tachycardia, temporary agitation Hypertension	112	130/80	13	PT: 16.5 sec.	Oral	No/19 hours	SC
3	15/Male	Uneasiness, restlessness	Anxiety	74	120/76	15	CK-MB: 29 U/L K: 3,1 mmol/L	Inhalation	No/21 hours	SC
4	16/ Male	Syncope, seizure	Tendency to sleep Temporary agitation Miosis	80	110/70	14	BSL: 107 mg/ dL PT: 16,9 sec.	Inhalation	No/12 hours	SC
5	13/Male	Chest pain, palpitation	Tachycardia	115	110/60	15	CK: 242 U/L CK-MB: 44U/L Troponin I: 0,033 µg/L	Oral	Yes	Marijuana
6	1/Male	Tendency to sleep	Tachycardia, Mydriasis	150	90/50	13	BSL: 124 mg/ dL CK-MB: 41 U/L	Oral	No/12 hours	SC
7	17/ Female	Nausea, Fatigue	Tendency to sleep, Hypotension, Tachycardia	121	90/60	13	K: 3,3 mmol/L BSL: 153 mg/ dL PT: 15,9 sec.	Inhalation	No/17 hours	SC
8	17/Male	Fever, Mental fog	Agitation Crying crisis Body temperature: 38.9	96	115/57	15	PT: 15,5 sec.	Inhalation	No/10 hours	SC
9	16/Male	Chest pain	Uneasiness ECG: ST elevation	88	113/78	15	CK: 936 U/L CK-MB: 106 U/L Troponin I: 2.9 µg/L LDH:394 U/L ALT: 61 U/L AST: 119 U/L	Inhalation	Yes	SC
10	17 Male	Found unconscious by police and transferred intubated	Unconsciousness Hypotension Tachycardia Conjunctival hyperemia	130	102/53	7	CK-MB: 153 U/L CK: 226 U/L	Inhalation	Yes	SC
11	9/ Male	Headache, Dizziness, Fatigue, Fever, Vomiting	Tendency to sleep, Tachycardia, Nausea Vomiting	132	110/80	15	BSL: 116 mg/dL PT: 15,9 sec.	Inhalation	No/6 hours	SC

Continuation of **Table 1**

12	18/ Male	He was found unconcious in his room	Tendency to sleep, Confusion, Hypotension ECG:ST elevation	80	80/50	13	BSL:119 mg/dL CK-MB: 33 U/L	Inhalation	No/8 hours	Marijuana+SC
13	17/ Male	Palpitation, Inappetent, Mouth dryness, Trembling hands	Agitation, Tremor, Thirst Tachycardia, Sweating	118	125/70	15	BSL: 109 mg/dL LDH:386 U/L AST:49 U/L CK-MB:68 U/L	Withdrawal syndrome	No/6 hours	SC negative
14	17/ Male	Found unconscious	Mydriasis, Confusion, Drowsiness	92	100/60	14	LDH: 300 U/L BSL:137 mg/dL	Inhalation	No/4 hours	SC
15	17	Vomiting, spasms, blank staring, unable to walk after taking bonzai	Tendency to sleep, Blank staring Nausea	58	95/55	15	CK-MB: 29 U/L	Inhalation	No/11 hours	SK+Ecstasy
16	16/Male	Sore throat, cervical swelling	Crepitation in palpation at cervical and supraclavicular region, subcutaneous emphysema	86	110/70	15	CK:470 U/L	Unknown	Yes	Morphine
17	9/Male	Dystonia on the neck, Deviation of the eyes	Torticollis Fixed glancing to external side Tachycardia İrritability Thirst Dizziness	138	100/80	15	BSL:117 mg/dL CK-MB:30 U/L	Unknown	Yes	SC

ECG: Electrocardiogram, LDH: Lactate dehydrogenase, CK: Creatine kinase, BSL: Blood sugar level, PT: Prothrombin time, K: Potassium, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SC: Synthetic cannabinoid

one patient used simultaneously Bonzai, cannabis, ecstasy and an unknown substance, the remaining patients had histories of cigarette use and alcohol consumption. One patient was brought intubated to the PED. This patient also had a previous history of intubation after Bonzai use. Two patients with no substance abuse history in admission to the PED confessed that they had consumed Bonzai after a positive screening test. One patient with a 3-year history of Bonzai use voluntarily admitted with symptoms of substance withdrawal (Case 13). The most common presenting symptoms among patients on admission were unstable cognitive conditions (drowsiness, clouding of consciousness, confusion and secondary aggression, anxiety and restlessness) and tachycardia. Only one patient had a GCS result lower than 8. Seven patients had GCS scores between 12-14 and 9 patients had GCS scores of 15. PSS results were as follows: 1 subject had grade 3, 8 subjects had grade 2 and 8 subjects had grade 1 scores. The most common clinical findings were tachycardia in 8 (47%), hypotension in 3 (17.6%), mydriasis in 3 (17.6%), chest pain in 2 (11.7%), hypertension in 1 (5.8%) and myosis in 1 (5.8%) patient. Laboratory analyses showed that most of the patients had high levels of creatine kinase (CK)-MB (53%, n=9, mean 69.6 U/L), followed by hyperglycemia (47%, n=8, mean 122.75 mg/dL), high lactic dehydrogenase (LDH) levels (24%, n=4, mean 351.25 U/L), high CK levels (24%, n=4, mean 472.6 U/L), slightly longer prothrombin time (24%, n=4, mean 16.14 sec), high troponin-I (18%, n=3, mean 0.99 µg/L), hypokalemia (12%, n=2, mean 3.2 mmoL/L), high aspartate aminotransferase (12%, n=2, mean 84 IU/L), high alanine aminotransferase (6%, n=1, mean 61 IU/L). Substance intake occurred mostly by inhalation. SCs were the most frequently detected substance in urine screening and confirmation tests. Other substances detected in the urine were ecstasy, cannabis and morphine. Hospitalization was required in 5 patients (general pediatrics ward, n=2; pediatric intensive care unit, n=2 and pediatric surgery service, n=1). The remaining 12 patients were discharged after observations at

Table II. Contunied
Possible findings on physical examination ındicating substance abuse
General findings
- Altered mood
- Poor dress/hygiene
- Inappropriate or strange behavior
Chronic substance abusers
- Mood swings
- Depression
- Paranoia
- Anxiety
- Poor hygiene
- Bizarre behavior
Vital signs
- Weight loss
- Hypertension (cocaine, amphetamine)
- Hypotension (heroine)
- Hyperthermia (cocaine, amphetamine)
- Hypothermia (heroine)
- Tachycardia (marijuana, cocaine, amphetamine)
Ear-nose-throat
- Red eyes (marijuana)
- Dilated pupils (marijuana, cocaine, amphetamine)
- Constricted pupils (heroine)
- Nasal irritation
Cardiac
- Arrhythmias (heroine, cocaine, amphetamine)
Abdomen
- Hepatomegaly
Skin
- Abscesses
- Tattoos
- Needle track marks
Neurologic
- Altered sensorium
- Poor coordination
- Ataxia (amphetamine)
- Nystagmus
- Hyporeflexia or hyperreflexia (marijuana, cocaine,amphetamine)

PED. The mean duration of the observation was 11.5 (4-21) hours. No mortality was observed.

Discussion

Illicit substance use is an important public health problem in Turkey (6). Based on our previous study and other published data, substance abuse among patients admitted to the PED is higher than the substance abuse rate derived from patient anamnesis. In our study, SCs was the most frequently abused substance. In Turkey, SCs are called "Bonzai". SCs, most commonly known as "spice" or "K2", have become popular substances because of their easy availability and their invisibility in routine drug tests (7). The most preferred method of SC use is by smoke inhalation which causes symptoms similar to cannabis (marihuana) (8). Herbal products usually contain more than one SCs compounds (9). SCs have also been detected in mixtures containing other psychoactive substances such as stimulants, hallucinogens and sedatives and can be sold as ecstasy tablets (3). SCs derivatives have a high affinity for cannabinoid receptors and are clinically 30-800 times more potent than cannabis (10). A survey assessing the knowledge of ED physicians on SCs clinical symptoms showed that 68% recognized the clinical profile variability, while 44% were unaware of the context (11). Other studies have also shown that the awareness of ED physicians regarding the symptoms of SCs use was low (12). Thus, awareness about SCs is needed, especially among ED physicians. Recent studies have shown that SCs addiction is linked to alcohol, cigarettes, hallucinogens, opiates, benzodiazepines, amphetamines and cocaine addiction (13,14,15). Studies have shown that the most frequent adverse effects of these substances are tachycardia, agitation, irritability, anxiety, hallucination, nausea, vomiting, hypertension, confusion, conjunctival hyperemia as well as others affecting the entire organ systems (3,5,7). Forrester et al. (16) evaluated 305 adolescents with SCs abuse and showed that the most frequent clinical symptoms were tachycardia (41.6%), drowsiness/lethargy (24.3%), agitation/irritability (16.4%), vomiting (13.1%), and hallucinations (10.8%). The remaining symptoms were observed in less than 10% of the patients. Our study reports confusion and tachycardia as the most frequent symptoms. Several studies showed that SCs use leads to increased creatinine kinase, lactic dehydrogenase, hyperglycemia, hypokalemia and acidosis, (17,18) which is similar to our study.

In our study, one patient had been using marijuana and had been complaining about intermittent chest pain and tachycardia for 1 year. Pediatric cardiology, gastroenterology

and neurology evaluations could not find any reason for the chest pain and tachycardia. After his urine was found positive for marijuana, further detailed past medical history revealed that (admitted the use of chickpea powder), it became clear that his symptoms were a side effect of cannabis/marijuana use. It is known that acute exposure to cannabis/marijuana increases heart rate, blood pressure and causes hypotension (19). The increasing availability of marijuana edibles, including hemp oil, candy, popcorn, and beverages has been associated with increased ED visits. Sometimes adults and children are not aware of the ingredients of the food they consume (20).

We speculate that more patients will be admitted to the ED in the future with withdrawal symptoms due to the increasing use of SCs. In our study, one adolescent patient with a 3-year use of SCs was admitted to the ED with complaints of agitation, lack of appetite, xerostomia and sweating. His symptoms were a result of deprivation of the substance for three days. The patient was prescribed benzodiazepine and discharged. Withdrawal symptoms are documented as agitation, anxiety, mood swings, tremor, palpitation, diaphoresis (sweating), hypertension, hyperventilation, headache, nausea and vomiting (20,21).

One adolescent male patient in our study was admitted to the ED with complaints of sore throat and swelling from his throat to his shoulders. After examination, it became clear that his symptoms had been present for at least 3-5 days and became more severe each day. Cutaneous and subcutaneous emphysema at the bilateral cervical and supraclavicular regions were found in physical examination and confirmed by radiology. Even though the patient's laboratory tests were normal and there was no clinical history of substance use, morphine metabolites were found in his urine. In the literature, pneumomediastinum and cervical emphysema are related to cocaine inhalation, marijuana inhalation, ecstasy ingestion and are indicators of withdrawal symptoms of illicit drug use (22,23,24).

The diagnosis of substance abuse can be confirmed by clinical history, physical examination and toxicological test results (10). Urine is the preferred sample type because it is non-invasive and easy to obtain in sufficient amount. Clinicians should be familiar with their specific laboratory limitations and common false negatives (e.g. when metabolites are at concentrations less than the established thresholds) and false positive results associated with substance abuse screening tests. A high index of suspicion for substance abuse is warranted in relevant clinical contexts for agents that are not present on routine toxicology screening, such as SCs. Detection of SCs requires specialized mass spectrophotometry capabilities (25). The confirmation test in our study was a high-specific specialized mass spectrophotometric test.

Indications for drug screening include emergent presentations of altered mental status, acute injuries, life-threatening symptoms that require a correct diagnosis to provide appropriate treatment, monitoring for abstinence in drug rehabilitation centers, and court ordered drug testing. Results of drug testing can be shared only with the patient unless permission is given or a substance is found that causes an acute medical problem, and additional care and monitoring are required (26). After the ED staff were educated regarding the symptoms of substance abuse more specific to SCs abuse, the number of patients diagnosed and treated in the ED for substance abuse doubled.

Study Limitations

The heterogeneous distribution of both patient group and their symptoms, the small number of patients and lack of a statistical analysis are the key limitations of our study. A similar study may provide a more accurate findings when administered on a larger group of patients.

Conclusion

In conclusion, substance abuse is very common among teenagers with SCs being the number one choice of substance. Substance abuse patients can easily hide it from their doctors. Thus, ED physicians must be educated regarding the symptoms of substance abuse because patients may present with various symptoms and may be treated symptomatically or referred to incorrect clinics and encounter delayed diagnosis. Also, community education such as TV, radio advertisements and social awareness campaigns should be performed to target the rise of substance abuse among the population.

Ethics

Ethics Committee Approval: The study was approved by the Trakya University Faculty of Medicine, Scientific Research Ethics Committee (approval no: 2018/366, decision no: 17/21, date: 15.10.2018).

Informed Consent: Oral informed consent was obtained from the patients and/or their parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.A.Ç., Concept: N.A.Ç., T.E., Y.K., Design: N.A.Ç., Data Collection or Processing:

N.A.Ç., T.E., Y.K., Analysis or Interpretation: N.A.Ç., T.E., Y.K., Literature Search: N.A.Ç., T.E., Y.K., Writing: N.A.Ç.

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Original Article

Anxiety Levels and Needs of Fathers of Children Hospitalized in Pediatric Surgery Intensive Care Units

Nurdan Akçay Didişen[1], Atiye Karakul[2], Sevinç Ertürk[3], Zafer Dökümcü[4]

[1]Ege University Faculty of Nursing, Department of Pediatric Nursing, İzmir, Turkey
[2]Katip Çelebi University Facult of Medicine, Department of Pediatric Nursing, İzmir, Turkey
[3]Pediatric Surgery Intensive Care Unit, İzmir, Turkey
[4]Ege University Faculty of Medicine, Department of Pediatric Surgery, İzmir, Turkey

ABSTRACT

Aim: The purpose of this study was to determine the anxiety levels and needs of those fathers whose children were hospitalized in a pediatric surgery intensive care unit.

Materials and Methods: This cross-sectional study was conducted with the fathers of children hospitalized in a pediatric surgery intensive care unit in 2016/2017 by using the critical care family needs inventory (CCFNI), and State and Trait Anxiety scale. Setting: Turkey, a university hospital.

Results: This study included 113 fathers. The fathers' mean age was 36.6±6.31 years. There was a weak positive correlation between the scores the fathers obtained from the State Anxiety scale and the CCFNI. There was a difference between the fathers' intensive care needs in terms of their education levels. While ''feeling that hospital personnel are attentive to the patient'' was important for 92% of the fathers, ''being sure that as much care as possible is given'' was important for 88.5% and ''being informed about the patient at least once a day'' was important for 85.8%.

Conclusion: The anxieties and needs of the fathers of the patients staying in a pediatric surgery intensive care unit were high, particularly in those with a low educational level. Health professionals should be aware of the fathers' feelings, needs and stressors so that they can provide interventions specific to fathers.

Keywords: Anxiety, father, needs, pediatric surgery, intensive care

Introduction

A child's admission to a surgical clinic or intensive care unit has many effects on their parents (1). Many stressors arising due to intensive care affect not only family functions but also the physiological and psychosocial well-being of families (2-4). The activities of daily living of families whose children stay in intensive care units are disrupted and families have difficulty in fulfilling their responsibilities (5). This study provides an understanding of the anxiety levels and needs of the fathers.

Background

Stress may result from such situations as fear of the unknown, fear of death, fear of not waking up after anesthesia, loss of control, pain, isolation, separation from loved ones or being deprived of social life. In addition to these, many other factors such as the strangeness of

Address for Correspondence
Nurdan Akçay Didişen Assistant Professor, PhD, RN, Ege University Faculty of Nursing, Department of Pediatric Nursing, İzmir, Turkey
Phone: +90 232 311 55 61 E-mail: nakcayyy@gmail.com / nurdan.akcay@ege.edu.tr ORCID: orcid.org/0000-0002-4371-6020
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the hospital setting, health care team's use of unfamiliar medical terms, the use of unfamiliar devices (e.g. monitors, ventilators, infusion pumps) or alarm sounds and lights from these devices are indicated to affect individuals' anxiety levels (6-9). The leading causes of stress and anxiety in these families are the history of the disease, fear of losing a loved one, issues resulting from moving to a new place, financial concerns, role changes and separation from other family members (10). Mild anxiety can increase spontaneous attention, courage and assertiveness. An individual's ability to perceive, comprehend and make decisions decreases as the level of anxiety increases. Parents' suffering intense anxiety can be prevented from understanding the information given about the child appropriately, interpreting the events realistically, making appropriate decisions, participating in the child's care or remembering the proper coping methods they had utilized previously (11). In the literature, it has been reported that parents whose children stay in surgical clinics experience various emotional conditions such as stress and anxiety (12,13). Parents of a child who is admitted to a surgical intensive care unit experience a crisis due to the child's sudden illness or planned major surgical intervention (5).

Parents of children admitted to an intensive care unit want to stay with their children constantly, to take part in the child's care, to receive accurate information about the child's disease and the prognosis of the disease, to be informed about any change in the child's condition, to be helped and supported by health professionals, and to be in constant contact with health professionals (6,14,15). Parents also want to be sure that the members of the healthcare team regard their child as an individual and try to treat their child in the best way (3,9,14,16,17).

Aim

The aim of this study was to determine the anxiety levels and needs of those fathers whose children were hospitalized in a pediatric surgery intensive care unit.

Materials and Methods

This cross-sectional study was conducted with fathers who had children hospitalized in the pediatric surgery intensive care unit of a university hospital for at least 48 hours between November 1, 2015 and March 1, 2017 and who also agreed to participate in the study. During this period, 237 patients were admitted to the pediatric surgery intensive care unit. The power analysis was used to calculate the sample size for finite population and it was decided to include 147 fathers at a 95% confidence interval with a margin of error of 0.05. Of the 147 fathers included in the study, 24 were excluded because they filled in the questionnaires incompletely or incorrectly. Thus, 113 fathers comprised the study sample.

Measuring Instruments

In this study, the sociodemographic characteristics questionnaire, state and trait anxiety inventory, CCFNI and child information form were used.

Sociodemographic Characteristics Questionnaire

This questionnaire including 12 items questioning the fathers' sociodemographic characteristics was developed by the researcher in line with the relevant literature (1,3,6,8,9,13,16,18-20).

State and Trait Anxiety Inventory (Self-report form) STAI form TX-1,2

The STAI developed by Spielberger et al., and adapted to Turkish by Öner and LeCompte (21) (1985) includes 40 items. Of these items, 20 assess state anxiety and the other 20 assess trait anxiety. Responses to each item in the state anxiety inventory have 4 options: 1) not at all, 2) somewhat, 3) much, and 4) completely.

Critical Care Family Needs Inventory

In 1991, Leske evaluated the construct validity of this scale through factor analysis and reported that its Cronbach's alpha reliability coefficient was 0.9. The scale consists of 4 subscales including 44 items questioning the needs of the family members (22). The results of İşeri's study revealed that the reliability and validity of the scale was high for Turkey (8). To use the scale in the present study, written permission was obtained from its author.

Child Information Form

This form was developed by the researcher to collect data about children staying in the intensive care unit. The form includes items questioning the child's age, gender, nutrition style, respiratory support, and length of stay in the intensive care unit. The form was filled in by the researcher.

Procedure

In the data collection process of the fathers, those who met the inclusion criteria and agreed to participate in the study were informed about the purpose and method of the study using a face-to-face interview technique, and their written informed consent was obtained.

After the fathers were informed, the sociodemographic characteristics questionnaire, developed by the researcher

in line with the relevant literature, was used to collect data on their socio-demographic characteristics such as place of residence, educational status, social security status, monthly income status, history of previous hospitalizations, the CCFNI was used to determine the needs of the participating fathers, the STAI form was used to determine the fathers' anxiety levels, and the child information form was used to collect data.

Ethics

This study was approved by the Ege University Nursing Faculty Scientific Ethics Committee of the University (approval number: 2015-110) and the clinic where the study was to be conducted. After the fathers included in the research were informed about the purpose of the study, their written consent indicating that they agreed to participate in the study was obtained.

Statistical Analysis

The SPSS for Windows 22.0 package program was used for the statistical analysis of the study data. The socio-demographic characteristics of the fathers included in the study were assessed in numbers and percentages. Whether the data was normally distributed or not was determined with the Kolmogorov-Smirnov test. As the data was normally distributed, Mann-Whitney U test and Kruskal-Wallis test were used to analyze the data. To examine the relationship between the scales, the Pearson correlation analysis was performed. The results were considered statistically significant at the $p<0.05$ level (95% confidence interval).

Results

The mean age of the participating fathers was 36.6±6.31 (min=22, max=57) years. While 58.4% of the fathers had spent 2/3 of their lives in a city, 24.8% spent it in a district/town and 16.8% in a village. While their children were in the intensive care unit, 40.7% of the fathers stayed in the hospital, 38.1% in their own home, 15.9% in a relative's home, 3.5% in a hotel and 1.8% in a friend's home. Of the fathers, 66.4% had a nuclear family, 26.5% had an extended family, 4.4% had a traditional family, 2.7% had a fragmented family. In terms of family size, 34.5% had one child, 39.2% had two children, 20.4% had three children. In terms of educational status, 39.8% were primary school graduates, 24.8% were high school graduates and 29.2% had a higher education. In terms of financial security, 91.2% had social security and 61.9% had an income equal to expenses. Additionally, 56.6% did not have a previous hospitalization experience and 47.8% had no chaperone experience previously (Table 1).

According to the socio-demographic characteristics of the children of the fathers included in the study sample, the children's mean age was 5.37±4.67 (min=1, max=17)

Table I. Sociodemographic characteristics of fathers

	Number (n)	Percentage (%)
Place of residence		
City	66	58.4
District/town	28	24.8
Village	19	16.8
Place stayed in during child's hospitalization		
Hotel	4	3.5
A relative's home	18	15.9
A friend's home	2	1.8
Hospital	46	40.7
His/her own home	43	38.1
Family type		
Nuclear	75	66.4
Extended	30	26.5
Traditional	5	4.4
Fragmented	3	2.7
Education		
Illiterate/low literacy	7	6.2
Elementary/secondary school	45	39.8
High school	28	24.8
University or higher	33	29.2
Social security		
Yes	103	91.2
No	10	8.8
Income status		
Income less than expenses	27	23.9
Income equal to expenses	70	61.9
Income higher than expenses	16	14.2
History of previous hospitalizations		
Yes	49	43.4
No	64	56.6
History of being chaperone previously		
Yes	59	52.2
No	54	47.8
Total	101	100.0

years. Of the children, 34% were girls, 58.5% had parenteral nutrition, 13.2% had oral and parenteral nutrition, 11.3% had oral and enteral nutrition, 9.4% had parenteral and enteral nutrition, 65.4% did not receive oxygen support, and 3.8% were intubated.

The mean score obtained from the CCFNI by the participating fathers was 147.61±1.55 (min=02, max=05). The mean scores obtained from the subscales of the CCFNI were 46.11±0.68 (min=25, max=60) for the Support and Proximity Need subscale, 36.14±0.31 (min=27, max=40) for the Information Need subscale, 24.33±0.44 (min=13, max=32) for the Comfort Need subscale, and 33.68±0.21 (min=27, max=36) for the Assurance Need subscale (Table 2).

The items responded to as "very important" by the participating fathers were as follows: to feel that hospital personnel care about the patient (92.5%), to be assured that the best possible care is being given (88.5%), to receive information about the patient at least once a day (85.8%), to have questions answered honestly (84.1%), to feel there is hope (84.1%), to know the facts about the patient's progress (83%), to receive understandable explanations (80.5%), to know the reasons for the interventions the patient undergoes (78.8%), to know exactly what is being done for the patient (77%), to talk to the doctor every day (77%), to be called at home about changes in the patient's condition (76.1%), to know the expected outcome (76.1%), to know how the patient is being treated medically (74.3%), to have directions about what to do when they are at the bedside (72.6%), and to be informed about the environment in the critical care unit before going there (70.8%).

The items responded to as "not important" by the participating fathers were as follows: to have another person with you when visiting the critical care unit (32.7%), to be visited by a hodja (25.7%), to have a bathroom near the waiting room (17.7%), to know which staff members could give what information (17.7%), to be informed about religious services (16.8%), to have a telephone near the waiting room (15%), to change visiting hours in case special conditions arise (14.2%), to be alone whenever you want to (10%) and to have someone to help with family problems (10.6%).

Table II. Distribution of the mean scores for the critical care family needs inventory and its subscales

CCFNI Subscales	The number of the items	X	SS	Cronbach's alfa coefficient
Support and proximity need	15	46.11	0.68	0.836
Information need	12	36.14	0.31	0.782
Comfort need	8	24.33	0.44	0.812
Assurance need	9	33.68	0.21	0.702
CCFNI total	44	147.61	1.55	0.921

CCFNI: Critical care family needs inventory

While the mean trait anxiety score obtained by the fathers was 46.76±0.60 (min=31, max=67), the mean state anxiety score was 41.93±0.59 (min=28, max=66) (Figure 1).

The comparison of the fathers' socio-demographic characteristics with the scores they obtained from the CCFNI and its subscales are shown in table 3. There was a statistically significant relationship between the education variable and the fathers' overall CCFNI scores and Comfort Need subscale scores ($p<0.05$). As the fathers' education levels increased, so did their critical care needs. There was a difference between the fathers with higher education and the illiterate and primary school graduate fathers, and between high school graduate fathers and illiterate fathers ($p<0.05$). There was a statistically significant relationship between the education variable and the fathers' Support and Proximity Need subscale scores ($p=0.029$) (Table 3). As the fathers' education levels increased, so did their support and proximity needs.

There was a statistically significant relationship between the education variable and the fathers' trait anxiety scores ($p=0.04$). There was a difference between those fathers with higher education and those who only received primary school education ($p<0.05$) (Table 3).

Discussion

Parents whose children are admitted to the critical care unit are faced with many stressors. Among these stressors, the deterioration of family integrity is the leading one.

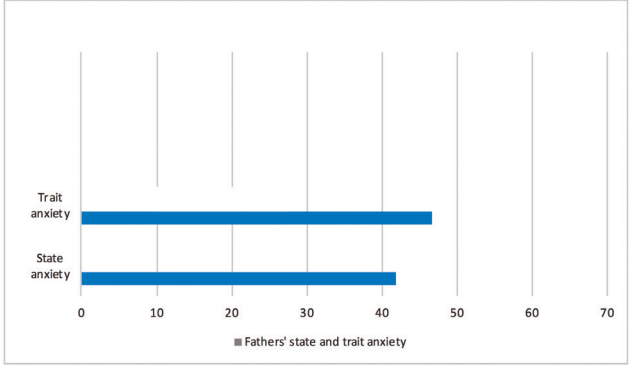

Figure 1. Mean scores fathers obtained from the State and Trait Anxiety scale

Table III. Comparison fathers' socio-demographic characteristics with the scores they obtained from the ccfni and its subscales

Socio-demographic characteristics		Support and proximity need		Information need		Comfort need		Assurance need		Total score for the overall scale		State anxiety score	
	n	X±SD	Statistical value	X± SD	Statistical value	X± SD	Statistical value	X± SD	Statistical value	X± SD	Statistical value	X± SD	Statistical value
Place of residence													
City	19	45.93±0.87	KWS:0.95*	36.04±0.41	KWS:0.16*	22.70±0.54	KWS:3.12*	33.54±0.28	KWS:1.31*	146.27±1.83	KWS:0.46*	42.21±1.37	KWS:0.27*
District/Town	28	45.64±1.61	p=0.65	36.07±0.73	p=0.92	24.64±1.07	p=0.20	33.82±0.50	p=0.59	148.71±4.10	p:0.79	42.32±1.48	p:0.87
Village	66	47.42±1.42		36.57±0.54		25.78±0.89		33.94±0.46		144.45±2.94		41.69±0.69	
The Place Stayed In Izmir													
Hotel	4	44.25±4.90	KWS:4.70*	36.00±2.67	KWS:6.22*	26.00±2.94	KWS:2.27*	34.25±0.85	KWS:6.11*	147.50±11.89	KWS:3.51*	41.50±3.92	KWS:2.84*
A relative's home	18	44.55±1.80	p=0.31	37.00±0.67	p=0.18	24.77±1.10	p=0.87	33.55±0.45	p=0.19	146.88±3.76	p:0.47	40.88±1.05	p:0.59
A friend's home	2	43.00±2.00		39.50±0.50		22.50±2.50		33.00±3.00		145.50±3.50		37.00±5.00	
hospital	46	45.23±0.98		35.58±0.48		24.04±0.64		33.39±0.31		145.26±2.03		42.43±0.94	
His/her own home	43	48.02±1.15		36.23±0.52		24.39±0.77		34.02±0.41		150.53±2.92		42.11±1.03	
Family Type													
Nuclear	75	46.44±0.87	KWS:3.10*	35.94±0.40	KWS:0.88*	24.38±0.57	KWS:1.25*	33.92±0.27	KWS:5.67*	148.20±2.06	KWS:1.55*	42.57±0.70	KWS:2.08*
Extended	60	45.80±1.21	p=0.37	36.66±0.51	p=0.82	24.50±0.70	p=0.74	33.20±0.39	p=0.12	147.10±2.40	p:0.67	40.53±1.24	p:0.55
Traditional	5	41.40±2.48		36.80±1.35		21.80±2.20		32.80±1.24		139.80±6.55		41.00±2.91	
Fragmented	3	49.00±5.03		34.66±2.90		25.66±3.28		34.00±1.15		151.00±12.01		41.66±0.33	
Education													
Illiterate / Literate	7	51.14±1.85	KWS:10.64*	37.00±1.71	KWS:54.86*	29.14±1.20	KWS:18.37*	34.28±0.52	KWS:4.06*	159.57±3.06	KWS:12.72*	43.28±2.87	KWS:3.98*
Elementary/Secondary	45	47.95±0.98	p=0.01	36.42±0.44	p=0.18	25.62±0.61	p=0.000	34.06±0.34	p=0.25	152.17±2.34	p:0.005	43.02±1.07	p:0.26
High School	28	44.85±1.29		36.78±0.52		24.14±0.73		33.50±0.32		146.10±2.50		40.82±0.96	
University or Higher	33	43.60±1.14		35.03±0.67		21.72±0.85		33.18±0.49		140.12±3.20		41.12±0.94	
History of previous hospitalizations													
Yes	49	46.00±1.08	MWU:-.73**	36.75±0.40	MWU:-1.44**	24.40±0.64	MWU:-.18**	33.89±0.31	MWU:-.82**	148.06±2.16	MWU:-.30**	41.04±0.77	MWU:-.1.4**
No	64	46.20±0.89	p=0.94	35.67±0.45	p=0.15	24.28±0.60	p=0.85	33.51±0.30	p=0.41	147.26±2.20	p:0.94	42.62±0.85	p:0.15
History of being chaperone previously													
Yes	59	45.94±0.89	MWU:-.20**	36.47±0.42	MWU:-1.30**	24.30±0.54	MWU:-.03**	33.81±0.31	MWU:-.85**	147.44±1.94	MWU:-.77**	41.47±0.68	MWU:-.77**
No	54	46.29±1.05	p=0.83	35.77±0.46	p=0.19	22.94±0.71	p=0.97	33.53±0.31	p=0.39	147.79±2.49	p:0.91	42.44±0.98	p:0.43

*Kruskal-Wallis test
**Mann-Whitney U test, SD: Standard Deviation

Coping with the problems arising from the child's admission to an intensive care unit and dealing with the child/family holistically are very important if quality patient care is to be achieved. In meeting the patients' and their parents' needs, primary responsibility lies with health professionals. In this study, conducted to determine the fathers' critical care needs and anxiety status, the vast majority of the fathers stated that their needs were very important or important.

In studies conducted by Stremler et al. (15), anxiety levels of parents with children receiving intensive care were high. In the study conducted by Board (2004), fathers were reported to suffer high levels of anxiety due to the intensive care setting, children's appearance and behavior, and intensive care procedures (23). In Dudley and Carr's study (2004), families were determined to experience feelings of anxiety, shock and uncertainty about their children (18). Chui and Chan (2007) interviewed parents whose children were in the intensive care unit and found that parents' anxiety levels were quite high (6). In the current study, the fathers' status and trait anxiety levels were high. To reduce parents' anxiety levels, environmental arrangements can be made. Currently, in Turkey, parents cannot stay with their children in the intensive care unit. However, in North America, parents can stay with their children (24). In the literature, it has been reported that parents' staying with their child in the intensive care environment reduces their anxiety level (18,19,25). In a study by Colville et al. (26) (2009), parents reported that their anxiety regarding their child's condition was greater than their anxiety regarding their child's condition when they were healthy. The parents also stated that their stress increased when they could not communicate with anybody about their child's progress. In Majdalani et al. (27) study (2014), families stated that they needed to be informed about the condition of their child to reduce their anxiety. Thus, it is very important for families to be regularly informed by health personnel.

There was no significant relationship between the parents' anxiety levels and their critical care needs. The fathers' anxiety levels were high, and their needs were a lot. It is important that caregivers are aware of the needs of the fathers. It is also necessary to consider that the father may be anxious. Initiatives to reduce the anxiety of parents and meet their needs should be planned. Fathers participating in this study rated the item 'the need for information' as very important. This result is similar to previous studies, which identified the importance of information (9,21,28). McKiernan and McCarthy stated that daily information given to family members increased the satisfaction of these family members (28).

In Uzun et al. (10) study (2002), the first three needs indicated by family members were ''to be assured the best possible care is being given''. In Tokur et al. (20) study (2016), while 90% of the patients' relatives wanted to see their patients every day, 96% wanted to be informed about their patient's condition every day. In the present study, the fathers considered the following items very important: ''to feel that hospital personnel care about the patient'', ''to be assured that the best possible care is being given'', ''to receive information about the patient at least once a day'', ''to have questions answered honestly'', ''to feel there is hope'', and ''to know the facts about the patient's progress''.

As the fathers' education levels increased, so did their critical and support/proximity needs. In a study performed by İşeri (2010), no correlation was determined between the participants' educational status and their assurance, support and proximity, information and comfort needs (8). In their study, Medonca and Warren (17) determined that the illiterate participants had a higher expectation of support.

In Maxwell's study (2010), families obtained the highest mean scores from the assurance, proximity, information, comfort and support need subscales respectively (9). In Majdalani et al. (27) study, the families described their experience relating to the intensive care setting, their child's prognosis and expectations of health professionals as a journey into the unknown. Board (2004) reported that the father's communication with health professionals was poor and that they did not know how to help their children (23). In a study conducted by Berube et al. (29) (2014), they concluded that the parents whose children were in the intensive care unit felt exhausted, wanted to feel that they were supported by others and wanted to be informed of their child's condition. Also the families' support and proximity needs were high.

In a study conducted by Carlson et al. (30), of the parents whose children were in intensive care units, 20% were satisfied with their communication with physicians and nurses, being informed about their children's condition, and receiving emotional support. Uzun et al. (10) reported (2002) that many of the patients' families regarded their need to be informed about the patient's condition and to receive psychological support as more important than their personal/physical needs. Clinical protocols should be developed to meet the needs of the father in line with these requirements.

Limitation of the Study

Our study had several limitations. The first one is that the study was performed only in the surgical intensive care

unit in one center. In addition, the majority of the participating fathers' economic status, social security and education levels were good. Therefore, the results of study cannot be generalized to other centers as priorities may change.

Conclusion

In conclusion, the anxiety levels and needs of those fathers whose children were admitted to the pediatric intensive care unit were high. The fathers wanted to know that their child received the best possible care from the hospital staff, and to receive clear, understandable and accurate information about their child. In order to improve the conditions and the quality of care in the existing pediatric surgery intensive care units in Turkey, hospital and/or clinical protocols should be developed to meet the needs of the fathers and to establish effective communication with them.

Ethics

Ethics Committee Approval: This study was approved by the Ege University Nursing Faculty Scientific Ethics Committee of the University (approval number: 2015-110) and the clinic where the study was to be conducted.

Informed Consent: A consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., Z.D., Concept: N.A.D., A.K., S.E., Z.D., Design: .A.D., A.K., S.E., Z.D., Data Collection or Processing: S.E., Analysis or Interpretation: A.K., Literature Search: N.A.D., A.K., S.E., Z.D., Writing: N.A.D., A.K.

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Original Article

The Effect of Mother's Lullaby on Preterm Infants' Physiological Parameters

Elham Shafiei[1], Zahra Daneshvar Ameri[2], Hojjat Sheikhbardsiri[3], Mahdi Yaseri[4], Hamideh Baniasadi[5],

[1]Tehran University Medical of Sciences Student, Faculty of Nursing and Midwifery, Tehran, Iran
[2]Tehran university Medical of Science, Faculty of Nursing and Midwifery, Public Health Depatment, Tehran, Iran
[3]Kerman University of Medical Sciences, Department of Emergency Operation Center, Disasters and Emergencies Management Center, School of Medicine, Kerman, Iran
[4]Tehran Medical University Faculty of Public Health, Department of Research Center for Modeling in Health, Tehran, Iran
[5]Kerman University Medical of Sciences Student, Department of Public Health's Nursing, Razi Faculty of Nursing and Midwifery, Kerman, Iran

ABSTRACT

Aim: Inappropriate auditory stimulants lead to neonatal stress and changes in physiological parameters. Nowadays, particular emphasis is placed on the developmental aspects of the care of preterm infants. The lullaby is a suitable auditory stimulus for preterm infants, which as a subtype of developmental care decreases stress responses. This study investigates the effects of lullabies in the mothers' own voices on preterm infants' physiological parameters.

Materials and Methods: This single group study is a randomized clinical trial. Forty study-qualified hospitalized infants were included in the study, during a lullaby stage and a non-lullaby stage. Their physiological parameters including respiratory rate, heart rate and oxygen saturation level were recorded. Their mothers' lullabies were played for them during the lullaby stage. No intervention was performed in the non-lullaby stage and only the infants' variables were recorded. Infants were assessed for four successive days, two days for each stage. Data was collected and recorded every 2 minute. Data was statistically analysed after gathering and entering into the SPSS.22 by means of Friedman's and paired sample t-test.

Results: In this study of 40 case studies, 45% were female and 55% were male, with an average gestational age of new-borns of 32.43 weeks and mean birth weight of 2,189.36 gr. In the intervention group, during the time that the lullaby was played, mean rates of heart beat were significantly decreased (p=0.03) and SaO_2 was increased (p=0.039), which were significantly different from their base recorded levels at the beginning and those of the control stage, but there was no significant difference between two stages in the mean of respiratory rates (p=0.070).

Conclusion: Since a mother's lullaby has significant effects on physiological parameters, we hope that nurses will tell mothers to use the lullaby as a supportive developmental care for infants to assist improving the physiological state of preterm new-borns.

Keywords: Preterm infant, lullaby, heart rate, respiration rate, oxygen saturation, physiological parameter

Introduction

Birth before the 37th gestational age week is preterm birth (1). Prematurity is an important indicator for a society's health and infant survival has a direct relationship with gestational age and birth weight (2). Preterm infants are very vulnerable due to physiological restrictions (3). Along with the increased infant survival, damage growth is rising. Developmental and cognitive function disorders and

Address for Correspondence
Hamideh Baniasadi MD, Kerman University Medical of Sciences Student, Department of Public Health's Nursing, Razi Faculty of Nursing and Midwifery, Kerman, Iran
Phone: +98 913 662 20 59 E-mail: Baniasadi.98po69@gmail.com ORCID: orcid.org/0000-0003-2883-2901
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sensoneural problems are seen in many of these babies (4).

Many studies show that the cause of these problems is the effect of the neonatal intensive care unit (NICU) environment on the central nervous system (5). Also believes that the preterm infant is hospitalized for a long time at a place that is different from his/her mother's womb and faces many sensory stimuli in the NICU environment. Prolonged care in this new place is beyond the immature nervous system's tolerance (6). At the same time, physical and environmental conditions and inappropriate care in the NICU and also unstable haemodynamic body conditions and challenges to immature organs cause stress in preterm infants (7). Also, separation from the mother's supportive uterine environment and the continuation of this separation by hospitalization of the infant and the mismatch of the NICU environment with uterine conditions cause stress (8). Heart rate disorder, changed skin colour, hypoxia, diminishment of SpO_2 and apnoea attacks are caused by stress, which lead to prolonged hospitalization and increased costs of hospitalization, and finally have bad effects on parent-infant relationships (9-11). Irritating environmental auditory stimulation is a common concern in NICU wards, which interferes with neonatal development (12).

The auditory environment is considered a part of the structure of the NICU, and its changes can affect neonatal development because the immaturity of vital organs and unfavourable physical and environmental care have great impact on growth and development (13). Then, preterm infants exposed to environmental noise show increased heart rate, blood pressure and respiratory rate as physiological changes. Managing noise in the ward is one of the aspects of developmental care (14) .With this in mind, one can define a programme called developmental care as a supplemental clinical care, providing a similar environment to uterine conditions for the neonate as the most important factor to reduce neonatal stress (15). Music as a subset of developmental care and a desired auditory stimulation can be heard and learnt by the neonate. Before birth, it affects the development process, and after birth, covering noises can facilitate balance and infant neurodevelopmental (12). The use of music to promote health has been proved by recent medical research. The effectiveness of music therapy has been demonstrated to improve mental-physical diseases, pain control, anxiety and stress (16,17). Prolonged auditory stimulation with a harmony-like lullabies acts as a sedative in infants and can lead to unstable physiological parameters like the heart rate being coordinated by the relaxed rhythm of music and so lead to a slow heart rate (18). It is important to note that the most natural sound for an infant is his/her mother's (14). This sound is the first sound that an infant hears and it affects his/her auditory system (19). The infant is completely dependent on his/her mother for physical and growth health (20). In human research, denial of maternal contact causes increased stress in the neonate (21). In the Discenza (22) study, it was shown that preterm infants fed while listening to a lullaby have more success in learning to and continuing to feed. Also, another study demonstrated that in a period when mothers talk to their infants compared to when this auditory sound did not occur, the level of arterial oxygen saturation is greater and the heart rate is lower in these infants (23), but Wenszell (24) found that after music, heart rate, arterial oxygen saturation and crying in infants with gastroschisis did not demonstrate significant differences.

Given the increasing number of preterm births and long-term hospitalization as a result of this, information can be given to caregivers that this is a harmless and economically affordable method and possible for use in the ward. A lullaby with the mother's sound is considered a choice to improve neurodevelopmental consequences and can lead to diminished stress following the improvement in physiological parameters. To date, very few studies have examined the effect of the mother's lullaby on physiological parameters in preterm infants. In the Iranian context, the lullaby is rooted in popular culture, and no research has examined its effects on infants.

Materials and Methods

This single group study is a randomized clinical trial conducted in Tehran, Iran. The sample of infants in this study was selected from a single hospital under the supervision of Tehran University of Medical Science. Forty study-qualified hospitalized infants were included in the study-once during the lullaby stage and once during the non-lullaby stage. All infants were assessed before intervention. Inclusion criteria were (1) a gestational age of 28-34 weeks at birth, (2) no congenital anomalies, (3) not having undergone surgery, (4) Apgar scores of more than 6 at 5 minute, (5) the accuracy of infant hearing health with confirmed OAE auditory test (this test was performed after the third day after birth to reduce false negative results) and (6) no use of phototherapy or mechanical ventilation for the infant.

Approval was obtained from the heads of NICU prior to the collection of data. The study proposal was also reviewed and approved by the office of the Centre of Research Ethics in Tehran Medical Science University (IRCT-201501296316N5). The parents signed a written informed consent form. The

consent form explained that participation was completely voluntary, and that they could withdraw from the study at any time. They were informed about the purpose of study and procedure, both verbally and with written information. For confidentiality, there was no personal information on the scale.

Infants entered the group during the third day after hospitalization. The infant, during the study, was in the differential thermal analyser incubator (YP-9 OA model), and his/her position was supine and such a way that the ears were free for hearing and there were no barriers to hearing sounds (25). Before the observation pulse, an oximeter probe was attached to the right foot of the infant. Two speakers at 30-centimetre distance from the neonate head were placed at two corners of the incubator. The intensity of ambient sound in the double wall incubator was determined with a decibel meter and sound intensity was adjusted to 50 decibels to consider the scope of sound that would be able to cover the ambient sound and also prevent transfer of sound from one neonate to another. A Sony MP3 player was attached to the speakers. Between infant feeding and the start of the observation, there was always a gap of approximately 1 hour, and nursing care was done at least half an hour before intervention. To record the mother's sounds, a fixed text was given to the mother and then her sound was recorded: they were recorded as they emitted sound in another room when they were alone and thinking about their infant. Each infant was studied for four consecutive days, and for this intervention, two stages were considered: one stage with lullaby (2 days) and another stage without lullaby (2 days). Every day, one infant was studied for 40 min and also according to Lubetzky (26) one period (24 hours) wash out considered for did not rest of lullaby affect. Putting infants in the lullaby stage or non-lullaby stage was randomized by the use of two cards (A and B) that were of the same shape and size. Then a person who was not aware of the meanings of the cards was asked to choose one of them; if Card A was chosen, the lullaby was played on the first and second days, and if Card B was chosen, the non-lullaby stage was selected for the first and second days, and two days later, the other stage with the lullaby was applied. In the lullaby stage, the infant was observed 10 minute before, during and 10 minute after playing the lullaby; the playing time was 20 minute. During 40 minute, physiological parameters such as heart rate, respiratory rate and SPO2 were recorded. In the non-lullaby stage, no intervention was made: these parameters were recorded in the checklist every 10 minute. The values were recorded in the relevant checklist. Data was collected for 5 months.

Statistical Analysis

Data was analysed using SPSS22. Quantitative and qualitative variables were respectively reported as mean (SD) and frequency (percentage). Friedman test for determination of the relationship between them before, during and after interventions was used. P-values less than 0.05 were considered significant.

Results

A descriptive analysis of the background information indicated that the premature infants had a gestational age of 28-34 weeks with a mean age of 32.43 weeks. They were mostly males (52%). Concerning type of delivery, both of normal vaginal delivery (NVD) and cesarean section (CS) were equal (n=20, n=20, respectively). The group's mean birth weight was almost 2,189.36 g. The mean score of Apgar for the group was 7 (Table 1).

Statistical analyses showed a significant difference between oxygen saturation across the two stages (p=0.039). There was no significant difference observed between respiratory rate of the interventional and control groups (p=0.07) but it showed a downward trend, and with respect to heart rate, there was a significant difference between the two stages (p=0.03) (Table2).

Discussion

In infants whose mothers were depressed, there was a delay in the start of change in response to music and heart rate fluctuation were more than in other infants (27), while listening to music, girls receive oral feeding sooner than boys and their mean of hospitalization days was less than for boys (28). If the mother had a history of addiction, there

Table I. Characteristics of the study sample (n=40)

Characteristics	**n (%) or Mean (SD)**
Sex	
Male	22 (55%)
Female	18 (45%)
Delivery type	
NVD	20 (50%)
C/S	20 (50%)
Gestational age (weeks)	32.43 (±2.7)
Birth weight (grams)	2,189.36 (±212.53)
Apgar score (5min)	7 (±1.3)

Table II. Oxygen Saturation, respiratory rate and heart rate before, during and after mother's lullaby across 4 days

Groups		Before Mean (SD)	During Mean (SD)	After Mean (SD)	p
Oxygen Saturation	Int. Cont.	89 (±3) 90 (±1)	94 (±5) 90 (±2)	91 (±2) 90 (±2)	0.039
Respiratory Rate	Int. Cont.	57 (±2) 57 (±2)	55 (±1) 57 (±2)	57 (±4) 57 (±2)	0.070
Heart Rate	Int. Cont.	154 (±6) 156 (±5)	149 (±2) 156 (±8)	151 (±1) 155 (±6)	0.03

were changes in physiological parameters and sleep states. Apnoea, tachypnoea, hypertension, irritability, increase in sudden responses to auditory stimulation, sleep disorders, rapid changes in the waking state and decreased reaction to human sounds were seen in infants of mothers addicted to alcohol and drugs (29). In the current study, based on patient documentation, none of the mothers mentioned addiction or depression, and so, this issue could not affect results.

The mean of heart rate during intervention (20 minute lullaby playing) was observed to be less than the base level before the lullaby stage. It was a significant difference. Also, the heart rate after intervention was observed to be less than the heart rate beforehand, but statistically not significant. According to the results, it can be concluded that the effect of lullabies on heart rate causes it to fall while hearing a lullaby. Possibly, the cause of this lullaby effect is explained by the fact that lullaby affects the nervous system (limbic and autonomic systems), leading to pacification, easiness, a decrease in stress and heart rate, respiratory regulation and an increase of oxygenation.

Music facilitates parasympathetic effects on the sympathetic system and finally, due to diminished heart rate, there is regular deep breathing, sleep and repeated induction of brain alpha waves that are produced in the awakened and aware state. This concept matches with Aron's study that found heart rate is less in a preterm infant group that has live music played to it than in two other groups who heard recorded music. They concluded that live music has more effect than recorded music in preterm infants (30). Also, Amini et al. (25) demonstrated that lullabies can cause a reduction in heart rate during intervention compared to the base level, and this agrees with our results (25).

Accordingly, coping with stress in preterm babies occurs due to improved physiological parameters such as heart rate. This finding is similar to Cevasco's (31) work, in which he had assessed the effect of a mother's lullaby on coping and its relationship with neonatal stress. He found that the infant who heard his/her mother's sound was discharged earlier than the control group by an average of 2 days (31).

Cassidy's (32) study found that music did not affect heart rate, this difference may be due to the music type (Mozart/lullaby), and the short duration of the observation period before and after music (4 minutes before, during and 4 minutes after) (32). Likewise, Hodge and Wilson (33) showed that music did not have any effect on physiological parameters; it could be justified that this incompatibility with our results is due to the time of playing the music, data collection interval, and music type (33).

In Farhat's (34) work, music did not produce any difference with the heart rate either. This difference might have been caused by the lullaby type. The researcher concluded that the mother's sound is the same for the infant and the palliative effect of that is more than a stranger's (another woman's) sound. Another parameter assessed in this study was the respiratory rate: The respiratory rate during intervention and afterwards was diminished. It can be concluded that lullabies can cause a decrease in heart rate. This is compatible with the work of Farhat (34) and Keith (35). They found that music causes a diminished rate of respiration (34,35). However, Coleman (36) found that music leads to an increase in respiratory rate, and the cause of this difference may be that the infants in the control and interventional groups in his study were not homogenous in terms of clinical diagnosis as neonates with different diagnosis could have other hemodynamic conditions that may have affected physiological parameters and disturbed the results (36).

The results of this study showed that SPO_2 increases after hearing a lullaby. This finding may be due to the soothing effect of the lullaby, which causes decreases in the sympathetic system's activity and tension, and this is shown by its calming effect on physiological parameters like respiratory rate, pulse, blood pressure, oxygen consumption, etc. According to the results and the decrease in respiratory rate, this finding may support the idea that lullabies, through the impact of deep breathing and the rate of breathing, leads to respiratory efficiency and finally increases oxygen saturation. It should be noted that reduced oxygen consumption is one of the reasons for the increase in and therefore higher levels of blood oxygen saturation without increases in patient oxygen uptake. This is one important goal that could diminish oxygen complications. Earlier studies supported this finding that infants experienced high level of oxygen saturation after hearing music (12,34,35).

In contrast, some researches indicated that there was no significant difference between music and oxygen saturation: This difference might be caused by the music type and number of participants compared to this study in which it is stated that a mother's sound may exert more effect on physiological parameters.

Conclusion

In this study, attempts were made to assess the effect of a mother's lullaby on the physiological parameters of the preterm neonate. This study found positive effects of such lullabies. Considering the notion that physiological instability is a sign of neonatal stress and autonomic stability is one of the most important factors that affect developmental outcomes, a lullaby is one of the cost-effective supplemental cares that we may use in NICU. All information on the risks and benefits as well as the best intervention strategies before this intervention is conducted should be included in the educational programmes. Further studies are suggested to examine NICU nurses' views on this intervention, and its advantages and disadvantages as well.

Ethics

Ethics Committee Approval: The study proposal was also reviewed and approved by the office of the Centre of Research Ethics in Tehran Medical Science University (IRCT-201501296316N5).

Informed Consent: The parents signed a written informed consent form.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S., Concept: E.S., Design: Z.D.A., Data Collection or Processing: H.S.B., Analysis or Interpretation: H.B., Literature Search: M.Y., Writing: H.B.

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Original Article

Ultrasonographic Screening and the Determination of Risk Factors involved in Developmental Dysplasia of the Hip

Gizem Ürel Demir[1], Eyüp Sarı[1], Selmin Karademir[2], Çiğdem Üner[3], Yasemin Taşcı Yıldız[3], Ulaş Onay[4], Şenol Bekmez[4]

[1]Dr. Sami Ulus Obstetrics and Gynecology Children's Health and Disease Training and Research Hospital, Clinic of Pediatrics, Ankara, Turkey
[2]Dr. Sami Ulus Obstetrics and Gynecology Children's Health and Disease Training and Research Hospital, Clinic of Pediatric Cardiology, Ankara, Turkey
[3]Dr. Sami Ulus Obstetrics and Gynecology Children's Health and Disease Training and Research Hospital, Clinic of Radiology, Ankara, Turkey
[4]Dr. Sami Ulus Obstetrics and Gynecology Children's Health and Disease Training and Research Hospital, Clinic of Orthopedics and Traumatology, Ankara, Turkey

ABSTRACT

Aim: Developmental dysplasia of the hip is an orthopedic problem which is a spectrum of disorders from the instability of the hip joint to total dislocation. Developmental dysplasia of the hip is frequently seen and has good prognosis when diagnosed and treated early. The aim of our study is to examine the risk factors leading to developmental dysplasia of the hip and to assess the value of hip ultrasonography.

Materials and Methods: In our research, 9.102 imagings of hip ultrasonography from 4.551 infants were analyzed retrospectively. One hundred and fifty-one infants who were diagnosed with developmental dysplasia of the hip and 170 healthy infants as a control group were compared in terms of birth order, being the firstborn, type of delivery, gestational age, birth weight, oligohydramnios, multiple pregnancy, breech presentation, swaddling, family history and existence of foot anomalies.

Results: Prematurity, oligohydramnios and a positive family history were observed to be significant risk factors for developmental dysplasia of the hip.

Conclusion: It is possible to prevent the complications and necessity of surgical treatment with early diagnosis. Therefore, we propose screening for developmental dysplasia of the hip for all infants.

Keywords: Developmental dysplasia of the hip, hip dislocation, hip dysplasia, hip instability, hip ultrasonography

Introduction

Developmental dysplasia of the hip (DDH) is defined as a disruption of the relationship between the acetabulum and the femoral head. The traditional term congenital hip dislocation, suggesting a pathology due to the prenatal malposition, has been replaced by the term DDH, as Klisic proposed, emphasizing the dynamic course of the disease (1).

The estimated incidence of hip instability during the newborn period ranges from 1/1.000 to 3.4/100, whereas

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Address for Correspondence
Gizem Ürel Demir MD, Dr Sami Ulus Obstetrics and Gynecology, Children's Health and Disease Training and Research Hospital, Clinic of Pediatrics, Ankara, Turkey
Phone: +90 505 256 36 88 E-mail: gizemurel@gmail.com ORCID: orcid.org/0000-0002-9928-3236
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the prevalence of hip dislocation ranges from 1 to 1.5 per 1.000 live births (2).

Various etiological factors including ligamentous laxity, prenatal positioning, postnatal positioning, and racial predilection may lead to DDH (2). Hormonal, genetic and environmental factors have been described in the etiology. DDH in a first-degree relative, breech presentation, swaddling, and congenital calcaneovalgus foot deformities were identified as the strongest risk factors in DDH, whereas female sex, coexistence of torticollis and being the firstborn child were associated with having weaker effects on DDH (3).

The hip joint should be evaluated during routine examination of the newborn.

Ultrasonography is the most reliable imaging method for the diagnosis of DDH before femoral head epiphyseal nucleus ossification. The aim of the treatment is to maintain the normal relationship between the femoral head and the acetabulum and to sustain the reduction until the pathological changes are over.

The purpose of our study is to examine those risk factors leading to DDH and to assess the diagnostic value of hip ultrasonography.

Material and Methods

In our hospital, 9.102 imagings of hip ultrasonography data performed between January 2012 and January 2013 from 4.551 babies were retrospectively analyzed. The records of 170 babies, diagnosed with DDH, were obtained from our hospital registration system.

ToshibaAplio 800, ToshibaAplio 500, General ElectricsLogiq S6 brand ultrasonography devices and 11 MHz linear probes were used for the ultrasonographic examination of the hip. Ultrasonographic classification of the hip joint was performed according to the Graf method (2,4).

Type I: alpha angle: >60° beta angle: <55°,

Type IIa: alpha angle: 50°-59° beta angle: >55° (less than 3 months),

Type IIb: alpha angle: 50°-59° beta angle: >55° (greater than 3 months),

Type IIc: alpha angle: 43°-49° beta angle: <77°,

Type D: alpha angle: 43°-49° beta angle: >77°,

Type IIIa: alpha angle: <43° beta angle: >77° (hypoechoic cartilage acetabular roof),

Type IIIb: alpha angle: <43° beta angle: >77° (hyperechoic cartilage acetabular roof),

Type IV: alpha angle: <43° beta angle: >77° (Pressed downwards, perichondrium is horizontal or dips caudally).

The physical examination findings of patients were evaluated in terms of 'pili asymmetry' and 'limited abduction'. Interviews were held via telephone with the parents to evaluate the follow-up. Data on birth order, sex, type of delivery, gestational age, birth weight, oligohydramnios, multiple pregnancy, breech presentation, swaddling, family history, and foot anomalies were obtained from the hospital registry system and family interviews. In order to determine the relationship between risk factors and DDH, 170 control cases were randomly selected from those infants who underwent hip ultrasonography between January 2012 and January 2013 in our hospital. The control group were questioned concerning the presence of risk factors of DDH and the information was recorded.

Ethics committee approval was received for this study from the Ethics Committee of Ankara Keçiören Training and Research Hospital (25.01.2017/1301). Verbal informed consent was obtained prior to the interviews.

Statistically Analysis

Statistical analyzes were performed using the SPSS for Windows Version 22.0 package program. Categorical variables were compared by chi-square or Fisher's exact test. The significance level was taken as $p<0.05$.

Results

The ultrasonographic findings of 9.102 hips of 4.551 cases, who underwent hip ultrasonography for screening, were examined. We identified a total of 170 cases of whom DDH was detected. Among them, follow-up data could not be obtained for 18 patients. Additionally, one patient was excluded because of the diagnosis of spinal muscular atrophy.

One hundred sixty-nine infants were accepted into this study giving a total of 338 hips. Of the total number of patients, 138 (81.7%) were female and 31 (18.3%) were male. Hip ultrasound examination was performed between the ages of 46 and 188 days (80.3±20.3 days). DDH was detected right sided in 89 cases and left sided in 125 cases. In 45 cases, DDH was bilateral. Ultrasonographic type distribution of each hip (338 hips in total) revealed that 124 (36.7%) were type Ia-b (normal), 16 (4.7%) were type IIa-, 133 (39.3%) were type IIa+, 33 (9.8%) were type IIb, 19 (5.6%) were type IIc, 5 (1.5%) were type D, and 8 (2.4%) were type IIIa. Type IIIb and type IV hips were not detected in any cases (Table I).

In order to evaluate the risk factors, we compared 170 cases constituting the control group with 151 cases who were diagnosed with DDH. Eighty-seven (51.2%) of the control cases were male, and 83 (48.8%) were female. In the control group, hip ultrasound examination was performed between the ages of 54 and 108 days (73±9 days).

On physical examination of those cases diagnosed with DDH, limited abduction was noted in 22 cases (14.6%) and pili asymmetry in 14 cases (9.3%). Physical examination findings of 115 patients (76.1%) were normal. All 7 patients with type IIIa hips had limited abduction, indicating a significant difference. No significant relationship was found between the pili asymmetry and the hip types.

The risk factors commonly associated with DDH including birth order, sex, type of delivery, gestational age, birth weight, oligohydramnios, multiple pregnancy, breech presentation, swaddling, family history, and the existence of foot anomalies were explored. Among these factors, prematurity, oligohydramnios and a positive family history were demonstrated to have a statistically significant association with DDH. A total of 135 patients had at least one risk factor, of whom 103 cases had positive physical examination signs for DDH. The relation between hip types and risk factors is shown in table II and the effect of risk factors on DDH is summarized in table III.

Follow-up information revealed that 52 of the DDH cases were followed up without treatment, 73 were treated with Pavlik harness, 4 with abduction orthosis, 12 with both Pavlik harness and abduction orthosis, 4 with open reduction, 4 with closed reduction and 2 had an operation plan at the time of writing.

Discussion

DDH is an orthopedic problem which is a spectrum of disorders ranging from the instability of hip joint to

Table I. Ultrasonographic type distribution of all hips

	Right hip		**Left hip**		**All hips**	
Type	**Number**	**%**	**Number**	**%**	**Number**	**%**
Ia-b	80	47.3	44	26	124	36.7
IIa-	8	4.7	8	4.7	16	4.7
IIa+	53	31.3	80	47.3	133	39.3
IIb	18	10.7	15	8.9	33	9.8
IIc	6	3.6	13	7.7	19	5.6
D	2	1.2	3	1.8	5	1.5
IIIa	2	1.2	6	3.6	8	2.4
Total	169	100	169	100	338	100

Table II. The relation between hip types and risk factors

	Type Ia-Ib (normal)		**Type IIa**		**Type IIb**		**Type IIc**		**Type D**		**Type IIIa**	
Risk Factors	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Firstborn	75	44.1	50	47.6	8	32	5	45.5	2	66.7	3	42.9
Female sex	83	48.8	86	81.9	21	84	10	90.9	0	0	6	85.7
Caesarean section	83	48.8	44	41.9	17	68	5	45.5	3	100	6	85.7
Prematurity	4	2.4	5	4.8	3	12	1	9.1	2	66.7	1	14.3
Oligohydramnios	8	4.7	10	9.5	4	16	1	9.1	2	66.7	0	0
Multiple pregnancy	2	1.2	4	3.8	1	4	1	9.1	1	33.3	0	0
Breech presentation	6	3.5	11	10.5	1	4	1	9.1	1	33.3	0	0
Swaddling	49	28.8	34	32.4	5	20	5	45.5	0	0	1	14.3
Family history	14	8.2	27	25.7	4	16	4	36.4	0	0	3	42.9
Family history (First degree)	2	1.2	8	7.6	1	4	2	18.2	0	0	1	14.3
Foot anomaly	3	1.8	3	2.8	2	8	0	0	1	33.3	1	14.3

Table III. Impact of risk factors on developmental dysplasia of the hip

	DDH group		Control group		p
Risk factors	n	%	n	%	
Firstborn	68	45	75	44.1	0.869
Firstborn girl	49	32.5	40	23.5	0.075
Caesarean section	75	49.7	83	48.8	0.880
Prematurity	12	7.9	4	2.4	0.030
Oligohydramnios	17	11.3	8	4.7	0.048
Multiple pregnancy	7	4.6	2	1.2	0.089
Breech presentation	14	9.3	7	4.1	0.101
Swaddling	45	29.8	49	28.8	0.848
Family history	38	25.2	14	8.2	0.000
Family history (First degree)	12	7.9	2	1.2	0.007
Foot anomaly	7	4.6	3	1.8	0.199

DDH: Developmental dysplasia of the hip

total dislocation. DDH is a common deformity among the musculoskeletal system abnormalities and successful outcomes can be obtained with early diagnosis and intervention. If not treated early, the cost of treatment and the need for surgery increases exponentially and the chances of success decline (5).

The incidence of DDH has been reported to be between 0.08% and 5.2% in previous studies (6-8). The estimated prevalence of DDH in Turkey ranges between 0.5% and 1.5% (6). The incidence determined by hip ultrasonography screening ranges between 0.86% and 17% (9-16). In our research, the frequency of DDH was found to be 3.71%.

All newborn infants should be examined for DDH during routine examination. DDH in the neonatal period can be diagnosed by eliciting the Ortolani or Barlow sign. By the second month of life, other signs of DDH might become obvious, including limited abduction, asymmetry of thigh folds, Galeazzi sign and pistoning of the hip (2). We did not regard the Ortolani and Barlow tests because our patients had passed the neonatal period. The most reliable examination finding after the newborn period is limited abduction (6,10,11). In our study, limited abduction was noted in 14.6% of infants.

Demirhan et al. (12) detected the ratio of the coexistence of abnormal ultrasonography and pathologic physical examination findings as 40% whereas the ratio of abnormal ultrasonography without clinical evidence was 60%. In the study of Karapınar et al. (13), 15,000 babies were screened regarding physical examination findings and risk factors. Among them, 482 infants with positive physical examination findings and risk factors were assessed with hip ultrasonography and pathologic ultrasonographic findings were observed in 73 (15.1%) cases. Bache et al. (17) reported that only 20% of those patients with abnormal ultrasound findings at 6 weeks of age were found to have unstable hips in the initial examination. Tönnis (18) stated that all newborns should be screened because many pathologies can be detected by ultrasonography rather than other clinical procedures. In our study, we observed that 76.1% of the patients did not display evidence of hip instability on physical examination. Furthermore, we did not find any clinical evidence on 74.7% of infants with dysplasia who required treatment. This suggests the necessity of ultrasonographic screening for DDH even if physical examination findings are normal.

Imaging methods, such as hip ultrasonography, plain pelvis radiography, computed tomography, magnetic resonance imaging, and arthrography, can be used for the diagnosis and monitoring of DDH (2). The specificity and sensitivity of hip ultrasonography in diagnosing DDH is over 90% (19,20). There are various opinions about the time of the screening and postnatal 6th week is defined as a period in which minor transient anomalies of the hip may resolve spontaneously, and early detection of permanent anomalies can be provided (21). Barlow (22) suggested that 60% of unstable hips noted at birth resolved within the first week and 88% in two months. In our hospital, hip ultrasonography is applied as a routine screening program and is usually performed after the first two months of life.

The etiology of DDH is multifactorial, including mechanical structural, mechanical environmental, and

genetic factors (2). In the study of Ömeroğlu et al. (10), infants who had at least one risk factor conducive to DDH were found to have a three times higher occurrence rate of DDH compared to those who did not carry any risk factors. In the same study, breech presentation and positive family history were determined to be the most common risk factors associated with DDH. The incidence of DDH was 27% in infants with at least one risk factor and 9% in infants without any risk factors. (10) In the study of Akman et al. (23), female gender, oligohydramnios, and swaddling were defined as risk factors for DDH. Uslu et al. (24) found that the frequency of hip immaturity among a group of patients exposed and unexposed to the risk factors at 25.2% and 9.9%, respectively. The same study also indicated that the incidence of hip dysplasia was 5.29% in the risk group, whilst no hip dysplasia was encountered in the control group. Furthermore, they demonstrated a correlation between the number of risk parameters and the incidence of immature or dysplastic hips during the newborn period. According to a study by Çakır et al. (5), the most frequent risk factor was identified as being a firstborn girl, followed by breech presentation, multiple pregnancy, and oligohydramnios. Breech presentation, oligohydramnios, female sex, and primiparity were determined to be risk factors for DDH in the study of Chan et al. (25). The meta-analysis of De Hundt et al. (26) indicated that breech presentation, female sex, positive family history, and clicking hips at physical examination were the most potent risk factors for DDH. In our study, prematurity, oligohydramnios, and positive family history were confirmed as statistically significant risk factors. Birth order, being a firstborn, type of delivery, birth weight, multiple pregnancy, breech presentation, swaddling, and the presence of foot anomalies were not found to be statistically significant for DDH.

In the literature, DDH is found to be 4-6 times more common among girls than boys (17,27,28). In our study, the female/male ratio was 4.4/1, which is consistent with the literature.

Delays in diagnosis and treatment resulting in sequelae increase the cost of treatment. Furthermore, total hip arthroplasty may be necessary owing to the development of coxarthrosis. This condition prolongs the treatment process and leads to serious labor force loss. In cases of early diagnosis and conservative treatment, the necessity of surgical treatment can be reduced. Therefore, hip ultrasonography has been included in the screening program and adopted as a health policy in various countries. In our country, within the national early diagnosis and treatment program for DDH, it is aimed to perform a routine hip examination during the newborn period, identify high risk and clinically suspected groups and to initiate early and appropriate treatment (29). Additionally, in our hospital, hip ultrasonography is applied to all infants as a part of the routine screening program.

Study Limitations

The limitations of our study include the small number of patients and the presence of patients whose follow-up information was not available. Additionally, there is a possibility that the information received from the parents of the patients may be incorrect due to misremembering.

Conclusion

Hip joint evaluation with regard to DDH in each visit, careful follow-up of infants with risk factors and family education about the influence of swaddling are important measures to prevent the development of DDH. Awareness concerning DDH among health professionals and parents plays a key role in preventing this condition. Training of health personnel in the identification of those high-risk babies is required for the early diagnosis and treatment of DDH.

Ethics

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara Keçiören Training and Research Hospital (25.01.2017/1301).

Informed Consent: Verbal informed consent was obtained prior to the interviews.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Ü.D., S.K., Concept: G.Ü.D., S.K., E.S., Design: G.Ü.D., Y.T.Y., U.O., Ş.B., Data Collection or Processing: E.S., U.O., Ş.B., Analysis or Interpretation: G.Ü.D., S.K., Ç.Ü., Y.T.Y., Literature Search: G.Ü.D.,U.O., Ş.B. E.S., Writing: G.Ü.D., E.S., S.K., Ç.Ü., Y.T.Y., U.O., Ş.B.

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Original Article

Professional Values and Job Satisfaction Levels of Pediatric Nurses and Influencing Factors: A Cross-sectional Study

Ayla Kaya[1], Derya Çelik[2], Ayşegül İşler Dalgıç[1]

[1]Akdeniz University Faculty of Nursing, Department of Pediatric Nursing, Antalya, Turkey
[2]Akdeniz University Hospital, Antalya, Turkey

ABSTRACT

Aim: The aim of this cross-sectional study was to investigate the perceptions of professional values and job satisfaction levels of pediatric nurses and their influencing factors.

Materials and Methods: This study was conducted with 134 nurses working in the pediatric clinics of three hospitals in Turkey. Nurses' Professional Values scale and Minnesota Job Satisfaction Questionnaire were used to collect the data.

Results: It was found that the pediatric nurses had high professional values and that job satisfaction scores were moderate. It was further noted that pediatric nurses who were single, received their education in a nursing high school, had professional experience of 11-15 years in pediatric clinics, were working as clinical responsible nurse, and were working during the day shift regularly had higher scores of professional values. It was found that the job satisfaction of the pediatric nurses who were married, received their education in a nursing high school, had professional experience of 11-15 years in pediatric clinics, were working as clinical responsible nurse, and were working at day shift regularly, was significantly higher than the others. The results also indicated a positive and high correlation between pediatric nurses' perception of professional values and job satisfaction levels.

Conclusion: It was concluded that promoting professional values among nurses would eventually result in increasing levels of job satisfaction. We believe this study provides substantial data in this particular field in Turkey and it is hoped that it may be used to guide nursing managers to design well-established and unbiased programs for pediatric nurses.

Keywords: Pediatric nursing, professional values, job satisfaction, cross-sectional study

Introduction

Today, globalization, migration, nursing scarcity, new diseases, the aging population, and high quality care are complex issues that result in ethical problems for nurses (1,2). For this reason, it is expected that nurses should be aware of professional values and use them in decision making processes while dealing with ethical problems (2,3). Professional values are standard guidelines, directions for professional actions, and clinical decision-making (4).

Contemporary nurses are expected to pay attention to professional values and reflect such values in their care practices (5-7). The results of several studies have shown that professional values enable nurses to assess care quality sensitively and enhance their care performances

Address for Correspondence
Ayla Kaya PhD, Akdeniz University Faculty of Nursing, Department of Pediatric Nursing, Antalya, Turkey
Phone: +90 536 321 00 29 E-mail: aylakayaakdeniz@gmail.com ORCID: orcid.org/0000-0002-0281-0299
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(3,8-10). Therefore, it is extremely important to enhance professional values among nurses in order to improve and professionalize nursing practices (10). When nurses raise awareness of professional values, they can successfully transfer these values into their professional practices, which eventually results in enhanced patient care and increased job satisfaction (11-13).

Job satisfaction is characterized by the rapport between professional expectations and gains and this primarily signifies the professional attitudes, beliefs, knowledge, emotions, behaviors, and judgements of employees (14,15). Job satisfaction is important in a nurse's work life (15). Nurses constitute the majority of human resources in medical care with 24-hour medical service. As nurses spend most of their days in their workplaces, job dissatisfaction will absolutely lead to life dissatisfaction in turn. In this case, physical, mental and social well-being might be impaired in the long-term. Consequently, nurses may experience job dissatisfaction and Burnout syndrome that manifests itself as distraction from their professional responsibilities, intentions to leave the profession, and high turnover rates (12,16). It has been recently revealed that nurses with high levels of job satisfaction report more positive feelings and professional attitudes (14,15,17).

Pediatric nurses support children by addressing important issues and dealing with their problems. In addition to meeting the child's needs, nurses communicate and collaborate with families and also fight with them. Pediatric nurses are responsible for enabling and facilitating ethical decision making in both children and their parents (9) as well as providing counseling and support to children and their parents to promote and maintain their health (1). Pediatric nursing is a special field of nursing that focuses on providing medical care particularly for children and their parents from infancy to late adolescence (3,18,19). Especially pediatric nurses may be at higher risk due to the fact that children are usually seen as helpless and vulnerable (17). The major concerns that may affect job satisfaction in pediatric nurses are the difficult work conditions and the relatively more intensive care needed for pediatric patients (20). Therefore, pediatric nurses should raise awareness concerning professional values in order to ensure developed nursing practices, quality nursing care, professionalization, and enhanced job satisfaction. Studies to date have examined mainly nurses working with adult patients and their professional values and job satisfaction (11,12,15).

It has been widely determined that the perception of professional values and job satisfaction play a great role in the professional careers of nurses. It has also been reported that developing professional values significantly improves the care satisfaction of patients and job satisfaction of nurses, enhances care quality and decreases the intent to leave the profession (11,12). Although recent studies have suggested a correlation among the concepts such as job satisfaction, professional values, and care quality, there is still a need for evidence-based studies to elaborate these correlations. This study also was conducted to pave the way for further studies by providing comprehensive data in this field. It is essential for nurses to integrate professional values into their professional practices in order to ensure professionalization and enhanced job satisfaction (11,12). However, professional values of pediatric nurses had not been thoroughly investigated to date. The aim of this study, therefore, was to provide data and pave the way for future studies and focus on perceptions of professional values and job satisfaction levels of pediatric nurses in particular and their influencing factors.

Materials and Methods

Research Design

This study was conducted with a cross-sectional design.

Participants and Setting

The study was conducted with 134 pediatric nurses working in three public hospitals in Turkey. All pediatric nurses (Total=175) in the city were included in the study. Therefore, no sampling method was used. Some nurses said that they were too busy and so did not want to participate in the study. The response rate was 93.7%.

Data Collection

The data were collected between February 2016 and August 2016. Before the data collection, the participants were informed about the aim of the study. Given that their participation in the study would be voluntary, their written consents were obtained. The researchers distributed and collected the data forms on the same day. There was no time limitation for the participants to complete the forms.

Data Collection Tools

The personal information form, the Nursing Professional Values scale (NPVS), and the Minnesota Satisfaction Questionnaire (MSQ) were administered. The personal information form included questions about the descriptive characteristics of the participants such as age, gender, marital status, and their number of children as well as their educational status, current position at work, duration

of service in the pediatric unit, and their shift work. The NPVS was used to analyze the professional values of the pediatric nurses. Developed by Weis and Schank (21), the NPVS is a five-point Likert scale with five subscales. In 2005, Orak adapted the scale into Turkish and conducted its reliability and validity testing (22). The scale has a total of 36 items and five subscales, namely dignity, responsibility, taking action, security and autonomy (22). The arithmetic mean was used to evaluate the total scores of the scale. An average score above 3.5 indicates high professional values. Higher scores signify that pediatric nurses place a great emphasis on professional values. The Cronbach's Alpha coefficient of the scale was found to be 0.95 (22). In the present study, the Cronbach's Alpha coefficient of the scale was found to be 0.92. The MSQ was used to assess job satisfaction levels of the pediatric nurses. Its original version with three subscales was developed by Weiss, Dawis and England (23). The reliability and validity study of the Turkish version of the questionnaire was conducted by Baycan (24). The Cronbach's alpha coefficient of the questionnaire was found to be 0.77. The total score of the scale and subscales were evaluated using the arithmetic mean. An average score above 3.5 indicates high job satisfaction. Sabancioguları and Dogan (15) reported that the Cronbach's Alpha coefficient of the questionnaire was 0.90 (15). In the present study, the Cronbach's alpha coefficient of the scale was 0.88.

Statistical Analysis

The data were analyzed using the Statistical Program, version SPSS 23.0. The demographic characteristics of the pediatric nurses in the study were assessed. Professional values and job satisfaction scales were tested for reliability with Cronbach's Alpha coefficient. The data analysis was conducted with frequency, percentage distribution, arithmetic mean, analysis of variance, t-test, Tukey test, and Pearson correlation analysis. The analysis of the results was predicated on the basis of a significance level of 0.05. Ethical principals were followed in the study.

Ethical Considerations

Ethical approval for this study was given by Akdeniz University Clinical Trials Ethics Committee (approval number: 70904504-23). The participants were informed about the study. Written permission from the hospitals and written consent from the participants were obtained.

Results

The results of the study revealed that the average age of the pediatric nurses was 32±0.77 years (min=18 max=51), the average duration of working in the professional service was 15±1.44 years (min=2, max=32), and the average duration of working as pediatric nurse was 7±1.36 years (min=1, max=18). It was also found that 97.8% of the participants were female and 45.5% were aged between 26-36 years. While 73.1% of the participants were married, 38.1% had no child. It was also reported that 71.6% of the participants received education in a nursing high school. 87.3% of the participants were clinical nurses, 75.4% had been working as a pediatric nurse for 10 years or less, and 59% were working in day and night shifts.

It was concluded that the professional values scores of the pediatric nurses were high; whereas, the job satisfaction scores were at moderate levels. Table 1 shows the NPVS and MSQ scores of the pediatric nurses. Table 2 shows the factors influencing the professional values and job satisfaction levels of the pediatric nurses.

The results also indicated a positive and high correlation between pediatric nurses' perception of professional values and their job satisfaction levels (Table 3).

Discussion

As a result of the study, it was found that the pediatric nurses perceived their professional values as high. This was satisfying in terms of reflecting the professionalism of the pediatric nurses. In a limited number of studies conducted with pediatric nurses, it was determined that the professional values scores of the nurses were high (3,9,25). Professional values are important in the development of nursing care quality (3,8-10). In addition, pediatric nurses

Table I. Mean Scores of Nursing Professional Values Scale and Minnesota Satisfaction Questionnare (n=134)

Scales	Mean	SD	Min	Max
NPVS				
Total score	3.87	0.58	2.47	5.00
Dignity	3.99	0.64	2.27	5.00
Responsibility	3.89	0.89	2.44	5.00
Taking action	3.94	0.94	2.38	5.00
Security	4.10	0.64	2.50	5.00
Autonomy	4.08	0.75	1.75	5.00
MSQ				
Overall satisfaction	3.40	0.71	1.60	5.00
Internal satisfaction	3.53	0.53	1.58	5.00
External satisfaction	3.20	0.78	1.38	5.00

NPVS: Nursing Professional Values scale, MSQ: Minnesota Satisfaction Questionnaire, SD: Standart Deviation, Min: Minimum, Max: Maximum

are responsible for supporting the families of the patients in many cases (1,9). Pediatric nurses can provide effective care by being aware of the needs of the children and their families as well as the means of optimum healthcare services and opportunities of families under all circumstances. Children are different from adults in terms of biological, psychological, and social aspects and they are also more vulnerable than adults in terms of exposure to violations of rights. Ethical issues caused by all of these main differences in pediatric nursing have brought new discussions into the open (26). At this point, it is important for pediatric nurses to perceive professional values as high in order to make correct decisions. Therefore, it is thought that pediatric nurses perceive professional values as high, reflect them in practices and implement them in order to protect and promote the child's health. In the present study, the job satisfaction level of the pediatric nurses was found to be moderate. According to studies in different countries, job satisfaction levels of nurses are moderate (12,13,20,27). In a limited number of studies conducted with pediatric nurses, it was determined that their job satisfaction scores were moderate (14,17,28). Our results are compatible with the literature.

Table II. Factors influencing the professional values and job satisfaction levels of pediatric nurses (n=134)

Descriptive characteristics	n	%	NPVS X ± SD	MSQ X ± SD
Marital status				
Married	98	73.1	3.65±0.51	3.69±0.39
Single	36	26.9	3.91±0.58	3.33±0.69
			p=0.01	p=0.04
Educational level				
Vocational high school of nursing	12	9.0	3.75±0.54	3.39±0.71
Vocational college	14	10.4	3.78±0.70	3.25±0.79
BSN	96	71.6	4.20±0.16	3.54±0.68
MSN	12	9.0	3.87±0.57	3.14±0.93
			p=0.01	p=0.02
Total service as pediatric nurse (years)				
≤10	81	60.4	3.71±0.57	3.34±0.73
11-15	36	26.9	4.06±0.64	3.59±0.79
≥16	17	12.7	3.56±0.63	3.50±3.64
			p=0.01	p=0.03
Position at work				
Clinical nurse	117	87.3	3.86±0.60	3.54±0.72
Chief nurse	17	12.7	4.08±0.29	3.39±0.72
			p=0.02	p=0.04
Work type				
Daytime	48	35.8	3.98±0.58	3.62±0.64
Night	7	5.2	3.77±0.41	3.50±0.62
Shift	79	59.0	3.72±0.60	3.31±0.75
			p=0.01	p=0.04

p<0.05, SD: Standart deviation, NPVS: Nursing Professional Values scale, MSQ: Minnesota satisfaction questionnaire

Table III. Nursing Professional Values Scale, Minnesota Satisfaction Questionnaire (n=134)

		NPVS
MSQ	r	0.831
	p	0.01

p<0.05, NPVS: Nursing Professional Values scale, MSQ: Minnesota satisfaction questionnaire

The pediatric nurses who were single, had a bachelor's degree, had been working in child nursing for 11-15 years, were in the position of clinical nurse specialist and working on the daytime shift had higher professional value scores. There are different statuses for nursing education in Turkey. Pediatric nurses with 4 years of university education may be considered to have higher professional values than others. In the study conducted by Yazıcıoğlu Sorucuoğlu and Güdücü Tüfekci (3) with 224 pediatric nurses, they stated that the professional values of those nurses who were single and nursing nurses were significantly higher (3). In another study conducted with pediatric nurses, professional value scores of post-graduate and day shift nurses were found to be high (25). The results of the present study are partially consistent with the literature. Those pediatric nurses who were married, had a bachelor's degree, had been working in child nursing for 11-15 years, in the position of clinical nurse specialist and working on the daytime shift had higher a job satisfaction level. In studies on the job satisfaction levels of pediatric nurses (14), job satisfaction levels of nurses who were working continuously in daytime work and were graduates (27) were higher than others.

The fact that nurses strive to provide quality care to patients, look out for them, advocate for them, and support them to make conscious decisions can be achieved only with an adoption of professional values and high job satisfaction (13,29). The results of this study also suggested a positive and moderately significant correlation between the perception of professional values and job satisfaction. In the study conducted by Yarbrough et al. (11), they found that attempts to improve the professional values of nurses

resulted in enhanced job satisfaction. Similarly, it was reported that there was a positive significant correlation between professional values and job satisfaction in nurses (12). This result was compatible with the results of previous studies. It can be reasonably suggested that raising awareness concerning professional values will improve the job satisfaction of nurses.

Study Limitations

The present study has several limitations. One of the limitations is that the data were obtained only from three public hospitals in Antalya, Turkey. Future studies with larger sample groups are needed in Turkey. Another limitation of this study is that the majority of the participants were female. For this reason, the results of this study cannot be generalized to mixed gender groups.

Conclusion

The mean scores of the professional values of the pediatric nurses were high and their job satisfaction scores were moderate. Marital status, education level, working duration in pediatric nursing, working position, and shift were related to the professional values of pediatric nurses and their job satisfaction. It was found that there was a positive and moderate correlation between the perception of professional values and job satisfaction in pediatric nurses.

In the light of the results of this study, it is recommended that the professional values and job satisfaction of pediatric nurses are improved. Additionally, it is considered to be crucial to implement new strategies to maintain professional values in order to increase job satisfaction levels. Nevertheless, there is still an urgent need to conduct further studies investigating the professional values of pediatric nurses. It is also suggested that the factors that influence the professional values of pediatric nurses are analyzed, and thus the professional values of pediatric nurses are improved. Further studies are needed to validate the results of this study and to evaluate the possible impacts of interventions to enhance professional values and job satisfaction. It is recommended that educational and promotional programs are designed to enhance the pediatric nurses' perceptions concerning professional values.

The results of this study will be valuable for nursing managers of pediatric units to understand current levels of professional values and job satisfaction. These have significant implications for policy makers in re-examining aspects of management and nursing practice. These findings can guide pediatric nursing managers to highlight the importance of awareness on professional values among pediatric nurses as caregivers with high job satisfaction. Nursing managers play an important role in the formation of safe working environments and the enhancement of job satisfaction due to their tasks and responsibilities as well as their authorizations. This study, therefore, is thought to provide substantial data in this field in Turkey and to guide the Ministry of Health, nursing managers, hospital management, and non-governmental organizations to design well-established and unbiased programs for pediatric nurses. Finally, it is recommended that similar studies with pediatric nurses in different medical settings are conducted so that nursing managers can evaluate the validity of the test results.

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Ethics

Ethics Committee Approval: Ethical approval for this study was given by Akdeniz University Clinical Trials Ethics Committee (approval number: 70904504-23).

Informed Consent: Written permission from the hospitals and written consent from the participants were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.K., D.Ç., A.İ.D., Design: A.K., D.Ç., Data Collection or Processing: A.K., D.Ç., Analysis or Interpretation: A.K., A.İ.D., Literature Search: A.K., D.Ç., Writing: A.K., D.Ç., A.İ.D.

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Original Article

Mortality Rate and Causes of Death in Children Aged 1-59 Months in Northeastern Iran During 2011-2017

Mehdi Safarpour[1], Amir Tiyuri[2], Parvin Mohamadzade[3], Maryam Dadjoo[3], Seyed Ahmad Hashemy[3], Masume Mohamadzade[4], Ehsan Shahrestanaki[5]

[1]Iran University of Medical Sciences, Faculty of Public Health, Department of Epidemiology, Tehran, Iran
[2]Student Research Committee, Iran University of Medical Sciences, Tehran, Iran
[3]Health Deputy, North Khorasan University of Medical Sciences, Bojnurd, Iran
[4]Health Deputy, Babol University of Medical Sciences, Babol, Iran
[5]Tehran University of Medical Sciences, Faculty of Public Health, Department of Epidemiology and Biostatistics, Tehran, Iranw

ABSTRACT

Aim: The mortality rate indicator for children is one of the important indicators of population health and socioeconomic development of countries. In addition, to reduce the mortality in children, it is essential to determine causes of death. This study aims to determine the mortality causes in children aged 1-59 months in Northeastern Iran.

Materials and Methods: This population-based cross-sectional study was conducted based on data from the child mortality surveillance system, from March 2011 to March 2017. The mortality rate was evaluated according to demographic variables (sex, place of residence and mother's education). Causes of death were coded according to the International Classification of Diseases. Chi-square and Mann-Whitney U tests were applied to investigate the relationships.

Results: The mortality rate in children aged 1-59 months was 8.2 per 1,000 live births (CI 95%: 7.6-8.8) from 2011 to 2017. Totally 53.2% of mortalities occurred in boys (p=0.07). The frequency of death in the age group of 1-11 months was 1.7 times more than the age group of 12-59 months. The highest mortality rates occurred in rural areas and among children with illiterate mothers. During the study period, on average, the mortality rate decreased by 0.7 per 1,000 live births every year. The most common causes of death were unintentional accidents (33.8%) and congenital or chromosomal abnormalities (22.1%).

Conclusion: Improving maternal education is among the key strategies for reducing child mortality. Therefore, it is necessary to raise the level of education and awareness regarding childhood mortality, especially in rural areas.

Keywords: Children, mortality rate, causes of death, maternal education, Iran

Introduction

The mortality rate for children has received more attention as an indicator of population health and a country's development especially in the last decade (1). This issue holds great importance which has led to the Millennium Development Goals (MDGs) aim to reduce child mortality with a target of reducing under-five mortality rates by two thirds over the period 1990-2015 (2). The child

Address for Correspondence
Masume Mohamadzade MD, Babol University of Medical Sciences, Health Deputy, Babol, Iran
Phone: +989155847626 E-mail: masume_mohamadzade@yahoo.com ORCID: orcid.org/0000-0002-4911-2017
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mortality rate in communities has been decreased due to economic and social developments and carrying out effective interventions (3). According to the World Health Organization (WHO), substantial global progress has been made in reducing child deaths since 1990. Worldwide, the number of under-5 deaths declined from 12.5 million in 1990 to 5.6 million in 2016. In other words, 35,000 deaths per day in 1990 compared with 15,000 in 2016. During these years, the under-5 mortality rate dropped by 56% worldwide, in other words, 93 deaths per 1,000 live births in 1990 to 41 in 2016 (4). According to the results of the global burden of disease study, lower respiratory infections (20.1%), diarrheal diseases (17.4%), malaria (11.8%), other no communicable diseases (8.1%), and nutritional deficiencies (6.7%), were reported to be the most important causes of death in children aged 1-11 months. Furthermore, malaria (20.8%), lower respiratory infections (12.4%), diarrhea (11.9%), chronic non-communicable diseases (9.9%) and nutritional disorders (7.2%) were the most prevalent causes of death among children aged 1-4 years old (5). According to the WHO, more than half of these early child deaths are due to conditions that could be prevented or treated with access to simple, affordable interventions. Strengthening health systems to provide such interventions to all children will save many young lives (4). The results of a variety of studies in Iran indicate that the under-five mortality rate has decreased in recent years (6,7). Given that reducing the mortality rate of this age group has been consistent with international goals as a national and academic priority, and due to the lack of data in this regard, this study was conducted to determine the mortality rate and causes of death in children aged 1-59 months in North Khorasan province, northeastern Iran, from March 2011 to March 2017.

Materials and Methods

In this population-based cross-sectional study, we considered all actual and recorded deaths through the child mortality surveillance system, from March 2011 to March 2017, to investigate the mortality rate and causes of death in children aged 1-59 months in North Khorasan Province, Located in Northeastern Iran, which had a population of 863,092 according to the 2016 national census. This province covers an area of 28,434 square kilometers and contains 8 counties with Bojnurd as its provincial capital. Due to the importance given to the registering of child mortality in the health care system of Iran, all deaths should be reported and reviewed by the child death committee. Therefore, the database of child deaths in the health department is a comprehensive and valid source. Iranian nationality and residence in North Khorasan province were the eligibility criteria, in contrast, inadequate and misleading information were considered as exclusion criteria (however, there were no missed cases). In this study, we performed a secondary analysis of the data collected by the health department of North Khorasan University of Medical Sciences. These data were obtained from the health department de-identified and without the confidential information of individuals. Therefore, informed parental consent was not obtained due to the design of this study.

The data needed for this study including gender, age, place of residence, mother's education and cause of death were extracted from the standard checklist of the Children's Health Department of the Ministry of Health in the health department of North Khorasan University of Medical Sciences. This checklist investigates the history of each child death since the beginning of the first signs of risk to death and includes four sections: an overview of family health status, outpatient medical measures, hospitalized medical measures and a specialized checklist examines the cause of the death of each child aged 1 to 59 months, which is completed by a Pediatrician after reviewing the previous checklists. The process of recording and reporting a child's mortality is as follow: when the death has occurred in the hospital, the main criterion for the leading cause of death in hospitals is under the supervision of the death committee, but when the death is reported by a physician at a health center in cases where death occurred outside the hospital, reports were examined by relevant experts at the health department and causes of death were coded according to the International Classification of Diseases. The mortality rate was estimated in each year as deaths which occurred in the age group of 1-59 months per 1,000 live births. To report the results, the frequency was used to describe qualitative variables and the mean and 95% CI for quantitative variables. Pie charts are used to display the causes of death in each age group (1-11 months and 12-59 months).

Statistically Analysis

The frequency of mortality is represented in a table according to demographic variables. Chi-square and Mann-Whitney U tests were applied to examine the relationship between qualitative variables and comparison of median age at death. The statistical significance level was set at less than 0.05. Additionally, the mortality trend was also investigated using linear regression, which was the line gradient considered as the average of the changes in mortality during the period.

Table I. Distribution of deaths by demographic characteristics				
Age groups (months)				
Variable	**1-11**	**12-59**	**1-59**	**p**
Gender n (%)				
Male	256 (52.0)	158 (55.2)	414 (53.2)	0.07
Female	236 (48.0)	128 (44.8)	364 (46.8)	
Place of residence n (%)				
Urban	149 (30.3)	82 (28.7)	231(29.7)	<0.001
Rural	343 (69.7)	204 (71.3)	547 (70.3)	
Mother's education n (%)				
Illiterate	159 (32.3)	88 (30.8)	247 (31.7)	
Elementary	134 (27.2)	97 (34.0)	231(29.7)	<0.001
Secondary	106 (21.5)	48 (16.7)	154 (19.8)	
High school	73 (14.8)	42 (14.6)	115 (14.8)	
Academic	20 (4.2)	11 (3.9)	31 (4.0)	

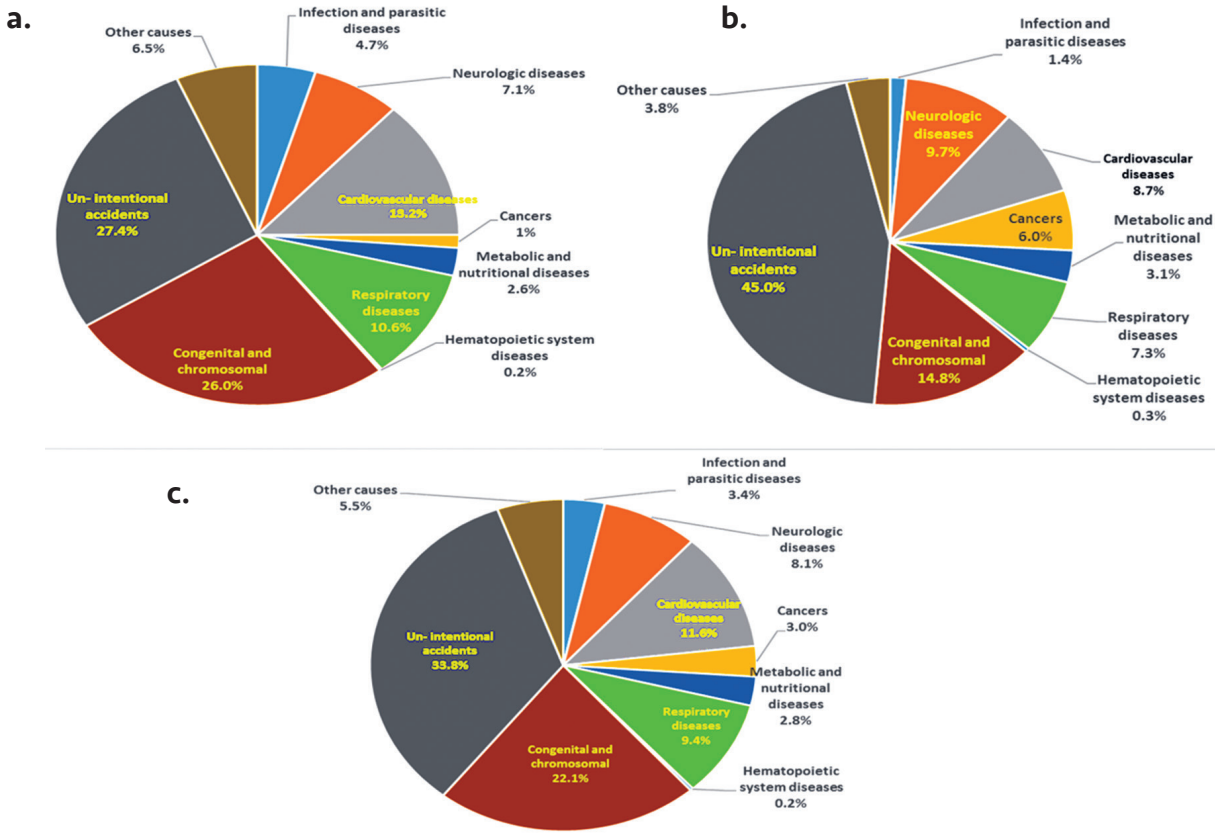

Figure 1. a) Distribution of deaths among children age 1-11 months, by cause. b) Distribution of deaths among children age 12-59 months, by cause. c) Distribution of deaths among children aged 1-59 months, by cause

Results

According to the table I, 778 deaths were recorded in children aged 1-59 months and that 414 (53.2%) of them occurred in boys and 364 (46.8%) in girls (p=0.07). Totally, 63.2% of deaths (492 cases) occurred in the age group of 1-11 months. In other words, the mortality rate in the age

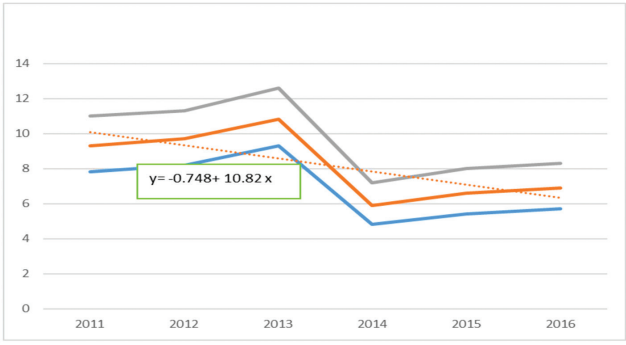

Figure 2. Trend of mortality rate with confidence interval 95% children 1-59 months in the study period

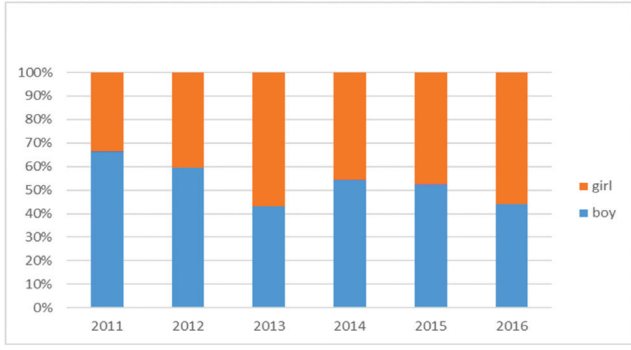

Figure 3. Frequency of deaths among children aged 1-59 months by gender in the study period

group of less than one year (1-11 months) was 1.7 times more than the age group of 12-59 months. The median age at death for boys and girls was 7 months (Interquartile: 16.0) and 6 months (Interquartile: 14.3) respectively (p=0.8). The childhood mortality in the rural areas (547 cases) was 2.3 times more than in urban areas (p<0.001). This significant difference was observed in both age groups and death cases in rural areas in the age groups of 1-11 and 12-59 months was 2.3 and 2.4 times more than urban areas respectively. The mortality rate of children with illiterate mothers was higher than children with mothers with elementary and academic education (p<0.001). In addition, 31.7% of mothers were illiterate and 81.3% of them lived in rural areas. Regarding the records of 94,501 new birth cases during the study period, totally, the mean annual mortality rate for children was estimated to be 8.2 per 1,000 live births (95% CI: 7.6-8.8). Figure 1 show the causes of death in age groups. Unintentional accidents, congenital and chromosomal abnormalities, cardiovascular diseases, respiratory diseases, and nervous system diseases are noted as the top five leading causes of death in the age group of 1-11 months. The top five leading causes of death in the age group of 12-59 months were unintentional accidents, congenital and chromosomal abnormalities, nervous system diseases, cardiovascular diseases, and respiratory diseases respectively. Also, in the top ten causes of death, the median of age of death was lower than 12 months except for cancers and hematopoiesis system diseases.

Figure 2 indicates the mortality rate from 2011 to 2017; the highest and lowest mortality rates occurred during 2013 and 2014, with 10.8 and 5.9 deaths per 1,000 live births, respectively. From 2011 to 2017, the mortality rate declined in the age group of 1-59 months, from 9.3 deaths per 1,000 live births in 2011 to 6.9 in 2017. Figure 3 shows that the frequency of deaths for boys was higher than for girls in the study period, except in 2013 and 2016.

Discussion

The findings of the present study suggests that child mortality in rural area was higher than urban areas. In contrast, according to a study of Izadi et al.(8) in Kermanshah province, child mortality was higher in urban areas. Also, according to the results of the present study, unintentional accidents were the leading cause of death in children aged 1-59 months, whereas Rahbar et al. (7) in their study reported that the most common cause of mortality were the congenital and chromosomal abnormalities in Iran.

With the end of the era of the MDGs, the international community agreed on a new framework, the sustainable development goals (SDGs). The SDGs target for child mortality represents a renewed commitment to the world's children: with an end date of 2030, all countries aim to reduce neonatal mortality to at least as low as 12 deaths per 1,000 live births and under-five mortality to at least as low as 25 deaths per 1,000 live births for preventable mortality (9). In the last few decades, childhood mortality rates have decreased in most countries (10). Despite the significant improvements made in reducing child mortality, child survival remains an urgent concern. In spite of the availability of interventions to preserve life, it is unacceptable that 15,000 children die from preventable and treatable diseases every day. Furthermore, according to the 6th development plan of the Islamic Republic of Iran, by 2021, the aim is to reduce the mortality rate of children under five years to at least as low as 11.3 deaths per 1,000 live births, while this rate was 15.1 according to the latest report of the Ministry of Health in 2017 (11). The results of the present study showed that there was a decline in the trend of mortality in children aged 1-59 months in the North Khorasan province, which is consistent with the results of other studies in other provinces of Iran (8,12,13). Although the results of the study indicated that there is a relative success in achieving the SDGs, unfortunately, the death rate of children aged 1-59 in

this province is higher than the national average (5.1 deaths per 1,000 live births) and the second lowest rank belongs to this province after Sistan and Baluchestan province (11). Soori et al. (6) compared the rates and causes of under-five mortality in Iran with the Eastern Mediterranean region and the world. Between 1990 and 2012, the under-five mortality rate in Iran dropped from 56 deaths per 1,000 live births to 18 deaths per 1,000 live births, and so ranked 11th among the 21 Eastern Mediterranean countries.

Based on the results, the death rate reached its highest level (10.8 deaths per 1,000 live births) in 2013. Under further scrutiny, it was found that the main contributing cause was due to the increase in central nervous system diseases and opioid poisoning along with traffic accidents compared to the previous year. In contrast, this rate unexpectedly dropped by 46% in the next year (5.8 deaths per 1,000 live births). This decline perhaps was due to low reporting or a lack of sufficient sensitivity of the health system in recording deaths due to shifting and relocation of experts on children's programs at health centers and health department. As well as this, the reduction may be actual and attributable to the effect of the rapid interventions by the health system such as increasing awareness, improvements in the care system and so on, which should be specifically investigated in other studies.

According to the study of Frey and Field (14), improvements in socioeconomics, education, housing, nutrition, health care, and sanitation have contributed to reducing childhood mortality. According to the results, a major part of the deaths occurred in rural areas, which is consistent with the results of previous studies (7,15). Koffi et al. (16) in their study entitled the social determinants of mortality among children aged 1-59 months reported that three quarters of deaths occurred in rural areas. Based on another study in Iran (17), the mortality for children in rural areas was higher than in urban areas. Unequal income distribution and facilities between the rural and urban areas which may affect mortality in children through a number of factors including low maternal education, malnutrition in both the mother and child, a lack of proper access to health services and facilities especially during pregnancy and the low quality of medical services particularly infant medical care can account for the difference between these two areas (18). In addition, the results of the present study showed that the educational level of mothers in rural areas was lower than in urban areas. Evidence suggests that girls with minimal primary education when they reach adulthood, compared to illiterate girls, are likely to better manage their desired family size based on their capacity and there is a strong probability that they provide better care for their children (19). The distribution of mother's educational levels among deceased children in the present study showed that more than three quarters of deaths were found in children of mothers who were illiterate mothers or only had elementary education, which is consistent with the results of other studies (7,15,17). It has been proven by several studies that maternal education plays an important role in increasing health awareness, adopting appropriate fertility behaviors, the better use of health services related to pregnancy, child nutrition, and health and medical care (20,21). Similar to the results of other studies, the frequency of deaths in boys was higher than in girls in our study (8,15-17). According to some previous studies, gender differences in child mortality are due to complex interactions of biological, genetic, social, and environmental factors (22,23). However, the causes of gender differences in childhood mortality can be explained by two biological and environmental mechanisms. According to the biological perspective, higher rates of mortality in boys can be attributed to their poor biological structure (22) that was confirmed by a report from the United Nations (23) on the existence of some biological factors favorable to female survival compared to males. Girls are less vulnerable to perinatal conditions, such as intrauterine injuries, intrauterine hypoxia, choking, prematurity, Respiratory Distress syndrome, intestinal and lower respiratory tract infections compared to boys. In the environmental factors approach, there is the emphasis on modifiable external factors that affect under-five morbidity and mortality, including mother and infant feeding, gender preference, infant care, breastfeeding, environmental health threats at home and socioeconomic levels (24). In our study, five factors including unintentional accidents, congenital and chromosomal anomalies, cardiovascular diseases, respiratory diseases, and neurological diseases have been noted as the leading causes of death in children aged 1 to 59 months. In addition, more than two-thirds of the deaths were also attributable to the three leading causes of death, and that the contribution of unintentional accidents was 50 percent. Unintentional accidents and congenital and chromosomal anomalies were the main causes of death in both age groups (7). However, according to the 2017 report from the United Nation Inter-agency Group for Child Mortality Estimation, the leading causes of death in this age group were malaria, diarrhea, injury, pneumonia and others (9). In other studies in Iran, similar to the results of the present study, congenital and chromosomal anomalies and unintentional accidents were reported as the leading causes of death in this age group. The low

mortality rate due to infectious diseases in comparison with some studies reflects the relative success of children's infectious disease prevention programs. Furthermore, since non-communicable diseases became the leading cause of death in children aged 1 to 59 months, it seems that a variety of interventions and strategies are needed to reduce the mortality rate in these children.

Study Limitations

Despite being population-based and having full coverage of the deaths as the strengths of the present study, our study has several limitations worth noting: the inability to access other variables that affect child death, such as birth weight, birth order, maternal age, pregnancy status, pre and postnatal care and environmental factors including the family's socioeconomic status. Other limitations of this study were due to its retrospective design and the use of secondary data that can affect the data quality as incorrect records may cause misclassification or the low quality of recorded data may lead to classification bias. A further limitation and a potential source of bias in our study was the change in the population of urban and rural areas due to changes in country divisions that made it difficult to calculate the death rate. In addition, the shifting and relocation of experts on children's programs at health centers and health departments is one of the sources of bias that may have affected the quality of data.

Conclusion

Considering the causes of death among children is very important for the development of health plans, the assessment of ongoing programs and monitoring and prioritizing interventions. Improving maternal education is among the key strategies for reducing childhood mortality. Therefore, it is necessary to raise the level of education and awareness regarding childhood mortality, especially in rural areas.

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Ethics

Ethics Committee Approval: In this study, we performed a secondary analysis of the data collected by the health department of North Khorasan University of Medical Sciences. These data were obtained from the health department de-identified and without the confidential information of individuals.

Informed Consent: Informed parental consent was not obtained due to the design of this study.

Peer-review: Externally peer-reviewed

Authorship Contributions

Concept: M.S., A.T., M.D., E.S., Design: M.S., A.T., P.M., M.M., Data Collection or Processing: P.M., M.D., S.A.H., M.M., Analysis or Interpretation: A.T., E.S., Literature Search: M.S., S.A.H., M.M., Writing: M.S., P.M., M.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

The Effectiveness of Heated Humidified High-flow Nasal Cannula in Children with Severe Bacterial Pneumonia in the Emergency Department

Ali Yurtseven[1], Eylem Ulaş Saz[1]

[1]Ege University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey

ABSTRACT

Aim: The provision of appropriate respiratory support has a great role in outcome of patients presenting to the emergency department (ED) with respiratory distress (RD) associated with severe pneumonia. In recent years, heated humidified high-flow nasal cannula (HHHFNC) therapy has become one of the most popular non-invasive respiratory support modalities in all pediatric settings. In this study, we aimed to assess whether the use of HHHFNC therapy is associated with reduced RD and improvements in hypoxemia among children with severe bacterial pneumonia (SBP) presenting to the ED.

Materials and Methods: We performed a prospective observational study of patients with SBP admitted to a tertiary children's hospital pediatric ED who received HHHFNC therapy within the 2 year study period. The primary outcome was accepted as treatment failure (It was defined as a clinical escalation in respiratory status) and an increase in peripheral capillary oxygen saturation (SpO_2). Secondary outcomes covered a decrease of respiratory rate (RR), heart rate (HR), and rates of weaning, intubation and intensive care unit (ICU) admission.

Results: Fifty-six patients were included in this analyses. Treatment failure was 21.5% (12/56). Among these patients, 9 (16%) were intubated and 3 (5.5%) placed on bilevel positive airway pressure. The mean initial RR values were significantly higher in the non responders group than the responder group (p=0.027). Significant variation in the intubation rate or the ICU admission rate was not determined. At the 2nd hour, the fall in RR (p<0.001), HR (p<0.001), and the increase of SpO_2 (p<0.001) were significantly evident when compared with the beginning.

Conclusion: HHHFNC therapy reached treatment success in a majority of the patients with SBP and provided an early effect. Patients with higher RRs responded less to HHHFNC. Further larger studies are needed to assess the impact of HHHFNC compared with other possible therapies.

Keywords: Pediatric emergency department, hypoxia, oxygenation, pneumonia, high-flow nasal cannula

Introduction

Severe bacterial pneumonia (SBP) is a common life-threatening disease for the pediatric population, and is more common in infants and young children (1). Respiratory distress (RD) due to SBP, which is one of the most common reasons for emergency department (ED) presentations, causes millions of hospital admissions and hundreds of thousands of deaths every year worldwide (1-3). In the 1980s, the World Health Organization (WHO) developed a case management strategy aiming to reduce deaths from pneumonia (4). While it suggests that in severe pneumonia cases, the cornerstones of management are antibiotic and supportive therapy, the most important basis for the

Address for Correspondence
Ali Yurtseven MD, Ege University Faculty of Medicine, Department of Pediatrics, İzmir, Turkey
Phone: +90 505 205 21 44 E-mail: aliyurtseven1605@gmail.com ORCID: orcid.org/0000-0002-8302-0204
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management strategy was hypoxemia which is common and potentially associated with increased risk of death (4-7). Early detection of hypoxemia, and administration of oxygen therapy also improves the outcome of children with SBP (7). The most effective way to treat hypoxemia is oxygen supplementation (6). There have been various oxygen treatment options for a long time but these may be insufficient. Heated humidified high-flow nasal cannula (HHHFNC) therapy has recently started to become an alternative oxygen giving method for the treatment of acute RD due to pneumonia (7).

HHHFNC can be set up quickly and is a reliable non-invasive respiratory support therapy method (8). Even though HHHFNC delivers high flow oxygen, owing to humidification and heating it doesn't damage the respiratory mucosa (9). HHHFNC also creates a positive-end expiratory pressure (8,9).

HHHFNC oxygen treatment, which has been reported to be more effective than standard oxygen, decreases the rate of intubation/invasive ventilation in severe pneumonia (10-12). Although it probably has some helpful effects, there is limited evidence on using this treatment option in patients with pneumonia (8,9).

There are already a few studies which evaluate the treatment success of HHHFNC for children with SBP with almost all of them being conducted in the intensive care unit (ICU) (13,14). The goal of this prospective clinical study was to determine whether the use of HHHFNC therapy is associated with a reduction in severity among children with SBP presenting to the ED.

Materials and Methods

This study was done as a prospective observational study in a pediatric ED. The study period was between May 2017 and April 2019. The ED is a tertiary-care teaching center and approximately 80,000 patients are admitted annually. The local Institutional Review Boards approved the study, and we obtained written informed consent for each patient. We maintained patient confidentiality during all processes of the study.

The diagnosis and the severity of pneumonia were made based on the Pediatric Infectious Diseases Society clinical practice guideline (15). All patients who were included in the study had fever or fever history, tachypnea, alveolar infiltration or consolidation on chest X-ray and high serum biomarkers values (procalcitonin level >0.25 ng/mL and/or C-reactive protein level >40 mg/L and/or absolute neutrophil count >10,000/mm^3) supporting bacterial infection (16-18). Patients who were diagnosed with bacterial pneumonia, aged between 0-18 years and having at least one of clinical features of severe pneumonia [1- Moderate to severe RD (RR >70 breaths/minute for infants, RR >50 breaths/minute for older children, moderate/severe suprasternal, intercostal, or subcostal retractions (<12 months), severe difficulty breathing (≥12 months), grunting, nasal flaring, apnea, significant shortness of breath) 2- Cyanosis 3- Altered mental status 4- Hypoxemia (sustained oxygen saturation <90 percent in room air at sea level) 5- Not feeding (infants) or signs of dehydration (older children) 6- Capillary refill ≥2 seconds) with temperature ≥38.5°C and tachycardia were included in this study.] Patients who were intubated and/or admitted to the ICU on arrival at the ED; patients who had PCO_2 (venous) greater than 55 prior to HHHFNC initiation; patients who presented with severe septic shock; and patients who were complicated with pneumothorax or nasal trauma were excluded.

Pediatric emergency medicine specialists examined the patients for acute life-threatening conditions caused by pneumonia after the triage assessment. Following this stage, a nurse monitored vital signs [SpO_2, blood pressure, RR, heart rate (HR)], achieved vascular access, and obtained venous blood gas. After obtaining parental consent and confirmation of eligibility for study inclusion, HHHFNC therapy was initiated. Initially, a flow rate of 10 kg 2-L/kg/min and thereafter a flow rate of 0.5 L/kg/min for every kilogram was delivered via nasal cannula. The total flow range was arranged as 6-50 L/min. FiO_2 was adjusted to a minimum value to ensure SpO_2 within a range of 94-99% and the humidifier was auto-set at 37°C. Optiflow of Fisher & Paykel Healthcare Auckland, New Zealand which is a heated and humidified HHHFNC delivery system was used. The optiflow junior nasal cannula (neonatal, infant and pediatric size) and the optiflow nasal cannula (adult size) which provides up to 50 L/min flow rate were utilized on all participants. All children also received standard management for bacterial pneumonia, including parental antibiotics and supportive care treatment. In addition, if necessary, patients were given therapy for comorbidities.

After HHHFNC initiation, the nurse and ED physician recorded hourly the clinical parameters (RR, HR and SpO_2). Achievement of all of the following criteria was accepted as weaning criteria. The criteria were: decreased RR (for infants ≤2 months <60 bpm, 2-12 months <50 bpm, 1-5 years <40 bpm and >5 years <20 bpm); absence of dyspnea including accessory muscle use, retractions, nasal flaring, and grunting; SpO_2 reached ≥90% with FiO_2 <30%; no confusion. If severe RD and/or SpO_2 <90% with FiO_2 > 50%

continued, ICU admission was required. HHHFNC therapy was continued in patients who had HHFNC failure or insufficient response, until their transfer to the ICU. If needed, intubation was performed at any stage of observation. The protocol continued for at least 24 hours and all stages of treatment [requirement of another modality of non-invasive ventilation (NIV), invasive ventilation, weaning, restart of HHHFNC therapy] were observed.

If one or more of the following criteria within 24 hours of initiation HHHFNC therapy were observed, it was considered as treatment failure. These criteria were; SpO_2 <90% continued even if FiO_2 >50%; persistent tachypnea (patients aged 0-12 months with RR >70 bpm and for >12 months >50 bpm); development of hypoventilation; PCO_2 sustained over 50 mmHg. Patients who had treatment failure received bilevel positive airway pressure (BiPAP) or intubation. The primary outcome was defined as treatment failure within 24 hours after HHHFNC initiation and recovery in SpO_2 (after two hours of the treatment). It was reported that the highest risk of failure is within the first 24 hours of the therapy and the expected potential benefits of HHHFNC therapy are improvement in RR and HR, achievement of weaning and the avoidance of intubation or ICU admission (9,19). Additionally, secondary outcomes were reduction of RR and HR, a rise of SpO_2 and the rate of weaning after two hours of the treatment; rates of intubation and ICU admission within the first 24 hours.

The investigators trained the ED nurses and physicians about HHHFNC therapy before starting the study. This study was approved by Ethics Board of Ege University (approval number: 17-4/6).

Statistical Analysis

SPSS for Windows (ver. 22.0 SPSS Inc., IL, USA) was used for all analyses. Wilcoxon's test was performed to compare the changes in SpO_2, RR, HR, and the rate of weaning. Student's t-test, chi-squared and Mann-Whitney U test were used to analyze the differences of the baseline characteristics of responder and non-responder groups (age, sex, admitted season, comorbidity, the initial values of SpO2, RR, HR, PCO_2, PO_2, and pH) as appropriate. A two-tailed probability value (p) of less than 0.05 was accepted as significant.

Results

During the study period, 92 patients presented to the ED with a diagnosis of SBP and 56 of them (61%) were assessed as eligible for the final analysis (Figure 1). The mean age was 45.3±41.2 (2-168) months, and 55.4% (n=31) were male. In the study group, 30 (53%) patients had chronic illnesses; 11 (20%) neuromuscular diseases, 8 (14%) chronic lung diseases, 5 (9%) chronic cardiac disease, 4 (7%) immunodeficiency, 1 (2%) malignancy and 1 (2%) malnutrition. The mean initial RR values of the non-responder group were significantly higher than the responder group (p=0.027). The other baseline characteristics of the responder group were similar to non-responder group (Table 1).

Among the 12 (21.4%) patients with treatment failure, 9 (16%) were intubated. BiPAP was successfully used to treat the remaining 3 patients. A total of 12 (21.5%) patients were admitted to the ICU. There was no statistical difference between patients who had chronic illnesses and others in terms of intubation rate, ICU admission rate and treatment failure.

At the second hour of the therapy, 21 (37.5%) patients received the weaning protocol, HHHFNC therapy continued in 23 patients (41%). The reductions in RR (p<0.001), and in HR (p<0.001), and the increase in SpO_2 (p<0.001) were significantly higher at the second hour of evaluation when compared with the baseline (Table 2).

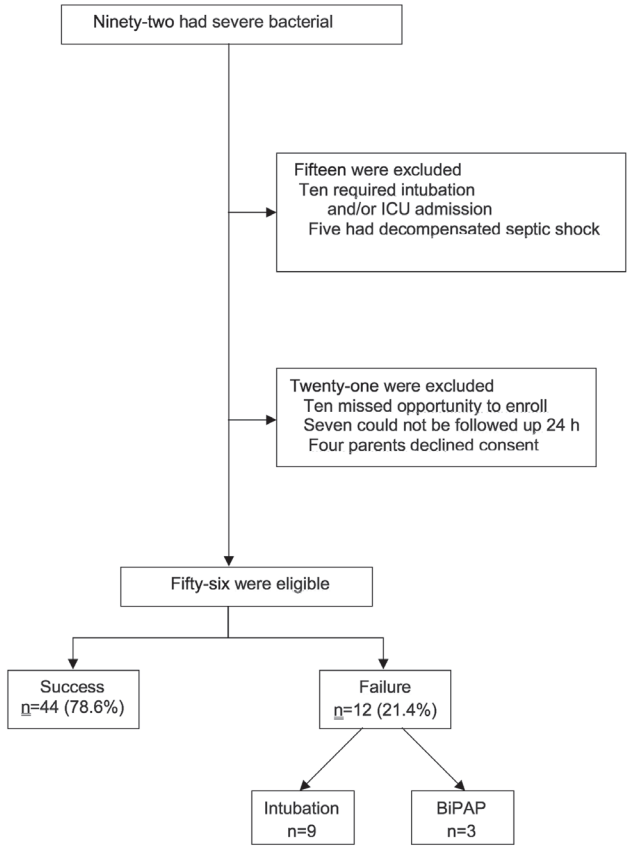

Figure 1. Flowchart of the study population and the primary outcomes

Table I. Comparison of patient characteristics at admission between responder and non-responder groups

	Responder group (HFNC therapy success) (n=44)	Non-responder group (HFNC therapy failure) (n=12)	Total (n=56)	p
Sex				
Male (%)	24 (54.5)	7 (58.3)	31 (55.3)	0.540
Mean age (months) (± SD)	45.7 (20)	43.7 (26)	45.3 (21)	0.878
Prematurity (<37 weeks)	9 (20.4)	3 (25)	12 (21.4)	0.707
Chronic illnesses	23 (52)	7 (58)	30 (53)	0.755
Admitted season				
Winter	22 (50)	4 (33)	26 (46)	0.451
Spring	9 (20)	4 (33)	13 (23)	
Autumn	7 (16)	1 (9)	8 (14)	
Summer	6 (14)	3 (35)	9 (16)	
Initial respiratory rate (breath/min)	59.7 (10.4) (40-80)	67.2 (9.1) (46-82)	61.3 (10.5) (40-82)	0.027
Initial heart rate (beat/min)	157.8 (21.9) (106-208)	157.1 (18.1) (135-211)	157.6 (21.1) (106-211)	0.918
Initial SpO_2ł (%)	91.3 (3.8) (75-100)	91 (3.6) (72-100)	91.2 (3.8) (72-100)	0.836
Initial venous PCO_2‡ (mmHg)	42.3 (7.5) (29-54)	43.2 (6.3) (33-54)	42.5 (7.5) (29-54)	0.707
Initial venous PO_2† (mmHg)	59.5 (14.4) (25-85)	56.7 (17.5) (33-87)	57.5 (15.5) (25-87)	0.622
Initial venous pH	7.35 (0.1) (7.21-7.52)	7.36 (0.1) (7.22-7.50)	7.35 (0.1) (7.21-7.51)	0.525

SD: Standard deviation, HFNC: High-flow nasal cannula, PCO‡: Partial carbon dioxide, PO†: Partial oxygen, łPeripheral capillary oxygen saturation

Table II. Secondary outcomes in the study cohort

	Initial values	At the 2nd hour of HFNC therapy	p	Mean difference
Reduction in RR‡	61.3 (10.5)	50.6 (11.8)	<0.001	-10.7 (-7.9, -13.5)
Reduction in HR†	157.6 (21.1)	141.4 (24.2)	<0.001	-16.2 (-11, -21.4)
Rise in SpO_2*	91.2 (3.8)	96.4 (4.3)	<0.001	5.2 (2.2-8.2)

Ranges in parentheses are SDSs, Values are mean, HFNC: High-flow nasal cannula, ‡Respiratory rate (breath/min), †Heart rate (beat/min), *Peripheral capillary oxygen saturation

No patient died and therapy-related side effects such as pressure injuries or pneumothorax had not developed within 24 hours.

Discussion

In this prospective observational study, we investigated the effectiveness of HHHFNC therapy and affecting factors in children with RD due to SBP in a tertiary care academic pediatric ED. The results of our study have shown that HHHFNC is a safe and effective form of noninvasive respiratory support method for patients with SBP. HHHFNC therapy was significantly efficient for RR, HR and SpO_2 at the second hour of the therapy, while treatment success was achieved in 78.5 % of patients. Therapy failure was more common in patients with a higher respiratory rate.

Although appropriate antibiotics and supportive care treatment are indispensable for children with pneumonia, it is stated that hypoxemia is one of the most important risk factors for mortality and morbidity in these patients (6,20). As shown in meta-analysis, hypoxemia, which is defined with a cut-off for SpO_2 below 90%, is associated

with significantly increased odds of death from acute lower respiratory infections (odds ratio: 5.47, 95%, confidence interval: 3.93 to 7.63) in children (21). Previously published data indicates that delays in diagnosis or management of hypoxemia due to pneumonia may be the main cause of these high rates in low-income countries (22,23). As expected NIV methods such as HHHFNC use are limited in these countries (23). Since our results indicate early and significant improvement in hypoxemia due to pneumonia, we can conclude that good outcomes are associated with HHFNC use. If HHFNC were used in low-income countries, death and disability could be prevented (24).

In recent years, HHHFNC has been preferred commonly for children with bronchiolitis/pneumonia/asthma in many pediatric departments around the world (9,25). However, there are still limited studies which have been conducted in the ED setting on the use of HHHFNC as a respiratory support method for children with pneumonia (8,9). Although the majority of patients included in these studies were infants with acute bronchiolitis, it has been reported that HHHFNC is also effective in children with pneumonia (10-12). In a unique, randomized controlled study, only including children with severe pneumonia, conducted in the ICU, comparing HHHFNC with nasal continuous positive airway pressure (nCPAP), Chisti et al. (24), have determined that there was no difference in treatment failure and intubation rate between an nCPAP group and HHHFNC group. In another study, Er et al. (26) evaluated 64 children aged 0-18 years with bacterial pneumonia receiving HHHFNC in an ED and found that the therapy success rate was 80%. Our findings are similar to the results of these studies.

It is very important to predict the determining factors of HHHFNC therapy failure in children with RD (13,14). That will enable us to identify patients who will not respond, and thus other treatment options will not be delayed. In our study group, non-responders had a higher respiratory rate at the beginning than responders which is consistent with previous studies (12,27). This may be a reason why HHFNC should not be selected in children with more severe RD.

Early response to HHHFNC is essential when treating a patient with RD and it also can be used as predictor for the main outcomes. A decline in HR and RR have been commonly considered as early signs of a good response to HHHFNC (10,28). Davison et al. (29) found that the surrogate markers (HR and RR) of RD decreased significantly after the first hour of HHHFNC treatment. Similarly, we found that there was a manifest improvement in RR and HR from the initial values to the second hour of therapy.

Since it has been reported that HFNC reduced the rate of intubation and ICU admission in children with RD, it has become increasingly popular in all pediatric settings (25). Our findings showed that the intubation rate for the present cohort was 16%. In a large study conducted with children with RD in an ED, Wing et al. (11), showed that there was an 83% reduction in the likelihood of intubation in patients receiving HFNC compared with patients who did not get HHFNC. A prospective pilot study has shown that PICU admission is four times less likely in children receiving HHFNC than the standard treatment group (30). In the study by Chisti et al. (24), a total of 79 patients with severe pneumonia were treated with HHHFNC and it was found that among these patients the rate of intubation was 13%.

Study Limitations

We have some limitations in this study. First, the findings of this study may not be generalizable to other settings because it was a single center study and had an insufficient number of cases. Second, since the study was performed in an ED, we thought 24-hour follow-up was enough. However, because of this decision, we may have lost some data. Third, due to time limitations, we could not evaluate possible confounding variables such as antibiotics, supportive care and so on. Lastly, the study was not a comparative study, hence the efficacy of HFNC therapy versus other treatment options could not be interpreted.

Conclusion

This study showed that HHHFNC therapy was clinically effective and well tolerated and led to an early impact on patients with SBP in an ED. Treatment failure was higher in patients with a higher respiratory rate. Multicenter, randomized controlled large studies are needed to confirm efficacy of this therapy more accurately for children with pneumonia.

Ethics

Ethics Committee Approval: This study was approved by Ethics Board of Ege University (approval number: 17-4/6).

Informed Consent: All of the parents of the patients gave their informed consent prior to their child's inclusion in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: A.Y., E.U.S., Concept: A.Y., E.U.S., Design: A.Y., E.U.S., Data Collection or Processing: A.Y., E.U.S., Analysis or Interpretation: A.Y., E.U.S., Literature Search: A.Y., E.U.S., Writing: A.Y., E.U.S.

Conflict of Interest: None of the authors had conflict of interest.

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Original Article

Open Globe Injury in Children

Sevinç Şahin Atik

Katip Çelebi University Atatürk Training and Research Hospital, Clinic of Opthalmology, İzmir, Turkey

ABSTRACT

Aim: To evaluate retrospectively the epidemiologic data and outcomes of pediatric open globe injury (OGI).

Materials and Methods: The medical records of all pediatric cases (<16 years old) diagnosed with OGI in İzmir Katip Çelebi University Atatürk Teaching and Research Hospital, Clinic of Ophthalmology between January 2009 and December 2018 were screened. Age, sex, history, cause of trauma, treatment received, visual acuity (VA) at presentation, and final VA were recorded.

Results: A total of 48 patients were included in this study. The mean age at the time of injury was 10.72±4.74 years, ranging from 1 to 16 years. Game-related accidents were the most common cause of all pediatric OGI patients with a frequency of 58.3% (n=28). Of the OGIs 56.3% (n=27) were in zone I, followed by zone II (39.5%; n=19), and zone III (4.2%; n=2). Patients with vitreous hemorrhage or retinal detachment at admission were found to have a higher risk of poor prognosis. The principal predictor for a good visual outcome was found to be initial best-corrected VA over 20/200.

Conclusion: To predict the prognosis in the best way, every patient with OGI should be carefully evaluated both at the time of admission and during the follow-up period.

Keywords: Children, open globe injury, trauma, visual acuity

Introduction

Open globe injury (OGI) is defined as the complete laceration of the cornea or sclera, depending on trauma or other condition. It is one of the main causes of preventable monocular blindness in childhood. Despite the many important developments in ophthalmic surgery, the complete visual recovery after an OGI is almost impossible and OGIs often cause permanent visual loss. In underdeveloped and developing countries, the incidence of OGI in children is higher (1,2).

In this study, we aim to evaluate the visual outcome of OGI in pediatric cases and to analyze the epidemiologic data retrospectively.

Materials and Methods

After obtaining informed consent from patients and their families, the medical records of all patients aged 16 years or younger at the time of injury diagnosed with OGI in İzmir Katip Çelebi University Atatürk Teaching and Research Hospital, Clinic of Ophthalmology between January 2009 and December 2018 were retrospectively analyzed.

Demographic features including age, gender, cause and place of injury, date of injury, and eyes involved, were evaluated based on the clinical records. Initial visual acuity (VA), zone of injury, clinical signs, and associated features (hyphemia, lens injury, endophthalmitis, retinal detachment, laceration of eyelid/eyebrow, and vitreous hemorrhage) were recorded. Management, follow-up data including need for

Address for Correspondence
Sevinç Şahin Atik MD, Katip Çelebi University Atatürk Training and Research Hospital, Clinic of Opthalmology, İzmir, Turkey
Phone: +90 505 261 78 22 E-mail: drsevincsahin@yahoo.com ORCID: orcid.org/0000-0003-2566-8691
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additional surgery, and the final VA were noted.

The zone of injury was defined by the location of the globe opening: zone I injuries were confined to the cornea and limbus, zone II involved the anterior 5 mm of the sclera, and zone III injuries involved full-thickness scleral defects >5 mm posterior to the limbus. Initial and final VAs were classified as no light perception, light perception, hand motion, 1/200-19/200, 20/200-20/50, and ≥20/40. According to the differences between initial and final VAs, the patients were grouped into those with or without improvement in VA.

Statistical Analysis

Statistical analysis was performed on IBM Statistical Package for Social Sciences (SPSS) software (version 22, SPSS, Inc, Chicago, IL, USA). Continuous and categorical variables were displayed as mean ± standard deviation and percentages, respectively. The student's t-test was used to assess the differences between means. Differences between categorical variables were analyzed by chi-square test and the analysis of variance for continuous variables. P values <0.05 were considered to be statistically significant.

Results

A total of 48 patients, diagnosed with OGI, were included in the study. The mean age at the time of injury was 10.72±4.74 years, ranging from 1 to 16 years. This was 10.57±4.73 years for boys and 11.15±4.95 years for girls. Thirty-five of the cases were male (72.9%). Of the patients with OGI, 18 (37.5%) involved the right eye, and 30 (62.5%) involved the left eye.

Game-related accidents were the most common causes of all pediatric OGI patients with a frequency of 58.3% (n=28). Injuries resulted from home accidents in 18.7% (n=9), traffic accidents in 8.3% (n=4), work accidents in 6.2% (n=3), fighting in 6.2% (n=3) and falls in 2% (n=1). Of all cases, 91.6% (n=44) were admitted to our hospital within the first 24 hours of injury. Of the OGIs, 56.3% (n=27) were in zone I, followed by zone II (39.5%; n=19), and zone III (4.2%; n=2). Injuries were most often caused by glass (29.2%; n=14), wood (18.8%; n=9), pencils (8.3%; n=4), and knives (6,3%; n=3).

Hyphemia and iris prolapses were the most common signs on admission (58.3%, n=28 and 58.3%, n=28, respectively), followed by vitreous hemorrhage (25%; n=12), laceration on eyelid and/or eyebrow (16.7%; n=8), and retinal detachment (10.4%; n=5).

The mean follow-up time of the patients (n=48) was 232.37 days (median: 90 days; min 1- max 1.710 days). Traumatic cataract was noted in 39.6% (n=19) of cases during the follow-up period. No intraocular foreign bodies were detected in our cohort. In 3 eyes (6.3%), phthisis bulbi was noted. Nine patients (18.7%) required an additional operation after the primary repair.

The initial and final best-corrected visual acuity (BCVA) could be measured in 46 of 48 patients. The association between initial BCVA and final visual outcome is shown in Table 1. Patients with vitreous hemorrhage or retinal detachment at admission were found to have a higher risk of poor prognosis (Table 1).

Discussion

Disintegrity of the eye globe after a trauma is known as OGI. Rapid diagnosis and referral to a specialist for OGI is essential to improve the prognosis of the affected eye. This is also important for the pediatric age group. The overall incidence of OGI has been reported to be 2.8 to 3.9 per 100,000 (1,3-5). There are a few studies that report the incidence of pediatric OGIs in the literature. Batur et al. (1) reported that the annual incidence rates of OGI in the pediatric population was 5.16 per 100,000.

The incidence of OGIs in pediatric ages is generally reported to range from 6.6 years to 11.6 years. In our study, it was found to be 10.72 years. There was no statistically significant difference in mean age between girls and boys. In the literature, it was reported that boys were more susceptible to OGI than girls (1). The ratio of boys to girls with OGI ranges from 1.66:1 to 5.25:1. In accordance with this data, 72.9% of the cases were male in this study and the ratio of boys to girls was 2.69:1.

It was also reported that game-related accidents were the most common cause of pediatric OGIs. Consistent with the literature, in 58.3% of cases, game-related accidents were found to be responsible for the OGI in our study (6-9). The most common causative objects of the injuries were glass and pencil in this study. Both objects causing OGIs cumulatively accounted for 48% of all cases. Although some previous studies have reported similar results about causative objects (8), many of them have determined that knives and scissors were responsible for most cases (6,10,11).

The results of the studies regarding which eye is more commonly affected in OGIs suggests that pediatric OGI affects both eyes at similar rates (1,7,8,12,13). In our study, we showed only a slight difference between the right and left eyes. The left eye was more commonly affected than the right eye.

Table I. The association between initial best-corrected visual acuity and final visual outcome; and visual outcome in patients with various ocular findings

<20/200		**Final visual outcome**		
			≥20/200	**p**
Initial VA	<20/200 (n=15)	11	4	<0.001
	≥20/200 (n=32)	4	28	
Ocular findings		**No improvement in VA (n=15)**	**Improvement in VA (n=32)**	**p**
Iris prolapses	Yes	8	20	0.751
	No	7	12	
Hyphemia	Yes	9	19	1.000
	No	6	13	
Traumatic cataract	Yes	8	10	0.201
	No	7	22	
Vitreous hemorrhage	Yes	8	4	0.009
	No	7	28	
Retinal detachment	Yes	5	0	0.002
	No	10	32	
Laceration on eyelid and/or eyebrow	Yes	5	3	0.056
	No	10	29	
Zone of injury	I	6	20	0.056
	II	7	12	
	III	2	0	

VA: Visual acuity

Despite significant advances in microsurgery, pediatric OGI continues to cause visual morbidity. After an OGI, 30.4% of pediatric cases in this study were found to have a poor visual outcome. The main goal of this study was to define the factors that determine the final VA in pediatric patients with OGIs. The effects of all parameters evaluated in this study on prognosis were statistically analyzed. The principal predictor for a good visual outcome was found to be initial BCVA over 20/200. Vitreous hemorrhage and retinal detachment were also predictors of a poor visual outcome (Table 1). Lesniak et al. (6) reported that the presenting VA is the best predictor of final vision, which is consistent with our study.

In 2002, Kuhn et al. (14) developed an Ocular Trauma score (OTS). They suggested that final VA could be predicted using clinical features such as initial VA, the presence of globe rupture or perforating injury, endophthalmitis, retinal detachment, and/or relative afferent pupillary defect. However, Pediatric OTS was then developed because it was difficult to evaluate the afferent pupil defect in children (15). As one of the limitations of our study, we did not calculate OTS in our cohort.

In conclusion, here we report some clinical features and their indicating potential on visual outcome after an OGI in pediatric patients. To predict the prognosis most effectively, every patient with OGI should be carefully evaluated both at the time of admission and during the follow-up period. Appropriate safety measures and adult supervision may be recommended to reduce the incidence of ocular trauma in children.

Ethics

Ethics Committee Approval: Ethics committee approval was received.

Inform Consent: Retrospective stıudy.

Peer-review: Externally peer-reviewed.

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Original Article

Occurrence of Unexpected Adverse Reactions to Vaccines in Children with Mastocytosis

Hanna Abuhay, Alicia S. Clark, Melody C. Carter

A Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

ABSTRACT

Aim: Children with cutaneous or systemic mastocytosis may experience severe manifestations of mast cell mediator release including anaphylaxis. The perceived risk for adverse vaccine reactions creates concern among parents and pediatricians regarding modification of the routine vaccine schedule for safety.

Materials and Methods: Using the National Institutes of Health (NIH) Biomedical Translational Research Information System and Clinical Research Information System, we conducted a retrospective chart review of 94 children ≤18 years of age, evaluated at NIH with mastocytosis. Based on the recommended childhood immunization schedule, we estimated that these 94 patients received approximately 2,136 vaccinations. Post vaccination reactions were determined as expected or unexpected according to the centers for disease control (CDC) parameters for vaccine-associated events.

Results: Eighty-four patients (89.4%) had no reports of moderate-severe post-vaccination reactions. Eleven reactions after vaccination were reported in 10 of 94 patients (10.6%), of which four patients had unexpected reactions (4.3%). Unexpected reactions included facial swelling, flushing and exacerbation of skin lesions which are not reported as possible vaccine reactions by the CDC. One patient was treated for anaphylaxis 2 hours post-varicella vaccine administration. Five patients with a history of anaphylaxis and a mean tryptase level of 115 ng/mL did not report vaccine-induced reactions.

Conclusion: Children with mastocytosis in this study did not experience a higher rate of adverse vaccine reactions compared to the general population. Anaphylaxis to other causes was not a risk factor for an untoward vaccine response. In patients that experience a severe post-vaccination reaction such as anaphylaxis, a modified schedule with single vaccine administration is a safer approach.

Keywords: Pediatrics, mastocytosis, vaccines

Introduction

Mastocytosis is a disease of many variants characterized by abnormal aggregates of mast cells in tissues, most commonly the skin, bone marrow, liver, spleen, and lymph nodes (1). The clinical manifestations of disease include flushing, urticaria, pruritus, diarrhea, and abdominal pain (2). Disease onset may occur both in the pediatric and adult populations, with varying prognoses. Mastocytosis is classified into cutaneous and systemic mastocytosis (SM) based on the presence of mast cell infiltrates in the skin and/or extracutaneous organs, respectively. The serum tryptase value is usually a reflection of total mast cell burden and can range from normal (<11.4 ng/mL to significangly elevated in cutaneous and systemic disease. SM, which is commonly seen in adult-onset mastocytosis, may also present in the pediatric age group (1). Cutaneous

Address for Correspondence
Melody C. Carter, A Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD
Phone: 240-476-0872 E-mail: mcarter@niaid.nih.gov ORCID: orcid.org/0000-0003-0379-5366
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mastocytosis is most common in pediatric onset mastocytosis (3). There are three variants of cutaneous mastocytosis: mastocytoma (MTOMA), maculopapular cutaneous mastocytosis (MPCM), and diffuse cutaneous mastocytosis (DCM) (4). Some common non-immunologic triggers of disease symptoms include stress, change in temperature and exercise (2). Vaccines have been reported as possible triggers of symptoms which has created some concerns regarding the vaccination of patients with mastocytosis (5-7).

There have been a limited number of studies exploring the eliciting nature of vaccines resulting in excessive mast cell degranulation in patients with mastocytosis. Anaphylaxis after vaccination in a patient with DCM has been reported (8). There is a recent report of a patient with DCM that experienced blistering and urticaria following the administration of a live viral vaccine, which prompted a recommendation for premedation before live viral vaccines for patients with DCM (9).

In a separate study, there was a report of nine patients with mastocytosis who experienced mast cell activation triggered by vaccines (5). There have also been two reports of the development of a MTOMA at the site of injection (10,11). In another study, the occurrence of an adverse reaction due to the first administration of a hexavalent vaccine was reported in four patients and these included bullous lesions, urticaria and bronchospasm, which was not seen in the comparison control population (6). On this basis, the first administration of a vaccine to a patient with mastocytosis has been recommended to be done under additional clinical supervision (6). Premedication and single component vaccine administration has also been suggested for patients with DCM, as a preventive measure (6,7).

Previous reports of adverse reactions in patients with mastocytosis associated with vaccination did not identify specific components of vaccines responsible for triggering the release of mast cell mediators. With the exception of the hexavalent vaccine in one study, (6) there are no reports of a particular vaccine more commonly associated with adverse reactions in patients with mastocytosis. The rate of post-vaccination reactions in the general population depends on the type of vaccine. Symptoms such as swelling and redness at the site of injection for the diphtheria, tetanus, and pertussis (DTaP), pneumococcal conjugate vaccine (PCV), human papillomavirus (HPV)- Gardasil09, Td, and Tdap vaccines, range from 0.2 to 90% of all children (12).

Our current study examines the occurence of post-vaccination reactions in children with mastocytosis compared to the data available for the general pediatric population. In order to evaluate whether children with mastocytosis exhibit more reactions due to vaccination, we reviewed the relationship between the number, severity and type of reported reactions to vaccines in patients with mastocytosis. In addition, we looked for correlations with onset and variant of the disease, as well as the type of vaccine associated with the reactions.

Materials and Methods

Using the NIH Biomedical Translational Research Information System and the NIH Clinical Research Information System, we conducted a retrospective chart review of 94 children evaluated at NIH from 1984 to 2018 with mastocytosis. The age of the patients when vaccine history was deteremined was ≤18 years of age. Informed consent to participate in the IRB-approved and NIH Ethics-approved protocol (NCT00044122) was obtained from all parents and also children ≥6 years of age. Mastocytosis variant was determined according to the WHO criteria for cutaneous and systemic disease (4). We queried using the search terms "immunizations", "vaccination" and "vaccines".

The total vaccines administered to patients born between 1994 to 2018 obtained from annual visit questionnaire while at NIH, was determined using the centers for disease control (CDC)'s recommended childhood immunization schedule of the patient's date of birth (13). The vaccine count for patients born between 1984 to 1988 and 1989 to 1993 was determined according to the 1984 and 1989 CDC's immunization schedule, respectively. Haemophilus influenzae type b vaccine (HbCV/Hib) was only counted for patients born after 1989. For patients born in 1989, one administration of HbCV was counted. The third administration of Hib administered at six months was counted for patients born in 1994 and patients born after 2007. Hepatitis B was counted for patients born after 1990. The second administration of measles, mumps and rubella (MMR) was counted for patients born after 1994. The third administration of Hib was counted for patients born in 1994 and patients born after 2007. The first administration of the varicella vaccine was counted for patients born after 1996 and the second administration was counted for patients born after 2007. Rotavirus vaccine was counted for patients born in 1999 and patients born after 2007. PCV was counted for patients born after 2001. Hepatitis A was counted for patients born after 2006. The changes made

in CDC's recommended age for administration of specific vaccines between 1984-2018 was taken into account for the vaccine count of patients. Newly added vaccines to the immunization schedule were counted for patients that were of age to receive the vaccine by the time it was administered (Supplemental Figure).

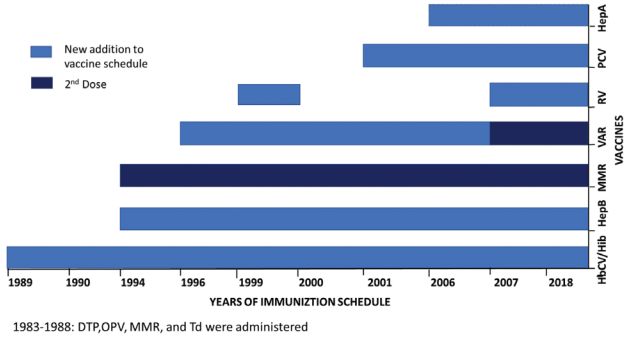
Using the CDC reports, we identified possible side effects to vaccinations based on data from the general population and designated these as expected or as unexpected, the latter of which are reactions not listed in the CDC's report of possible mild or moderate side effects for a given vaccine. Common mild symptoms include fever (100 °F), redness or swelling at the injection site, extended swelling beyond the injection site, fussiness, headache or tiredness. Moderate symptoms are those associated with an interference of usual activities and include fever (102 °F), nausea and vomiting. Based on CDC reports, severe adverse allergic reactions are those that require medical attention such as a serious allergic reaction, can be caused by any medication and are estimated to occur at about 1 in a million and thus, classified as unexpected for our study.

Statistical Analysis

A univariate analysis was used to describe the distribution of mean age in years for each disease group and measure the standard deviation.

Results

Ninety-four patients with macular papular cutaneous mastocytosis (MPCM) (59%), DCM (14%), MTOMA (5%) and indolent systemic mastocytosis (ISM) (22%) were estimated to have received a total of 2136 separate administrations of vaccines. When considering adverse vaccine reactions, overall there was no difference in gender distribution amoung those with mild-severe reactions; and patients with MPCM had fewer reported reactions based on total number of vaccines received (Table I). Eighty-five patients (90%) had the onset of mastocytosis before the age of two years old, of which nine (10%) patients had reported reactions to vaccines (Table IIA). Nine patients had onset of the disease after two years of age, of which one patient (11%) reported a reaction to a vaccination. Twenty-three patients at the time of their annual visit and vaccinaiton questionnaire were less than two years old, 15 patients were between the age of 2-6 years old and 56 patients were between the age of 6-18 years old (Table IIB). According to the current



Supplemental Figure. Changes in CDC Vaccination Schedule 1989-2018
1983-1988: DTP, OPV, MMR, and Td were administered. Six new vaccines, HbCV/Hib, HepB, VAR, RV, PCV, and HepA have been added since 1988. Administration of the RV vaccine was discontinued between 2000 to 2007. A second administration of the MMR and Varicella vaccines was added in 1994 and 2007, respectively.
RV: Rotavirus vaccine, PCV: Pneumococcal conjugate vaccine, MMR: Measles, mumps and rubella, OPV: Oral poliovirus vaccine, CDC: Centers for disease control

Table I. Demographics of pediatric patients with mastocytosis who received vaccination

Variant	MPCM	DCM	MTOMA	ISM	Total
Number of patients	55	13	5	21	94
Gender F/M	28/27	4/9	1/4	8/13	41/53
Current age in years (mean ± SD)	17.13±7.3	11.27±7.4	14.40±7.7	15.54±7.1	15.84±7.3
Number of patients with reported reactions	4	3	1	2	10

MPCM: Maculopapular cutaneous mastocytosis, DCM: Diffuse cutaneous mastocytosis,
MTOMA: Mastocytoma, ISM: Indolent systemic mastocytosis, SD: Standard deviation

Table IIA. Age of onset of mastocytosis

Age of onset	Before 2 years	After 2 years
Number of patients	85	9
Number of patients with reactions	9	1

Table IIB. Vaccine history related to age

Age Group	Birth -2 years	2-6 years	6-18 years
Number of patients	23	15	56
Total Vaccine doses/patient	23	6	1
Total Vaccine types/patient	8*	5†	1‡

Various ages are represented in each age range and not reflective of total vaccines administered. * :DTaP, IPV, Hep A, Hep B, Hib/HbCV, MMR, PCV, VAR; †: Hep A DTap, IPV, MMR, VAR; ‡: Tdap
DTaP: Diphtheria, tetanus, and pertussis, IPV: Inactivated polio vaccine, MMR: Measles, mumps and rubella, VAR

vaccination recommendation, a total of 23 administrations of eight different vaccines are to be given before age 2 years. Between the two groups (2-6 and 6-18 years), a total of seven administrations of six different vaccines are recommended (Table IIB). At the time of data collection, patients through age 6 years (60%) had received 96% of the recommended vaccines and thus the data reflects the majority of possible reported events.

Eighty-four (89.4%) of the 94 patients did not have any moderate-severe reactions to vaccinations. Ten patients were reported to have a total of 11 expected and unexpected reactions associated with vaccination after onset of mastocytosis. The time of occurrence of a post-vaccination reaction was specified for one reaction associated with anaphylaxis. The mastocytosis variant of the six patients with expected reactions included MPCM, DCM, ISM and MTOMA, with tryptase levels ranging from 3.4 -139 ng/mL (data not shown). The four patients that experienced unexpected vaccine reactions had tryptase values ranging from 5.1-62.9 ng/mL (Table III). Thus, the serum tryptase level was not predictive of an adverse reaction in our cohort.

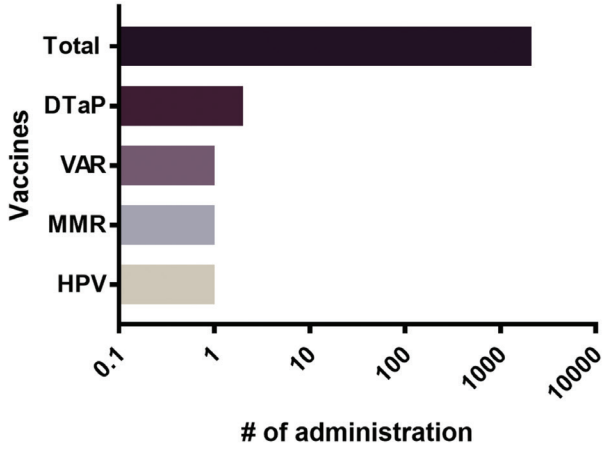


Figure. Total Vaccine administrations and vaccines associated with unexpected reactions (URs)
2136 vaccines were administered to 94 patients (Total bar), of which 4 administrations were associated with URs (remaining bars). In 3 patients with
URs, DTap was associated with one alone; MMR and HPV with DTaP in one and VAR with one. In the fourth patient, the eliciting
vaccine was not identified (data not shown), MMR: Measles, mumps and rubella, HPV: Human papillomavirus, DTaP: Diphtheria, tetanus, and pertussis, VAR:

Four patients (4%) had reactions that were associated with unexpected symptoms including anaphylaxis, urticaria or exacerbation of skin lesions, flushing, facial swelling and GI symptoms beyond the common expected side effects enlisted by the CDC, such as fever, redness and swelling at the site of injection (Table III). Four vaccinations (DTaP, MMR, HPV and Varicella) out of the 2136 (0.18%) administered were reported as responsible for the unexpected reactions (Figure). Patient 1 with MPCM was reported to have experienced flushing, abdominal pain, vomiting, wheezing, dizziness and to have had an anaphylactic episode two hours after receiving the second varicella vaccine. The patient was treated with epinephrine. A second patient (patient 2) with MPCM, experienced eye swelling and flushing with the DTaP vaccine. Similarly, a patient 3 who had ISM experienced facial swelling, flushing and accentuation (swelling) of lesions of MPCM following the administration of HPV, DTaP and MMR. A patient with DCM, patient 4, reported mild flushing and urticaria, but the eliciting vaccine was unknown (Table III). These reactions were unique to patients with mastocytosis and not reported as common adverse reactions in the general population.

There were five other patients with a history of anaphylaxis who did not have any vaccine-induced reactions (Table IV). One of these patients had experienced anaphylaxis

Table III. Clinical data of patients with unexpected reactions to vaccination

Patient	Age of disease onset	Tryptase level (ng/mL)	Variant	Reaction inducing vaccine	Reaction	Treatment
1	Birth	5.1	MCPM	varicella	flushing, abdominal pain, vomiting, wheezing and dizziness (anaphylaxis)	epinephrine
2	5 months	6.1	MCPM	DTaP	eye swelling, flushing	N/A
3	15 years	62.9	ISM	HPV DTaP MMR	facial swelling, flushing and exacerbation of MPCM lesions	N/A
4	Birth	23.4	DCM	N/A	mild flushing and urticaria	N/A

NA-not available; Normal serum tryptase £11.4 ng/mL,
MCPM: Maculopapular cutaneous mastocytosis, ISM: Indolent systemic mastocytosis, DCM: Diffuse cutaneous mastocytosis, DTaP: Diphtheria, tetanus, and pertussis, HPV: Human papillomavirus, MMR, Measles, mumps and rubella

Table IV. Anaphylaxis history

	Number of patients	Trigger	Age at time of episode
Non-vaccine associated anaphylaxis	5	Idiopathic anaphylaxis* Fire Ant†	≥2 years
Vaccine associated anaphylaxis	1	Varicella vaccine	5 years

*: One episode each of idiopathic anaphylaxis in four patients; †: Two episodes of fire ant-induced anaphylaxis in one patient

to fire ant and the remaining four were diagnosed with idiopathic anaphylaxis. Although previous anaphylaxis to a vaccine is reported to be associated with an increased risk of subsequent severe reactions, anaphylaxis to other causes was not associated with the same increase risk in our study.

Discussion

The prevalence of vaccine-induced reactions was not greater in our patients with mastocytosis compared to the general population and the unexpected reactions occurred in 4.2% of our patients. With the exception of anaphylaxis, the unexpected reactions in patients with mastocytosis were illustrative of mast cell-medicated symptoms associated with their primary disease and therefore not reported in the general population. Eighty-nine percent of the patients in this study did not have a history of post-vaccination reactions and only 0.18% of vaccine administrations were associated with unexpected reactions (Figure). Most pediatric vaccines (77%) are administered before the age of two. Since 75% of our patients are in the age group (>age 2 years) that received most of the recommended vaccines, we feel this data is reflective of a low risk for unexpected post-vaccination reactions.

Expected reactions to vaccines are reported in the general population. The mild and moderate symptoms associated with specific vaccines occur at varying prevalence reported as 0.2% to 90% depending on the vaccine (12). Only seven patients (7.4%) in our cohort had reports of symptoms such as fever, localized rash, swelling and redness at site of injection, which are expected reactions identified by the CDC as commonly reported side effects. Thus, the safety profile in our patients with mastocytosis did not suggest an increased risk of severe reactions to vaccines.

Unexpected reactions were reported in four patients (4.2%), of which one patient had a report of second expected reaction as well. Four vaccines, HPV, DTaP, MMR, and Varicella were reported to be associated with these unexpected reactions (Figure). Although the adverse event to the second dose of varicella in patient one was severe enough to require administration of epinephrine, the patient suffered no prolonged or residual side effects and was able to tolerate subsequent vaccines. Anaphylaxis to vaccines reportedly identifies patients as high risk for subsequent vaccinations (14). Vaccine components such as, yeast, egg, gelatin, and latex have been linked to some post-vaccination allergic reactions in the general population (14). Thus, it has been suggested that patients with anaphylaxis to vaccines be evaluated for the responsible allergen as a preventive measure (14). Additionally, the administration of single vaccines has been widely recommended for patients with mastocytosis to include extended post-vaccination medical supervision for 30 minutes to 2 hours (6,14). Based on our experience, we think a post-vaccination observation period, as recommened in previous studies, is a reasonable approach.

Five patients reported episodes of anaphylaxis that were not attributed to any vaccines. These reactions in these patients were noted to have occurred at ≥2 years, after they had received the majority of their vaccines. According to the risk assessment for adverse vaccine reactions published by the European Academy of Allergy and Clinical Immunology (14), patients who have experienced anaphylaxis unrelated to vaccines are not thought to be at higher risk to an adverse vaccine response (14). Our data also supports this observation and these patients do not have to opt out of receiving vaccines.

There was no particular trend with respect to mastocytosis variant or serum tryptase level noted amongst patients with post-vaccination reactions. Patients with extensive cutaneous involvement such as DCM and elevated serum tryptase levels have been reported to be at a higher risk for severe mast cell activation episodes (5). Although patients with DCM represent a smaller number (14%) in our study, the number of reactions was similar to the patients with MPCM (59%) (Table 1). It is, however, important to note that the most severe reaction occurred in a patient who would not have been predicted to be at high risk for severe mast cell activation reactions. This patient has MPCM, a tryptase level of 5.1 ng/mL and no previous adverse reaction to vaccine administration. On the contrary, the five patients with a history of anaphylaxis and a mean tryptase level of 115 ng/mL had no reports of reactions due to vaccines.

Our study limitations are based on limited sample size for the variant, DCM, MTOMA and ISM and thus a quantitative comparison in the number of reactions was not

made between variants as a result. The vaccine responsible for the unexpected reaction in patient 4 was not available in our medical chart. In addition, the temporal association between three of the unexpected reactions and vaccine administration was not precisely identified.

Conclusion

Collectively, our data agrees with the literature and does not indicate patients with mastocytosis to be at an overall greater risk for vaccine-induced reactions. Patients with DCM may be at higher risk for more severe reactions to a variety of triggers including vaccines as noted in several case reports (5,7,9). However, vaccines were not a trigger in several of our patients indicated to be at higher risk for severe mast cell activation episodes. Nonetheless, precaution such as prolonged medical supervision (30 minutes-2 hours) following vaccination should be taken when vaccinating as there are a few reports of patients with unexpected reactions, which can be severe. This is particularly important in patients with a history of a previous expected moderate reaction or an unexpected reaction of any severity.

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Ethics

Ethics Committee Approval: National Institutes of Health Ethics- approved protocol (NCT00044122)

Informed Consent: Informed consent to participate in the IRB-approved protocol (NCT00044122) was obtained from all parents and also children ≥6 years of age.

Peer-review: Externally peer-reviewed.

Authorship Contributionss

Design: A.S.C., H.A., M.C.C., Data Collection or Processing: H.A., Analysis or Interpretation: A.S.C., H.A., M.C.C., Writing: H.A., M.C.C

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

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Erratum

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