Clinical Effects of L-Carnitine Supplementation on Apnea and Growth in Very Low Birth Weight Infants

Jonathan Whitfield, MBChB*; Twyala Smith, RD‡; Heather Sollohub, RD‡; Lawrence Sweetman, PhD§; and Charles R. Roe, MD§

ABSTRACT. *Objective.* **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. This study was undertaken to examine the effect of carnitine supplementation in premature infants.**

Methods. **Eighty preterm infants <1500 g were enrolled in a prospective, double-blind, placebo-controlled study of carnitine supplementation within 96 hours of delivery. Growth, length of hospital stay, and frequency and severity of apnea were the primary outcome measures.**

Results. **Weight gain and change in length, frontooccipital head circumference, mid arm circumference, and triceps skinfold thickness were similar between the carnitine-supplemented and placebo groups. The amount and severity of apnea and the overall length of hospitalization were also similar between the 2 groups. The carnitine levels in the supplemented group were significantly higher than in the placebo group at 4 and 8 weeks after study entry.**

Conclusion. **Although preterm infants <1500 g have low carnitine levels, routine supplementation with carnitine has no demonstrable effect on growth, apnea, or length of hospitalization and thus seems to be unnecessary.** ***Pediatrics*** **2003;111:477–482;** ***carnitine supplementation, very low birth weight infants, apnea, growth.***

ABBREVIATIONS. VLBW, very low birth weight; LOS, length of stay; NICU, neonatal intensive care unit; PCG, pneumocardiogram.

Carnitine, a quaternary amine synthesized from the amino acid lysine, is essential in β oxidation to transport long-chain fatty acids across the inner mitochondrial membrane.[1] Carnitine also binds excess acyl groups created during β oxidation to form acyl carnitines, which are renally excreted. Unbound acyl groups may inhibit cellular enzymatic activities, causing metabolic acidosis.[2] Carnitine deficiency may present with apnea and apparent life-threatening events, delayed development, gastrointestinal dysmotility, peripheral myopathy, and cardiomyopathy.[3–5]

The fetus probably obtains exogenous carnitine via placental transport.[6,7] Carnitine is stored in fetal tissue in increasing amounts over the latter part of gestation, and tissue carnitine stores at birth are directly related to gestational age.[8,9] Endogenous synthesis of carnitine is limited in the neonate by low levels of α-butyrobetaine hydroxylase, the enzyme that catalyzes the final step of the carnitine synthetic pathway. Without an exogenous supply of carnitine, preterm infants cannot achieve carnitine homeostasis.

Very low birth weight (VLBW) infants are at high risk of carnitine deficiency when receiving parenteral nutrition or unsupplemented infant formulas, such as soy-based preparations.[10] Carnitine can be viewed as a conditionally essential nutrient in the preterm infant, primarily because of immaturity of biosynthetic capability and the dependence on exogenous sources. Enteral infant formulas have carnitine added and provide 2 to 5 mg/kg/d when on full enteral feeds. This is similar to the amounts contained in breast milk.[11] Infants receiving parenteral nutrition have no exogenous source of carnitine.

Assessing an infant's carnitine status is complicated. Blood levels alone are not indicative of the total metabolic pools of carnitine, eg, those found in red cells, muscles, and liver stores. Full-term neonates experience a decrease in plasma carnitine concentrations in the first 2 weeks of life. Without enteral feeds and carnitine supplementation of parenteral nutrition, preterm infants' plasma carnitine levels fall to one third of the value found in full-term infants at birth.[12,13]

Previous studies of carnitine supplementation have shown varying results, with some studies suggesting benefit and others showing no benefit. One study presented in abstract form demonstrated a beneficial effect on preterm infants with apnea. That study showed less apnea, a shorter mechanical ventilator course, and better growth in the carnitine-supplemented group.[14] However, lack of consistent dosing, lack of consistent caloric and protein intake, small sample size, and lack of consistent measures of growth make the studies difficult to interpret.[15–19] Most studies of carnitine supplementation have been short term and have focused on intravenous lipid tolerance.[12,20–26]

From the *Division of Neonatology, Department of Pediatrics, ‡Department of Nutrition Services, and §Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas.

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Reprint requests to (J.W.) Division of Neonatology, Department of Pediatrics, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246. E-mail: jonathaw@baylorhealth.edu

This study was designed to test the hypothesis that carnitine supplementation within 96 hours of delivery in VLBW infants has a beneficial effect on apnea, growth, and length of hospitalization.

PATIENTS AND METHODS

A power analysis was conducted to determine sample size using a power of 80% and α of <0.05. The following were assumptions about the primary outcome variables: 1) apnea: to decrease the incidence at 32 weeks' gestational age for significant apneic episodes (>20 seconds) from 70% to 30% required a total of 64 patients; 2) length of stay (LOS): to demonstrate a 7-day reduction in LOS required a total of 60 infants; and 3) weight gain: to show an increase in weight gain by 10 g per day required a total of 32 patients.

Neonates <1500 g were enrolled in the study between June 1998 and May 2000. Infants with congenital malformations, chromosome abnormalities, inborn errors of metabolism, end-stage liver disease, peritoneal dialysis, or severe intraventricular hemorrhage (grade IV) were excluded from the study. All patients were enrolled at Baylor University Medical Center in Dallas, which has a level 3 neonatal intensive care unit (NICU). The protocol underwent institutional review board approval, and parental informed consent was obtained by the investigators for each subject.

Participants were recruited within 96 hours of birth. The study was masked to the clinical caretakers and investigators. The research pharmacist conducted the randomization using an Excel spreadsheet (Microsoft Corp, Redmond, WA) with randomization into blocks of 10 patients.

Laboratory tests included prestudy plasma free and total carnitine levels and subsequent levels every 4 weeks until discharge from the NICU or 36 weeks' postconceptional age. The assay used was stable isotope dilution tandem mass spectrometry of butyl ester derivatives by either fast atom bombardment or electrospray ionization, modified from Kodo et al[27] and Rashed et al.[28] These laboratory results were not available to the clinical care team. In addition, acyl carnitine profiles in dried blood spots and urine organic acids were analyzed at enrollment to rule out a possible inherited metabolic disorder (none detected).

Patient characteristics were recorded, including birth weight, route of delivery, Apgar scores, sex, gestational age as determined by attending neonatologist, length, fronto-occipital head circumference, mid arm circumference, and triceps skinfold thickness. Weekly measurements of weight, fronto-occipital head circumference, and length were recorded from the bedside NICU flowsheets completed by the registered nurse. The mid arm circumference and triceps skinfold thickness were measured weekly by the research dietitian. A large skinfold caliper was used, and measurements were rounded to the nearest 1 mm. An admission severity of illness score (Score for Neonatal Acute Physiology) was calculated on each infant at 24 hours of life using vital signs and other data from the NICU flowsheet and chart.[29]

Carnitine Supplementation

Infants were randomly assigned to receive intravenous infusions of L-carnitine (15 mg/kg/d) or no supplementation. Infusions were initiated within 96 hours of birth. When full enteral feeds were established (120–150 mL/kg/d), 100 mg/kg/d of L-carnitine was given orally in 4 divided doses. The control infants received an osmotically matched placebo prepared in an identical manner. The placebo was supplied by the research pharmacist and given in 4 doses each day. The bedside nurse did not know whether carnitine or placebo was given.

The carnitine was supplied by Sigma-Tau Pharmaceuticals, Gaithersburg, Maryland.

Nutritional Regimens

Infants were given maintenance fluids initially, usually with 10% dextrose, and parenteral nutrition was started within 72 hours. Fluids and the caloric content of parenteral nutrition and feeds were ordered according to the preference of each attending neonatologist. There was no set protocol.

Evaluation for Apnea

Apnea was evaluated in 4 ways:

1. The bedside NICU flowsheet recordings of apneic spells identified by the bedside nurse. Three categories of apnea were recorded: type 1 required no intervention, with the infant recovering spontaneously; type 2 required stimulation; and type 3 required bagging to restore heart rate and normal respiratory effort.
2. A pneumocardiogram ([PCG]; Aquetron Medical 5100) using leads for heart rate, respiratory rate, and oxygen saturation, which was scored by trained respiratory therapists blinded to the patient allocation. The recordings were scored for percentage of periodic breathing, number of apnea of 15 to 20 seconds, and number of apnea of >20 seconds. The number of desaturation episodes <85% for >5 seconds was also recorded. A PCG was done at 32 weeks' postconceptional age (or within 1 week of extubation if the patient was still intubated at 32 weeks) and then at predischarge from the nursery. The results were normalized for the varying durations of the PCG studies and reported per 12 hours.
3. Recording of the administration of xanthines (caffeine or aminophylline) and length of xanthine treatment. No protocol limiting the use of xanthines for study patients was in place during the study. Administration of xanthines was based on the preference of each neonatologist. In general, the practice at the time was to use xanthines to facilitate extubation. After extubation, a trial of stopping the medication was done at ~34 weeks' gestational age.
4. The length of ventilation (intermittent mechanical ventilation plus continuous positive airway pressure days).

Statistical Analysis

Categorical variables were analyzed using the Fisher 2-sided exact test for simple 2×2 tables. A likelihood ratio was used for larger tables. Continuous variables were analyzed with the Wilcoxon 2-sample test.

RESULTS

Of the 80 randomized patients, 64 completed the study (Fig 1). The main reason for transfer of 7 infants was either lack of NICU space or parental request. Five infants withdrew because of parental change of mind after initially signing consent. There were no significant differences in demographic characteristics between the 31 placebo patients and 33 carnitine patients (Table 1).

As expected, the carnitine supplementation greatly affected carnitine levels. All study participants had low carnitine levels at the beginning of the study. In the placebo group, these levels climbed to low-normal by 4 weeks and to normal by 8 weeks. Levels in the supplemented group were significantly higher at 4 and 8 weeks (Fig 2).

Despite the higher carnitine levels in the study group, there were no significant differences in growth or intake (Table 2) or in apnea when evaluated with both clinical spells and PCG (Table 3). Both groups had equal incidence of apneic spells >20 seconds. All placebo and 32 of 33 carnitine-supplemented patients received xanthines at some time during the study. The number of days on caffeine was 28 ± 13 in the placebo group and 30 ± 15 in the carnitine group; the number of days on aminophylline was 16 ± 7 in the placebo group and 15 ± 9 in the carnitine group.

DISCUSSION

The infants in this study were fed either breast milk or cow's milk formulas, both of which contain

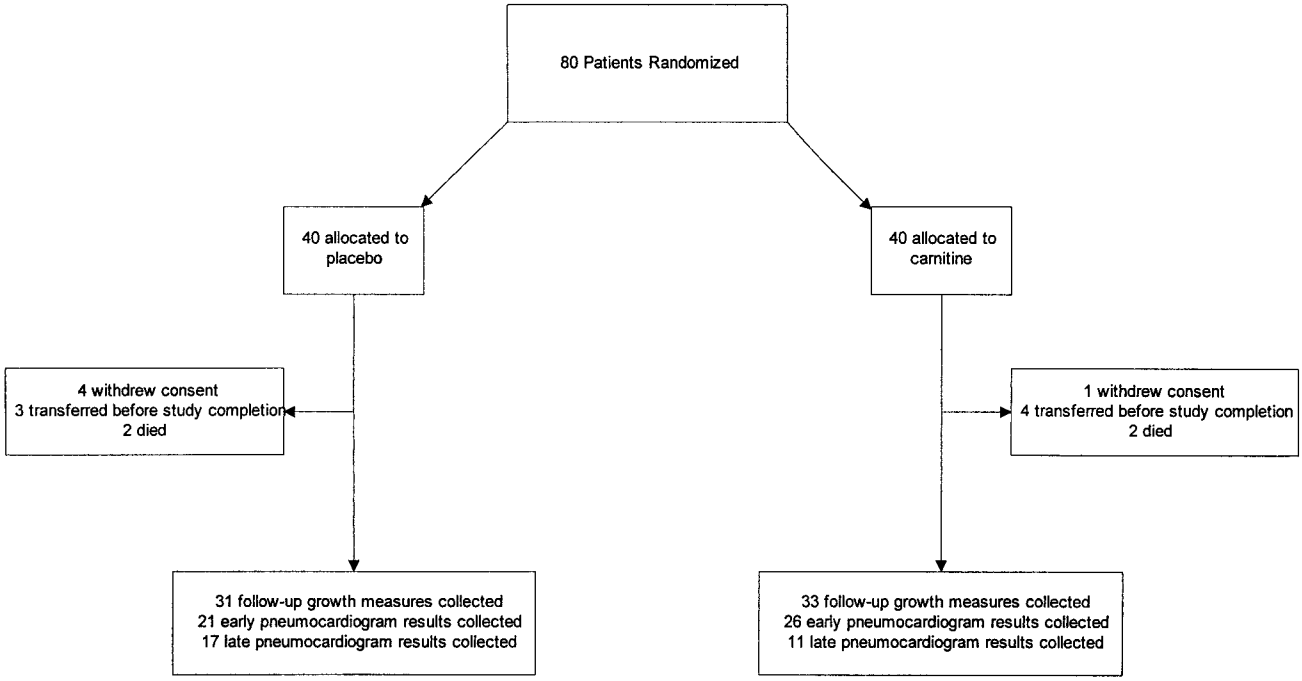

Fig 1. The number of enrollees and final study participants.

TABLE 1. Demographic Characteristics of the Study Patients

Characteristic	Placebo (n = 31)	Carnitine (n = 33)
Birth weight (g)		
Mean ± SD	967.1 ± 193.2	1002.3 ± 270.7
Median (IQR)	1013.0 (316.0)	970.0 (420.0)
Gestational age (wk)		
Mean ± SD	27.5 ± 2.0	27.9 ± 2.1
Median (IQR)	27.0 (3.0)	28.0 (3.0)
Cesarean section		
n (%)	22 (71.0)	22 (66.7)
Apgar score at 1 min		
Mean ± SD	6.2 ± 2.3	5.9 ± 2.6
Median (IQR)	7.0 (3.0)	7.0 (4.0)
Male		
n (%)	14 (45.2)	11 (33.3)
SNAP*		
Mean ± SD	25.3 ± 9.2	24.2 ± 7.3
Median (IQR)	25.0 (14.0)	25.0 (9.0)

SD indicates standard deviation; IQR, interquartile range; SNAP, Score for Neonatal Acute Physiology.
* Calculated from variables taken from the bedside NICU flowsheet on the day of admission.

carnitine.[11] Under the conditions of this study, there is a steady rise in carnitine levels in preterm infants, even when not supplemented (placebo group). In fact, the levels in the placebo group are low-normal initially and rise over the course of the study into the "normal" range (normal total: 46 ± 13 μmol/L). This suggests that the exogenous sources in the breast milk or preterm formulas and/or endogenous synthesis are sufficient to maintain carnitine homeostasis.

The supplemented group had levels that were 4 to 5 times higher than that of the control group. Despite these high levels, no growth advantage was observed in these infants. In 1 study, carnitine levels of almost 200 μmol/L after supplementing 48 mg/kg/d in a group of preterm infants on parenteral nutrition were associated with increased nitrogen excretion, higher metabolic rate, and lower weight gain.[21] No other studies have reported adverse effects of carnitine supplementation.

Our study did not demonstrate any beneficial effect on growth as measured by weight, fronto-occipital head circumference, length, mid arm circumference, or triceps skinfold thickness. Cairns and Stalker[34] recently reviewed all published articles of carnitine supplementation in parenterally fed neonates, with the primary outcome measure being weight gain. Fourteen trials were found, but 8 were excluded because of lack of randomization. Of the 6 studies in which randomization was considered appropriate, only 1 showed a significant effect in the second week of supplementation, and this effect was noted only in infants of 1001 to 1500 g.[18] This beneficial effect on growth was not sustained. None of the other studies showed any effect on weight gain.

Apnea of prematurity is one of the most common disorders of the VLBW infant, affecting >50% of VLBW infants.[35,36] Methylxanthines (theophylline and caffeine) are the mainstay of pharmacotherapy for idiopathic apnea of premature infants. All 3 types of apnea, ie, mixed, obstructive, and central, respond to this therapy.[37] Despite this treatment, many infants continue to have episodes of apnea with associated bradycardia and hypoxia that are believed to be clinically significant with potentially harmful physiologic changes. The infant who fails to respond adequately to methylxanthines is a challenge for the physician. The use of continuous positive airway pressure may eliminate the need for intubation in many infants, but occasionally intubation and mechanical ventilation are required.

A study by Iafolla and Browning[14] reported decreased apnea and the need for mechanical ventila-

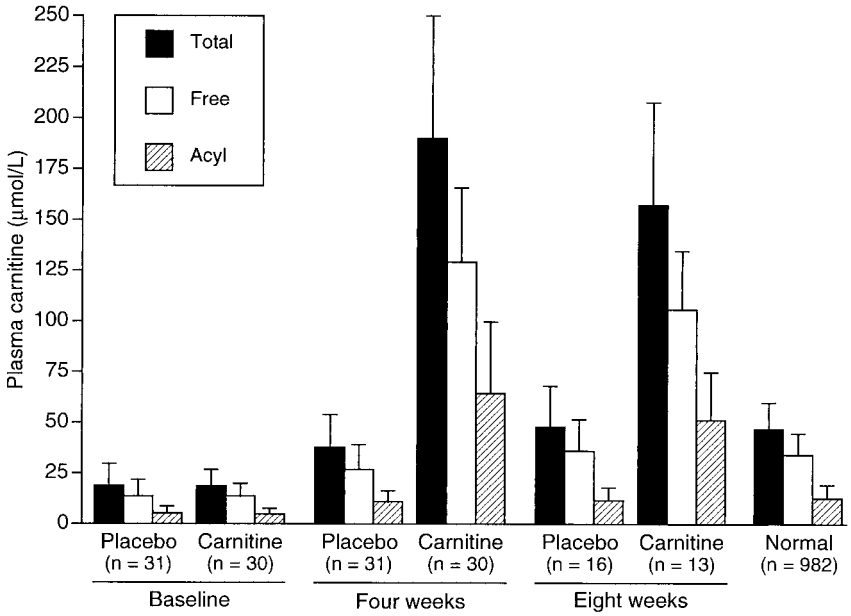

Fig 2. Plasma carnitine levels. Normal values were taken from reference 30. $P < .001$ for the supplemented group versus placebo group for all values (acyl, free, and total carnitine) at both 4 and 8 weeks.

TABLE 2. Growth Parameters Taken at 36 Weeks' Postconceptional Age

Characteristic	Placebo (n = 31)	Carnitine (n = 33)
Weight (g)		
Mean ± SD	1912.5 ± 239.5	1873.4 ± 292.6
Median (IQR)	1925.0 (352.0)	1887.0 (303.0)
Length (cm)		
Mean ± SD	41.7 ± 1.9	41.2 ± 3.0
Median (IQR)	42.0 (2.5)	41.5 (3)
Fronto-occipital head circumference (cm)		
Mean ± SD	30.5 ± 1.5	30.5 ± 2.1
Median (IQR)	30.0 (2.0)	30.3 (1.0)
Mid-arm circumference (cm)*		
Mean ± SD	8.0 ± 0.8	7.9 ± 0.8
Median (IQR)	8.0 (1.0)	8.0 (1.0)
Triceps skinfold thickness (mm)*		
Mean ± SD	3.8 ± 0.9	3.9 ± 0.9
Median (IQR)	4.0 (1.0)	4.0 (1.0)
Total length of hospital stay (d)		
Mean ± SD	71.6 ± 23.1	66.4 ± 24.7
Median (IQR)	66.0 (34.0)	63.0 (22.0)
Total caloric intake (kcals/kg/d)†		
Mean ± SD	107.6 ± 11.6	109.9 ± 11.1
Median (IQR)	109.0 (14.0)	110.0 (16.0)
Protein intake (kcals/kg/d)		
Mean ± SD	2.8 ± 0.3	2.9 ± 0.4
Median (IQR)	2.9 (0.5)	2.8 (0.4)

SD indicates standard deviation; IQR, interquartile range.
* Normal mid-arm circumference and triceps skinfold thickness values in full-term infants at 1 month are 10.54 cm ± 0.86 and 5.6 mm ± 0.12, respectively.[31–33]
† Mean intake over the course of the study from birth to 36 weeks' postconceptional age; takes into account both parenteral and enteral sources of calories and protein.

tion in carnitine-supplemented infants <33 weeks' gestation. The study also demonstrated improved growth in supplemented infants compared with control infants (weight gain of 14 g/kg/d vs 21 g/kg/d). The authors speculated that preterm infants have many of the symptoms of carnitine deficiency, such as apnea, hypotonia, poor weight gain, delayed development, and gastrointestinal reflux. Supplementation with carnitine was associated with decreased apnea and a decreased need for mechanical ventilation. These observations were made despite the concurrent use of xanthines in all of the infants studied. The carnitine-supplemented infants were weaned more quickly from xanthines than the control infants. The caregivers in that study were not blinded to the carnitine supplementation. Based on these observations, we hypothesized that if carnitine does have such a salutatory effect on apnea of prematurity, the effect would be seen despite concurrent use of mechanical ventilation and xanthines. For this reason, no attempt to control the use of xanthines was made. In general, our practice at the time of this study was to use xanthines to facilitate extubation and to trial weaning off xanthines by 33 to 34 weeks' gestation.

TABLE 3. Evaluation of Apnea

Characteristic	Placebo (n = 31)	Carnitine (n = 33)
Apneic spells (type 1–3) identified by the bedside nurse		
Mean ± SD	1.4 ± 0.8	1.4 ± 0.8
Median (IQR)	1.0 (1.2)	1.2 (1.1)
Early PCG results	Placebo (n = 21)	Carnitine (n = 26)
Periodic breathing (% sleep)		
Mean ± SD	1.2 ± 0.5	1.0 ± 0.4
Median (IQR)	1.2 (0.1)	1.2 (0.1)
Apneic episodes of 15–20 sec*		
n (%)	7 (33.3)	4 (15.4)
Mean ± SD	1.3 ± 3.1	0.5 ± 1.6
Median (IQR)	0.0 (1.0)	0.0 (0.0)
Apneic episodes of >20 sec*		
n (%)	6 (28.6)	6 (23.1)
Mean ± SD	1.2 ± 3.7	1.3 ± 3.4
Median (IQR)	0.0 (0.9)	0.0 (0.0)
Saturation episodes <85% for >5 sec*		
n (%)	14 (66.7)	14 (53.9)
Mean ± SD	30.3 ± 46.7	14.5 ± 24.9
Median (IQR)	6.5 (23.4)	2.8 (14.6)
Late PCG results	Placebo (n = 17)	Carnitine (n = 11)
Periodic breathing (% sleep)		
Mean ± SD	1.1 ± 0.3	1.2 ± 0.1
Median (IQR)	1.1 (0.2)	1.2 (0.0)
Apneic episode of 15–20 sec*		
n (%)	6 (35.3)	1 (9.1)
Mean ± SD	1.0 ± 2.3	0.1 ± 0.3
Median (IQR)	0.0 (1.0)	0.0 (0.0)
Apneic episodes of >20 sec*		
n (%)	4 (23.5)	2 (18.2)
Mean ± SD	0.3 ± 0.8	0.2 ± 0.4
Median (IQR)	0.0 (0.0)	0.0 (0.0)
Saturation episodes <85% for >5 sec*		
n (%)	12 (70.6)	5 (45.5)
Mean ± SD	17.8 ± 30.6	9.7 ± 13.1
Median (IQR)	5.9 (12.7)	1.0 (17.1)

SD indicates standard deviation; IQR, interquartile range.
* Means and medians summarize number of episodes per patient per 12 hours time. No statistically significant differences were observed in either clinical or PCG evaluation of apnea.

A weakness of this study design was lack of control over xanthine therapy. Our prestudy power analysis assumed a 70% incidence of apnea. In fact, attributable most likely to xanthine administration the incidence was only 28% (Table 3). Much larger numbers and a very profound effect (28% reduced to 0%) would have been required to show a beneficial effect of carnitine. PCG recordings were not available on all infants. Lack of PCG machines or nonavailability of technicians at time of discharge were the principal reasons for lack of recordings. This occurred in random fashion and affected both placebo and carnitine-supplemented groups equally. Given these factors, we were unable to demonstrate any beneficial clinical effect of carnitine on apnea in our study. The study design does not allow us to conclude that there is no effect. More subtle effects of carnitine on apnea may have been masked by the concurrent use of xanthines. The total number of clinical episodes and of PCG apneic episodes >20 seconds as well as the percentage of periodic breathing in both groups were similar. Likewise, the length of mechanical ventilation was similar in the supplemented and placebo group. This latter observation was dramatically different in the Iafolla study, in which all the supplemented patients were extubated significantly earlier than the placebo patients.

CONCLUSION

Because carnitine supplementation of VLBW infants seems to have no demonstrable effect on clinical apnea, growth, or length of hospitalization, routine carnitine supplementation of VLBW infants is not necessary.

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