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Original Article

Lack of Effect of L-Carnitine Supplementation on Weight Gain in Very Preterm Infants

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OBJECTIVE

Carnitine transfer across the placenta occurs predominantly during the third trimester. Unless L-carnitine is provided, very preterm infants develop carnitine deficiency. Although breast milk and infant formulas contain L-carnitine, parenteral nutrition solutions do not routinely provide L-carnitine. We hypothesized that prolonged L-carnitine supplementation in very preterm infants would improve weight gain and shorten length of stay in the hospital.

STUDY DESIGN

The study was a double-blind parallel placebo-controlled randomized clinical trial. Eligible patients were <29 weeks of gestation, <72 hours of age, and did not have a potentially life-threatening congenital malformation or hereditary metabolic disorder. Patients were stratified by gestational age (23 to $25^{6/7}$ and 26 to $28^{6/7}$ weeks), and randomized to receive, either L-carnitine at a dose of 50 μmol/kg/day, or placebo. Carnitine was provided intravenously until the infants tolerated 16 ml/day of feeds. The sample size was calculated to have 80% power to detect a 10% increase in weight gain from birth until 36 weeks of postmenstrual age or discharge from the hospital. Secondary outcome variables included food efficiency (defined as weight gain divided by caloric intake), weight gain at 4 weeks of age, time to regain birth weight and length of stay.

RESULTS

Among the 63 infants enrolled in the trial, 32 were randomized to L-carnitine and 31 to placebo. L-Carnitine supplementation did not significantly affect average daily weight gain from birth until 36 weeks or hospital discharge, or any of the secondary outcome variables.

CONCLUSION

Prolonged supplementation of L-carnitine did not improve long-term weight gain in very preterm infants.

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INTRODUCTION

Carnitine is an amino-acid derivative that facilitates transport of fatty acid across mitochondrial membranes, thereby improving the availability of fatty acids for beta-oxidation,[1] regulating the free CoA to acylCoA ratio and scavenging potentially toxic organic compounds before they accumulate in the mitochondria. Patients with carnitine deficiency may develop lipid storage myopathy, weakness and myalgias, cardiomyopathy, failure to thrive, hepatomegaly, abnormal liver function tests, recurrent infections, elevated serum levels of triglycerides, hypoglycemia, hypoketonemia, and pancytopenia.[2,3] Placental transport of carnitine to the fetus occurs primarily during the third trimester of pregnancy.[4] Carnitine deficiency develops among very low birth weight (VLBW) infants who do not receive exogenous supplementation for 2 to 4 weeks.[5] This is related to minimal body stores at birth, limited carnitine production, high carnitine loss in the urine and lack of L-carnitine supplements in standard parenteral solutions.[4,6] Human milk and most infant formulas contain L-carnitine.[7] However, the most metabolically stressed neonates typically receive only parenteral alimentation (TPN). Thus, they are the infants at greatest risk for significant alterations of energy metabolism due to inadequate intake of exogenous carnitine.

Among preterm infants, short-term low L-carnitine supplementation doses (50 to 70 μmol/kg/day) have been shown to improve lipid tolerance, ketogenesis, and short-term weight gain.[8–14] However, one study using high doses, 300 μmol/kg/day,[15] of L-carnitine supplementation showed increased protein oxidation and decreased weight gain. In 2000, only one randomized controlled study had evaluated the effect of long-term use of carnitine on growth in VLBW infants,[16] and this study had been conducted without sample size analysis. Preliminary data from a national survey indicated that approximately one-third of the

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neonatal intensive care units in the USA routinely supplemented TPN with L-carnitine.[17] The current study was then undertaken to test the hypothesis that L-carnitine supplementation in very preterm infants would improve weight gain and shorten length of stay (LOS). In the mean time, two other long-term randomized controlled studies[18,19] have been completed and published; neither of them showed any benefit of carnitine supplementation on growth and several other outcome variables in very preterm infants.

MATERIALS AND METHODS

Patients

Eligible patients were <29-week gestational age (GA), ≤72-hour postnatal age and admitted to the neonatal intensive care unit at Weiler Hospital, Albert Einstein College of Medicine, Bronx, NY. GA was assigned based on the best obstetrical estimate if available, or else by the modified Ballard score, which was performed after 12 to 48 hours of life. We excluded infants with potentially life-threatening congenital anomalies or hereditary metabolic disorders. An informed consent was obtained. The Institutional Review Board (IRB) of Montefiore Medical Center approved the protocol. A Data Safety Monitoring Board designated by the IRB monitored the trial.

Procedures

Parenteral and enteral nutrition. TPN was begun on the first day of life, with 1.5 g/kg/day of amino acids (Trophamine, B. Braun Medical, Inc., Irvine, CA), glucose at 4 mg/kg/minute and 1.25 ml/day of multivitamins (Pediatric MVI, Astra Pharmaceuticals, Wilmington, DE). Amino-acid intake was increased daily by 1 g/kg/day, up to 3.5 g/kg/day. Glucose intake was increased, as tolerated, up to a maximum of 13 mg/kg/minute. Intralipid 20% (Fresenius-Kabi Clayton, Nutrition AB, Clayton, NC) was provided as a continuous infusion, started at 0.5 g/kg/day at 24 hours of life, and later increased to a maximum of 3 g/kg/day; the dose was adjusted to maintain serum triglyceride level equal to or less than 150 mg/dl. Trophic feeds were started (10 ml/kg/day divided into three aliquots) in most infants once the vital signs were stabilized and the infant no longer required vasopressor support. Enteral feedings were given every 3 hours using the infant's own mother's milk or a 20 calories per ounce (cal/oz) premature formula (Enfamil Premature 20). When more than 100 ml/kg/day were tolerated, human milk was supplemented with Similac human milk fortifier (Ross Products Division, Abbott Laboratories). Formula-fed infants were advanced to a 24 Cal/fl oz premature formula (Enfamil Premature 24) as tolerated. The caloric content of the feedings was increased as needed up to 30 cal/oz in order to achieve a daily weight gain of at least 20 g/day and a total caloric intake of at least 120 kcal/kg/day. When the infant's weight reached 1800 g, the formula-fed infant was changed to a 22 Cal/fl oz premature formula. Infants with a direct bilirubin >5 mg/dl were changed to Pregestimil 20 or 24 Cal/fl oz.

Randomization and intervention. Enrolled patients were stratified by GA (23 to $25^{6/7}$ and 26 to $28^{6/7}$ weeks), and randomized by the pharmacist using a computer-generated table of random numbers. Codes were unblinded only after all patients had reached the study end point. Neonates assigned to the treatment group received L-carnitine (Carnitor®, Sigma-Tau Pharmaceuticals, Gaithersburg, MD) until 36 weeks postmenstrual age (PMA) or the time of hospital discharge, whichever occurred first. In case of multiple gestations, each infant was randomized independently. The carnitine solution did not contain any D-carnitine, which has been associated with myasthenia syndrome. L-Carnitine supplementation was initiated within 72 hours of life, starting as early as possible following enrollment in the study. L-Carnitine was initially provided as a continuous infusion in the parenteral nutrition. When infants were able to tolerate at least 2 ml of enteral feedings every 3 hours for a minimum of 12 hours, L-carnitine was provided enterally at the same daily dose, divided three times per day. If during the course of hospitalization, oral feedings were interrupted for more than 12 hours, parenteral supplementation was resumed. Patients in the control group received placebo (5% glucose solution) by the same route and at the same volume as those in the treatment group.

Outcome Variables

The main outcome variable was the average daily weight gain (grams per day) from birth until 36 weeks PMA or hospital discharge, whichever occurred first. Secondary outcome variables included food efficiency (defined as weight gain divided by caloric intake, thereby allowing to compare weight gain between groups while taking into account any disparity in caloric intake), weight gain at 4 weeks of life, time to regain birth weight and LOS. We also assessed potential toxicity of L-carnitine.

Statistical Analysis and Sample Size

Sample size was determined using Sample Power (Version 2, SPSS Inc., Chicago, IL). The total P-value of 0.05 was partitioned between the main outcome variable ($p = 0.04$) and each of the four secondary outcome variables ($p = 0.01/4 = 0.0025$). We needed 26 patients in each group to detect a weight gain difference of 2 g/day between the two groups with a power of 0.80 and a two-tailed alpha error of 0.04. We selected a difference that would correspond to ~10% of the average daily weight gain observed in very preterm infants in our neonatal intensive care unit in 1999, that is, 18.5 ± 2.4 g/day (mean ± SD), and thus shorten LOS accordingly. We enrolled 63 patients taking into account potential attrition due to infants' death at >24 hours or withdrawal from the study.

All analyses were performed on an intent-to-treat basis using SPSS version 10 (SPSS Inc) and StatXact 5.0 (Cytel Statistical Software, Cambridge, MA). Values with normal distribution are presented as mean ± SD, while the other continuous variables and

ordinal variables are presented as median (range). For each variable, we first tested if GA affected the response to therapy; if not, we compared treatment group and control group without stratification.

Continuous variables with normal distribution were compared between the treatment group and the placebo group by two-way analysis of variance (ANOVA) taking into account stratification by GA if homogeneity of variance was verified, and by Student's *t*-test if ANOVA failed to show any effect of GA. Continuous variables in which ANOVA assumptions were violated were compared by two-way ANOVA by ranks using Puri and Sen's L-statistic,[20] and, if the latter test failed to show an effect of GA, by using the Mann–Whitney test (Monte Carlo approximation of the exact test). Frequencies were compared using the Cochran–Mantel–Haenszel test (exact test)[21] and the Fisher's exact test.

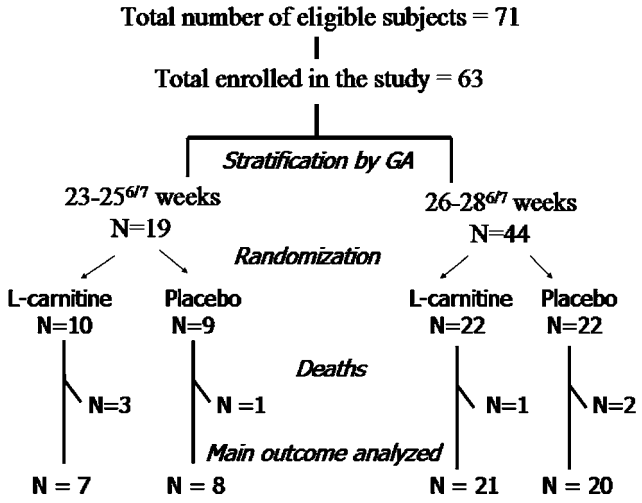

Figure 1. Flow diagram.

RESULTS

Description of the Patient Population at Study Entry

Among the 71 babies <29 weeks of GA admitted to the neonatal intensive care unit at Weiler Hospital between November 2000 and January 2002, 63 babies were enrolled in the study (Figure 1). Reasons for nonparticipation included: patient's death before 24 hours ($n = 2$), refusal of consent ($n = 3$), mother's illness ($n = 1$) and failure to approach the mother within 72 hours after delivery ($n = 2$). All demographic and baseline variables were similar between the two allocation groups using bivariate analysis, except for mean airway pressure (MAP) at 24 hours, which was significantly higher in the L-carnitine group than in the placebo group (Table 1).

Outcome Variables

Seven patients died before reaching the study end point, leaving 56 patients (89% survival) for analysis of the main outcome variable (Figure 1; Table 2). Carnitine supplementation was provided intravenously for a median of 11 days (range 4 to 56) and placebo for 10 days (4 to 50). Daily weight gain until end point was greater

Table 1 Demographic and Baseline Data in Study Population

Parameter	Placebo ($n = 31$)	Carnitine ($n = 32$)
Birth weight (g) (mean ± SD)	912 ± 214	894 ± 277
Length (cm)	34.9 ± 2.6	35.3 ± 4.3
Head circumference (cm)	24.3 ± 2.3	24.7 ± 1.9
Gestational age (weeks) (mean ± SD)	26.6 ± 1.6	26.2 ± 1.8
Cesarean section (yes/total)	23/31	21/32
Apgar score at 1 minute: median (range)	5 (1–9)	6 (1–9)
Apgar score at 5 minutes: median (range)	8 (4–9)	8 (2–9)
Gender (female) (yes/total)	17/31	14/32
CRIB score: median (range)	4(1–16)	6(0–20)
Maternal infection (yes/total)	12/31	8/32
Prenatal steroids (yes/total)	25/31	24/32
Pregnancy-induced hypertension (yes/total)	10/31	11/32
Small for gestational age (yes/total)	2/31	4/32
Number of surfactant doses: median (range)	1 (0–2)	1 (0–3)
Intubated at 24 hours (yes/total)	19/31	23/32
MAP at 24 hrs (kPa)*: median (range)	0.7 (0.5–1.0) ($n = 19$)	0.8(0.5–1.6) ($N = 23$)
Use of vasopressors (yes/total)	17/31	14/32
Number of boluses for hypovolemia: median (range)	1 (0–4)	1 (0–8)

*Mean airway pressure at 24 hours of life (patients requiring respiratory support).

in patients with GA greater or equal to 26 weeks than in more immature infants (contrast versus <26 week GA infants: 4.4 g/day, 95% confidence interval 0.8, 8.0, $p = 0.017$). However, daily weight gain was not affected by L-carnitine (contrast versus placebo: −0.2 g/day, confidence interval −2.7, +2.3, $p = 0.870$). There was no significant difference between the two groups in any of the planned secondary outcome variables (Table 3) or potential toxicity (Table 4).

Table 2 Average Daily Weight Gain Until End Point

Gestational age	Group allocation	Mean	SD	*N*
<26 weeks	Placebo	14.1	3.4	8
	Carnitine	15.6	4.1	7
≥26 weeks	Placebo	20.2	3.8	20
	Carnitine	20.0	4.5	21
Total	Placebo	18.5	4.6	28
	Carnitine	18.9	4.7	28

The number of patients reaching end point was 28/32 in the carnitine group and 28/31 in the control group.

Post Hoc Analyses

Patients in the treatment group and those in the control group received similar caloric intake until end point (i.e., 36 weeks PMA or hospital discharge), 167±22 versus 177±44 kCal/day, respectively. Carnitine supplementation did not significantly affect PMA at end point (35.4±1.0 weeks, $n = 28$, in the treatment group versus 35.3±0.9 weeks, $n = 28$, in the control group), size at end point (weight 2056±357 versus 2010±289 g, length 43.0±2.8 versus 42.6±2.0 cm, and head circumference 30.8±2.3 versus 30.3±1.6 cm, respectively), or weight at 36 weeks PMA (2032±416 g, $n = 19$, versus 1972±397 g, $n = 11$). Serum triglyceride levels while receiving 3 g/kg of lipid intravenously were not significantly affected by carnitine supplementation (79 mg/dl, range 41 to 93 in the treatment group, $n = 8$, versus 86 mg/dl, range 17 to 205 in the placebo group, $n = 13$). Only one infant had a serum triglyceride level greater than 150 mg/dl.

Since we observed a trend towards an increased need for surgical ligation of the patent ductus arteriosus (PDA), we compared the incidence of ductal ligation after failure to respond to indomethacin. None of 11 patients (0%) in the control group required ductal ligation, compared with 5 of 14 (36%) in the treatment group ($p = 0.046$).

Table 3 Secondary Outcome Variables

Parameter	Control	Carnitine	Significance*
Food efficiency (g of body weight/kCal)	0.11±0.02 ($n = 28$)	0.11±0.02 ($n = 27$)	NS
Weight gain until 4 week† (g/day) (mean±SD)	12.2±4.3 ($n = 29$)	11.5±5.0 ($n = 29$)	NS
Days to regain birth weight†: median (range)	11 (6–19) ($n = 29$)	11 (2–22) ($n = 30$)	NS
Length of stay (days)‡: median (range)	56 (39–144) (28)	69 (32–151) (27)	NS

*Using Bonferroni correction (significance asserted if $p < 0.01/4 = 0.0025$).
†Surviving until outcome is reached or obtained.
‡Patients surviving until discharge.

Table 4 Potential Toxicity

Parameter	Control	Carnitine	Sig
Mortality before hospital discharge (yes/total)*	3/31 (10%)	5/32 (16%)	NS
Gastrointestinal perforation (yes/total)	3/31 (10%)	3/32 (9%)	NS
PDA ligation (yes/total)	2/31 (6%)	8/32 (25%)	NS
O_2 requirement at 36 weeks† (yes/total)	12/28 (43%)	16/28 (57%)	NS
Severe IVH (grade III or IV) (yes/total)	6/31 (19%)	9/32 (28%)	NS
Laser surgery for ROP† (yes/total)	4/29 (14%)	6/31(19%)	NS

Abbreviations: PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; SIG: significance (*p*-value) using exact test.
*One patient with a GA <26 weeks and randomized to L-carnitine died after reaching trial end point; this patient was included in the analysis of the primary and secondary outcomes.
†Surviving until outcome is reached or obtained.

Table 5 Randomized Clinical Trials of Carnitine Supplementation in Preterm Infants

Author (date)	Participants	Intervention	Results
Schmidt-Sommerfeld (1983)	GA 29–37 weeks, birth weight 1200–2490 g, PNA 6–10 days, $n = 29$	Treatment: carnitine 62.5 μmol/kg/day in TPN over 5 hours. Control: no supplement	Greater increase in acyl carnitine level and lower free fatty acid/D-beta-hydroxybutyrate ratio after lipid infusion (1 g/kg over 4 hours)
Coran (1985)	GA 32–42 weeks, TPN for $\geq$1 week, Major surgery within first days, birth weight 1.60–4.28 kg, $n = 12$	Treatment: carnitine 70 μmol/kg/day enterally 7 days. Control: placebo	Higher serum carnitine levels. No effect on clearance of triglycerides or free fatty acids after lipid infusion (0.5 g/kg over 2 hours); no effect on serum levels of ketone bodies
Melegh (1986)	GA 29–34 weeks, 1180–1860 g, PNA 1–2 weeks, $n = 10$	Treatment: carnitine 60 μmol/kg/day enterally 7 days. Control: no supplement	Increased baseline ketone bodies serum levels; higher ketone bodies and lower free fatty acid serum levels after lipid infusion (0.25 g/kg over 20 minutes)
Helms (1986)	GA 32–40 weeks, birth weight 0.70–3.30 kg, PNA 39–292 days, prolonged TPN, $n = 14$	Treatment: carnitine 50 μmol/kg/day enterally for 7 days. Control: placebo	Higher serum carnitine levels. Enhanced fatty acid oxidation after lipid bolus (0.5 g/kg over 2 hours)
Larsson (1990)	GA <33 weeks (27–32), 790–2090 g, PNA 5–21 days, $n = 12$	Treatment: carnitine 62.5 μmol/kg/day into Intralipid solution; TPN stopped when feedings >75% of recommended intake. Control: placebo	Elevated serum level of beta-hydroxybutyrate on day 2 of treatment, sign of transient increase in fatty acid oxidation
Helms (1990)	GA 31.7±4.5 weeks, birth weight 1.49±0.67 kg, limited enteral intake (<15% of total cal & protein), PNA 2.4±1.4 weeks, $n = 43$	Treatment: carnitine 50 μmol/kg/day i.v., 7 days, then 100 μmol/kg/day enterally, 7 days. Control: no supplement	Greater nitrogen and carnitine balance, better weight gain during 2nd (but not 1st) week; on day 14, higher ketone bodies/free fatty acid ratios and lower tri-glyceride levels after lipid infusion (0.5 g/kg over 2 hours)
Bonner (1995)	Birth weight 750–1500 g, <48 hours, Stratifed by birth weight (751–1000 and 1001–1500 g); $n = 20$	Treatment: carnitine 50 μmol/kg/day i.v. until 50% of calories given enterally. Control: no supplement	Higher serum levels of beta-hydroxybutyrate; in 1001–1500 g birth weight group: better weight gain after 2 weeks and fat tolerance
Shortland (1998)	28–34 weeks, 885–2545 g, <72 hours, stratified by GA, $n = 86$	Treatment: carnitine 156 μmol/kg/day until 40 weeks PMA. Control: placebo	No effect on: (1) short-term & long-term weight gain, (2) Incidence of hypoglycemia during the first week
Crill (1999)*	GA 27.5±2.2 weeks, birth weight 1.0±0.3 kg, PNA 2.9±1.1 days, $n = 21$	Treatment: carnitine 124 μmol/kg/day for 8 weeks, initially in TPN; later in enteral feedings. Control: placebo (water)	Increased plasma carnitine levels
O'Donnell (2002)	$\leq$32 weeks, TPN, <1.5 kg, <48 hours, $n = 44$	Treatment: carnitine 187.5 μmol/kg/day in TPN until tolerating 120 ml/kg/day enteral feedings then 187.5 μmol/kg/d orally until 34 weeks of PMA. Control: placebo	No effect on: (1) Apnea (1ry outcome): days on ventilator, days on continuous positive airway pressure, need for O_2 at 28 days PNA or 36 weeks PMA, (2) Nutrition: time to regain birth weight, time to enteral feeds 120 ml/kg, discharge weight, (3) LOS, PMA at discharge

Table 5 Continued

Author (date)	Participants	Intervention	Results
Whitfield (2003)	<1.5 kg ≤96 hours $n=80$ (64 completed)	Treatment: 93.8 μmol/kg/day in TPN until 120–150 ml/kg/day enteral feedings then 625 μmol/kg/day in four divided doses until 36 weeks of PMA or discharge. Control: placebo	No effect on: (1) Growth (weight, length, head circumference, anthropometry (2) LOS (3) Amount and severity of apnea
Storm (2003)*	GA: 27.2±2.1 weeks; birth weight 1.0±0.3 kg, PNA ≤6 days, $n=30$	Treatment: carnitine 124 μmol/kg/day. initially in TPN; later in enteral feedings. Control: placebo (water)	Shortened time to regain birth weight: 12.7±6.4 days versus 17.4±6.0 days

Abbreviations: cal, calories; d, days; GA, gestational age; LOS, length of stay; NS, not significant; PMA, postmenstrual age; PNA, postnatal age; TPN, total parenteral nutrition.
*Could represent one or two trials.

Discussion

This double-blind randomized trial failed to show evidence of benefit of carnitine supplementation on weight gain in very preterm infants at 36 weeks post menstrual age or at hospital discharge. There are several possible limitations to this study. First, we may have missed an effect of L-carnitine supplementation on carnitine depletion and/or carnitine stores, because most infants received partial or full enteral feedings containing L-carnitine. Under these conditions, carnitine levels in the control group were expected to increase to normal values by approximately 2 months of age.[19] To our knowledge, no investigator has assessed the effect of L-carnitine supplementation in neonates receiving TPN as their sole nutrition source for more than 3 weeks. Second, we did not measure serum carnitine levels because they may not accurately reflect tissue levels. The dose of L-carnitine supplementation, 50 μmol/kg/day (8 mg/kg/day), was consistent with calculated daily in utero accretion[6] and with the estimated intake from 150 ml/kg/day of pooled breast milk.[2,7] Supplementation of preterm infants using doses of 50 to 60 μmol/kg/day significantly increases serum carnitine levels to values at least three times those in controls.[10,11,13,14] Third, in contrast with other studies[18,19] we used the same relatively low dose of carnitine of 50 μmol/kg/day both intravenously and enterally, because mean serum carnitine levels in studies using this enteral dose (90.2±28.7 nmol/ml[10]; 30–40 nmol/ml[11]) in preterm infants were well above those associated with carnitine deficiency (<20 nmol/ml).[22] Using higher doses of carnitine might have yielded serum levels that would have been higher than normal.[19] Fourth, we may have missed a true difference in any of the secondary outcome variables for which a power of 0.80 was calculated but with a very stringent alpha error (0.0025). Fifth, we did not assess lipid tolerance, that is, the dose of intralipid resulting in serum triglyceride levels of 150 mg/dl. Nevertheless, serum triglyceride levels obtained during a continuous lipid infusion at 3 g/kg/day were not affected by carnitine supplementation. Finally, a 10% difference in weight gain may seem too small to be clinically significant; however, a 10% reduction in LOS might have been important, given the high cost of neonatal intensive care.

Using the keywords ''Clinical Trial'' and ''Carnitine'' to search Medline and the Cochrane Database and our our own personal files we found ten randomized clinical trials[8–14,16,18,19] (Table 5) and one nonrandomized trial[15] assessing the effects of L-carnitine supplementation in preterm infants. On March 25, 2005, we conducted an updated Medline search using the keyword ''Carnitine'', limited to ''Clinical Trial'' and ''All Infant: birth to 23 months'' and a search of the Cochrane Central Register of Controlled Trials (The Cochrane Collaboration 2005, issue 1. Published by John Wiley & Sons, Ltd.) using the keyword ''Carnitine.'' This yielded two additional abstracts from the same institution (randomized trial(s)).[23,24] Whereas three studies showed

improved short-term growth,[13,14,24] none of the three published long-term studies[16,18,19] showed any effect of carnitine on growth. The systematic review conducted by Cairns (2005, issue 1 version)[25] showed no effect of carnitine on weight gain in VLBW infants; however, meta-analysis of long-term weight gain only included the results from one study. We conducted a meta-analysis (fixed effect model) of weight at 36 weeks of PMA, including data from O'Donnell et al.,[18] Whitfield et al.,[19] and our own data: the weighted mean difference in weight gain associated with carnitine supplementation ($n = 134$, including 72 patients randomized to carnitine and 62 to control treatment) was not significantly different from zero: −24.1 g (95% confidence interval −136.7, +88.5), and there was no significant heterogeneity (χ^2 0.35, $p = 0.84$).

None of the previously published randomized trials of carnitine supplementation in preterm infants showed any evidence of toxicity. In our study, there was no observed effect of carnitine supplementation on weight gain or other outcome variables. However, an increase in PDA ligation among infants treated with indomethacin was seen. This post hoc observation may well have resulted from chance. Alternatively, it could have been the result of an interaction between carnitine and indomethacin. Closure of a PDA is mediated by apoptosis, a process that is enhanced by indomethacin.[26] Carnitine has been shown to reduce apoptosis in different models, including ischemia–reperfusion injury.[27] These data would suggest that an epidemiologic analysis be considered to assess a possible effect of carnitine on PDA in very preterm infants.

The current study is the fourth randomized trial that fails to show any benefit of long-term carnitine supplementation in preterm infants. Although none of the three previous studies showed a significant change in any of several other outcomes, it is possible that rare benefits or side effects could have been undetected, for example, reduced ototoxicity. Until more data become available, the best evidence, based on four long-term studies including the current one, is that routine long-term L-carnitine supplementation does not appear to improve weight gain in preterm infants at doses greater than or equal to 50 μmol/kg/day.

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