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Evaluation of the Effect of Oral Carnitine Supplementation on Apnea of prematurity in Premature Neonates in Hospitals Affiliated to Shiraz University of Medical Sciences

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Abstract

Background and objective: Premature neonates are at increased risk for carnitine deficiency, and carnitine supplementation can be effective in preventing and treating apnea. However, there is not enough information to support the effect of carnitine on the treatment of apnea. Thus, this study was conducted to evaluate the effect of oral carnitine supplementation on prevention of apnea of prematurity in premature neonates in hospitals affiliated to Shiraz University of Medical Sciences. Methodology: In this study, a total of 112 neonates with birth weight equal to or less than 1500 grams or with gestational age equal to or less than 32 weeks of age were included into the study with the consent of the parents. Out of these 112 neonates, 60 were placed in the control group and 52 were placed in the intervention group. During the first 72 hours of life, oral carnitine syrup was administered to the intervention group and placebo was given for the control group. Finally, the data were analyzed using SPSS 14 software. Results: The apnea cases were 42.3% and 10.2% in the intervention group and the control group (10.2%), respectively, which showed a significant difference (P≤0.001). In addition, the percentage of need for CPAP in neonates of intervention group and control group was obtained 40% and 28.3%, respectively. Mechanical ventilation was used 4% in intervention group and 18.3% in control group, reflecting the reduction in the severity of apnea as a result of using carnitine supplementation (P ≤0 / 001). Moreover, an increase in the average height from 13.3% to 36.5% during two weeks was seen in the intervention group compared to control group. Conclusion: The results of this study revealed that oral carnitine supplementation can reduce the severity of apnea and its severity and it can be effective in increasing height in neonates.

Key words: AOP, PM, IBW

Introduction

One of the common problems in premature neonates is apnea deficiency, which is defined as a stop in breathing for more than 15-20 seconds. Apnea deficiency occurs in 85% of neonates born before the gestational age of 34 weeks (Atik et al., 2016; Miller and Martin, 2011). The first episode of apnea deficiency can occur in the first 24 hours of life in neonates who have spontaneous breathing without RDS, but it occurs later in neonates who receive mechanical ventilation (Carlo et al., 1982). In AOP (Apnea of prematurity) neonates, periodic respiratory distress is longer than that in neonates without AOP and the general time spent on periodic breathing is longer. Both of these factors lead to the exacerbation and more prevalence of bradycardia along with a loss of oxygen saturation (SPO2) (American Academy of Pediatrics, 1987). The prevalence of apnea has inverse relationship with gestational age and birth weight, and apnea attacks are more prolonged in the gestational age of 28-24 weeks. Apnea can occur from the first day of life in neonates without RDS and a few days later in neonates with ROD. The duration and number of apnea cases decrease with an increase in the age of the neonate and disappears at the age of 42-38 weeks (Eichenwald, Aina and stark, 1997).

The results of various studies have revealed that apnea deficiency occurs due to the lack of maturity of the respiratory control mechanisms, including reduced sensitivity to CO2 and hypoxia, and larynx closure due to larynx stimulation. Recent evidence has also shown that inflammation in the central nervous system (CNS) may be also involved in development of apnea deficiency (Morton and Smith, 2016). AOP medical treatment includes supportive care and drug therapy. Supportive care includes tactile stimulation, changing the status of disease to maintain open airway and ventilation support such as O2, CPAP and mechanical ventilation (Bhatid, 2000). Some studies have shown that the use of methylxanthines, theophylline, caffeine and doxapram may be effective in the treatment of apnea in premature neonates (Kua and Huey, 2017; Zulqarnain et al., 2019). Additionally, dietary supplements such as carnitine and keratin are also used in AOP treatment. Carnitine facilitates the transfer of fatty acids into the mitochondria to produce ATP. Lack of energy production in premature neonates due to carnitine deficiency causes hypotension, apnea, and reduced growth (Mhairi et al., 2005). Human fetus receives exogenous carnitine from placenta at late pregnancy, and is stored in various tissues such as the brain and its level in brain is directly associated with gestational age (Whitfield et al., 2003). Thus, due to the high importance of presence of enough

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carnitine in premature neonates in order to prevent apnea as well as lack of comprehensive studies on the effect of carnitine on

prevention of apnea in premature neonates, this study was conducted with the aim of evaluating the effect of oral carnitine supplementation in prevention of apnea in premature neonates in hospitals affiliated to Shiraz University of Medical Sciences.

Methodology

In this study, based on statistical counsellor view and T-test, α=0.05 and 1-β=90, a total of 112 neonates with birth weight equal to or less than 1500 grams or with gestational age equal to or less than 32 weeks were was included into study with consent of the parents. Out of these 112 neonates, 60 patients were randomly placed in the control group and 52 patients were placed in the intervention group. During the first 72 hours of life, oral carnitine syrup at dose of 100mg/ kg/day along plus oral nutrition with gastric catheter were administered to the intervention group and placebo was given to control group. It should be noted that the volume of placebo was equal to the volume of carnitine syrup administrated. The duration of the study was 2 weeks or until 34 weeks of gestational age. The exclusion criteria of study included neonates with sepsis, congenital and chromosomal anomalies, intracerebroventricular hemorrhage with grade 3 or 4, or lack of consent of the parents of the neonates. Patients' data included birth weight, delivery method, gestational age, Apgar score, gender, the use of corticosteroids before birth, causes of prematurity, associated illnesses and carnitine deficiency symptoms were recorded before the study. The head circumference, weight and height of the neonates were measured once per week.

Apnea cases were recorded using NICU flowsheet at the bedside of the nurses by each nursing staff in each work shift, and bradycardia and respiratory distress more than 20 -15 sec (mild apnea) and respiratory distress for more than 20 seconds (moderate), and drop in SPO2 below 85% for 5 minutes by Puls oximetery were recorded by staff at each work shift (three times per day). Simultaneously, the apnea response to their current treatments as response to stimulation and the need for CPAP and mechanical ventilation in flowsheet were recorded. The complications of oral carnitine were recorded by staff in the medical record. The conventional treatments for prematurity and related illnesses related to antibiotics, methylxanthines, and even CPAP or mechanical ventilation continued for neonates in both groups. Finally, the data were analyzed using SPSS 14 software.

Results

In terms of demography, out of 112 neonates studied, 63 (56.3%) were male and 49 (43.8%) were female. The mean weight of neonates was 1.9667 g and 1.5000 g in the control group. With regard to delivery method, 49 (83.1%) people had caesarian section and 11 (11.9%) people had vaginal delivery in the control group and 36 (69.2%) people had caesarian section and 16 (30.8%) people had vaginal delivery in the intervention group. The results of this study showed that Apgar score in control group was more than 8 in 14 people (23.3%), between 6 and 8 in 34 people (56.7%) and below 6 in 12 people (20%). In the intervention group, it was above in 17 people (32.7%), between 6 and 8 in 30 people (57.7%) and below 6 in 5 people (9.6%). With regard to gestational age, in the control group, it was reported 30-32 weeks in 15 people (25%), 28-30 weeks in 28 people (46.7%) and below 28 weeks in 17 people (28.3%). In intervention group, it was reported 30-32 weeks in 24 people (46.2%), 28-30 weeks in 21 people (40.4%), below 28 weeks in 7 people (13.5%), and in the whole study, it was reported 30-32 weeks in 39 people (34.8%), 28-30 weeks in 49 people (43.8%) and below 28 weeks in 24 people (21.4%). in the control group, the cause of prematurity and preterm delivery was due to PROM in 35%, PLP in 27%, multiple pregnancy in 25%, and in the intervention group, it was due to PROM in 33%, PLP in 25%, and multiple pregnancy in 33%, and in the whole study, it was due to PROM in 34%, PLP in 26% and multiple pregnancy in 29%. The most common associated illness in both groups was respiratory distress syndrome (RDSL). However, TTN cases were higher in the intervention group. With regard to the symptoms of carnitine deficiency, 90 (85%) of neonates had symptoms of hypotension, low growth, and apnea in both groups. In general, all premature neonates had symptoms of carnitine deficiency. Complications seen as a result of carnitine treatment included lethargy in 38 people (73.1%) and frequent vomiting in 5 people (9.6%) in 9 people (17.3%) and no complication was reported in 5 people. With regard to the presence of absence of apnea in the control group, 6 people (10.2%) had no apnea, 21 people (35.6%) had mild apnea, 13 people (22%) had moderate apnea, 7 people (11.9%) had both mild and moderate apnea, and 11 people (18.6%) had moderate apnea with bradycardia and one person (1.7%) had mild apnea associated with bradycardia, and in the intervention group, 22 people (42.3%) had no apnea, 21 people (40.4%) had mild apnea, 8 people (15.4%) had mild and moderate apnea, and 1 person (1.9%) had moderate apnea with bradycardia. In response to apnea treatment in the control group, 6 people (10%) recovered without treatment, 17 people (28.3%) responded to stimulation, 17 people (28.3%) required CPAP, 11 people (18.3%) needed mechanical ventilation, 8 (13.3%) needed CPAP and then mechanical ventilation, and one person (1.7%) was treated with CPAP and then with stimulation, and in the intervention group, 21 people (42%) did not need treatment, 5 patients (10%) were treated with stimulation, 20 people (40%) needed CPAP, 2 people (4%) needed mechanical ventilation, and 2 people (4%) needed stimulation, and then, CPAP. Weight gain was done during 2 weeks of study. In the control group, 51 people (85%) gained weight by 100 g and 9 people (15%) gained weight by more than 150 g. In the intervention group, 39 people (75 %) gained weight by 100 g and 12 people (23.1%) gained weight more than 150 g. in addition, one case of death was seen. In total, 90 (80.4%) weights were 100 grams and 21 (18.8%) weights were more than 150 grams (Table 1).

Table 1- Weight gain in 2 weeks: 1) 100 g weight gain, 2) above 150 g weight gain

		Weight gain			Total
		.00	1.00	2.00	
GROUP	Control count	0	51	9	60
	% within GROUP	0.0 %	85.0 %	15.0 %	100 %
GROUP	Case Count	1	39	12	52
	% within GROUP	1.9 %	75.0 %	23.1 %	100.0 %
Total	Count	1	90	21	112
	% within GROUP	0.9 %	80.4 %	18.8 %	100.0 %

With regard to an increase in head circumference during 2 weeks, in the control group, 52 people (86.7%) had a 1 cm increase in head circumference and 8 people (13.3%) had a 2 cm increase in head circumference, and in the intervention group, 43 people (82.7%) had a 1 cm increase in head circumference and 8 people (15.4%) had a 2 cm increase in head circumference. In general, 95 people (84.8%) had a 1 cm increase in head circumference and 16 people (14.3%) had a 2 cm increase. P-value was about 0.525 which is not significant (Table 2).

Table 2- Increase in head circumference over 2 weeks: 1 - 1 cm, 2 - 2 cm

		Increase in head circumference			Total
		.00	1.00	2.00	
GROUP	Control count	0	52	8	60
	% within GROUP	0.0 %	86.7 %	13.3 %	100 %
GROUP	Case Count	1	43	8	52
	% within GROUP	1.9 %	82.7 %	15.4 %	100.0 %
Total	Count	1	95	16	112
	% within GROUP	0.9 %	84.8 %	14.3 %	100.0 %

Measurement of height during two weeks of the study also showed that in the control group, 52 people (86.7%) had a 1cm increase in height and 8 people (13.3%) had a 2cm increase in height, and in the intervention group, 32 people (61.5%) had a 1 cm increase in height and 19 people (36.5%) had a 2cm increase in height. P-value was about 0.003 which was significant (Table 3).

Table 3- increase in height over 2 weeks: 1 - 1 cm, 2 - 2 cm

		Increase in height			Total
		.00	1.00	2.00	
GROUP	Control count	0	52	8	60
	% within GROUP	0.0 %	86.7 %	13.3 %	100 %
GROUP	Case Count	1	32	19	52
	% within GROUP	1.9 %	61.5 %	36.5 %	100.0 %
Total	Count	1	84	27	112
	% within GROUP	0.9 %	75.0 %	24.1 %	100.0 %

Discussion

Apnea is one of the most common problems in premature neonates hospitalized in the neonatal intensive care unit in hospitals (Eichenwald, 2016). Premature neonates are at the increased risk of carnitine deficiency, and carnitine supplementation can be effective to prevent and treat apnea. However, there is no sufficient information to support the effect of carnitine on apnea treatment (Kumar, Kabra and Paes, 2004). Thus, this study was conducted with the aim of evaluating the effect of oral carnitine supplementation on prevention of apnea in premature neonates in hospitals affiliated to Shiraz University of Medical Sciences. The analysis of the results obtained from both control and intervention groups and their comparison showed that reduction in the occurrence of apnea attacks and severity of attacks in the intervention group, compared to the control group .The apnea cases showed a significant reduction in the intervention group compared to the control group, and the neonates without apnea were reported more in the intervention group, but they were almost similar in mild and moderate apnea. The percentage of neonates required apnea treatment other than conventional treatments were more in the intervention group than that of the control group and the percentage of need for CPAP in the intervention group was higher compared to the control group. In other words, the severity of apnea was lower and did not require mechanical ventilation. The use of mechanical ventilation was 4% in the intervention group and 18.3% in the control group, indicating a reduction in the severity of apnea due to carnitine supplementation.

In a study conducted by IaFolla et al (1996), the results similar to the results of current study were reported, since IaFolla et al (1996) reported that the use of carnitine reduces the occurrence of apnea attacks and reduces the need for mechanical ventilation and CPAP and improves the growth of premature neonates. However, in studies conducted by Kumar et al (2004; 2004) and O'Donnell et al (2002), no difference was reported between control and intervention groups in terms of reducing apnea cases and their severity. The factors making this study to be distinguished from previous studies are the number of studied children and the use of higher dose of carnitine supplementation, which improves the results. In addition, the use of pre-natal corticosteroid therapy has increased in recent years, which

leads into maturity of central respiratory centers. Accordingly, it leads to appropriate central and environmental responses to the level of blood CO2 level and hyperoxia or hypoxia in premature neonates.

The gestational age in this study was higher in the carnitine supplementation group than that in the control group, which this difference was statistically significant. The percentage of neonates with higher gestational age was more and it is one of the reasons for our study success. The results of our study are in line with those of the research conducted by O'Donnell et al (2002) who showed that the effect of carnitine at gestational age over 34 weeks was more significant. Another factor that was evident in this study was the association of more cases of transient tachypnea of the newborn (TTN) in the intervention group compared to the control group, indicating a decrease in the severity of pulmonary diseases in the neonates of the intervention group. However, the number of neonates with RDS was almost similar in both groups .The results of this study showed that vaginal or normal delivery was more in the intervention group than that in the control group and it could be effective in reducing the apnea cases without the effect of carnitine in the intervention group and explain a decrease in the severity of apnea. With regard to the effect of gender, the results inconsistent with the results of previous studies were obtained in this study, and the percentage of male neonates in the current study was higher than that of other studies, which could be due to increased use of induction methods of reproduction and IVF, which select more boy fetuses and the odds of having a preterm delivery is also higher in these cases.

Conclusion

The results of this study showed that oral carnitine supplementation may be more effective in neonates with higher gestational age, the neonates who received corticosteroid before birth, the neonates born with vaginal delivery, and the neonates with higher Apgar score. It is also effective in reducing the apnea cases and its severity and increasing the height of the neonates. It is recommended that more extensive and multi-central studies to be conducted in order to evaluate the use of carnitine as a nutritional supplement for the treatment of apnea.

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