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Original Article

Evaluation of the Effect of L-Carnitine Supplementation in Preterm Neonates Suffering from Respiratory Distress Syndrome

Safaa Adel Beshir [1]*, Mohamed Abdel-Salam Zannoun [2], Mohamed Ibrahim El Samanoudy [2], Hesham Samir Abd Al-Samee [3]

[1] Department of Pediatrics, Damanhour Medical National Institute, Ministry of Health, Egypt

[2] Department of Pediatrics, Damietta Faculty of Medicine, Al-Azhar University, Egypt

[3] Department of Clinical Pathology, Damietta Faculty of Medicine, Al-Azhar University, Egypt

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*Corresponding author

Email: safaa.mahmoud2606@gmail.com

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ABSTRACT

Background: Carnitine is one of hydrophilic amino acid derivatives participating in pulmonary surfactant production in infants. The deficiency of Carnitine might lead to the incidence and severity of respiratory distress syndrome [RDS] in preterm infants.

Aim of the work: The aim of this work is the assessment and evaluation of L- carnitine therapy effect on the prognosis of respiratory distress syndrome.

Patients and Methods: The study included a total number of 90 preterm infants with RDS, categorized into two groups; group I [40 cases] with sufficient level of l-carnitine and group II [50 cases] with deficient l-carnitine. Both groups are subdivided into two subgroups; intervention group [received carnitine] and control group. Patients with sufficient carnitine levels received Carnitine supplementation at a dose of 10 mg/kg/day. Patients with deficient carnitine levels received Carnitine therapy at a dose of 30 mg/kg/day Follow-up was carried out to assess the need of respiratory support, oxygenation, hospital stay and mortality.

Results: The mean gestational age was 31.62 ± 2.18 wks. The mean birth weight was 1.58 ± 0.41 Kg. Newborns with deficient carnitine level were had lower birth weight [1.68 ± 0.42 Kg vs. 1.50 ± 0.39 Kg; P=0.046] and exhibited more frequency of mechanical ventilation [P=0.021]. In the sufficient Carnitine group, carnitine supplementation was associated with improvement of weight [P=<0.001] and early onset of enteral feeding [P=0.013]. In the deficient carnitine group, carnitine supplementation was associated with lower need [P=0.031] and short duration [P=0.006] of mechanical ventilation.

Conclusion: The supplementation of Carnitine for infants with sufficient carnitine has a significant positive effect on their growth and weight gain. Carnitine therapy for infants with deficient carnitine significantly reduces mechanical ventilation requirement and duration, improved chest X- ray, shortened duration to reach full enteral feeding and the duration of neonatal intensive care unit [NICU] stay.

Keywords: L-Carnitine; Preterm; Neonates; Respiratory Distress Syndrome; Surfactant.

INTRODUCTION

Respiratory distress syndrome [RDS], or hyaline membrane disease, almost occurs in premature infants. The severity and occurrence of RDS are related inversely to the gestational age of the newborn infant [1].

The impaired surfactant synthesis and secretion lead to the incidence of RDS resulting in ventilation-perfusion [V/Q] inequality, atelectasis, hypo-ventilation with resultant hypoxemia and hypercarbia [2].

Pulmonary surfactant is produced and secreted by type II epithelial cells in the alveolus. It is composed of phospholipids predominantly di-palmitoylphosphatidylcholine [DPPC] with lesser amounts of other phospholipids [3], including phosphatidylglycerol [PG], phosphatidylethanol-amine, and phosphatidylinositol. Surfactant lines the alveolar surface and prevents atelectasis at end-expiration by minimizing surface tension on air-water surfaces, so a deficiency or dysfunction of pulmonary surfactant resulting in inadequate pulmonary function and respiratory failure [4].

Carnitine is one of the hydrophilic amino acid derivatives produced in the liver and kidney from lysine and methionine; its function is to facilitate and enable the transport of long-chain fatty acids through the mitochondrial membrane so as to make them available for beta-oxidation. Carnitine is present in human and cows' milk formula, but parenteral nutrition solutions do not usually contain carnitine [5].

Carnitine is crucial for the fetus provided via placental transport. Fetal tissues store an increasing amount of carnitine as long as the gestational age increases; yet, preterm infants are at an increased risk of carnitine deficiency as a result of low levels of α-butyrobetaine hydroxylase, a catalyzing enzyme in the final step of the carnitine biosynthetic signaling pathway. Thus, preterm infants require exogenous carnitine supplementation for carnitine homeostasis [6, 7].

THE AIM OF THE WORK

It has been suggested that L-carnitine given to RDS patients may be used for surfactant synthesis, but the effect of Carnitine prophylaxis or therapy on the outcome of RDS is not established yet. Due to the frequency of preterm deliveries and the subsequent occurrence of RDS, the present study was conducted to evaluate the effect of L- carnitine therapy or supplementation on the clinical outcomes of respiratory distress syndrome.

PATIENTS AND METHODS

This randomized clinical trial included 90 preterm [gestational age ≥ 28 to ≤ 36 weeks] newborns with RDS selected randomly in a consecutive sampling way and followed up in Al-Azhar University Hospital, New Damietta at the neonatal intensive-care unit over a period of 12 months between January 2020 and January 2021. The gestational age of infants was calculated from the date of the last menstrual period of their mothers, confirmed using the New Ballard score [8].

Exclusion criteria: Neonates received surfactant in early post-delivery before enrollment in the study, neonates with apparent congenital anomalies, clinical and/or laboratory picture of sepsis, birth asphyxia or congenital pneumonia, maternal medical conditions [chorioamnionitis, endocrinal diseases such as diabetes mellitus, thyroid or adrenal dysfunction, received any hormonal therapy or drugs during pregnancy [except corticosteroids for lung maturation]].

Patient grouping: Grouping of patients was based on the measured level of l-carnitine, then evaluation of the efficacy of L-carnitine supplement-ation through a prospective cohort study. Ninety preterm infants with RDS were divided according to the measured level of serum total l-carnitine [within 6 hrs. from delivery] into two main groups: **Group I [sufficient group]:** with normal level of L-Carnitine, and **Group II [deficient group]:** with low level of L- Carnitine. Each main group was further subdivided into two subgroups:

The sufficient group [I] was divided into: Group IA: received L-carnitine in a supplementary dose [10 mg/kg/day, three times per day] and, Group IB: didn't receive supplementation [9].

The deficient group [II] was divided into: Group IIA: received l- carnitine in a therapeutic dose [30 mg/kg/day, three times per day] and, Group IIB: didn't receive any carnitine therapy [9].

Carnitine was intravenously given to the infants during breastfeeding, and then it was administered via the enteral route when the patient began enteral feeding. All the cases which received L- carnitine either in supplementary or therapeutic does continued to receive the treatment until either discharge or death.

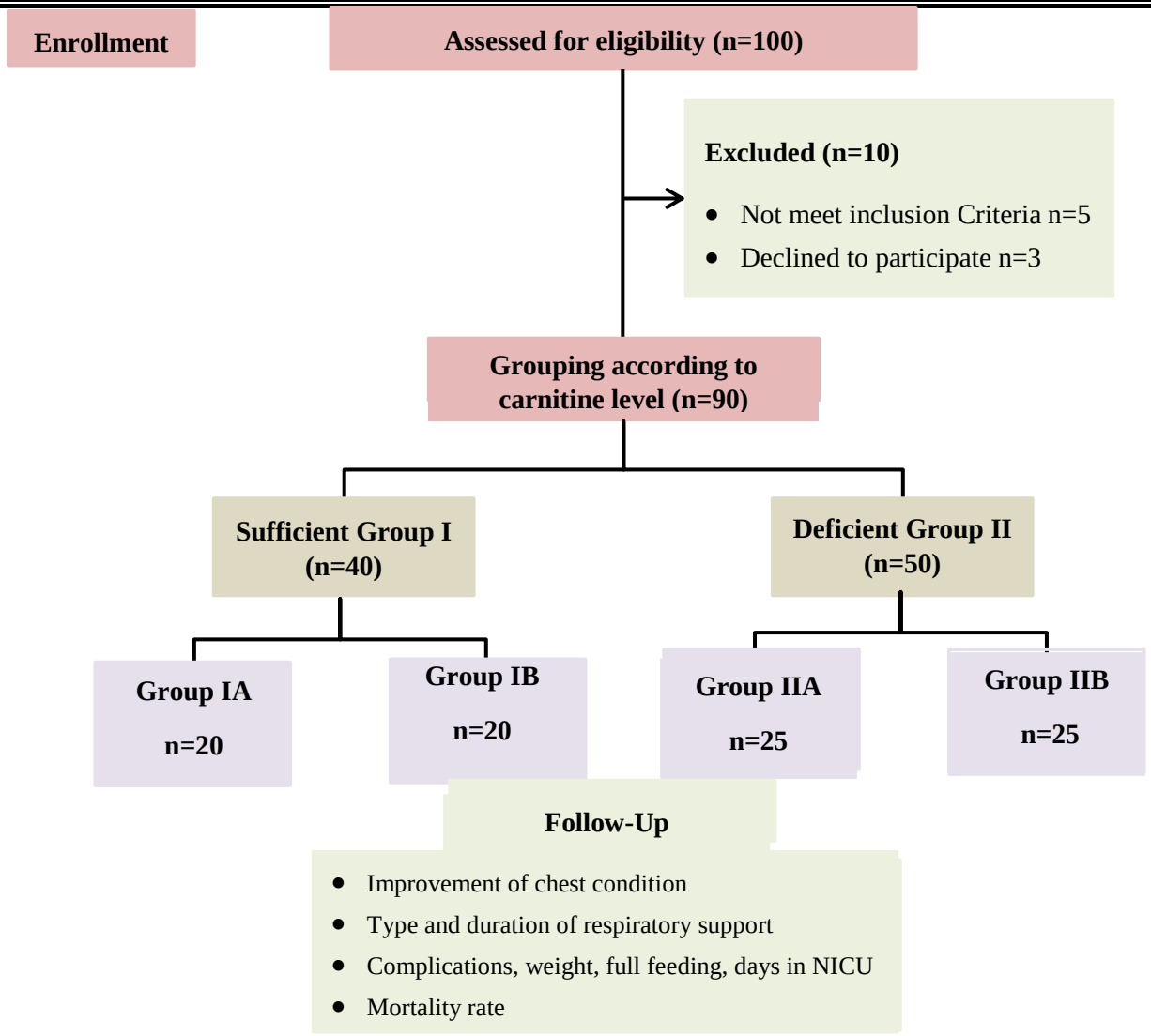

Figure [1]: Diagram of patient grouping in the present study

Serum Carnitine level was measured in all infants during the first 6 hrs. following birth using ELISA assay. The principle of the used kit in the current study depended on an enzyme-linked immune-sorbent assay [ELISA].

Respiratory support: All neonates diagnosed with RDS were treated with respiratory support according to their RDS degree [clinically and radiologically]. Patients with mild RDS required a fraction of inspired oxygen [FiO2] lower than 0.3 for target saturation 88% to 93% were initially supported by nasal cannula. Patients which more distressed required [FiO2] more than 0.3 to sustain the target saturation were supported by nasal continuous positive airway pressure [CPAP], with a positive end expiratory pressure ranged from 5-8 cm H_2O. Patients that required FiO2 of >0.35 0.40 on CPAP to sustain optimal blood O_2 saturation [PaO2, >50 80 mmHg], SpO2 of 88 93% [as determined via pulse oximeter] were intubated using an endotracheal tube and ventilated according to their RDS degree and provided with surfactant replacement therapy if needed [in case of bilateral opacities of the lung]. The total dose of surfactant was 100 mg phospholipids/kg birth weight [4 ml/kg], which was subsequently divided into four quarter-dose aliquots. Surfactant replacement therapy was repeated after 6–24 h when improvement of clinical and laboratory RDS results were not observed. The patients were then subjected [weaned] to NCPAP following the improvement of their respiratory condition. The aim of the therapy was to maintain SpO2 of 88 93% [10].

Outcomes

Primary outcome: clinical improvement of respiratory pathology as indicated by need and duration of mechanical ventilation

Secondary outcomes: initiation of enteral feeding, incidence of complications, weight gain, NICU duration, improvement of CXR and patient mortality.

Ethical Consideration

Consent from the parents of the infants has been orally obtained after explaining the objectives, as well as methodology of study. Each parent had the right to refuse or withdraw consent at any time. The approval of the ethics Committee at the Institute of Postgraduate Childhood Studies [IPGS] has been also obtained foe the protocol of the present study.

Statistical Analysis

Data has been analyzed using IBM SPSS software package version 20.0. [Armonk, NY: IBM Corp]. Qualitative data were described using number and percent. In order to verify the normality of distribution, the Kolmogorov-Smirnov test was used. Quantitative data were described using range [minimum and maximum], mean and standard deviation. For categorical variables, Chi-square test was used to compare between different groups. Fisher's Exact test was used as a correction for chi-square when more than 20% of the cells have expected count less than five. Student t-test was used for normally distributed quantitative variables, in order to compare both of the studied groups. As for abnormally distributed quantitative variables, Mann Whitney test was used to compare between the studied groups. And to detect the most parameters affected by the level of L-carnitine, Logistic Regression was used. Significance of the obtained results was judged at the 5% level.

RESULTS

The present study included 90 preterm infants with RDS, 45 females and 45 males. The mean gestational age was 31.62 ± 2.18 weeks [range, 28–36 weeks]. The average birth weight of the infants was [1.58 ± 0.41 kg], Those infants were separated into Group I [40 cases 44.4%] with sufficient level of l-carnitine [39.64 ± 3.53] and group II [50 cases 55.6%] with deficient l-carnitine [17.04 ± 4.19].

There was no significant difference between sufficient and deficient groups regarding age, sex and mode of delivery. Regarding the mean weight of the two groups, it was significant statistically lower in the deficient group than the sufficient group [P=0.046]. The main initial respiratory support was CPAP in both of sufficient and deficient group. Regarding the mechanical ventilation, 15 cases in the deficient group were initially supported by the mechanical ventilation in contrast to only 4 cases in the sufficient group with statistically significant difference between the two groups [P=0.021] [table 1].

Table [2] demonstrates the comparison between two subgroups of group I [sufficient level of L-carnitine]: group IA, sufficient cases received L-carnitine supplementation, group IB, sufficient cases didn't receive supplementation. There were no statistically significant differences between the two groups regarding general characteristics, type of respiratory support or incidence of complications. Regarding the end prognosis of both groups; group IA had a mean of 5.05±0.69 days to achieve full enteral feeding in comparison to 5.55±0.51 days in group IB with statistically significant difference between two groups [P=0.013]. Also, the weight at the 5th day was significantly higher in group IA [1.98 ± 0.23 kg] than group IB [1.64 ± 0.30 kg] [P<0.001]. The mean duration in NICU was 6.95±1.10 and 7.30±1.49 days in group IA & IB respectively with no statistically significant difference between the two groups. Regarding mortality rate two cases [10%] died in group IB in contrast to one case [5%] in group IA.

Table [3] demonstrates comparison between two subgroups of group II [deficient level of L-carnitine]: group IIA, deficient cases which received L-carnitine therapy, group IIB: deficient cases didn't receive L-carnitine therapy. There were no statistically significant differences between the two groups regarding demographic data. Regarding respiratory support, 44% [11 cases] of group IIB was initially supported by MV for a mean duration of 7.45 ± 1.44 days in comparison with only 16% [4 cases] of group IIA for a mean duration of 4.50 ± 1.29 days with statistically significant difference between the two studied groups. As regard the end prognosis of both groups: Group IIA had a shorter duration of 4.68±0.63 days to achieve full enteral feeding in comparison to 5.44±0.77 days in group IIB with statistically significant difference between the two groups [P<0.001]. Also, the weight at the 5th day was significantly higher in group IIA [1.74 ± 0.21 kg] than group IIB [1.50 ± 0.24 kg] [p<0.001]. The mean duration in NICU was [7.80±2] and [9.04±2.15] days in group IIA and IIB respectively with statistically significant difference between the two groups [P=0.009]. Regarding mortality rate, was 2 [8%] and 3 [12%] in group IIA and IIB respectively with no significant difference between two studied groups [P > 0.05].

Table [4] summarizes the prognostic effect of administration of L-carnitine in a supplementary dose to 20 cases in the sufficient group [group IA] which shows statistical significant difference from the other group that did not receive L-carnitine supplementation [group IB] regarding duration to reach full enteral feeding and weight at the 5th day, otherwise there is no statistical significant difference

between the two groups regarding type and duration of respiratory support , complications, improvement of chest x-ray , days in NICU and mortality rate. Regarding the prognostic effect of administration of L-carnitine in a therapeutic dose to 25 cases in the deficient group [group IIA], there was statistical comparison indicated that group IIA [received L-carnitine] required significantly less mechanical ventilation support for a shorter duration compared with group IIB [didn't receive L-carnitine]. Regarding improvement of RDS grade chest x-ray on the 5th day was significantly improved in group IIA [88% became normal] in contrast to only 36% of group IIB. The table also shows that L-carnitine therapy significantly decreased the duration to achieve full enteral feeding in group IIA [received L-carnitine] compared with group IIB which didn't receive L-carnitine therapy with significant higher weight in infants received carnitine therapy [group IIA]. As regard complications and mortality, there was no statistically significant difference between the two groups.

Table [1]: Comparison between sufficient and deficient carnitine groups regarding demographic data and respiratory support

		Sufficient [GI] [n = 40]	Deficient [GII] [n = 50]	P
Sex	Male Female	18 [45%] 22 [55%]	27 [54%] 23 [46%]	0.396
Gestational age [weeks]		31.83 ± 2.15	31.46 ± 2.22	0.433
Birth weight [kg]		1.68 ± 0.42	1.50 ± 0.39	0.046*
Mode of delivery	Cesarean NVD	36 [90%] 4 [10%]	45 [90%] 5 [10%]	FEp= 1.000
Maternal age [years]		26.43 ± 2.86	26.16 ± 3.27	0.688
Type of respiratory support	Nasal cannula	6 [15%]	4 [8%]	FEp=0.330
	CPAP	30 [75%]	31 [62%]	0.190
	MV	4 [10%]	15 [30%]	**0.021***

*: significant; NVD: Normal vaginal delivery; CPAP: Continuous positive airway pressure; MV: Mechanical Ventilation; FEp: Fisher's Exact test

Table [2]: Demographic data, respiratory support and outcomes in relation to carnitine supplementation among Carnitine-sufficient group

		Carnitine-sufficient group		P
		Group IA [n = 20]	Group IB [n = 20]	
Sex	Male Female	9 [45%] 11 [55%]	9 [45%] 11 [55%]	1.000
Gestational age [weeks]		31.60 ± 2.06	32.05 ± 2.26	0.515
Birth weight [kg]		1.62 ± 0.39	1.73 ± 0.45	0.384
Mode of delivery	CS NVD	16 [80%] 4 [20%]	20 [100%] 0 [0%]	FEp= 0.106
Maternal age [years]		27.25 ± 2.99	25.60 ± 2.54	0.068
Type of respiratory support	Nasal cannula	3 [15%]	3 [15%]	FEp=1.000
	CPAP	16 [80%]	14 [70%]	0.465
	MV	1 [5%]	3 [15%]	FEp=0.605
Complication	Pulmonary HTN	9 [45%]	10 [50%]	0.752
	Pneumothorax	1 [5%]	0 [0%]	FEp=1.000
	Apnea	3 [15%]	5 [25%]	FEp=0.695
Full enteral feeding		5.05 ± 0.69	5.55 ± 0.51	**0.013***
Weight at 5th day		1.98 ± 0.23	1.64 ± 0.30	**<0.001***
Days in NICU		6.95 ± 1.10	7.30 ± 1.49	0.947
Outcome	Discharged Died	19 [95%] 1 [5%]	18 [90%] 2 [10%]	FEp=1.000

*: significant; NVD: Normal vaginal delivery; CPAP: Continuous positive airway pressure; MV: Mechanical Ventilation; HTN: hypertension; NICU: neonatal intensive care unit; FEp: Fisher's Exact test

Table [3]: Demographic data, respiratory support and outcomes in relation to carnitine therapy among Carnitine-deficient group

		Carnitine-deficient group		P
		Group IIA [n = 25]	Group IIB [n = 25]	
Sex	Male Female	15 [60%] 10 [40%]	12 [48%] 13 [52%]	0.395
Gestational age [weeks]		31.28 ± 2.35	31.64 ± 2.10	0.571
Birth weight [kg]		1.52 ± 0.36	1.49 ± 0.42	0.784
Mode of delivery	CS NVD	22 [89%] 3 [12%]	23 [92%] 2 [8%]	^{FE}p= 0.100
Type of respiratory support	Nasal cannula	3 [12%]	1 [4%]	0.609
	CPAP	18 [72%]	13 [52%]	0.145
	MV	4 [16%]	11 [44%]	**0.031***
Duration of respiratory support [days]	Nasal cannula	3.0 ± 1.0	4.0	-
	CPAP	4.39 ± 1.33	4.85 ± 1.34	0.352
	MV	4.50 ± 1.29	7.45 ± 1.44	**0.006***
Complication	Pulmonary HTN	16 [64%]	19 [76%]	0.355
	IVH	2 [8%]	4 [16%]	^{FE}p=0.667
	Apnea	4 [16%]	7 [28%]	0.306
Full enteral feeding		4.68 ± 0.63	5.44 ± 0.77	**<0.001***
Weight at 5th day		1.74 ± 0.21	1.50 ± 0.24	**<0.001***
Days in NICU		7.80 ± 2.0	9.04 ± 2.15	**0.009***
Outcome	Discharged Died	23 [92%] 2 [8%]	22 [89%] 3 [12%]	^{FE}p=1.000

*: significant; NVD: Normal vaginal delivery; CPAP: Continuous positive airway pressure; MV: Mechanical Ventilation; HTN: hypertension; NICU: neonatal intensive care unit; ^{FE}p: Fisher's Exact test

Table [4]: Univariate Logistic regression analysis for the parameters affected by administration of L-carnitine in the sufficient and deficient groups

	Effect of carnitine supplementation [Group IA vs. group IB]		Effect of carnitine therapy [Group IIA vs. group IIB]	
	OR [95%C.I]	P	OR [95%C.I]	P
Mechanical ventilation	0.298 [0.028 – 3.146]	0.314	0.242 [0.064 – 0.916]	**0.037***
Duration of MV	1.352 [0.141 – 12.932]	0.793	0.285 [0.087 – 0.939]	**0.039***
Normal CXR at 5th day	3.353 [0.318 – 35.364]	0.314	13.04 [3.04 – 55.9]	**0.001***
Full enteral feeding	0.250 [0.078 – 0.804]	**0.020***	0.200 [0.070 – 0.571]	**0.003***
Weight at 5th day	113.46[4.837 – 2661.3]	**0.003***	92.665[5.168 – 1661.4]	**0.002***
Days in NICU	0.806 [0.491 – 1.325]	0.395	0.721 [0.515 – 1.009]	0.056
Mortality	0.474 [0.039 – 5.688]	0.556	0.638 [0.097 – 4.188]	0.639

*: significant; OR: odds ratio; C.I: Confidence interval MV: Mechanical Ventilation; NICU: neonatal intensive care unit.

DISCUSSION

Recently, numerous factors associated with the development and/or the severity of RDS have been studied; the presence of low serum carnitine in preterm infants with RDS [11] has been identified.

Preterm infants in this study were divided into Group I with sufficient level of l-carnitine and group II with deficient level of l-carnitine, with high prevalence of L-carnitine deficiency [50/90; 55%] among preterm infants with RDS in concordance with Taman *et al.* [12] study. It has been proven that carnitine has a crucial function in the cellular metabolic processes, such as aerobic catabolism of glucose and beta-oxidation of free fatty acids. The diaphragmatic muscle requires carnitine for contractility because of its importance in metabolism. Premature infants may have lower glycogen levels, and as a result they use more carnitine for fatty acid oxidation, resulting in a decrease in carnitine levels [9].

The present study showed no correlation between sex and carnitine deficiency, which comes in agreement with Ozturk *et al.* [9] and Taman *et al.* [12] study where the serum carnitine levels of all patients were evaluated on day 1, and no correlation was observed between carnitine levels and sex.

Regarding the gestational age and birth weight, carnitine deficiency was associated with lower birth weight, but not related to gestational age. Actually, L-carnitine transport to the lungs of the premature infants likely increases for surfactant synthesis, which may lead to a reduction in the level of carnitine in the premature infants with RDS [13].

Carnitine causes lung maturation via membrane phospholipid repair activity and has been reported to have surfactant like properties so its deficiency may have a further negative effect on decreased surfactant synthesis in lung tissue; hence the infant quickly consumes carnitine for fatty acid oxidation and surfactant synthesis [14].

As regard the end prognosis of both groups, Carnitine-deficient patients who received carnitine therapy had a shorter duration of days to achieve full enteral feeding. In addition, carnitine therapy has a positive effect on growth and weight gain in infants with RDS, which was in agreement with Crill *et al*. [15] who reported that carnitine therapy has a positive effect on catch-up growth, and may improve periodic breathing in premature neonates.

The present study showed that group IIA [treated with carnitine] stayed in NICU for shorter duration than group IIB, which came in agreement with Said *et al*. [16] who stated that L-carnitine administration was associated with a significant reduction in the duration of hospital stay.

Conclusion: Carnitine supplementation at a dose of [10 mg/kg/day] for infants with RDS and sufficient level of serum carnitine has a significant positive effect on their growth and weight gain, while carnitine therapy at a dose of [30 mg/kg/day] for infants with RDS and deficient level of serum carnitine much reduces mechanical ventilation requirement and duration. Thus, L-carnitine maybe used for preterm infants with RDS to decrease the need of mechanical ventilation and oxygen requirements in addition to its role in growth.

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