Clinical Effects of Carnitin Supplementation on Hypoglycemia, Apnea and Sepsis in Very Low Birth Weight Neonates

Ashraf Mohammadzadeh MD1* Ahmad Shah Farhat, MD2 Rana Amiri, MSC3 Habibollah Esmaeli, PhD4

1,2- Neonatal Research Center, School of Medicine, Emam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
3-Masters of pediatric nursing, Neonatal Research Center, School of Medicine, Mashhad, University of Medical Sciences, Mashhad, Iran
4- Neonatal Research Center, School of Medicine, Mashhad, University of Medical Sciences, Mashhad, Iran

Abstract

Background
Systemic carnitine deficiency may present with apnea, hypotonia, and poor growth. Premature infants often manifest these symptoms and are at risk of developing carnitine deficiency because of immaturity of the biosynthetic pathway, lack of sufficient predelivery transplacental transport, and lack of sufficient exogenous supplementation.

Objective
This study was undertaken to examine the effect of carnitine supplementation on hypoglycemia, apnea and sepsis in premature infants.

Methods
In this clinical study 60 preterm infants less than <1500 g birth weight were enrolled. The subjects in the carnitine group received 20 mg/kg/day oral supplemental by nasogastric tube in addition to routine nursing care within 96 hours of birth. Episodes of apnea, hypoglycemia and sepsis were the primary outcome measures recorded. The control group received routine nursing care.

Results
Episodes of apnea and the hypoglycemia were similar between the two groups. (P=0.55 and 0.69 respectively).

Conclusion: In this study treatment with carnitine supplementation had no effect on apnea, hypoglycemia and sepsis in very low birth weight neonates.

Key word
Carnitin supplementation, hypoglycemia, apnea, sepsis, very low birth weight neonates

Introduction
Experimental evidence from several investigators suggests that carnitin is a conditionally essential nutrient for neonates. The metabolic functions of carnitine are varied and important in several aspects of neonatal physiology.1) Carnitine, a nutrient normally synthesized from methionine and lysine in the liver and kidney, has been gaining increasing attention as a therapeutic agent since 1960.2) Neonates have a low ability to synthesize carnitine, primarily due to a diminished amount of protein-bound trimethyllysine and decreased activity of the enzyme gamma butyrobetaine hydroxylase, which is necessary for the conversion of gamma butyrobetaine to carnitine. In addition, due to decreased tissues stores and placental transfer of carnitine occurring during the third trimester, premature neonates are at risk of developing carnitine deficiency.3-5) Since premature neonates and infants may not adequately synthesize endogenous carnitine, they must rely on exogenous intake to prevent deficiency.3-6) In addition, carnitine supplementation has been found to be important for weight gain in the neonatal population.7) Carnitine deficiency may be an etiological factor in the limited ability of premature babies to utilize parenteral lipid. In vitro studies have suggested that fatty acid oxidation is impaired when the tissue carnitine levels fall below 10% of normal. Therefore
relative carnitine deficiency may impair fatty acid oxidation.\(^{(8)}\) Carnitine deficiency may have important effects on the premature neonate. Ketone production provides a critical energy source for the developing brain and nervous system. Similarities exist between complications that are common in premature neonates and those that develop from carnitine deficiency syndromes occurring outside the neonatal period, specifically respiratory and gastrointestinal dysfunction, hypotonia, hypoglycemia, failure to thrive, and increased infection risk.\(^{(9-11)}\)

We hypothesized that many of the complications seen with prematurity may be actually secondary to carnitine deficiency or insufficiency. The objective of this study was to evaluate the effect of oral carnitine supplementation on hypoglycemia, apnea and sepsis in very low birth weight neonates.

**Methods**

This was a prospective, randomized and blind trial study enrolling neonates from neonatal intensive care units (NICU) in Mashhad-Iran. The ethics committee of our university approved this study. Informed parental consent was obtained prior to enrollment. Neonates were eligible for enrollment if they were 3 days of age, had a birth weight of 1500 g, appropriate for gestational age and had stable condition. Neonates were excluded from the study if they had inborn errors of metabolism, chromosomal abnormality, respiratory distress or cardiovascular problem. Neonates were studied for catch up birth weight. Randomization into carnitine or control groups was conducted based on a list of random numbers. The subjects in the carnitine group received 20 mg/kg/day oral supplemental carnitine by nasogastric tube in addition to routine nursing care. Controls received routine nursing care. Episode of apnea, hypoglycemia and occurrence of sepsis were checked daily. Sepsis was evaluated by clinical signs and symptoms and positive blood or CSF cultures. Episodes of apnea were documented by the nursing staff or physicians records from pulse oximetery if they had breathlessness for more than 20 seconds or heart rate less than 100 beat/minute. Hypoglycemia was checked by glucometer in the morning at 5 am. If they had blood sugar less than 50 mg/dl. Statistical analysis of data between groups was conducted with Student t-test (reported as mean± standard deviation) for continuous data and \(\chi^2\) or Fisher exact tests for categorical data. Repeated measures analysis of variance with multiple comparison testing was used to determine differences between groups. Kruskal–Wallis analysis of variance on ranks was utilized for parametric data. Data with P-values 0.05 were considered significant.

**Results**

Sixty neonates were enrolled in the study between August 2007 and May 2008. Patient characteristics (Table1) were similar between the two groups.

**Discussion**

Methylxanthines (theophylline and caffeine) are the mainstay of pharmacotherapy for idiopathic apnea in premature infants. All 3 types of apnea, i.e. mixed, obstructive, and central, respond to this therapy.\(^{(12)}\) Apnea of prematurity is one of

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=30)</th>
<th>Carnitine (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>29± 1.9</td>
<td>28.2 ± 2</td>
<td>0.16</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1147.3 ± 185.2</td>
<td>1129.6 ± 205.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Apgar score *</td>
<td>7.12± 1.52</td>
<td>6.8± 2.12</td>
<td>0.45</td>
</tr>
<tr>
<td>Male No. (%)</td>
<td>17 (56.7)</td>
<td>12 (40)</td>
<td>0.19</td>
</tr>
<tr>
<td>Cesarean section No. (%)</td>
<td>17 (56.7)</td>
<td>14 (45.6)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Data are mean±standard deviation (range).
the most common disorders of the VLBW infant, affecting >50% of VLBW infants\cite{13, 14}. Despite this treatment, many infants continue to have episodes of apnea associated with bradycardia and hypoxia that are believed to be clinically significant with potentially harmful physiologic changes. So in this study we evaluated effect of carnitine on apnea, hypoglycemia and sepsis of low birth weight neonates. Our results showed that episode of apnea and the hypoglycemia were similar between the two groups. Previous studies of carnitine supplementation have shown varying results, with some studies suggesting benefit and others showing no benefit. A study by Iafolla and Browning demonstrated a beneficial effect on preterm infants with apnea\cite{15}. O’Donnell et al designed to evaluate the role of carnitine in apnea of prematurity, as well as to evaluate the role of carnitine in potentially improving other outcomes. In this trial, infants who received supplemental carnitine did not achieve any reduction in apnea of prematurity whether assessed by CRG data or nursing recorded events.\cite{16} Whitfield et al completed a similar study, and their preliminary findings indicated that carnitine supplementation did not significantly reduce apnea of prematurity.\cite{17} Results in O’Donnell and Whitfield’s study with respect to the response of apnea and the carnitine levels in their carnitine-treated infants are very similar to those observed in our study. Kumar et al had done a study to determine the role of carnitine supplementation in premature infants on apnea of prematurity. Result showed that there was no difference among the groups.\cite{18} Hino et al did a study to assess L-carnitine inhibition of hypoglycemia-induced brain damage in the rat. Their results suggested that l-carnitine prevents hypoglycemia-induced neuronal damage in the hippocampus, presumably by preserving mitochondrial functions. Thus, l-carnitine may have therapeutic potential in patients with hypoglycemia.\cite{19} Increased oxidation of fat is an important host response to sepsis, and carnitine is essential for long-chain fatty acid oxidation. Because neonates have low levels of carnitine, their ability to respond to a septic insult may be impaired.\cite{20}

**Conclusion**

Because in our study carnitine supplementation of VLBW infants seems to have no demonstrable effect on clinical apnea, hypoglycemia and sepsis, prescription of routine carnitine supplementation in VLBW infants requires further study.

**Acknowledgement**

This study was funded by the University of Mashhad. We thank the dedicated nursing and respiratory therapy staffs of the NICU at Imam Reza Hospital and Dr. Sadati for follow up of patients, Miss Mojdeh Mahmoodi and Miss Najme Saberi for collecting data and typing.

**References**

4. Schmidt-Sommerfeld E, Penn D, Sodha RJ, Progler

---

Table 2. Apnea, hypoglycemia and morbidity in the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (N=30)</th>
<th>Carnitine (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode of Apnea No. (%)</td>
<td>23(70)</td>
<td>23(76.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Episode of Hypoglycemia No. (%)</td>
<td>15(51.7)</td>
<td>14(46.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>Positive CSF culture</td>
<td>1(3.3)</td>
<td>2(6.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>Positive Blood Culture</td>
<td>3(10)</td>
<td>4(13.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3(10)</td>
<td>4(13.3)</td>
<td>0.68</td>
</tr>
</tbody>
</table>
15. Iafolla AK, Browning IB. Carnitine deficiency in infantile apnea. Pediatr Res, 1996; 38:312A