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Original Article

The effects of early nutritional contents in premature infants on the development and severity of retinopathy: A retrospective case-control study

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ABSTRACT

Objectives: Poor weight gain during the first weeks of life in preterm infants is associated with the risk of developing retinopathy of prematurity (ROP). Our study aimed to evaluate the effect of energy, macronutrient intake, and weight gain during the first 4 weeks of life on the risk of ROP.

Methods: This study was designed as a single-center, retrospective, and case-control trial. Premature babies, born before the 30th week of gestation, were included in our study. The infants were divided into three groups: control (without ROP), mild ROP, and severe ROP groups. Possible nutritional risk factors for ROP were compared.

Results: ROP was found in 32 (29.5%) of 108 infants included in this study. The first enteral feeding day, full enteral feeding day, and total duration of parenteral nutrition were significantly higher in infants with level 3-4 ROP than the others ($p < 0.05$). The risk of severe ROP increased in infants who gained less than 8 g/day and who received less than 91 kcal/kg of calories ($p < 0.05$). It was found that infants with severe ROP received statistically ($p < 0.05$) less breast milk, but there was no difference in formula intake ($p > 0.05$).

Conclusions: We showed that low energy intake during the first 4 weeks of life is an independent risk factor for severe ROP. This implies that the provision of adequate energy from parenteral and enteral sources during the first 4 weeks of life may be an effective method to reduce the risk of severe ROP in preterm infants.

Keywords: Retinopathy of prematurity, total parenteral nutrition, weight gain, premature

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading causes of morbidity in preterm infants. As a preventable condition, the diagnosis and monitoring of ROP are especially important. ROP is defined as abnormal vascular proliferation in the vascular-avascular junction of the immature retina, which has not completed vascularization.[1] The reported prevalence of ROP among preterm infants under 27 weeks of gestational age is between 10% and 35% in developed countries.[2] In a multicenter study conducted by the TR-ROP Study Group including 6115 infants at 69 neonatal intensive care units in Türkiye, the prevalence of ROP regardless of the stage was 27% and that of severe ROP was 6.7%.[3]

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Although the etiopathogenesis of ROP has not been fully elucidated, certain mechanisms have been proposed and numerous risk factors have been identified.[4-9] Risk factors for ROP have been studied in detail and identified risk factors include gestational age, low birth weight, hypoxia, oxygen therapy, hypercapnia, asphyxia, hypothermia, acidosis, mechanical ventilation longer than a week, bronchopulmonary dysplasia (BPD), intracranial bleeding, transfusion, hyperglycemia, erythropoietin (EPO) use, and multiple pregnancies.[7-9] In addition, in recent years, there has been a focus on the possible link between nutrition and ROP. Among other risk factors, malnutrition and late initiation of feeding have been examined.[10-12] It has been determined that in preterm infants with low caloric intake or delayed feeding after birth, vascularization is interrupted due to a decrease in the synthesis of growth factors, especially insulin-like growth factor 1 (IGF-1). A comparison of infants with ROP showed that those with lower energy intake had more advanced ROP.[10] Based on the hypothesis that ROP is less prevalent or less severe in infants who are well and aggressively fed during the first 28 days of life, this study was conducted to identify risk factors for ROP and to investigate the relationship between ROP and nutrition.

METHODS

This single-center, retrospective, case-control study included preterm infants born before 30 weeks of gestation in the Hacettepe University Faculty of Medicine Neonatal Unit between the years 2000 and 2016. The infants were divided into 3 groups: the non-ROP healthy control group, the early-stage ROP group, and the advanced ROP group. Variables that may influence the development of ROP, such as energy intake in the first 28 days, drugs used, procedures performed, and duration of mechanical ventilation, were compared among the groups.

Study population

The study included preterm infants born before 30 weeks of gestation and admitted to Hacettepe University Faculty of Medicine for treatment between 2000 and 2016. Infants born before 2000, those with congenital anomalies, those whose files did not include information on caloric intake in the first 28 days or had missing drug and weight data, and those who died were excluded.

Data collection

Data were collected by retrospective chart review. Clinical data related to the patient included sex, date of birth, gestational age at birth, birth weight, length, and head circumference, mode of delivery, presence of meconium aspiration, premature rupture of the membranes (PROM), complications of prematurity (e.g., necrotizing enterocolitis [NEC], ROP, intracranial hemorrhage), positive blood culture, sepsis, pneumonia, pneumothorax, patent ductus arteriosus (PDA) and history of medical/surgical PDA treatment, retinopathy, age at retinopathy diagnosis (days), and total hospital length of stay. Respiratory data included the presence of perinatal hypoxia, Apgar score, need for neonatal resuscitation, a number of surfactant treatments in the intensive care unit, duration and mode of mechanical ventilation (e.g., high-frequency oscillatory ventilation [HFOV], synchronized intermittent mandatory ventilation [SIMV], nasal continuous positive airway pressure [CPAP]), and presence of apnea requiring medical treatment. Nutritional data included amounts of parenteral and enteral feeding during the first 28 days, calorie, protein, and fat intake in the first 28 days, duration of total parenteral nutrition (TPN), and rate of weight gain. Maternal data were collected on gravity and parity, diseases, pregnancy-related conditions, and history of drug use. These parameters were evaluated both in patients diagnosed with ROP and in the control group.

ROP staging was done according to the definition in the TR-ROP study.[3] NEC was diagnosed in the presence of excessive gastric residual volume, abdominal distention, positive fecal occult blood test, radiological findings of pneumatosis intestinalis or portal vein gas, and discontinuation of oral intake for these reasons.[11] Patients who received more than 30% oxygen and were given surfactant were evaluated as having respiratory distress syndrome (RDS)[12], and those who needed oxygen for at least 28 days were evaluated as bronchopulmonary dysplasia (BPD).[13] Patients were classified as having PDA if evaluated as hemodynamically significant by a cardiologist and received medical treatment/ligation. Sepsis was diagnosed in patients exhibiting clinical signs and elevated acute phase reactants, with or without a positive culture.

After collecting the data, enteral protein, lipid, and calorie intake were calculated based on the following values per 100 ml: 1.4 g protein, 3.9 g lipids, and 67 kcal for breast milk; 2.2 g protein, 3.9 g lipids, and 82 kcal for fortified breast milk, and 1.4 g protein, 3.9 g lipids, and 80 kcal for formula.[14]

For infants on TPN, the daily energy intake was calculated as the sum of glucose and lipid intake was calculated. Calories were calculated using the following formula: (glucose infusion rate × 5.7) + (Lipids [g/kg] × 9).[15]

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY). Descriptive statistics were expressed as number (n) and percentage (%) for categorical variables, mean and standard deviation for normally distributed numerical variables, and median and (minimum–maximum) values for non-normally distributed numerical data. The Chi-square test was used to compare categorical data such as sex and the presence of comorbidities. The normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons of numerical data between groups were done with one-way ANOVA for normally distributed data and the Kruskal–Wallis test for non-normally distributed data, followed by post-hoc Dunn's test for pairwise comparisons to determine which group differed from the others. Receiver operating characteristic (ROC) curves were used for diagnostic data. Based on a 95% confidence interval, p-values less than 0.05 were accepted as significant.

RESULTS

The medical records of 745 patients born before 30 weeks of gestational age at our center between 2000 and 2016 were examined. Of these, 307 patients were excluded from the study due to mortality and 330 due to missing data or congenital anomalies. The 108 preterm infants included in the study were divided into 3 groups: 76 (70.3%) without ROP, 12 (11.1%) with early (stage 1-2) ROP, and 20 (18.5%) with advanced (stage 3-4) ROP. The median gestational age was 28 (24–29.4) weeks, the median birth weight was 1080 g (590–1750), and 51% were female.

There were no significant differences in maternal characteristics between the groups ($p>0.05$). Comparisons of patient characteristics between the groups are shown in Table 1. No significant differences were observed in gestational age at birth, sex, head circumference, small for gestational age (SGA) status, intraventricular hemorrhage (IVH), NEC, pneumonia, sepsis, positive blood culture, or C-reactive protein (CRP) level ($p>0.05$). However, the advanced ROP group had a more frequent need for resuscitation, lower Apgar scores, more frequent hypotension and need for inotropes, lower birth weight, longer duration of mechanical ventilation, and higher prevalence of RDS, hemodynamically significant PDA, and BPD ($p<0.05$).

No significant differences were found between the groups in terms of methylxanthine therapy, erythropoietin (EPO) therapy, phototherapy, platelet suspension therapy, fresh frozen plasma support, oxygen support, or discharge time. However, the stage 3-4 ROP group had significantly different rates of insulin use, intravenous immunoglobulin (IVIg) therapy, erythrocyte suspension therapy, and steroid therapy for the treatment of BPD compared to the other groups ($p>0.05$). The number of erythrocyte suspensions differed significantly between the stage 3-4 ROP group and the group without ROP, but there was no difference compared to the stage 1-2 ROP group ($p>0.05$).

The feeding characteristics and energy intake calculations of the groups are shown in Table 2. Infants in the advanced ROP group began enteral feeding later, received TPN support longer, and achieved full enteral feeding later than the other groups. The timing of first enteral feeding differed significantly between the advanced ROP and control groups only, whereas the duration of TPN and achievement of full enteral feeding differed significantly between the advanced ROP and control groups and between the advanced ROP and stage 1-2 ROP groups. There was no difference between the groups in terms of the amount of formula fed during enteral feeding, but the advanced ROP group received significantly less breast milk. Enteral protein intake (g/kg/day) was also significantly lower in the advanced ROP group, while there was no difference between the groups in terms of total (IV + enteral) protein intake (g/kg/day). Enteral and total (IV + enteral) lipid intakes (g/kg/day) were significantly lower in the advanced ROP group compared to the other groups.

The advanced ROP group also showed significantly lower total energy intake (kcal/kg/day) in the first 28 days, daily weight gain in the first 28 days, and weight on day 28 compared to the other groups.

Timing of full enteral feeding, duration of TPN, enteral total protein and lipid intake, total energy intake, daily weight gain, and weight on day 28 differed significantly between the advanced ROP group and the stage 1-2 ROP group, but not between the stage 1-2 ROP and control groups.

Comparisons of total protein and lipid intake, total daily energy intake (kcal/kg/day), weight gain, and weight on day 28 are shown in Figure 1. ROC curve analyses for the diagnostic use of the association between the development of severe ROP and daily weight gain and total daily energy intake are shown in Figure 2. Neither parameter was found to have a diagnostic value in ROP. A weight gain of 8.3 g/day had a 60% sensitivity and a 75% specificity for advanced ROP. When patients were grouped according to weight gain of 8.3 g/day, it was found that the risk of severe ROP was significantly increased in those with weight gain <8.3 g/day ($p=0.004$). A daily caloric intake of 91.4 kcal/kg/day had a 70% sensitivity and a 61% specificity for the development of advanced ROP.

Table 1. Comparison of neonatal characteristics between the groups				
Variable	**No ROP (n=76)**	**Stage 1-2 ROP (n=12)**	**Stage 3-4 ROP (n=20)**	**P value**
Gestational age (weeks)*	28 (26-29)	28 (26-29)	27 (24-29)	0.184
Sex				
Male	41 (53.90)	4 (33.30)	8 (40)	0.277
Female	35 (46.10)	8 (66.70)	12 (60)	
Birth weight (g) *	1100 (600-1750)	1155 (670-1480)	895 (590-1400)[+]	**0.027**
Resuscitation	4 (5.30)	0 (0)	6 (30)[·]	**0.002**
Hypotension	14 (18.40)	1 (8.30)	11 (55)[+]	**0.021**
Inotrope use	30 (39.50)	2 (16.70)	18 (90)[+]	**<0.001**
SGA	11 (14.50)	2 (16.70)	2 (10)	0.087
Apgar score (5-min)*	8 (2-10)	9 (7-10)	7 (3-9)[+]	**0.036**
Head circumference (cm)*	26.10 (23-30)	27 (22.50-29)	25.15 (22-28.50)	0.672
IVH	12 (15.80)	2 (16.70)	6 (30)	0.353
NEC	10 (13.20)	1 (8.30)	5 (25)	0.428
PDA	27 (35.50)	4 (33.30)	13 (65)[+]	**0.049**
Pneumonia	34 (44.70)	3 (25)	11 (55)	0.254
Sepsis	38 (50)	4 (33.30)	12 (60)	0.340
Positive blood culture	20 (36.30)	3 (25)	4 (20)	0.845
RDS	43 (56.60)	3 (25)	17 (85)[+]	**0.003**
Surfactant treatments*	1 (0-5)	0 (0-3)[+]	1 (0-6)	**0.007**
Ventilatory support (days)				
MV	4.05 (0-28)	2.08 (0-14)	13.45 (0-28)[+]	<0.001
HFOV	0.12 (0-8)	0	1.05 (0-16)[+]	0.047
CPAP	6.03 (0-21)	2.92 (0-9)	3.40 (0-9)	0.107
Free O_2	7.36 (0-26)	5.83 (0-15)	5.65 (0-21)	0.784
Total	17.55 (0-28)	10.83 (0-27)	23.55 (5-28)[+]	**0.002**
CRP (mg/dL)*	0.26 (0.01-13.50)	0.18 (0.01-5.87)	0.26 (0.01-6.82)	0.778
BPD	26 (34.20)	4 (33.30)	17 (85)	**<0.001**
Day of discharge*	39 (6-76)	41 (17-53)	61 (31-150)[+]	**<0.001**

Data are presented as *Median (minimum–maximum), other data are shown as n (%).
[+] Shows which group is significantly different.
Bold p values indicate statistical significance.

Table 2. Comparison of feeding characteristics between the groups				
Variable	**No ROP (n=76)**	**Stage 1-2 ROP (n=12)**	**Stage 3-4 ROP (n=20)**	**P value**
First day of enteral feeding*	2 (1-25)	3 (1-5)	4 (1-40)$^{+}$	**0.002**
Day of total enteral feeding*	15 (5-67)	13 (8-39)	31 (8-64)$^{+}$	**0.005**
Duration of TPN (days)*	14.50 (0-50)	12 (6-37)	27.50 (8-63)$^{+}$	**0.006**
Feeding (ml)*				
Breast milk	2084 (0-5896)	2041 (643-6319)	701 (0-6440)$^{+}$	**0.006**
Formula	19 (0-3585)	6 (0-2066)	17 (0-2852)	0.735
Enteral protein** (g/kg/day)	1.30±0.77	1.50 ±0.86	0.80±0.85^{+}	**0.006**
Enteral lipids** (g/kg/day)	3.07±1.44	3.52±1.42	1.90±1.86^{+}	**0.040**
Total protein (g/kg/day)**	3.04±0.98	3.45±0.80	2.91±1.16	0.373
Total lipids (g/kg/day)**	3.89±1.27	4.46±1.07	2.94^{+}±1.73	**0.007**
Total energy (kcal/kg/day)**	96.40±21	107.3 ±18.50	79.4±29^{+}	**0.003**
Weight gain (g/day)*	12.73 (-5.56-26.79)	13.91 (0-22.78)	6.96^{+} (-3.93-17.5)	**0.010**
Weight on day 28*	1470 (810-1860)	1535 (1010-1790)	1050^{+} (780-1850)	**<0.001**

Data are presented as *median (minimum–maximum), **mean±standard deviation values. $^{+}$ Shows which group is significantly different. Bold p values indicate statistical significance.

DISCUSSION

In this study, the effect of aggressive feeding on ROP in premature babies born less than 30 weeks was examined. It was determined that the patients' total lipid intake, total energy, and daily weight gain rate in the first 28 days were effective in the development of ROP. In addition, it is known that there are many comorbidities that affect the development of ROP. In our patient group, it would not be correct to attribute the development of severe ROP to nutritional parameters alone. What we want to draw attention to is that energy and lipid deficiency may be particularly effective in the development of severe ROP, so more caution should be taken in high-risk premature babies.

Although many risk factors for ROP have been identified, the strongest associations are with low birth weight and gestational age.[16] In a study comparing patients with active and inactive ROP, risk factors for active ROP, in particular, were birth before 26.4 weeks, low birth weight (mean 874 g), low Apgar scores, and longer duration of oxygen therapy.[7] In a study of preterm infants born before 28 weeks of gestation, low birth weight and gestational age were found to be independent risk factors for ROP. Other identified risk factors include intracranial hemorrhage, infections, BPD, hypoxia, hemodynamically significant cardiovascular conditions (e.g., PDA), transfusions, and multiple pregnancies.[17] Although the size of our sample group was acceptable compared to other studies, we were unable to perform logistic regression analysis of early and advanced ROP due to the small number of patients in the subgroup analysis. Therefore, pairwise comparisons were made between the groups. No significant difference was found between the groups in terms of gestational age. Infants with advanced ROP had higher rates of resuscitation, hypotension, inotrope use, insulin use, IVIg use, erythrocyte suspension therapy, PDA, RDS, and BPD, as well as a longer need for antibiotic therapy compared to the other groups. In general, the identified risk factors are interrelated and are common conditions in preterm infants. The prevalence of parameters such as hypoglycemia, RDS, hypotension, and infection increases with decreasing gestational age and birth weight. Although not found to be a significant factor in the present study, SGA has also been reported as a risk factor for ROP.[18]

In recent years, studies on the link between nutrition and ROP have highlighted the importance of providing breast milk, enteral nutrition, and adequate caloric support, and there is an extensive literature on this subject.[19-26] Although some studies have indicated that there is no significant link between breast milk and ROP[23-27], the protective and beneficial effects of breast milk are widely recognized. Coşkun et al.[20] reported low IGF-1 levels in 127 premature infants and emphasized that breast milk and good nutrition increase IGF-1 levels and may protect against ROP. Manzoni et al.[19] found a lower prevalence of ROP in infants who were breastfed compared to formula-fed infants (3.5% vs. 15.8%) and discussed the protective effect of breastfeeding against ROP (any stage). It is also known that premature infants

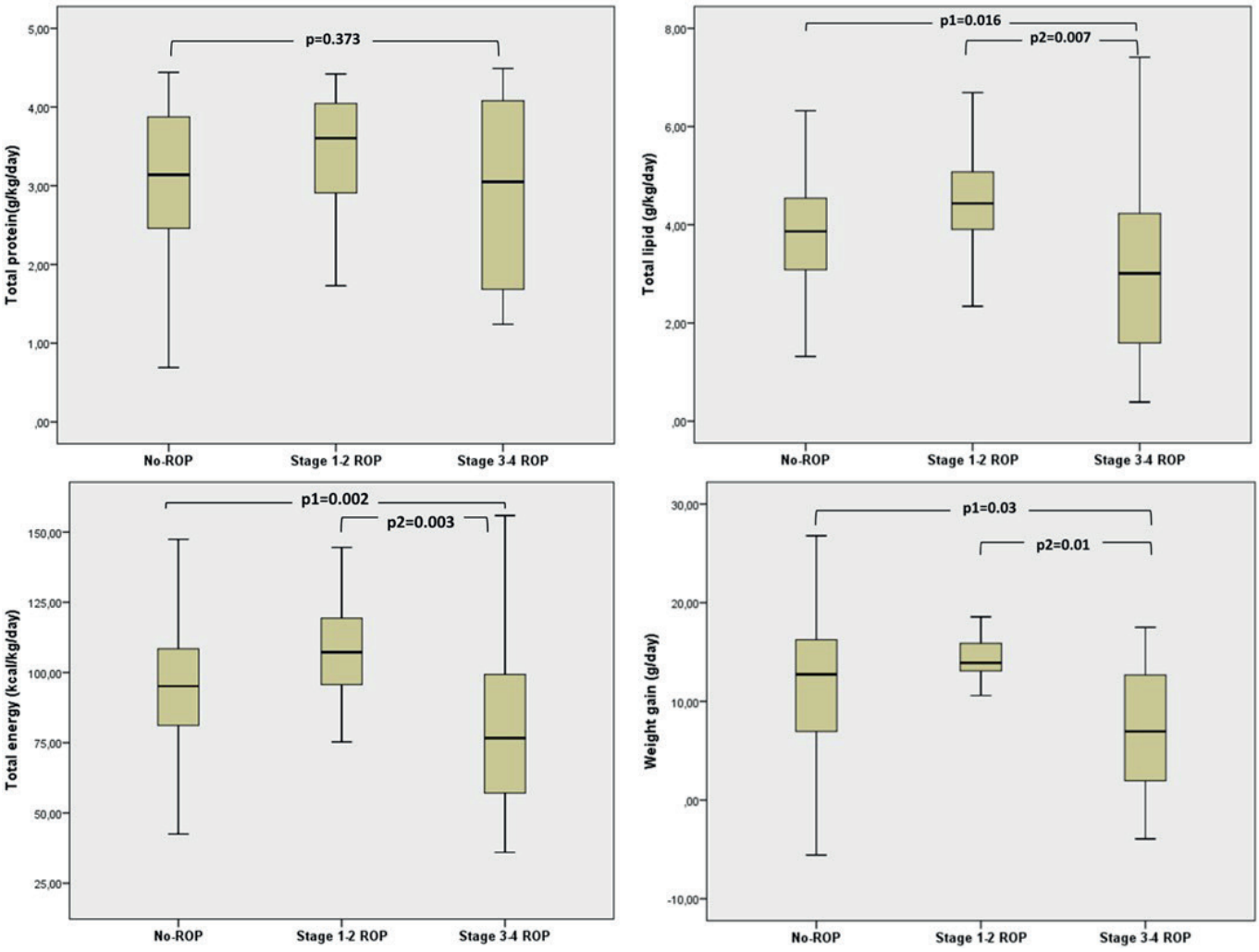
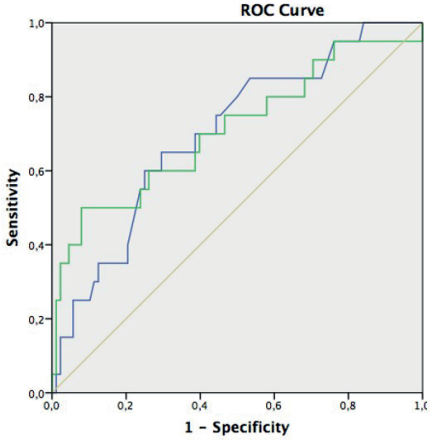


Figure 1. Comparison of total protein (g/kg/day), lipids (g/kg/day), and total calories (kcal/kg/day) and weight gain (g/day) between the groups

p1: Comparison of control group and stage 3-4 ROP group. **p2:** Comparison of stage 1-2 ROP and stage 3-4 ROP group

are exposed to oxidative stress because their antioxidant systems are still immature. Breast milk has been shown previously to provide partial protection against oxidative stress, and it has been suggested that it may also play a protective role against ROP via this mechanism.[24,25] In another study, 400 premature infants were divided into 2 groups, one fed breast milk, and the other fed formula, and rates of ROP and NEC were lower in the group that was fed breast milk.[26] In contrast, a meta-analysis including 21819 infants from 67 studies showed that breast milk was only found to be effective in observational studies and that randomized trials yielded different results.[25] In the present study, there was no significant difference between the ROP groups in terms of the number and proportion of infants who were fed enterally with breast milk. The median day of first enteral feeding was later for infants in the stage 3-4 ROP group (day 4) compared to the control group (day 2) and the stage 1-2 ROP group (day 3). Similarly, the achievement of full enteral feeding occurred later in infants with stage 3-4 ROP (day 31) compared to the control group and infants with stage 1-2 ROP (day 15 and day 13, respectively).

Determining the fluid, electrolyte, and energy requirements of preterm infants according to their birth weight and postnatal age requires precise calculations.[28] The goals of parenteral nutrition are to provide sufficient calories for energy and growth; to provide carbohydrates and lipids together in order to prevent hypoglycemia and meet energy requirements; to maintain a positive nitrogen balance to promote growth, and to this end, to provide adequate protein that also contains essential amino acids; to provide fatty acids in order to prevent essential fatty acid



	Sensitivity	Specificity	AUC	95% Cl		*p**
				Lower	Upper	
Weight gain of 8.3 g/day	60	75	0.702	0.57	0.82	**0.05**
Daily caloric intake of 91.4 kcal/kg/day	70	61	0.711	0.57	0.85	**0.03**

Figure 2. Relationship of daily weight gain and total daily energy intake (kcal/kg/day) to severe ROP development

***Green curve:** Daily weight gain, **Blue curve:** Daily calories per kg weight, **Brown curve:** Reference

deficiency and to increase non-protein-derived energy; and to provide the minerals, electrolytes, and trace elements necessary for growth.[29] Current publications demonstrate that aggressive feeding of preterm infants (earlier initiation of intravenous and enteral nutrition, earlier transition to full enteral feeding) is safe and effective.[29-33]

The literature on the relationship between aggressive nutrition and ROP includes a prospective randomized controlled trial by Can et al.[33] in which infants born before 32 weeks of gestation were divided into two groups, one that received conventional parenteral nutrition and one that received aggressive parenteral nutrition. The incidence of ROP was lower and IGF-1 levels were higher in the group that received aggressive nutrition. A meta-analysis showed that aggressive parenteral nutrition reduced the risk of ROP of any stage but did not reduce the risk of advanced ROP. The present study compared the nutritional characteristics of newborns with no ROP, early ROP, and advanced ROP. Nutritionally aggressive feeding of preterm infants has been implemented in our center since 2006. We observed that the incidence of ROP decreased in the first 4–5 years after increasing nutrition and did not change over the next 4–5 years. The decrease in mortality rate and the consistently low incidence of ROP since 2010 are related to both the improvement of other risk factors for ROP in premature infants and overly aggressive nutrition. Daily oral protein, oral lipid, total lipid, and total energy intakes, weight gain, and weight on day 28 were lower in infants with advanced ROP compared to the other groups, consistent with the literature. Preterm infants with advanced ROP have longer hospital stays and lower daily weight gain compared to other infants. In this study, weight gain in the advanced ROP group was 7.21 g/day, compared with 11.75 g/day and 13.88 g/day in the non-ROP and early ROP groups, respectively. Daily energy intake by weight was 96.4 kcal/kg/day in the control group, 107.3 kcal/kg/day in the stage 1-2 ROP group, and 79.4 kcal/kg/day in the stage 3-4 ROP group. However, we do not believe that the daily weight gain and energy intake found in this study should be compared with those in the literature, because the weight, gestational age, sex, ethnicity, and comorbidities (PDA, NEC, BPD, treatments received) of the sample groups will show substantial heterogeneity among the studies. Therefore, we believe it is more appropriate to interpret our sample group within itself.

Unlike other studies in the literature, we performed ROC curve analysis to evaluate whether daily weight gain and total energy intake could be used for diagnostic purposes in ROP. Based on our results, we concluded that these parameters are not useful in the diagnosis of ROP. On the other hand, we concluded that daily weight gain and total energy intake may play a predictive role in the diagnosis of advanced (stage 3-4) ROP. However, the sensitivity and specificity values for both parameters did not exceed 60–70%. Although the result was statistically significant, these two values alone were shown to have relatively low sensitivity and specificity for clinical use. Nevertheless, we would like to emphasize that premature infants with a daily weight gain of 8 g and a daily energy intake of less than 91.4 kcal/kg/day require closer monitoring for the development of ROP. Using daily weight gain or energy intake in combination with other risk factors may provide more reliable results. In addition, our findings need to be corroborated by studies with larger sample sizes.

Study Limitations

This study has a retrospective study design. Despite the adequate sample size compared to other studies, multivariate regression analysis could not be performed due to the small number of patients in the subgroups. The patient groups were not entirely similar in terms of comorbidities due to the clinical heterogeneity of preterm infants. There was no difference in terms of gestational age between the severe ROP group and the

other groups, but birth weights were lower in the severe ROP group, which is one of the limitations of our study. The study was planned as an analytical case-control study, and long-term follow-up results are not known. .

Ethical approval

This study has been approved by the Hacettepe University Ethics Committee (approval number 0016/137). Written informed consent was obtained from the participants.

Author contribution

Surgical and Medical Practices: MŞA, ŞY; Concept: MŞA, ŞY; Design: MŞA, ŞY; Data Collection or Processing: MŞA, ŞY; Analysis or Interpretation: MŞA, ŞY; Literature Search: MŞA, ŞY; Writing: MŞA, ŞY. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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