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[Intervention Review]

Carnitine supplementation of parenterally fed neonates

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ABSTRACT

Background

Carnitine, a quaternary amino acid, plays an important role in the oxidation of long chain fatty acids. Both breast milk and infant formulas contain carnitine. However, it is not routinely provided in parenteral nutrition solutions. Non supplemented parenterally fed infants have very low tissue carnitine levels. The clinical significance of this is uncertain. 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, thus reducing the available energy and impairing growth.

Objectives

The primary aim of this review is to determine whether carnitine supplementation of parenterally fed neonates will improve weight gain.

The secondary aims are to determine the effect on lipid tolerance and ketogenesis.

Search methods

Computerised searches were carried out by both reviewers. Searches were made of Medline, Embase, The National Research Register (UK), the Cochrane Controlled Trials Register and expert informants. The MeSH headings used were carnitine and parenteral nutrition.

Selection criteria

Only randomised trials were considered. Trials were included if they involved carnitine supplementation alone, parenterally fed newborn infants, and measured at least one outcome of interest (weight gain, plasma fatty acids, plasma triglycerides, quantity of lipid tolerated, respiratory quotient or beta hydroxybutyrate levels).

Data collection and analysis

The two reviewers searched the literature separately and reached a consensus for inclusion of trials. Data were extracted and evaluated by the two reviewers independently of each other. Authors were contacted if possible to clarify or provide missing data.

Carnitine supplementation of parenterally fed neonates (Review)

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Main results

Fourteen studies were identified, six met the selection criteria. The results of the review are limited by the fact that the studies were generally short term and studied different outcomes. One study examined short term and long term weight gain, three reported only short term weight gain, three reported biochemical results in response to a short lipid challenge, and two reported results obtained during normal parenteral nutrition.

Among infants supplemented with carnitine, there was no evidence of effect on weight gain, lipid utilization or ketogenesis.

Authors' conclusions

We found no evidence to support the routine supplementation of parenterally fed neonates with carnitine.

PLAIN LANGUAGE SUMMARY

Carnitine supplementation of parenterally fed neonates

Not enough evidence that carnitine supplements improve weight gain in parenterally fed newborns. Preterm newborns (born before 37 weeks) frequently need extra nutritional supplements parenterally (given other ways than by the mouth). Carnitine is an amino acid found in both breast milk and infant formulas but is not routinely given parenterally. It helps fatty acids to convert into energy and helps in growth. The review of trials found not enough evidence to show any benefit of parenteral carnitine supplements on weight gain or lipid tolerance in preterm newborns. More research is needed.

BACKGROUND

Preterm neonates are frequently dependent on parenteral nutritional support in the first few weeks of life. The use of intravenous lipid emulsion, usually in the form of long chain triglycerides, provides essential fatty acids and a concentrated, isosmolar source of energy. Unfortunately, limited ability to metabolize lipids may limit the quantity infused.

Carnitine, a quaternary amino acid, plays an important role in long chain fatty acid oxidation. It is essential for the transport of fatty acids across the inner mitochondrial membrane into the mitochondrial matrix where the enzymes for beta oxidation are located. This is achieved via a three-enzyme cycle with carnitine palmityl transferases on the outer and inner aspects of the inner mitochondrial membranes and carnitine translocase as a transport protein in between. Carnitine is formed in the liver from the hydroxylation of gamma butyrobetaine, which is synthesized in the kidney from lysine and methionine. The activity of gamma butyrobetaine is age dependent, being much lower in newborns than in older children and adults (Borum 1983).

Carnitine is concentrated within cells, the intracellular level being 10 - 50 times the extracellular level. The total body stores are regulated by renal excretion with carnitine excreted intact. The tissue

stores in newborn term and preterm infants are approximately 25-50% of adult levels (Shenai 1984) with those of preterm being lower than term (Penn 1985). Both breast milk and infant formulas contain carnitine. However, it is not routinely provided in parenteral nutrition solutions.

Neonates therefore have both reduced synthesis and reduced stores of carnitine. Given that they are also likely to have increased demand due to rapid growth, it is perhaps not surprising that non-supplemented parenterally fed infants have very low tissue carnitine levels within two weeks (Penn 1981). The clinical significance of this is uncertain. In vitro studies have suggested that fatty acid oxidation is impaired only when the tissue levels fall below 10% of normal (Long 1982). Clinical symptoms of carnitine deficiency in infants receiving prolonged nonsupplemented parenteral nutrition have not been described. Despite this, it is possible that relative carnitine deficiency impairs fatty acid oxidation. It would be expected that carnitine deficiency would limit the metabolism of lipid leading to a rise in plasma triglycerides and free fatty acids, and impaired ketogenesis. The available non protein energy would be impaired, amino acids would be increasingly used to meet endogenous energy needs and thus tissue growth would be impaired.

OBJECTIVES

The primary aim of this review is to determine whether carnitine supplementation of parenterally fed neonates will improve weight gain.

The secondary aim is to determine whether carnitine supplementation of parenterally fed neonates will improve lipid tolerance. This will be assessed in terms of fatty acid levels, triglyceride clearance and amount of lipid tolerated.

Subgroup analysis will be conducted to determine whether the results differ for infants requiring more than 14 days of exclusive parenteral nutrition.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials in which carnitine supplementation was compared to placebo.

Types of participants

Infants 28 days postnatal age or less receiving more than 50% of their daily calorie intake from parenteral nutrition.

Types of interventions

Intravenous or enteral carnitine supplementation compared to no supplementation. This includes any dose, duration or starting age.

Studies reporting response to a single dose of carnitine will be excluded.

Studies using nutritional co-interventions will be excluded.

Types of outcome measures

1. Weight gain, both short term (during the intervention period) and long term (after the intervention period)
2. Fatty acid levels
3. Triglyceride levels
4. Quantity of lipid tolerated
5. Respiratory quotient
6. Ketone body levels

Search methods for identification of studies

Computerised searches were carried out by both reviewers. Searches were made of MEDLINE (1966 to January 2000), EMBASE (1974-2000), The National Research Register (UK), the Cochrane Controlled Trials Register (2000 issue 1) and expert informants. The MeSH headings used were carnitine and parenteral nutrition.

Data collection and analysis

The criteria and standard methods of the Cochrane Collaboration and its Neonatal Review Group were used.

Data extraction was performed independently by each reviewer using a structured proforma; differences were resolved by discussion.

We transformed graphical data into numerical data using a millimetric ruler.

Two of the studies stratified randomisation by birth weight or gestation and reported outcomes within each stratum. Each stratum was entered independently in this review. Therefore Bonner 1995 and Bonner 1995 represent two birthweight strata from the same trial. [Schmidt-S. 1983a](#) and [Schmidt-S. 1983b](#) represent two gestational age strata from the same trial.

Statistical analysis was carried out using the standard method of the Cochrane Neonatal Review Group, using weighted mean difference and its 95% confidence interval, and a fixed effect model for meta analysis.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Fourteen trials looking at the effect of carnitine supplementation were identified. Five trials were excluded on the basis of non randomisation. Two were excluded because of the presence of a nutritional co-intervention. One trial was excluded because the main route of nutrition was enteral.

Excluded studies

[Magnusson 1997](#) performed a double blind randomised trial of a standard long chain triglyceride emulsion compared to a new fat emulsion containing carnitine and gamma-linolenic acid. The study group consisted of 20 neonates undergoing surgery; the intervention took place over five days and the nutrition was 100% parenteral. This study was excluded as a nutritional co-intervention was present.

[Melegh 1986](#) performed a trial of enteral carnitine supplementation in five neonates versus five controls. The intervention took

place over seven days and nutrition was more than 50% enteral. This trial was excluded as it was unclear whether or not randomisation had taken place and the nutrition was more than 50% enteral throughout the study.

[Orzali 1983](#) studied the effect of a single dose of carnitine (total 200mg/kg over six hours) on lipid tolerance in 11 newborns compared to 10 controls. This trial was excluded as it did not appear to be randomised and it examined the acute effect of a single dose of carnitine.

[Orzali 1984](#) studied the effect of a single dose of carnitine (total 200mg/kg over six hours) on lipid tolerance in 11 newborns. A lipid tolerance test was carried out after seven days of carnitine free parenteral nutrition and was repeated with supplemental carnitine. This trial was excluded as it was a single group, nonrandomised study which examined the acute effect of a single dose of carnitine.

[Rubecz 1984](#) studied the clearance of plasma triglycerides in five infants following a lipid infusion. This was repeated after carnitine supplementation for three days. This trial was excluded as it was a single group, nonrandomised study.

[Rubecz 1985](#) studied the effect of a four hour carnitine infusion on resting heat production and respiratory quotient in 10 enterally fed preterm infants. This study was excluded as it was a single group, nonrandomised study which examined the acute effect of a single dose of carnitine.

[Rubin 1995](#) performed a double blind randomised study in 49 neonates. They were randomised to receive long chain triglyceride emulsion, a 50:50 medium chain:long chain triglyceride emulsion or a new fat emulsion containing carnitine and gamma-linolenic acid for six days. The study was excluded as a nutritional co-intervention was present.

[Sulkers 1990](#) compared 12 infants receiving carnitine supplemented parenteral nutrition with 12 receiving parenteral nutrition alone. Metabolic rate, protein, glucose and fat oxidation were calculated. This study was excluded as the groups were not randomised.

Included studies

Details of the included studies are presented in the table "Characteristics of included studies". All studies, with the exception of [Shortland 1998](#), were very short term.

Population

The inclusion criteria for each study varied slightly but were largely homogeneous. All studies involved newborns requiring parenteral nutrition. [Helms 1995](#) included term post surgical neonates as did [Coran 1985](#); the other studies included only premature neonates (27-37 weeks). Extremely premature infants were not included in any study. [Bonner 1995](#) used very low birth weight as the entry criterion (750-1500g).

Intervention

Carnitine was the sole intervention in all of the included studies. In four studies supplementation was completely parenteral; [Coran 1985](#) used the enteral route and [Shortland 1998](#) used both. The dose used ranged from 50 micromol/kg/day ([Bonner 1995](#)) to

150 micromol/kg/day ([Shortland 1998](#)). The duration of the intervention was variable. [Schmidt-Sommerfeld 1983](#) commenced carnitine on day 2 of life; mean duration was 5.9 +/-1.3 days. Patients in [Larsson's](#) study received carnitine for six to twenty one days; results were reported for the first five days. The studies by both [Helms 1995](#) and [Bonner 1995](#) report results for two weeks of supplementation. [Shortland 1998](#) supplemented parenterally followed by orally once enteral feeds were established; supplementation continued until the equivalent of 40 weeks gestation. Results were reported until 6 months after the expected date of delivery. None of the studies reported the carnitine content or the actual quantity of the enteral feeds given.

Outcome measures

Primary Outcome

Weight gain

[Bonner 1995](#) reported weight gain (g/day) at 2 weeks. [Shortland 1998](#) reported weight gain in g/day over two week intervals for the first eight weeks and then at three and six months after the expected date of delivery. [Coran 1985](#) reported individual patient weights before and after two weeks of supplementation with either carnitine or placebo. [Helms 1995](#) reported weight gain in g/kg/day over the first and second week separately.

Secondary outcomes

The outcome measures reflecting lipid metabolism varied between studies. In three of the studies blood for biochemical analysis was taken at the end of a lipid tolerance test, either 1g/kg Intralipid over 4 hours ([Schmidt-Sommerfeld 1983](#)) or 0.5g/kg Intralipid over 2 hours ([Coran 1985](#), [Helms 1995](#)).

Two studies ([Bonner 1995](#), [Larsson 1990](#)) took samples during normal parenteral nutrition, [Larsson 1990](#) after a 4 hour lipid free period. The timing of samples is not stated by [Bonner 1995](#).

Fatty acids

Free fatty acids were measured by [Schmidt-Sommerfeld 1983](#), [Helms 1995](#) and [Coran 1985](#). [Helms 1995](#) and [Coran 1985](#) presented the results graphically.

Triglycerides

[Schmidt-Sommerfeld 1983](#) measured triglyceride response to a 4 hour lipid challenge. [Helms 1995](#) and [Coran 1985](#) measured triglyceride levels obtained in response to a 2 hour lipid tolerance test; the results were displayed graphically and the peak value at 2 hours used in this analysis.

[Larsson 1990](#) intermittently measured triglyceride levels after a 4 hour lipid free period over 20 days of the study. The results at day 5 were used for this analysis as parenteral nutrition still comprised more than 50% of the calorie intake at this stage.

Maximum amount of lipid tolerated

In the study by [Bonner 1995](#) the lipid intake was limited by the serum triglyceride levels obtained and the maximum lipid tolerated was reported.

Respiratory quotient

Respiratory quotient was not measured in any study.

Ketogenesis

Schmidt-Sommerfeld 1983, Helms 1995 and Bonner 1995 measured beta hydroxybutyrate at the end of a lipid tolerance test. Larsson 1990 reported beta hydroxybutyrate levels for days 2-5 during normal parenteral nutrition. Day five data were used for this analysis. Coran 1985 measured total ketone bodies.

Risk of bias in included studies

Three out of the six studies reported methods of randomisation. Larsson 1990 used a card system in blocks of four, Helms 1995 used a random digit table and Shortland used a predetermined random code. In two studies both the carers and assessors were blinded (Shortland 1998, Helms 1995), in two they were unblinded (Bonner 1995, Schmidt-Sommerfeld 1983) and in two it was unclear whether either the carers or assessors were blinded (Coran 1985, Larsson 1990). As previously stated randomisation was stratified in two studies. Results were obtained for between 86% and 100% of the enrolled infants. In the Helms 1995 study it was stated that all the study participants received at least seven days parenteral nutrition. It is not clear whether this represented all patients randomized or if those receiving shorter periods of parenteral nutrition were not subsequently studied.

Effects of interventions

Weight gain

Four trials examined early weight gain. Three of those reported weight gain over the first 2 weeks in g/day in a total of 58 treated neonates versus 57 controls. There was no difference in weight gain (WMD 0.74 g/day, 95% CI -1.88, 3.35). Bonner 1995 reported weight gain for the bigger infants (Bonner 1995b). They state that there was no difference between the treated and control group in the smaller infants (Bonner 1995a), but do not report the actual data. Helms 1995 reported weight gain separately for week one and week two in 20 supplemented neonates versus 23 controls. There was no difference for the first week (MD -1.1g/kg/day 95% CI - 9.20, 7.0). A significant effect was reported in the second week (MD 11.6g/kg/day, 95% CI 3.76, 19.44). Shortland 1998 found no difference in weight gain over the subsequent two weeks (MD 0.80, 95% CI -0.34, 4.94).

Shortland 1998 was the only study to report long term weight gain. There was no difference at one month post term (MD 0.80, 95% CI -3.81, 5.41) or at any stage between randomisation and three months post term.

Secondary Outcomes

Lipid tolerance was reported in response to a lipid challenge or during normal parenteral nutrition. Those studies reporting lipid tolerance in response to a lipid challenge were combined by meta analysis.

Plasma free fatty acids

Three studies reported free fatty acid levels in a total of 40 supplemented neonates versus 43 controls. There was no evidence of difference between groups (WMD -0.16 mmol/l, 95% CI -0.37, 0.05).

Plasma triglycerides

Three studies reported triglyceride levels in a total of 40 carnitine supplemented versus 43 controls. There was no evidence of difference between groups (WMD -0.69 mmol/l, 95% CI -1.84, 0.45). Larsson 1990 measured plasma triglyceride and fatty acid concentrations in a further 12 neonates after a four hour lipid free period during normal parenteral nutrition (lipid infused over 20 hours). There was no significant difference in either.

Amount of lipid tolerated

Bonner 1995 increased the lipid incrementally depending on the plasma triglyceride levels in 21 carnitine supplemented neonates versus 21 controls. The mean quantity of lipid infused therefore reflected tolerance. There was no evidence of difference between groups in the amount tolerated (WMD 0.09g/kg/day, 95% CI -0.20, 0.38). Thus, there was no evidence of improvement in lipid tolerance in neonates supplemented with carnitine.

Ketogenesis

Three studies reported beta hydroxybutyrate production in response to a lipid challenge in a total of 55 supplemented neonates versus 58 controls. There was a statistically significant improvement in beta hydroxybutyrate production (WMD 0.05mmol/l, 95% CI 0.03, 0.06). However, even a true difference of 0.06mmol/l would not be clinically significant. Larsson 1990 noted no difference in a further 12 neonates, six of which were carnitine supplemented.

Coran 1985 noted no difference in ketone bodies between the supplemented and nonsupplemented groups (6 in each).

A subgroup analysis of the effect of supplementation in infants requiring prolonged parenteral nutrition (more than 14 days) was not possible as data were not available.

DISCUSSION

The review did not demonstrate any evidence of benefit from parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain for neonates requiring parenteral nutrition. However, the studies were all small and reported different outcome measures.

The most important clinical outcome would be that of improved weight gain. It may be expected that any effect on weight gain would be seen during the first two weeks, as parenteral nutrition plays a diminishing role with time. Bonner 1995 reported that there was no difference in weight gain in the smaller birth weight group (Bonner 1995a, 750-1000g) and reported numerical weight gain data only for the larger infants (Bonner 1995b, birth weights 1001-1500g). In effect this produced a publication bias. Despite

this, no improvement in weight gain was demonstrated in the three studies reporting weight gain at two weeks. The only positive effect on weight gain in carnitine supplemented infants was noted by Helms 1995 for week two but not for week one. The rate of weight gain halved in the control group between week one and two, thus creating the difference. The authors state that there was no difference between the groups when the weight gain was analysed over the study period. It is possible that the carnitine status of the control group continued to fall, increasingly impeding growth, and hence the difference between weeks one and two could be real. However, this is not supported by the data obtained in the Shortland 1998 study which failed to show any difference in weight gain between the groups at any time during the study.

The longer term weight gain data are all obtained from the Shortland 1998 study. Although they did not show any difference in weight gain, data on calorie intake and feed supplementation were not provided. While the study was completely blinded it is possible that the control group was prescribed a greater calorie intake in response to poor weight gain. However, there is no evidence of even transiently impaired weight gain in the non supplemented group.

Biochemical evidence of lipid tolerance and utilisation were measured both during normal parenteral nutrition and in response to a lipid challenge. Despite the different conditions under which carnitine supplementation was compared, there was no difference between the groups. The small increase in ketogenesis in the carnitine supplemented group is unlikely to be of any clinical significance.

AUTHORS' CONCLUSIONS

Implications for practice

Despite plausible rationale, we found no evidence from randomised trials which justifies routine carnitine supplementation of neonates receiving parenteral nutrition.

Implications for research

Further research on carnitine supplementation should concentrate on those neonates or infants requiring long term total parenteral nutrition. Outcome measures should be robust and clinically important such as growth and lipid tolerance under conditions of normal parenteral nutrition.

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Shenai 1984

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bonner 1995a

Methods	Randomised, placebo controlled trial Blinding of randomisation:- Can't tell Blinding of intervention:- No Blinding of outcome assessors:-No Complete follow up:-Yes
Participants	Number entered into study =22, 11 in each group Inclusion criteria= birth weight 751-1000g requiring parenteral nutrition. Exclusion criteria=not expected to survive, recent blood transfusion, not expected to require parenteral nutrition for more than 1 week. Infants stratified by birth weight (750-1000g and 1001-1500g)
Interventions	50 micromol/kg/day carnitine as a continuous intravenous infusion vs placebo until >50% of caloric intake was enteral. Parenteral lipid was started at 0.5g/kg/day and increased gradually if serum triglyceride level was <1.7mmol/l
Outcomes	Outcomes were reported at 2 weeks of study. Weight gain in g/day Beta hydroxybutyrate levels (weekly) Serum carnitine (weekly) Mean quantity of lipid tolerated daily. Triglyceride levels
Notes	Same trial as Bonner 1995b

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bonner 1995b

Methods	Randomised, placebo controlled trial Blinding of randomisation:- Can't tell Blinding of intervention:- No Blinding of outcome assessors:-No Complete follow up:-Yes
Participants	Number entered into study =20, 10 in each group Inclusion criteria= birth weight 1001-1500g requiring parenteral nutrition. Exclusion criteria=not expected to survive, recent blood transfusion, not expected to require parenteral nutrition for more than 1 week

Bonner 1995b (Continued)

Interventions	50 micromol/kg/day carnitine as a continuous intravenous infusion vs placebo until >50% of caloric intake was enteral. Parenteral lipid was started at 0.5g/kg/day and increased gradually if serum triglyceride level was <1.7mmol/l	
Outcomes	Outcomes were reported at 2 weeks of study. Weight gain in g/day Beta hydroxybutyrate levels (weekly) Serum carnitine (weekly) Mean quantity of lipid tolerated daily. Triglyceride levels	
Notes	Same trial as Bonner 1995a	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Coran 1985

Methods	Randomised controlled trial Blinding of randomisation:-Can't tell Blinding of intervention:-Yes Blinding of outcome assessors:-Cant tell Complete follow up:-Yes	
Participants	Number entered into study =12, 6 in each group Inclusion criteria Newborn undergoing major surgery in first few days of life and expected to require parenteral support for at least 1 week. No exclusions stated	
Interventions	70 micromol/kg/day carnitine or placebo in divided doses every 3 hours enterally for 7 days	
Outcomes	Weight gain Plasma taken on days 1 and 8 for free fatty acids, triglycerides, total ketone bodies and carnitine	
Notes	Biochemical results obtained after a short lipid challenge (0.5g/kg intralipid over 2 hours) at 2,4,6 and 8 hours	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Helms 1995

Methods	Randomised controlled trial Blinding of randomisation:-Yes Blinding of intervention:-Yes Blinding of outcome assessors:-Yes Complete follow up:-can't tell
Participants	Number entered into study = 43, 20 in the carnitine group Inclusion criteria =Neonates requiring minimum of 7 days parenteral nutrition Mean gestational age was 31 weeks Exclusion criteria=receiving drugs known to affect carnitine or lipid metabolism
Interventions	50 micromol/kg/day carnitine by continuous intravenous infusion for 7 days then 100 micromol/kg/day for 7 days. It is unclear whether the control group received placebo or if the carnitine was added to the parenteral nutrition in the pharmacy. Participants were permitted <15% enteral nutrition with formulas containing little carnitine
Outcomes	Weight gain week 1 (derived from the slope of a linear regression plot of daily weight) nitrogen and carnitine balance at baseline, day 7 and day 14 of study. Plasma biochemistry on days 0,7 and 14 :- ketone levels, triglycerides, free fatty acids.
Notes	Biochemical results obtained after a short lipid challenge (0.5g/kg Intralipid over 2 hours)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Larsson 1990

Methods	Randomised placebo controlled trial Blinding of randomisation:-Yes Blinding of intervention:-Yes Blinding of outcome assessors:-Yes Complete follow up:-Yes
Participants	Number entering study= 14, one died, one excluded as on full feeds within 5 days, therefore results from 12 reported, 6 in each group Inclusion criteria= neonates with gestational age <33 weeks and anticipated need for at least 5 days parenteral nutrition. The mean gestational ages were 28.8 in th carnitine group compared to 30.7 weeks in the control
Interventions	Carnitine 60 micromol/kg/day or normal saline added to the lipid emulsion until on 75% of enteral feeds
Outcomes	Plasma taken on days 0, 2, 5, 10, 15, 20, for -triglycerides, free fatty acids, betahydroxybutyrate, lactate and plasma carnitine (total, free and acyl). These were taken 4 hours after the amino acid and lipid solution

Larsson 1990 (Continued)

	had been discontinued	
Notes		
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Schmidt-S. 1983a

Methods	Randomised controlled trial Blinding of randomisation:-Can't tell Blinding of intervention:-No Blinding of outcome assessors:-Can't tell Complete follow up:96%	
Participants	Number entering study=13, 7 in the carnitine group Inclusion criteria =appropriately grown neonates, 29-33 weeks gestational age and 1200-2490g birth weight requiring parenteral nutrition Exclusions=severe jaundice, sepsis, metabolic disturbance or intracerebral haemorrhage	
Interventions	60 micromol/kg/day IV carnitine infused over 5 hours while on parenteral nutrition. Control group not supplemented, the use of placebo is not stated	
Outcomes	An intravenous lipid challenge was carried out on days 6-10 before the start of enteral feeds Plasma was taken for - Betahydroxybutyrate, triglycerides, free fatty acids and carnitine	
Notes	Biochemical results obtained after a lipid challenge (1g/kg Intralipid over 4 hours) Same trial as Schmidt-S. 1983b	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schmidt-S. 1983b

Methods	Randomised, placebo controlled trial Blinding of randomisation:- Can't tell Blinding of intervention:- No Blinding of outcome assessors:-No Complete follow up:-Yes
Participants	Number entering study=15, 7 in the carnitine group Inclusion criteria =appropriately grown neonates, 34-37 weeks gestational age and 1200-2490g birth weight requiring parenteral nutrition Exclusions=severe jaundice, sepsis, metabolic disturbance or intracerebral haemorrhage
Interventions	60 micromol/kg/day IV carnitine infused over 5 hours while on parenteral nutrition. Control group not supplemented, the use of placebo is not stated
Outcomes	An intravenous lipid challenge was carried out on days 6-10 before the start of enteral feeds Plasma was taken for - Betahydroxybutyrate, triglycerides, free fatty acids and carnitine
Notes	Biochemical results obtained after a lipid challenge (1g/kg Intralipid over 4 hours) Same trial as Schmidt-S. 1983a

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Shortland 1998

Methods	Randomised placebo controlled trial Blinding of randomisation:-Yes Blinding of intervention:-Yes Blinding of outcome assessors:-Yes Complete follow up:-94% at 6 months post term, weight data while in hospital falls to 83% at 4 weeks of the study and 25% at 8 weeks reflecting infant discharge home
Participants	Number entering study =86. 1 withdrew consent, 1 had a nasopharyngeal teratoma, 1 died from an intraventricular haemorrhage and 1 died from sudden infant death after hospital discharge. This left 83, 42 in the placebo group and 41 in the carnitine group Inclusion criteria = appropriately grown infants gestational age 28-35 weeks and requiring parenteral nutrition. Randomisation was stratified by gestational age. The median gestational ages were 30.7 and 31.4 weeks in the carnitine and control group respectively
Interventions	Carnitine 150 micromol/kg/day or placebo intravenously until enteral feeds established and then orally until 40 weeks gestation. Infants remained in the study until 6 months after the expected date of delivery

Shortland 1998 (Continued)

Outcomes	Weight gain, length, head circumference and skinfold thickness. Plasma carnitine (total, free and acyl) Incidence of hypoglycaemia	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Magnusson 1997	Co-intervention present - lipid emulsion supplemented with carnitine was also supplemented with gamma linolenic acid
Melegh 1986	Carnitine supplementation was enteral, unclear if the study was randomised
Orzali 1983	Not randomised
Orzali 1984	Crossover study Single dose of carnitine Not randomised
Rubecz 1984	Not randomised
Rubecz 1985	Not randomised Not on parenteral nutrition
Rubin 1995	Co-intervention present - lipid emulsion supplemented with carnitine was also supplemented with gamma linolenic acid
Sulkers 1990	Not randomised

DATA AND ANALYSES

Comparison 1. Carnitine supplementation vs no supplementation

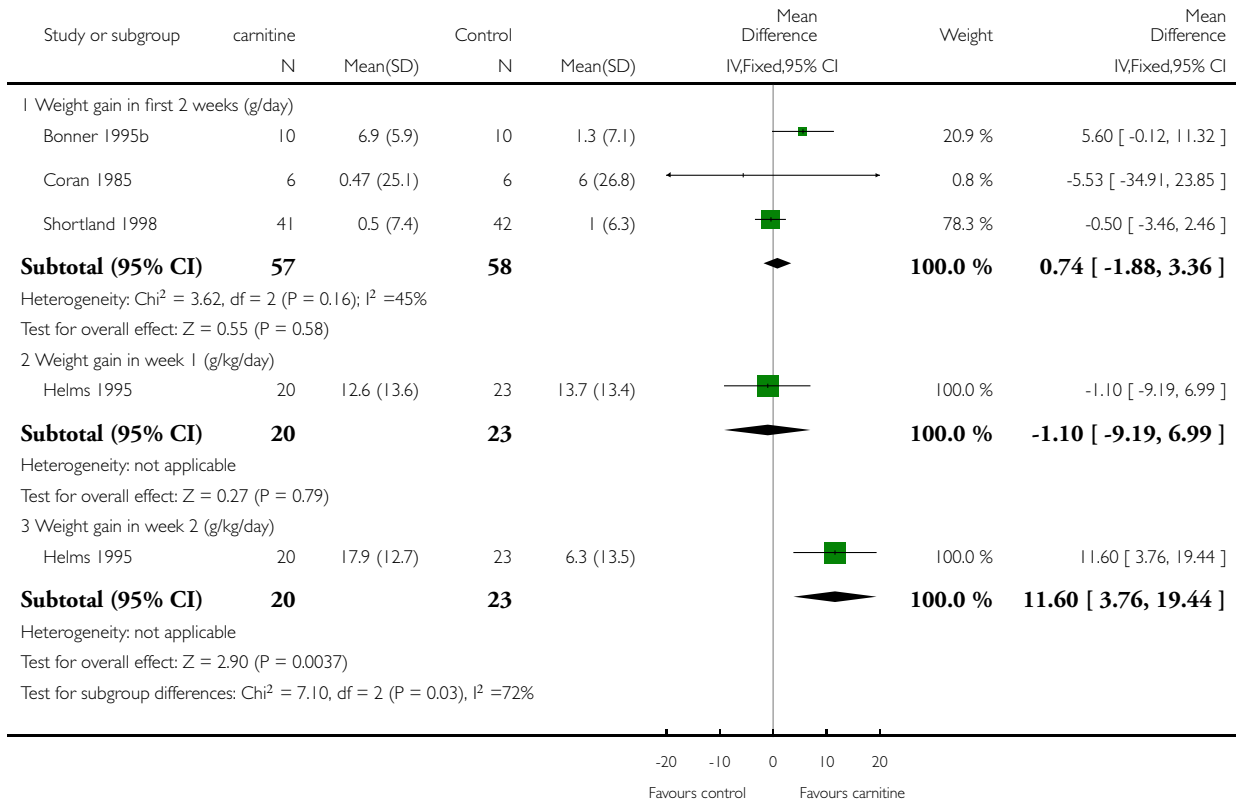
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight gain in first 2 weeks	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Weight gain in first 2 weeks (g/day)	3	115	Mean Difference (IV, Fixed, 95% CI)	0.74 [-1.88, 3.36]
1.2 Weight gain in week 1 (g/kg/day)	1	43	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-9.19, 6.99]
1.3 Weight gain in week 2 (g/kg/day)	1	43	Mean Difference (IV, Fixed, 95% CI)	11.60 [3.76, 19.44]
2 Weight gain 2-4 weeks (g/day)	1	69	Mean Difference (IV, Fixed, 95% CI)	0.80 [-3.35, 4.95]
3 Weight gain from hospital discharge to one month post term (g/day)	1	83	Mean Difference (IV, Fixed, 95% CI)	0.80 [-3.82, 5.42]
4 Free fatty acid levels (mmol/l)	4	83	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.37, 0.05]
5 Triglyceride levels (mmol/l)	4	83	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-1.84, 0.45]
6 Lipid tolerance - maximum amount of lipid tolerated (g/kg/day)	2	42	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.20, 0.38]
7 Ketogenesis - beta hydroxybutyrate levels (mmol/l)	5	113	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.03, 0.07]

Analysis 1.1. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 1 Weight gain in first 2 weeks.

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 1 Weight gain in first 2 weeks

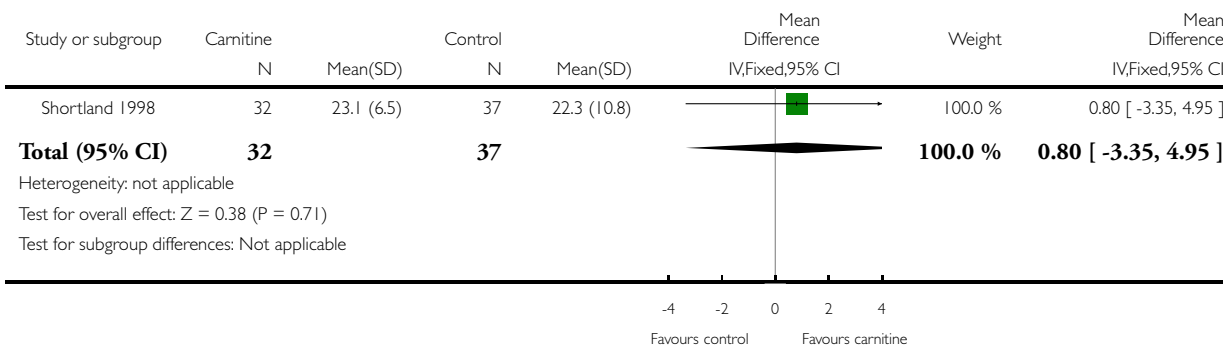


Analysis 1.2. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 2 Weight gain 2-4 weeks (g/day).

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 2 Weight gain 2-4 weeks (g/day)

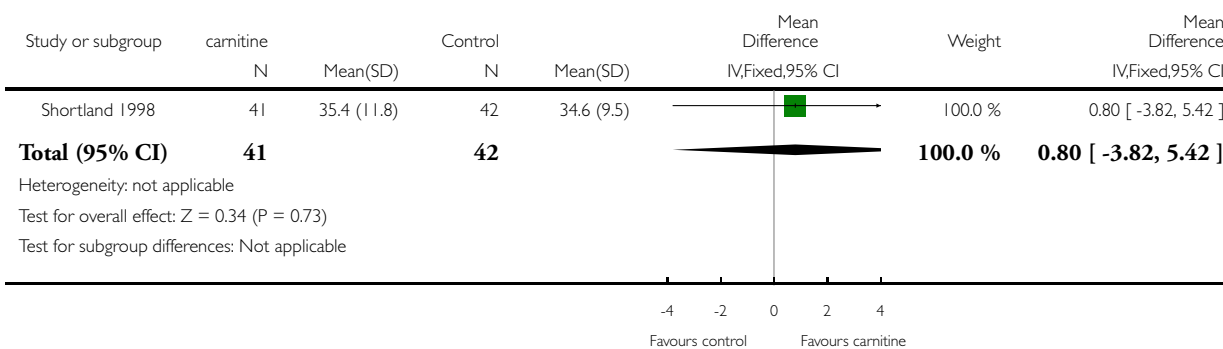


Analysis 1.3. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 3 Weight gain from hospital discharge to one month post term (g/day).

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 3 Weight gain from hospital discharge to one month post term (g/day)

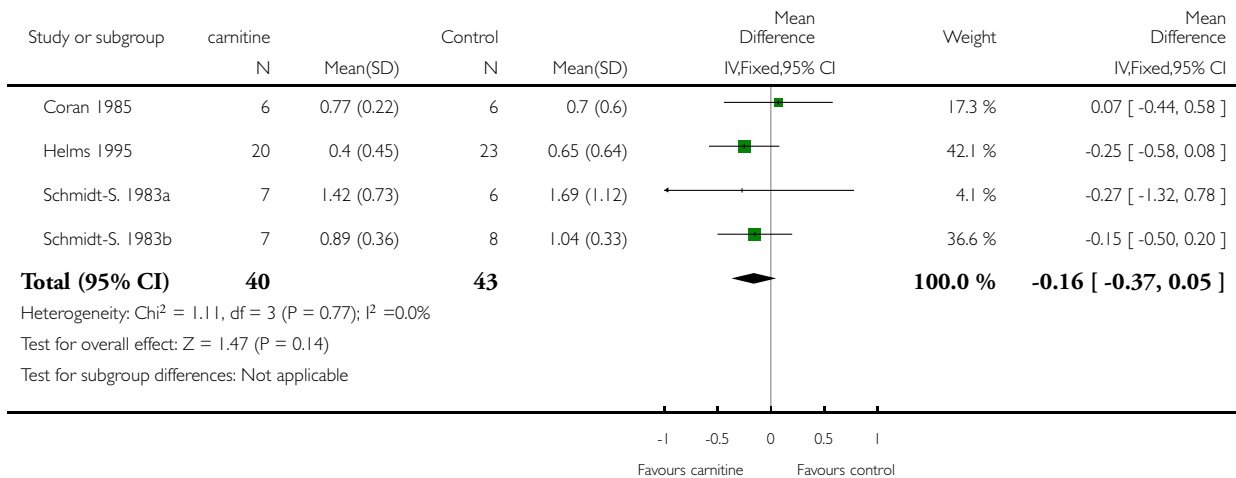


Analysis 1.4. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 4 Free fatty acid levels (mmol/l).

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 4 Free fatty acid levels (mmol/l)

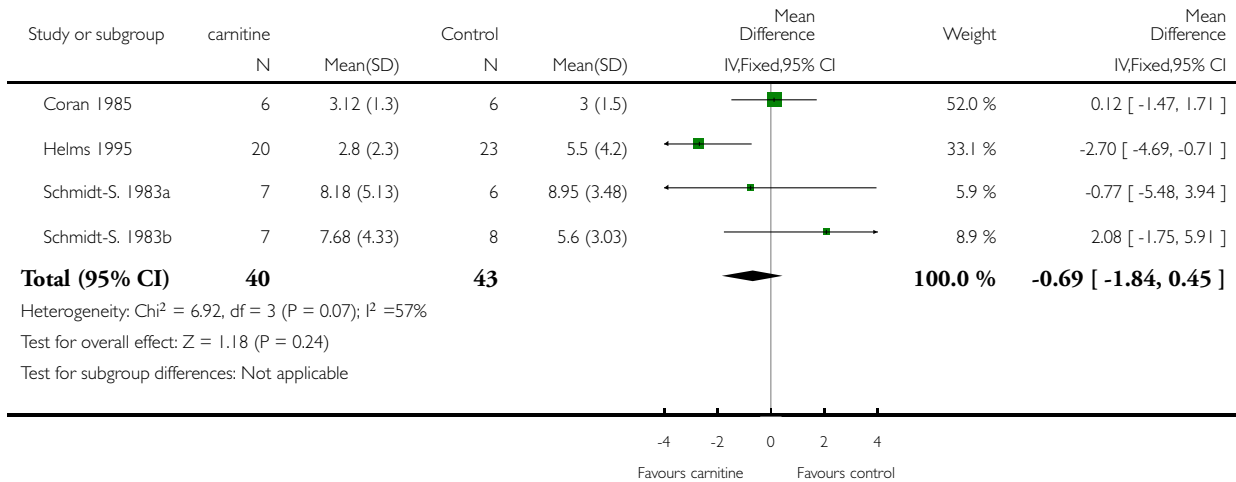


Analysis 1.5. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 5 Triglyceride levels (mmol/l).

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 5 Triglyceride levels (mmol/l)

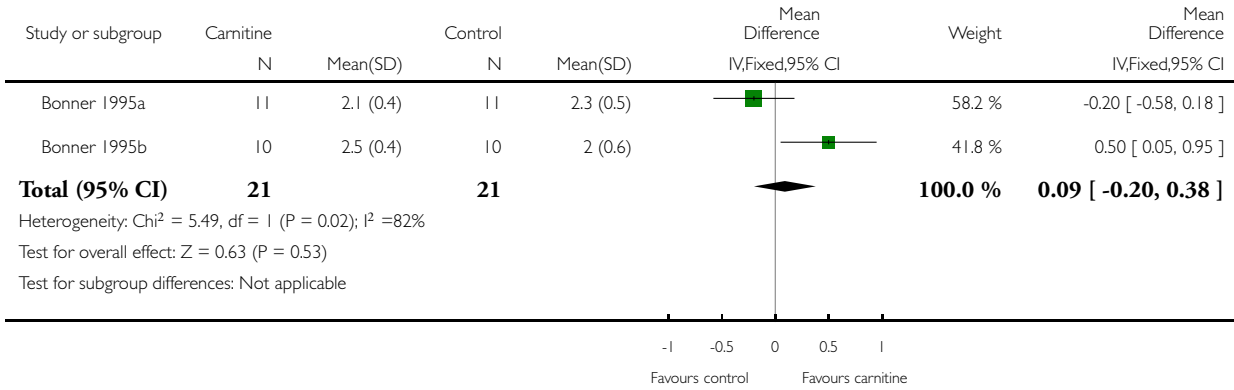


Analysis 1.6. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 6 Lipid tolerance - maximum amount of lipid tolerated (g/kg/day).

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 6 Lipid tolerance - maximum amount of lipid tolerated (g/kg/day)

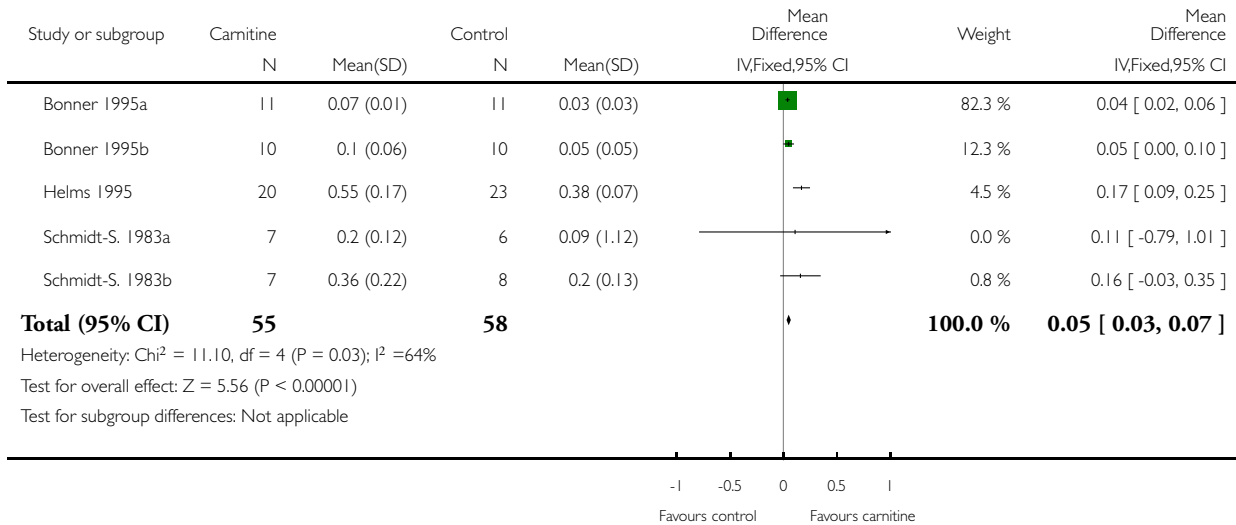


Analysis 1.7. Comparison 1 Carnitine supplementation vs no supplementation, Outcome 7 Ketogenesis - beta hydroxybutyrate levels (mmol/l).

Review: Carnitine supplementation of parenterally fed neonates

Comparison: 1 Carnitine supplementation vs no supplementation

Outcome: 7 Ketogenesis - beta hydroxybutyrate levels (mmol/l)



WHAT'S NEW

Last assessed as up-to-date: 9 August 2000.

Date	Event	Description
15 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 4, 2000

DECLARATIONS OF INTEREST

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Parenteral Nutrition; *Weight Gain; Carnitine [*administration & dosage]; Infant, Newborn; Randomized Controlled Trials as Topic

MeSH check words

Humans