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The protective effect of L-carnitine supplementation on retinopathy of prematurity: A retrospective cohort study

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Ethics Committee Approval
This research was approved Baskent University Institutional Review Board (Project No: KA-22/54, Date: January 25, 2022).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Retinopathy of prematurity (ROP) is important morbidity in premature infants and is the most common preventable cause of blindness in childhood. Carnitine is a key molecule in energy metabolism and in oxidation of fatty acids, which are the main structural component of phospholipid membrane of the brain and retinal cells. Premature babies are born with insufficient carnitine pools. This study aimed to evaluate the effect of carnitine replacement on ROP in premature infants aged < 34 gestational weeks.

Methods: Premature infant records between 2014 and 2019 were retrospectively examined. All premature infants at gestational ages < 34 weeks were included. Data from the two groups who received/did not receive carnitine supplementation in total parenteral nutrition (TPN) over two consecutive time periods and whose ROP examination was complete were recorded retrospectively. Fifty-eight out of 125 infants were in the carnitine group, and 67 formed the non-carnitine group (CG and NCG, respectively). The morbidity data from subjects, especially those with ROP, who received (CG) and did not receive carnitine (NCG), were compared.

Results: Of the 125 infants enrolled, no significant differences in gestational age (P = 0.323) or birth weight (P = 0.597) between the groups was found. The Cox regression analysis revealed that carnitine replacement in the premature infant was a protective factor for ROP (P = 0.045, B = −0.933, hazard ratio 0.393, 95% confidence interval 0.158–0.978).

Conclusion: Carnitine supplementation may offer protection from developing ROP during exposure to oxygen in premature infants.

Keywords: L-carnitine supplementation, Prematurity, Retinopathy of prematurity

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Introduction

Retinopathy of prematurity (ROP) is most important cause of preventable blindness in children [1]. Recent advances in neonatal intensive care have led to an improvement in survival rates for premature infants [2]. Consequently, the incidence of ROP has increased correspondingly. ROP is characterized by abnormal neovascular development in the retina of premature infants. These abnormal blood vessels cause a tractional retinal detachment, which is the main cause of visual impairment and blindness in ROP patients [3]. The main factors associated with ROP are low gestational age, low birth weight, and prolonged exposure to supplementary oxygen following delivery [4].

Carnitine is essential for long-chain fatty acid transport through the cell membrane and both the mitochondrial outer and inner membranes into the mitochondrial matrix in which fatty acid oxidation occurs. So, carnitine is crucial for energy production in tissues dependent upon fatty acid oxidation [5]. Fatty acids, such as docosahexaenoic acid (DHA), are important for nervous system development because these compounds are an integral component of the phospholipid membrane of the brain and retinal cells. DHA is accumulated in the rapidly developing brain and retina, especially during the last trimester of pregnancy and the first 24 months of life with ongoing accumulation throughout childhood [6–9]. High DHA concentrations in the retina and brain gray matter suggest that these fatty acids have important roles in retinal and neural functions. Animal studies have shown that the depletion of DHA from the retina and brain results in reduced visual function and learning deficits. Preterm babies, who suffer from numerous morbidities, including retinal and neurological issues, have more carnitine and essential fatty acid insufficiency due to preterm birth and nutritional problems. These data suggest that preterm infants are especially under risk because of imbalances in dietary fatty acid.

In the human body, fatty acids are mostly found in the central nervous system and then continues to the retina. It is known that premature babies born before the last trimester especially have insufficient levels of fatty acids and insufficient carnitine storage [10]. Consequently, carnitine plays a very important role in the transport of fatty acids from the cell cytosol into mitochondria, especially in premature babies. Our hypothesis was that replacement of carnitine in diets for premature babies with insufficient carnitine and fatty acid pool due to preterm birth and feeding difficulties may offer protection against ROP. This study aimed to evaluate the effect of carnitine replacement on ROP in premature infants < 34 gestational weeks.

Materials and methods

This double-center, retrospective cohort study was conducted at Baskent University Konya Hospital and Gaziantep Medical Park Hospital. This research was approved by Baskent University Institutional Review Board (Project No: KA-22/54). Premature infant records between 2014 and 2019 were retrospectively examined. All premature infants at gestational ages < 34 weeks were included. Clinical data and demographic information, including gestational age, gender, weight; antenatal steroid administration, respiratory distress syndrome (RDS), the day of oxygen exposure, bronchoalveolar dysplasia, maximum fractional inspired of oxygen, intraventricular hemorrhage (IVH), hemodynamically significant patent ductus arteriosus, treatment options of patent ductus arteriosus, whole blood cell count at admission, maximum C-reactive protein (CRP) levels during hospitalization, total days of parenteral nutrition, necrotizing enterocolitis, frequency of hypothyroidism, frequency of sepsis, frequency of ROP and stages, and duration of hospital stay were obtained from the medical records of the enrolled infants. Infants with comorbid complex congenital heart disease, genetic abnormalities, and other severe deformities were excluded from the study. Subjects were classified into two groups through matched case-control. Of the 125 infants enrolled, 58 were in the carnitine group (CG), and 67 were in the non-carnitine group (NCG) as shown in Table 1. The cases in the CG were older (2014–2017) than the NCG (2017–2019). To avoid selection bias, the characteristics of patients, such as gestational week and birth weight, were similarly chosen. Also, the cases were grouped as ROP and non-ROP to provide statistics to evaluate the association between carnitine replacement and premature retinopathy. Baseline characteristics (Table 3) and weight gain (Table 4) were examined based on ROP grouping.

In the CG, carnitine was given 25mg/kg by IV route in the first 6 hours of life with total parenteral nutrition (TPN) [11]. Carnitine supplementation was continued until TPN was stopped. Carnitine supplementation was not continued during enteral feeding. NCG did not receive any carnitine support. The first assessment of the state of patent ductus arteriosus in both groups was made on the third day of life. Treatment and follow-up of the patent ductus arteriosus were done as per our pediatric cardiology guidance. Cranial ultrasound was performed in the first week of life and at the end of the first month of life for staging IVH and cystic encephalomalacia, respectively. Ophthalmological examinations were initiated at the fourth week of life or at the 31st week of gestational age (whichever came later) and were repeated weekly or biweekly using the schedule for follow-up recommended by the American Academia of Pediatrics and American Academy of Ophthalmology [12].

Sample size calculation

The known incidence of ROP in infants < 34 weeks is 66% [13]. On the open access website, it was calculated that the administration of L-carnitine would lead to a reduction in ROP by 20%, with a power of 80%, a confidence interval (CI) of 95%, and 58 cases for each group at a 1:1 ratio (https://clincalc.com/stats/SampleSize.aspx).

Statistical analysis

Descriptive statistics of scale variables were presented as mean (standard deviation (SD)) or median (range) as appropriate. Demographic and clinical continuous variables were compared using the two-independent Student's t-test for normally distributed values and the Mann–Whitney U test for non-normally distributed values. Z-scores of skewness, kurtosis, and Shapiro–Wilk statistics were used to understand whether the continuous variables were normally distributed. Categorical variables were compared using Fisher's exact test. The univariate analyses to identify variables associated with ROP were investigated using chi-squared, Fisher exact, Student's T-, and

Mann–Whitney U tests where appropriate. Univariate Cox regression analyses were used to calculate the hazard ratios and 95% CI to determine the relationship between ROP and carnitine replacement during the period of total oxygen exposure. Statistics related to carnitine replacement (weight gain and weight gain in the ROP infants) were applied because a close relationship between carnitine and energy metabolism exists as shown in Tables 2 and 4. For all tests, the level of statistical significance was set at $P = 0.05$. SPSS 25 was used for all data analyses.

Results

Of the 125 infants enrolled, 58 (46%) and 67 (54%) were CG and NCG infants, respectively. No significant differences in gestational age, birth weight, gender, antenatal steroid administration, oxygen duration, TPN duration, number of packed red blood cells, maximum CRP levels, the transition time to fully enteral nutrition, whole blood cell indices, except for mean platelet volume (MPV), surfactant instillation, and bronchopulmonary dysplasia (BPD) (any stage) between the groups (Table 1). In the NCG, mechanical ventilation per day was significantly higher ($P = 0.001$), while the total oxygen exposure did not change between the groups. Although BPD at any stage did not differ between groups, when the subgroups were combined, moderate or severe BPD rates were found to be significantly higher in CG. This result, which was unexpected, was explained based on the finding that gestational week (28 (2) versus 30 (2); $P < 0.001$) and birth weight (1060 (206) versus 1420 (340) g; $P < 0.001$) were significantly lower in the moderate-severe BPD group. In other words, babies with lower birth weight and lower gestational age were collected in the group of moderate to severe BPD with receiving carnitine. While no difference was observed between the groups in terms of severe intracranial hemorrhage, grade I-II IVH was observed more in the NCG babies, but it was not significantly different from the CG infants ($P = 0.121$). As proven, sepsis was significantly higher in the NCG babies ($P = 0.025$), and congenital hypothyroidism was significantly higher in the CG babies ($P = 0.025$). Approximately two times more ROP was observed in the NCG, but this difference was not significant ($P = 0.089$). Similarly, advanced stage and laser-requiring ROP were higher in the NCG infants, but this difference was not at the statistically significant level ($P = 0.340$). The Cox regression analysis, in which the time variable was selected as total oxygen exposure day, revealed that carnitine replacement in the premature infant was a protective factor for ROP ($P = 0.045$, B = −0.933, HR: 0.393, 95% CI 0.158–0.978) as shown in Figure 1. Figure 1 and Cox regression results demonstrate that carnitine supplementation in premature infants protects against ROP development by approximately 2.5 times.

Figure 1: Figure shows a statistically significant decrease in retinopathy of prematurity (ROP) in premature infants who were supplemented with carnitine.

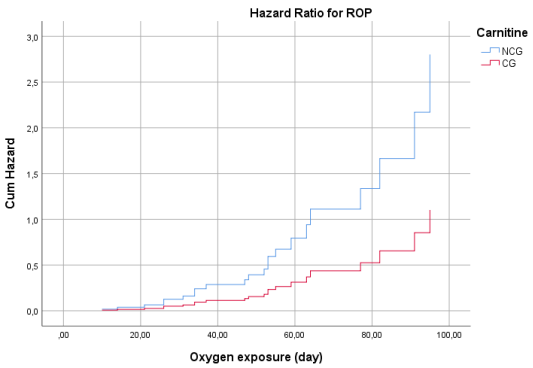

Table 1: Baseline characteristics of study groups

	Carnitine (n = 58)	Non carnitine (n = 67)	*P*-value
GW, mean(SD)	29.6 (2.08)	30 (2.34)	0.323
BW, mean(SD)	1357 (312)	1389(376)	0.597
Mechanical ventilation; day; median (min-max)	2 (0–107)	6 (0–47)	0.001
O2; day; median (min-max)	25 (0–107)	13 (1–116)	0.099
TPN; day; median (min-max)	9 (0–107)	10(0–50)	0.438
The number of packed RBC; median (min-max)	0.5 (0–6)	0 (0–5)	0.200
Max CRP (mg/dl), median (min-max)	5.87 (0.1–291.6)	4.5 (0.2–299)	0.907
The transition time to full enteral nutrition; day median (min-max)	11.5 (0–110)	12 (3–52)	0.870
WBC; median (min-max)	9.39 (2.2–47.3)	9.38 (2.59–38.1)	0.812
ANS median (min-max)	2.6 (0.13–48.9)	2.2 (0.05–15.4)	0.064
ALS median (min-max)	5.15 (0.93–45.5)	5.28 (1.05-31.9)	0.946
MPV median (min-max)	7.3 (6.07–9.2)	6.5 (4.88–9.7)	0.007
Plt median (min-max)	235 (28–670)	229 (48–396)	0.823
Gender; male; n (%)	30 (44.8)	30 (51.7)	0.438
Antenatal steroid administration; n (%)	13 (22.4)	31 (46.3)	0.005
Surfactant administration	17 (29.3)	23 (34.8)	0.510
Respiratory support; n(%)	34 (58.6)	58 (86.6)	0.001
RDS; n (%)	34 (58.6)	58 (86.6)	<0.001
BPD; n (%)	21 (36.2)	20 (29.9)	0.450
BPD moderate and severe; n(%)	15 (25.9)	1 (1.5)	<0.001
HsPDA; n (%)	12 (20.7)	6 (9)	0.062
IVH any grade; n (%)	1(1.7)	8(11.9)	0.037
IVH grade1-2; n (%)	1 (1.7)	6 (9)	0.121
Pnmtx; n (%)	0	2 (3)	0.499
Rop; n (%)	7 (12.1)	16 (23.9)	0.089
Laser or Anti-VEGF requiring ROP; n (%)	4 (6.9)	8 (11.9)	0.340
NEC; n (%)	11 (19.3)	6 (9)	0.095
Proven sepsis; n (%)	14(24.1)	29(43.3)	0.025
Hypotiroidy; n (%)	7(12.1)	1(1.5)	0.024
Exitus; n (%)	5(8.6)	1(1.5)	0.095

GW: Gestational week; BW: Birth weight, TPN: Total Parenteral Nutrition, RBC: Red Blood Cell, CRP: C reactive protein, WBC: White Blood cell, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, MPV: Mean platelet volume, Plt: Platelet, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, hsPDA: Hemodynamically significant patent ductus arteriosus, IVH: Intraventricular hemorrhage, ROP: Retinopathy of prematurity, NEC: Necrotizing enterocolitis.

When groups were examined in terms of weight gain, the first eight weeks of weight gain were significantly higher in the NCG ($P = 0.019$) as shown in Table 2. MPV was only significantly higher in the CG ($P = 0.007$). During the grouping in terms of ROP, surfactant use, BPD, mechanical ventilation support rate, TPN duration, the transition time for full enteral feeding, proven sepsis, hypothyroidism, total oxygen exposure, number of packed red blood cell transfusion, and maximum CRP levels were significantly higher in the group with observed ROP (Table 3). The reason for these results was the lower birth weights and gestational weeks of the cases in the group with observed ROP. Except for the significantly lower absolute neutrophil count (ANC) in the ROP group, no differences between the groups in whole blood indices were observed. Weight gain in the first eight weeks and weight gain between the second and fourth weeks were significantly higher in the non-ROP group (Table 4).

Table 2: The effect of carnitine replacement on weight gain

	Carnitine (n = 58)	Non carnitine (n = 67)	*P*-value
BW; mean(SD)	1357 (312)	1389 (376)	0.597
Weight gain in the first 2 weeks median (min-max)	30 (−190–550)	−40 (−300–350)	0.053
Weight gain in the first 4 weeks; mean(SD)	213.4 (180.4)	207.5 (148.3)	0.858
Weight gain in the first 8 weeks; mean(SD)	506.6 (267.2)	684.6 (232.6)	0.019
Weight gain between 2nd and 4th week; mean(SD)	198.2 (163.9)	250.8 (126.5)	0.081
Catch-up birth weight day; median (min-max)	17 (0–27)	17 (5–43)	0.299

BW: Birth weight, SD: Standard deviation

All findings found as risk factors for ROP seem to be related to lower birth weight and lower gestational age. In addition, the significant difference in TPN duration and transition time to full enteral feeding between ROP and non-ROP groups is another impressive finding revealing the relationship between nutrition and ROP.

Table 3: Retinopathy statistics

	ROP (n = 23)	Non-ROP (n = 102)	*P*-value
Gender; male; n (%)	9 (39.1)	51 (50)	0.346
Carnitine; n (%)	7(30.4)	51(50)	0.089
Antenatal steroid administration; n(%)	8 (34.8)	36(35.3)	0.963
Surfactant administration n(%)	12 (52.2)	28 (27.7)	0.024
Respiratory support; n(%)	22 (95.7)	70 (68.6)	0.008
BPD; n (%)	17 (73.9)	24 (23.5)	<0.001
BPD moderate and severe; n(%)	4 (17.4)	12 (11.8)	0.466
HsPDA; n (%)	2 (8.7)	16 (15.7)	0.523
IVH any grade; n (%)	4(17.4)	5(4.9)	0.059
IVH grade1-2; n (%)	2(8.7)	5 (4.9)	0.612
Pnmtx; n (%)	1 (4.3)	1 (1)	0.338
NEC; n (%)	5 (21.7)	12 (11.9)	0.095
Proven sepsis; n (%)	18(78.3)	25(24.5)	<0.001
Hypotiroidy; n (%)	4(17.4)	4(3.9)	0.037
Exitus; n (%)	1(4.3)	5(4.9)	1
GW mean(SD)	27.7 (1.7)	30.2(2.06)	<0.001
BW mean(SD)	1025 (256)	1453 (316)	<0.001
Mechanichal ventilation; day; median (min-max)	17 (0–91)	3 (0–107)	<0.001
O2; day; median (min-max)	52(10–116)	12.5 (0–107)	<0.001
TPN; day; median (min-max)	24 (11–91)	4.5(0–107)	<0.001
The number of packed RBC transfusion; median (min-max)	1 (0–5)	0 (0–6)	0.001
Max CRP (mg/dl), median (min-max)	28.4(0.2–9)	4 (0.1–299)	0.027
The transition time to full enteral nutrition	25 (12–93)	10 (0–110)	<0.001
WBC median (min-max)	7.5(4.37–8.1)	9.46 (2.59–47.3)	0.093
ANC median (min-max)	1.6(0.79–48.9)	2.4 (0.05–48.9)	0.028
ALC median (min-max)	4.9(1.99–45.5)	5.4 (1.05–45.5)	0.975
MPV median (min-max)	7.07(5.88–8.70)	6.6 (4.88–9.7)	0.319
Plt median (min-max)	228(48.7–336)	227 (92.4–396)	0.751

GW: Gestational week; BW: Birth weight, TPN: Total Parenteral Nutrition, RBC: Red Blood Cell, CRP: C reactive protein, WBC: White Blood cell, ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, MPV: Mean platelet volume, Plt: Platelet, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, hsPDA: Hemodynamically significant patent ductus arteriosus, IVH: Intraventricular hemorrhage, ROP: Retinopathy of prematurity, NEC: Necrotizing enterocolitis

Table 4: Weight gain between groups with and without retinopathy

	ROP (n = 23)	Non-ROP (n = 102)	*P*-value
BW; mean (SD)	1025 (256)	1453 (316)	<0.001
Weight gain in the first 2 weeks; median (min–max)	−40 (−210–550)	−30 (−200–340)	0.835
Weight gain in the first 4 weeks; mean (SD)	118.6 (130.2)	235.6 (162.1)	0.002
Weight gain in the first 8 weeks; mean (SD)	565 (210.5)	655.7 (285.5)	0.235
Weight gain between 2nd and 4th week, mean (SD)	114.7 (123.3)	261.7 (133.8)	<0.001
Catch-up birth weight day; median (min-max)	17.5 (5–31)	17 (7–43)	0.201

BW: Birth weight, SD: Standard deviation

Discussion

Carnitine transports fatty acids chains into the mitochondrial matrix, thus allowing the cells to derive energy from the stored fat reserves via β-oxidation of fatty acids [14]. DHA and eicosapentaenoic acid also play a role in anti-inflammatory eicosanoid/docosanoid synthesis, signaling events, gene expression, and cytokine expression. Infants with very low birth weight have low carnitine levels with impaired ketogenesis and are dependent upon parenteral nutrition for a prolonged period. Carnitine is accepted as essential for such infants [10]. Studies have shown that fatty acid oxidation is impaired when tissue carnitine levels fall below 10% of normal. Therefore, relative carnitine deficiency disrupts fatty acid oxidation, thus reducing its use, and problems associated with impaired energy and growth may be observed [10, 15]. Studies in which plasma carnitine levels were evaluated in preterm babies with respiratory distress syndrome (RDS) and the effects of carnitine supplementation on RDS were investigated. The researchers found that plasma carnitine levels were lower in premature infants with RDS and that carnitine supplementation in these infants caused a decrease in the duration of mechanical ventilation and surfactant requirement [16, 17]. Moreover, in some congenital fatty acid oxidation defects due to a genetic mutation that codes for long-chain acyl CoA dehydrogenase (LCAD), retinopathy, which is the unlikely pathophysiology of ROP, could be observed. Therefore, we examined the relationship between the risk of ROP and carnitine supplementation in this study.

In an experimental animal study that investigated the effects of L-carnitine on oxygen-induced retinopathy, the authors found that L-carnitine supplementation offered protection against retinopathy development, a finding that is in line with our findings [18]. Although ROP was observed to be approximately two times higher in the group that did not receive carnitine, this difference was not significant in our study. However, when the time variable was placed in the model, the observed significant difference suggested that the protective effect of carnitine became evident over time. Contrary to our hypothesis, an *in vitro* study showing that agents, such as etomoxir (irreversibly blocks fatty acid oxidation) that block fatty acid oxidation can stop angiogenesis in endothelial cells [19]. In contrast to the results of this study, a study in which the results of 75 LCAD-deficient patients were published reported that retinopathy was present in 43% of cases [20]. Simply put, retinopathy is a common finding in congenital fatty acid metabolism disorders. Additionally, in their study investigating the association of targeted metabolomic levels with ROP in premature infants, Yang et al. [21] found high serum glycine and malonyl carnitine levels to be predictive serum markers associated with the emergence of ROP. Consequently, conflicting results on the effect of carnitine on different retinopathy types can be found in the literature.

In a recently published systematic review on prophylactic administration of L-carnitine on the parenteral nutrition of premature infants, it was suggested that carnitine supplementation may help increase carnitine levels. However, no relevant improvements in the lipid profile, increase in weight gain, decrease in morbimortality, and reduction of hospital stay were found [22]. Results such as growth, weight gain, hospital

duration, ventilator dependency, and lipid profiles have been emphasized as primary outcomes in these studies. In our study, it was found that while carnitine replacement in premature infants led to a decrease in mechanical ventilation duration, weight gain had no positive effects and even had negative effects in the subsequent postnatal weeks. As in our findings, in a metanalysis that examined the effect of the carnitine on adult weight loss in obese patients, they concluded that receiving the carnitine resulted in weight loss [23]. Similarly, weight gain was shown to be higher in the group that did not receive carnitine at the end of the second and eighth weeks. In their randomized controlled study investigating carnitine supplementation on RDS, Ozturk et al. [16] showed that carnitine-supplemented babies spent less time on mechanical ventilation and had less surfactant requirements. Also, Korkmaz et al. [17] found that premature babies with RDS had low serum carnitine levels. Such effects may be related to the role of carnitine on the energy metabolism of respiratory muscles through fatty acid oxidation.

ROP is a disease specific to premature babies, and the greatest risk factors for ROP development are low birth weight, low gestational age, and the. need for oxygen to maintain life. The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study demonstrated that ROP is a disease that occurs in 66% of infants born < 1250 g and in 82% of infants born under 1000 g [24]. Moreover, in the WINROP study, which is a web-based screening software tool and was used to investigate ROP risk factors, low weight gain associated with serum insulin-like growth factor 1 (IGF-1) level was found to be one of the other risk factors [25]. Other specific postnatal factors that increase the risk for ROP include sepsis, blood transfusion, and IVH [26]. Similar to the findings in these studies, in our study, gestational week, birth weight, mechanical ventilation rate, total duration of oxygen exposure, BPD rates, proven sepsis rates, maximum CRP levels, and packed red blood cell transfusion rates were found to be significantly higher in the ROP group. Similarly, it was thought that the low ANC observed in the ROP group was related to the infants susceptible to sepsis, one of the risk factors for ROP. ANC significantly correlated with sepsis and CRP levels. Almost all results appear to be related to individuals with chronic lung disease associated with low birth weight and individuals susceptible to sepsis due to their vulnerability and weak immune response to pathogen microorganisms. Another result that we did not encounter in our study that has been found in other studies was the significantly higher number of congenital hypothyroidism cases in the group with observed ROP. This finding was not expected. When congenital hypothyroidism cases were examined in detail, it was observed that birth weight (1068 versus 1395 g) was significantly lower and oxygen exposure duration (51 versus 24 days) were significantly higher in those with hypothyroidism. The main reason for this result seems to be related to low birth weight. So, this result was interpreted as a confounding factor. Studies examining the relationship between weight gain, somatic growth factors, such as insulin-like growth factor 1 (IGF-1), and ROP have shown an inverse relationship between weight gain and ROP [27, 28]. IGF-1was used as a surrogate marker for postnatal growth in another study. Although IGF-1 levels were not measured in our study, significantly more ROPs in those with poor postpartum weight gain were observed similar to these studies. It was noticed that the differences in weight gain were significant in the first four weeks. Weight gains in the first four weeks and between the second and fourth weeks were significantly lower in the group with ROP.

The present study had some limitations. First, it was a retrospective study. It could have been a prospective randomized controlled study to predict risk factors associated with ROP, especially with respect to understanding the effects of carnitine replacement on ROP. Second, a different period may have influenced the results of such different approaches.

Conclusions

In conclusion, carnitine supplementation may offer protection against ROP development during exposure to oxygen in premature infants through the relationship between carnitine and angiogenesis, less mechanical ventilation and complications, and less exposure to oxygen. To explain these interactions, further prospective randomized controlled studies with a larger sample size should be conducted to understand the relationship between the supplementation of carnitine and ROP in premature infants.

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