



Effects of Enteral Olive Oil Supplement on Weight Gain, Length of Hospital Stay, and the Development of Some Complications in Preterm Infants: A Randomized Controlled Trial

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ABSTRACT

Aim: The objective of the present research was to compare the nutritional status, weight gain, length of hospital stay, and the development of some complications in very low birth-weight (VLBW) infants who received and those who did not receive olive oil supplementation enterally.

Materials and Methods: This study was a single-blind, randomized controlled trial with 96 VLBW infants (intervention: 48, control: 48) in a neonatal intensive care unit. In this study, those infants who met the inclusion criteria for the study were divided into two groups by using a random number table. The same feeding protocol (breast milk and/or formula milk) was applied to the infants in both groups. From the seventh day of life (after starting to take 25-30 mL/kg/day orally), 0.5 cc/30 mL of olive oil was added to the milk at each feeding of those infants in the intervention group.

Results: In comparison with the control group, the infants in the intervention group had a higher daily weight gain rate in the first month and a higher weight on the tenth day, a shorter transition time to full enteral feeding, a higher amount of calories on the day of transition to full enteral feeding, and a shorter length of hospital stay ($p<0.05$). Furthermore, the need for rectal enema and the prevalence of sepsis, gastrointestinal system intolerance, and bronchopulmonary dysplasia were significantly lower in the intervention group in comparison with the control group ($p<0.05$).

Conclusion: These findings suggest that olive oil supplementation administered enterally to preterm infants can be recommended since it positively affects the development of infants. Trial registration: This study was registered in ClinicalTrials.gov with the following ID: NCT05815849. This study was retrospectively registered on the 14th of April, 2023.

Keywords: Preterm infant, olive oil, neonatal intensive unit, nursing care

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Received: 06.11.2023 Accepted: 26.03.2024



Introduction

It is known that nutrition for very low birth-weight (VLBW, <1,500 g) neonates is as crucial as the treatment they receive in the neonatal intensive care unit in order to prevent problems which may develop in the long-term follow-ups and so to increase their quality of life. In order to support optimal growth, VLBW newborns require parenteral nutrition as a source of energy, and lipid emulsion is a crucial component of total parenteral nutrition (1). Due to preterm birth, VLBW neonates have a weakened immune system and antioxidant defense, which makes them susceptible to oxidative stress. Oxidative stress plays a significant role in the development of diseases such as retinopathy of prematurity (ROP), intraventricular hemorrhage, chronic lung disease, and necrotizing enterocolitis (NEC), all of which can increase the risk of morbidity (2,3). Prematurity also causes an insufficient supply of long-chain polyunsaturated fatty acids (LC-PUFAs), including eicosapentaenoic acid and docosahexaenoic acid, most of which are transferred to the fetus during the third trimester of pregnancy (4,5).

Providing parenteral and enteral feeding support in the early stages and maintaining this treatment regularly may allow the continuation of intrauterine growth and development in the extrauterine period (6). Research has shown that the best nutrition for newborns in all circumstances is breast milk. Unsupplemented breast milk can, however, be nutritionally insufficient for premature newborns for a variety of reasons, despite its many advantages. First, the nutritional contents in breast milk can change over time (7-9), and some nutrients needed to support preterm infants' fast growth are not present in sufficient amounts (7). Of these, fat is one of the most variable nutrients (10). When breast milk alone cannot meet these needs, it is recommended that special nutritional supplements in the form of powder or liquid be added to breast milk and given to the infant (11).

Due to its content, olive oil has antioxidant, cell regenerative, and anti-carcinogenic properties which help digestion (12). There are clear pieces of evidence indicating that parenterally administered oil emulsions can be well tolerated by VLBW and even extremely low birth-weight infants from the first day and even from the first 1-2 hours of life (13-15). The objective of the current research was to compare the nutritional status, weight gain, length of hospital stay, and the development of some complications [bronchopulmonary dysplasia (BPD), ROP, gastrointestinal system (GIS) intolerance, etc.] in preterm neonates who

received and those who did not receive olive oil enterally for calorie support.

Materials and Methods

Study Design

The sample of this experimentally designed study consisted of all premature babies (n=387) hospitalized in the Neonatal Care Unit of a hospital in between June, 2020 and March, 2021. The sample consisted of 96 preterm infants (intervention: 48, control: 48).

Sample selection criteria: Preterm infants between the 28th and 36th weeks of gestation at the time of delivery determined by the date of the mothers' last menstruation and obstetric evaluation results, weighing over 1,000 g during the study period, with stable vital signs and being able to consume 75% of the total protein and energy through an orogastric tube, fed with breast milk and breast milk fortifiers, not having any severe neurological condition, not using inotropic, muscle relaxants, sedatives, or analgesics drugs, and having spontaneous respiration were enrolled in this research.

Exclusion criteria: Preterm infants with NEC, pneumothorax, skull fracture, the presence of any major congenital anomalies, suspected or diagnosed metabolic disease, a history of pathological jaundice (jaundice developing in the first 24 hours), hospitalized for less than one month, and having a history of surgery which might affect the residual were not enrolled in this research.

Power analysis was conducted with the G*Power (3.1.9.2) program with the objective of determining the sample size. The effect size (d) was found to be 0.745 by utilizing the mean (28.29 and 20.33) and standard deviations (12.287 and 8.766) acquired from the lengths of hospital stay in the publication titled "A Randomized Controlled Clinical Trial of Olive Oil Added to Human Breast Milk for Weight Gaining in Very Low Birth Weight Infants" (16). Using the formula above, the required minimum sample size was found to be 78 preterm infants, 39 for each group. This study was completed with 96 preterm infants (intervention: 48, control: 48) (Figure 1).

A total of 96 infants forming the study sample were randomly divided in a controlled manner into two groups by their status of receiving or not receiving olive oil supplementation. The urn approach, which is comparable to complete randomization, was used to verify that the groups were randomly assigned (17).

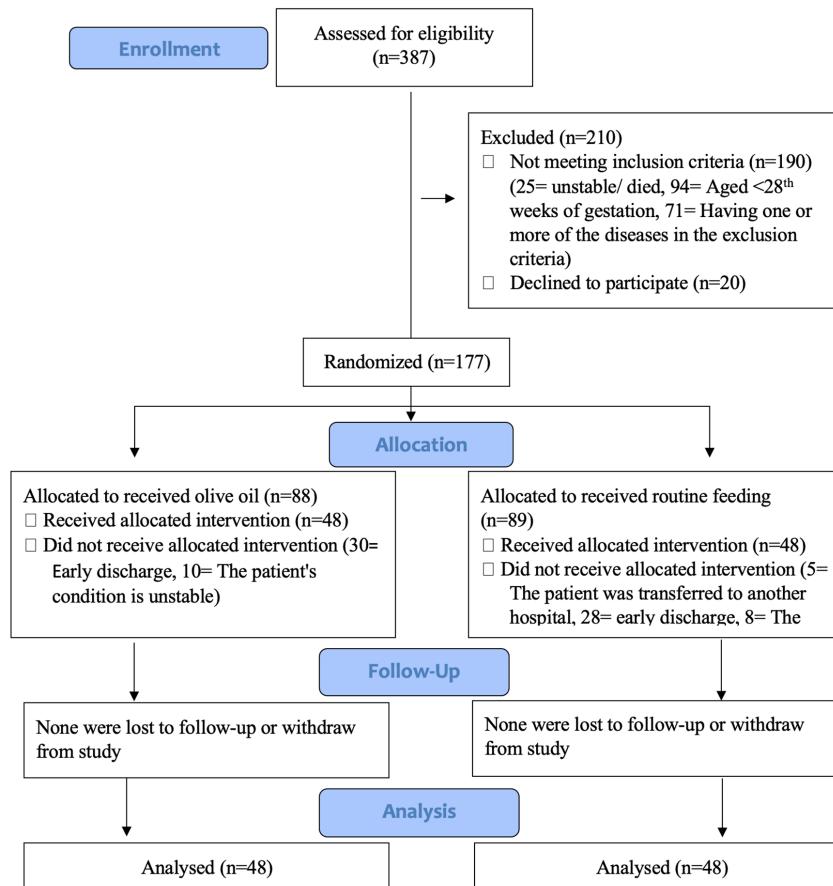


Figure 1. Flow chart of research

Variable Definitions

Demographic and clinical information was obtained from the electronic database of the hospital and patient charts. In sepsis scoring, according to the Turkish Neonatal Society and European Medicines Agency, positivity in at least two of the six clinical categories and at least two of the six laboratory categories was evaluated as clinical sepsis (18). Gastric intolerance (GI) was considered as the inability to digest more than 50% of the enteral nutrition presented as the gastric residual volume, or abdominal distention and vomiting, or both, and accordingly, the patient's nutritional plan being disrupted (6). In the findings of ROP, the ROP Diagnosis and Treatment Guidelines were considered, and it was evaluated as severe ROP in cases of ROP being stage 3 or higher in both eyes or in cases of the infant being treated with laser or anti-vascular endothelial growth factor therapy (19). BPD was graded according to the BPD Prevention and Follow-up Guidelines, and all mild/moderate/severe cases

were enrolled in this research. The jaundice levels of the preterm infants were studied by examining direct bilirubin in the blood. Those infants with a history of pathological jaundice were not included in this research (20).

Data Collection

Mother and infant information form: This form includes descriptive information about the mother and the infant (age, weight, birth mode, sex, diagnosis, etc.).

Infant follow-up form: In the said form, information such as the date on which olive oil supplementation was started enterally, vital signs measured before and after the intervention, and the development of complications in the infant were recorded.

Procedure

- Those families who wished to participate in this study received an informed consent form, which they reviewed and accepted. The data gathering forms were filled out.

- The same feeding protocol (breast milk and/or Low Birth-Weight Infant Milk Formula) was applied to the infants in both groups, and minimal enteral nutrition was started at 15-20 mL/kg/day (21). Prior to the procedure, the breast milk of the preterm babies in both groups was warmed in a regular food warmer and supplemented with eoprotein (one measure of eoprotein to 25 cc of breast milk).
- Approximately from the seventh day after starting to take 25-30 mL/kg/day orally, 0.5 cc/30 mL of olive oil (a brand easily available in the markets) was added to the milk at each feeding of the infants in the intervention group (9,16,22). The preterm infants were fed in this way for at least one week until discharge. The oil used for this purpose was stored in a special glass bottle with a label attached and protected from heat/light to prevent contamination. The olive oil and breast milk mixture was carefully shaken by a staff member previously trained for this project until the mixture turned into microlipids. The target was determined as being 150-160 mL/kg, and if growth was insufficient, it was determined as being 180-200 mL/kg (if tolerated).
- Prior to feeding, the babies in both groups had their vital signs measured (heart rate 100-160 beats per minute, axillary temperature 36.5-37.4 °C, respiration rate <60/min) (23).
- Following the placement of an OG or NG tube for position control, the neonates in both groups were fed while lying supine and had their heads elevated between 30 and 45 degrees.
- The infants' daily weight gain, GI, BPD, and ROP findings were monitored daily until discharge, and jaundice findings were evaluated by considering the bilirubin

levels on the 10th and 15th days and recorded in the infant follow-up form together with the other findings.

Ethical Considerations

The Clinical Studies Ethics Committee of Kahramanmaraş Sütçü İmam University in Turkey approved this study (date: 25.12.2019, approval no.: 15). All subjects provided written informed permission prior to inclusion in this research.

Statistical Analysis

In the study, 98 participants' data were analyzed and input into the IBM SPSS Statistics 23 application. The analysis of the participants' descriptive characteristics was carried out by utilizing frequency (n, %) for categorical variables and mean and standard deviation for continuous variables. A comparison of qualitative data was carried out using Pearson's chi-square test. The difference between two-group discontinuous variables was examined using the independent samples t-test. Statistical significance was considered at a p-value <0.05.

Results

When the individuals in the intervention and control groups were compared according to their birth weight, length, sex, week of gestation, and average head circumference at birth, the groups did not show statistically significant differences (p>0.05) (Table 1).

In terms of their length of hospital stay, weight growth, and feeding, there was a statistically significant difference found between the groups. Accordingly, in comparison with the control group, the participants in the intervention group had a higher daily weight gain rate in the first month and a higher weight on the tenth day, a shorter transition time to full enteral nutrition, a higher amount of calories on the day

Table I. Comparison of some descriptive and clinical characteristics by the groups

	Intervention group (n=48) Mean±SD	Control group (n=48) Mean±SD	Test value	p value
Week of gestation week	30.1875±2.98	29.10±2.43	t=1.948	0.054
Birth weight (gr)	1214.89±223.07	1128.54±219.48	t=1.912	0.059
Birth length (cm)	37.83±2.67	37.16±2.81	t=1.189	0.237
Head circumference at birth (cm)	27.72±2.18	27.6042±2.34	t=.270	0.788
Sex	n (%)	n (%)		
Female	30 (62.5)	22 (45.8)	χ^2 : 2.685	0.101
Male	18 (37.5)	26 (54.2)		
χ^2 : Pearson's chi-square test, t: Student's t-test, *p<0.05, **p<0.001 SD: Standard deviation				

of transition to full enteral nutrition, and a shorter length of hospital stay (Table 2).

When the participants were compared according to sepsis, rectal enema, BPD, GI intolerance, and bilirubin value, a statistically significant difference emerged between the groups. Accordingly, the participants in the intervention group had a significantly lower probability of receiving rectal enemas in comparison with the control group. Moreover, the participants in the intervention group had significantly less sepsis, GIS intolerance, and BPD than those in the control group. Additionally, the bilirubin levels on the 15th day were found to be statistically significantly lower in the

control group in comparison with the intervention group ($p < 0.05$). There was no statistically significant difference between the intervention and control groups in terms of the development of ROP and bilirubin levels on the 10th day ($p > 0.05$) (Table 3).

Upon comparing the participants in the intervention and control groups according to the time of discontinuation of respiratory support, a statistically significant difference was identified between the groups. Accordingly, the participants in the intervention group had a statistically significantly shorter time to the discontinuation of respiratory support in comparison with the control group ($p < 0.05$) (Table 4).

Table II. Comparison of weight gain, nutrition, and length of hospital stay in preterm neonates by the groups

Variables	Intervention group (n=48)	Control group (n=48)	Test value	p value
	Mean±SD	Mean±SD		
Daily weight gain rate in the first month (gr)	13.45±2.17	11.77±2.39	t=3.619	0.000**
Weight on the tenth day (gr)	1264.27±260.35	1125.10±222.00	t=2.818	0.006**
Weight at discharge (gr)	1924.16±124.00	1949.68±163.16	t=-0.863	0.390
Transition time to full enteral nutrition (days)	12.12±6.26	20.18±13.54	t=-3.743	0.000**
Calorie amount on the day of transition to full enteral nutrition	137.37±22.35	127.02±18.45	t=2.474	0.015*
Length of hospital stay (days)	52.00±21.32	73.22±22.79	t=-4.712	0.000**

t: Student's t-test, * $p < 0.05$, ** $p < 0.001$
SD: Standard deviation

Table III. Comparison of some complications in preterm neonates by the groups

Variables		Intervention group (n=48)	Control group (n=48)	Test value	p value
		n (%)	n (%)		
Status of receiving rectal enema	Yes	6 (12.5)	34 (70.8)	33.600	0.000**
	No	42 (87.5)	14 (29.2)		
Sepsis	Yes	8 (16.7)	23 (47.9)	10.720	0.001**
	No	40 (83.3)	25 (52.1)		
GI	Yes	7 (14.6)	26 (54.2)	16.670	0.000**
	No	41 (85.4)	22 (45.8)		
ROP	Yes	23 (47.9)	17 (35.4)	1.543	0.214
	No	25 (52.1)	31 (35.4)		
BPD	Yes	5 (10.4%)	16 (33.3)	7.375	0.007**
	No	43 (89.6%)	32 (66.7%)		
		Mean±SD	Mean±SD	Test value	p value
Bilirubin value on the 10 th day		4.88±2.58	4.24±2.30	1.283	0.203
Bilirubin value on the 15 th day		3.65±2.50	2.57±1.71	2.462	0.016

χ^2 : Pearson's chi-square test, t: Student's t-test, * $p < 0.05$, ** $p < 0.001$
GI: Gastric intolerance, ROP: Retinopathy of prematurity, BPD: Bronchopulmonary dysplasia, SD: Standard deviation

Table IV. Comparison of the time of discontinuation of respiratory support in preterm neonates by the groups

Variables	Intervention group (n=27)	Control group (n=34)	Test value	p value
	Mean±SD	Mean±SD		
Time of discontinuation of respiratory support (days) ^a	22.63±15.87	36.20±22.02	t=-2.694	0.009**

χ²: Pearson's chi-square test, t: Student's t-test, *p<0.05, **p<0.001
^a: The participants who did not receive respiratory support at all or whose respiratory support was discontinued within the first 7 days were excluded from the statistical analysis.

Discussion

Preterm infants are vulnerable to postnatal nutritional deficiencies, e.g., fat, since they do not receive the nutrients they need to store in the third trimester of pregnancy and cannot experience the rapid growth phase (4,24,25). Despite the numerous benefits of human milk for the said population, its fat content varies considerably and may be insufficient for optimum growth and development. Hence, the additional fat intake of the infant can be ensured by adding commercially prepared fat mixtures to a small amount of expressed breast milk. Fat taken with the diet is crucial to maintaining energy, growth, and long-term health in preterm infants. Nevertheless, in a systematic review published in the Cochrane Database by Amissah et al. (9), the researchers revealed no clear pieces of evidence for the benefits or harms of adding fat to breast milk in preterm infants (10). Therefore, there is a need for studies assessing these effects, including LC-PUFA supplementation.

The most suitable oils to add to neonatal nutrition nowadays are a combination of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs). Although LCTs contain a high amount of essential fatty acids which can be found in almost all vegetable oils, such as olive oil, MCTs cannot provide essential fatty acids. Nevertheless, the impacts of essential fatty acids (unsaturated) on the neurodevelopmental growth of infants have been proven (5,26,27). It is thought that the natural antioxidant effect of phenolic compounds and oleic acid, which is rich in unsaturated fats, in olive oil strengthens the infant's immune system and may also positively affect some physiological parameters in bone development (28). This study demonstrated that adding vegetable oil (olive oil) to the diet of preterm infants is highly effective in terms of weight gain and shortening the length of hospital stay due to improving the immune system. Along with the significant anti-inflammatory effects of olive oil and its bioactive compounds, the evidence of its effects on inflammatory bowel disease has also been emphasized in the recent literature (29,30). The lower level of BPD and the lower

incidence of GI in those individuals given olive oil in our study were thought to be associated with these properties of olive oil. Similar to our study, the study by Amini et al. (16) also determined that olive oil positively impacted the weight gain and length of hospital stay of infants. Furthermore, although the table did not display a statistically significant difference in complications related to GI and respiration, it was observed that they were more common in the control group in comparison to the intervention group. However, in another pilot study with a limited number of infants, Ecevit et al. (22) found no significant difference between the two groups according to weight gain, length of hospital stay, and oxidative stress-related diseases. In another study also conducted with a limited number of infants (n=14), Polberger et al. (32) stated that adding extra fat to breast milk for preterm infants did not have a clear benefit in terms of short-term weight gain, length growth, and head growth rates. However, they also found no pieces of evidence that adding additional fat increased the risk of feeding intolerance. In this respect, our study will contribute to the field due to it being an evidence-based randomized controlled trial which included a larger sample group compared to other studies on this subject.

Study Limitations

There were some limitations in this study. Firstly, follow-ups after long-term use of olive oil could not be performed due to the infants being discharged. Secondly, the amount of olive oil administered orally may vary depending on each infant's weight and health status. Further studies are needed on standardized usage amounts.

Conclusion

Olive oil is a very important natural antioxidant and anti-inflammatory nutrient, especially for premature infants. In conclusion, considering the current research results, the use of vegetable oils to increase caloric intake in preterm neonates appears to deserve further and more comprehensive investigation. As adding additional fat to breast milk is already carried out as part of multi-nutrient

supplementation, we urge that future studies look at the effects of the fat component on short- and long-term growth, body fat ratio, blood sugar, and brain development. Considering the differences depending on the season and agricultural areas where olive oil is produced, it is extremely important to present standard content in clinical routine use. Bioavailability studies of the bioactive components contained in olive oil need to be carried out, especially in this high-risk patient group. Furthermore, the correct amount and composition of the extra fat required for preterm infants, its potential side effects, and its impact on delivery practices are among the other issues which should be researched.

Ethics

Ethics Committee Approval: The Clinical Studies Ethics Committee of Kahramanmaraş Sütçü İmam University in Turkey approved this study (date: 25.12.2019, approval no.: 15).

Informed Consent: All subjects provided written informed permission prior to inclusion in this research.

Authorship Contributions

Surgical and Medical Practices: S.A., M.S., S.Y., Y.Ç., S.T., S.Y.Ç., Y.Ö., M.N.Y.İ., Concept: S.A., M.S., S.Y., Y.Ç., S.T., S.Y.Ç., Y.Ö., M.N.Y.İ., Design: S.A., M.S., Y.Ç., Y.Ö., M.N.Y.İ., Data Collection and/or Processing: S.T., S.Y.Ç., Y.Ö., M.N.Y.İ., Analysis and/or Interpretation: S.A., M.S., S.Y., S.T., S.Y.Ç., Literature Search: S.A., M.S., S.Y., S.T., S.Y.Ç., Y.Ö., Writing: S.A., S.Y., S.T., S.Y.Ç., Y.Ö., M.N.Y.İ.

Conflict of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

Financial Disclosure: Sponsored by the University Office of Scientific Research Projects.

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