

A systematic review about prophylactic L-carnitine administration in parenteral nutrition of extremely preterm infants

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REVIEW

A systematic review about prophylactic L-carnitine administration in parenteral nutrition of extremely preterm infants

Revisión sistemática sobre la suplementación profiláctica de L-carnitina en la nutrición parenteral de recién nacidos pretérmino

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Abstract

Objective: Preterm infants with total parenteral nutrition are at particular risk of developing carnitine deficiency with impaired tolerance of parenteral lipids. The objective was to review the scientific literature on potential benefits of prophylactic L-carnitine administration in parenteral nutrition of preterm newborns.

Methods: Selected scientific articles in MEDLINE/PubMed, Scopus, The Cochrane Library, British Library EThOS and TESEO databases were assessed for this systematic review. The terms used as descriptors were «Total Parenteral Nutrition» and «Carnitine». Jadad scale was chosen to evaluate the quality of them.

Results: 18 out of the 93 references retrieved were selected for reviewing after applying the inclusion and exclusion criteria, 4 of them were discarded for being considered of low quality. Almost all studies agreed on the analytical variables measured (free carnitine and acylcarnitine, triglycerides, free fatty acids and ketone bodies). Other clinical variables such as weight gain, apnea, or length of stay at hospital were also considered.

Conclusions: The present results prove that routine supplementation in the parenteral nutrition of preterm newborns may help to increase carnitine levels, but neither a relevant improvement in the lipid profile, or an increase in weight gain, or a decrease in morbimortality or reduction of hospital stay could be demonstrated. More studies are needed in preterm infants to know whether routine supplementation of L-carnitine in neonates requiring total parenteral nutrition for a long time would provide any clinical benefit.

KEYWORDS: Carnitine/deficiency++ Parenteral Nutrition++ Infant++ Extremely Premature.

Resumen

Objetivo: Los recién nacidos pretérmino con nutrición parenteral total tienen tanto una reducción de la ingesta de L-carnitina como de las reservas tisulares, lo que podría suponer una peor tolerancia de los lípidos parenterales. El objetivo fue revisar la literatura científica en busca de los posibles beneficios clínicos de su administración en la nutrición parenteral.

Métodos: Revisión sistemática de los documentos recuperados en las bases de datos MEDLINE/Pubmed, Scopus, The Cochrane Library, British Library EThOS y TESEO. Los términos utilizados como descriptores fueron «Total Parenteral Nutrition» y «Carnitine». La calidad de los artículos se evaluó mediante la escala de Jadad.

Resultados: Tras aplicar los criterios de inclusión y exclusión, se seleccionaron para la revisión 18 artículos de las 93 referencias recuperadas, de los cuales 4 fueron descartados al no ser considerados de alta calidad. Casi la totalidad de los estudios coincidían en las variables analíticas medidas (carnitina libre y acilcarnitina, triglicéridos, ácidos grasos libres y cuerpos cetónicos). Además, en algunos se tenían en cuenta otras variables clínicas, como la ganancia ponderal o la apnea.

Conclusiones: La suplementación rutinaria en la nutrición parenteral de recién nacidos pretérmino sí parece mejorar los niveles plasmáticos de carnitina, pero sin llegar a demostrar una mejoría significativa en el perfil lipídico, ni aumento de la ganancia ponderal, ni disminución de la morbi-mortalidad o reducción de la estancia hospitalaria. Son necesarios más estudios para demostrar si la suplementación sistemática a recién nacidos pretérmino que requieren nutrición parenteral total durante más de un mes aportaría beneficios clínicos.

PALABRAS CLAVE: L-carnitina, Suplementación, Nutrición parenteral, Recién nacido pretérmino, Deficiencia.

Introduction

Carnitine (4-trimethyl-amino-3-hydroxybutyrate) is a dipeptide widely distributed in all mammal tissues, and particularly abundant in muscle tissue¹, which is synthesized in the liver, kidneys and brain from two essential aminoacids, lysine and methionine. It appears as D and L isomer, and the latter is its biologically active form found in certain foods; and even though Disomer is not, it is able to compete with the former for binding sites, which increases the risk of L-carnitine deficiency. It acts as a shuttle for long-chain fatty acids, facilitating their entry in the mitochondrial matrix for lipid β -oxidation and the subsequent production of energy². To this aim, it binds with the activated fatty acid molecule (Acyl-CoA), generating acylcarnitine, and through a transporter enzyme of the internal mitochondrial membrane, it allows this molecule to get inside the mitochondria, where it is separated again so that the fatty acid will continue on its way and obtain adenosine triphosphate (ATP). Intracellular carnitine deficiency will deteriorate the ability to use fat as fuel. Specifically, it seems to limit lipid metabolism, leading to an increase in plasmatic triglycerides, fatty acids and ketone bodies (acetoacetic and β -hydroxybutyric acids), and therefore aminoacids would be used to satisfy the endogenous energy needs, as there would be an impact on the availability of energy non-originated in proteins, and this would affect new tissue growth formation³. There is no need in healthy children and adults for carnitine intake from food, as long as their liver, kidneys and brain are generating quantities enough to meet their daily needs. Some foods rich in this product are: red meat (particularly mutton), whey, fish, chicken, rice, bread, asparagus and avocados.

Digestive tract immaturity and frequent complications appearing during the first weeks of life will make it difficult to implement an enteral nutrition enough to meet the metabolic needs of the preterm newborn (PTNB); it will be required to adapt their energy and metabolic balance through parenteral nutrition (PN), which will often be required even for >1 month (prolonged PN: PPN). The L-carnitine reserves in a full-term

newborn (FTN) are approximately 25-50% of those in adults⁴, and the reserves in PTNBs are even lower than those in FTNs⁵. Both breast milk and baby formula contain carnitine, though it is not usually added to PN solutions. For this reason, PTNBs on total parenteral nutrition (TPN) have both a reduction in carnitine intake and in tissue reserves; and given that they tend to be more demanding due to their rapid growth, it is not surprising that newborns fed with PN without supplements will reach very low carnitine levels after two weeks of life⁶.

In the past, PTNBs were usually kept on a strict diet and received calorie intakes quite below their energy requirements for a prolonged time, during some days or weeks, for fear of presenting metabolic complications derived of an early enteral nutrition or a rapid increase in macronutrients. Currently, enteral nutrition practices with more accelerated advancement are considered safe⁷, as well as an administration of parenteral nutrients earlier than in the past, and with a higher volume of lipids since the first day of life⁸. Lack of carnitine can be an etiological factor in the limited ability of preterm newborns to use parenteral lipids. In vitro studies have suggested that fatty acid oxidation will be irregular when levels of tissue carnitine are below 10% of their normal level⁹. The objective of this study was to review literature in search of the potential benefits of the prophylactic administration of L-carnitine in the PN of PTNBs, such as a potential improvement in lipid profile, increase in weight gain, reduction in morbimortality, reduction in hospital stay, or development of apnea of prematurity.

Methods

A descriptive study and critical analysis of the articles retrieved, through a systematic technique, from the following databases: MEDLINE/Pubmed, Scopus, The Cochrane Library, British Library EThOS and TESEO (Doctoral Thesis Database of the Ministry of Education, Culture and Sport). It was decided to select for analysis those articles that met the following inclusion criteria: original documents, adequate to the search objectives (relationship between serum L- carnitine levels and an improvement in clinical parameters, such as a significant progress in the lipid profile, an increase in weight gain, or a reduction in hospital stay, among others), published in any country, by any institution or individual researcher, and in English or Spanish. The Medical Subject Headings (MeSH) developed by the U.S. National Library of Medicine was used to define the search terms. «Total Parenteral Nutrition» and «Carnitine» were considered adequate as descriptors (MeSH). The final search equation was developed through the use of boolean connectors for their use in the MEDLINE/Pubmed database, as follows: (“Parenteral Nutrition, Total”(Mesh) OR “Parenteral Nutrition Solutions”(Mesh)) AND “Carnitine”(Mesh) (English (lang) OR Spanish (lang)).

The same strategy was subsequently adapted to the characteristics of the remaining databases previously mentioned. The search was conducted

from the first date available and until December, 2017. Besides, the bibliographic list of the articles selected was reviewed, in order to identify any studies undetected during the database review. Those articles with a study population other than PTNBs were excluded, as well as any articles that were not original (exclusion criteria).

Article selection was conducted independently by two of the authors of this present review. Any discrepancies detected were solved through discussion, and in case that consensus was not reached, a third evaluator was asked to participate. The methodological quality of the studies was analyzed through the Jadad Scale or Oxford Quality Scoring System, a critical reading tool with 5 questions associated with clinical trial analysis, which classifies the study as of low quality if its score is below 3, and considers rigorous a randomized clinical trial with a score of 5¹⁰.

Results

The strategy for search in different databases reported 93 references in total. After the first duplicity review, 52 studies were obtained; and after applying the inclusion and exclusion criteria (Figure 1), 30 of these were rejected because they did not adjust to the topic of our review, 3 of them were reviews, comments, or other document types, and therefore did not meet the inclusion criteria, and another 2 because the study population were not PTNBs (exclusion criteria). When evaluating the quality of the 18 articles^{2,6,11-26} selected through the Jadad Scale, their scores ranged between 2 and 5, with a median score of 5 (Table 1). Those articles with a score <3 were rejected, and therefore 14 articles were left for our review^{2,6,11-22}, as shown in Figure 1. These articles had been published by international institutions and were written in English.

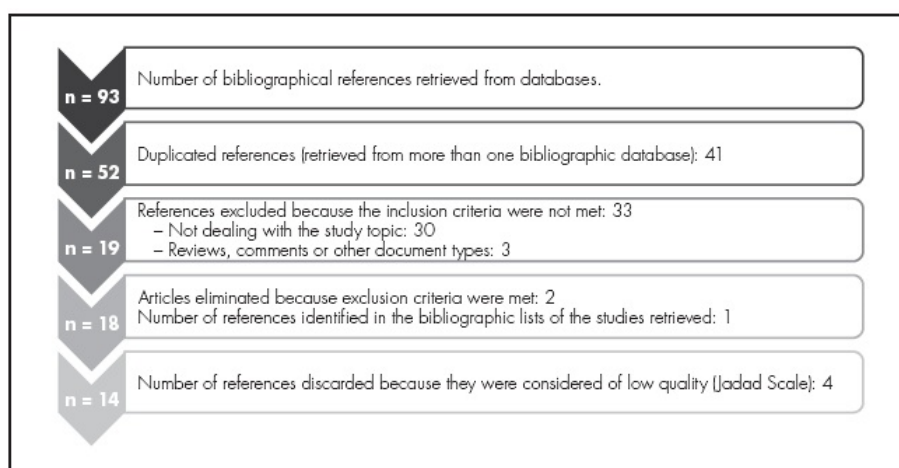


Figure 1
Flow diagram for article selection.

Table 1
Evaluation of methodological quality and risk of bias with the Jadad Scale

Study	Q1*	Q2*	Q3*	Q4**	Q5**	Total
Penn <i>et al.</i> , 1980 ¹¹	1	1	1	1	1	5
Schmidt-Sommerfeld <i>et al.</i> , 1983 ²³	1	0	1	1	-1	2
Coran <i>et al.</i> , 1985 ¹²	1	1	1	1	1	5
Larsson <i>et al.</i> , 1990 ¹³	1	1	1	1	1	5
Helms <i>et al.</i> , 1990 ¹⁴	1	1	1	1	1	5
Sulkers <i>et al.</i> , 1990 ¹⁵	1	1	1	1	1	5
Bonner <i>et al.</i> , 1995 ¹⁶	1	1	1	1	1	5
Shortland <i>et al.</i> , 1998 ¹⁷	1	1	1	1	1	5
Meyburg <i>et al.</i> , 2002 ⁶	1	1	1	1	1	5
O'Donnell <i>et al.</i> , 2002 ¹⁸	1	1	1	1	1	5
Whitfield <i>et al.</i> , 2003 ¹⁹	1	1	1	1	1	5
Honzik, 2005 ²⁴	1	0	1	1	-1	2
Pande <i>et al.</i> , 2005 ²⁰	1	1	1	1	1	5
Crill <i>et al.</i> , 2006 ²¹	1	1	1	1	1	5
Seong <i>et al.</i> , 2010 ²	1	1	1	1	1	5
Winther <i>et al.</i> , 2014 ²⁵	1	0	1	1	-1	2
Ozturk <i>et al.</i> , 2016 ²⁶	1	0	1	1	-1	2
Clark <i>et al.</i> , 2017 ²²	1	1	1	1	1	5

Score = *0: no; 1: yes; **-1: no; 1: yes; Q1-Q3: regarding the manner of patient randomization; Q2-Q5: regarding the use of double blinding; Q3: regarding the loss of individuals during the study. If the score is <3, the clinical trial is considered to have low quality.

All relevant data from each article were summarized in one table (Table 2 and Table 2 (cont)); specifically, these were coded according to the first author of the bibliographic reference and year of publication, population who received carnitine, variables measured, both clinical and analytical, primary endpoint, dosing and time during which the supplement was administered, as well as the final conclusion of the study.

Table 2
Characteristics of the studies evaluated about L-carnitine supplementation in PTNBs

Article	Study population	Variables measured	Primary endpoint	Dosing/Duration	Conclusion
Penn <i>et al.</i> , 1980 ¹¹	20 PTNBs	Plasma carnitine, urinary excretion	To determine if PTNBs that cannot receive oral nutrition present risk to develop carnitine deficiency	Non-supplemented PN	PTNBs are not able to generate enough carnitine to cover their daily needs
Coran <i>et al.</i> , 1985 ¹²	12 PTNBs	Plasma carnitine, TG, Free FAs, KBs	To determine the importance of carnitine supplementation in NBs receiving TPN with high lipid contents	70 µmol/kg/day (enteral administration/ non-supplemented PN) 7 days Control: placebo	Serum carnitine levels were significantly high in the supplemented arm, though no differences were observed in serum TG and free FAs in both arms
Larsson <i>et al.</i> , 1990 ¹³	12 PTNBs with 27-32 GWs	Total carnitine, free carnitine, acylcarnitine, TG, Free FAs, β-HB, lactate	To study the effect of carnitine supplementation in the metabolism of lipids and glucose of PTNBs receiving PN	10 mg/kg/day until reaching 75% of enteral nutrition. Control: placebo	Carnitine supplementation seemed to improve FA oxidation, though the effect observed in the study was temporary
Helms <i>et al.</i> , 1990 ¹⁴	43 PTNBs with 31 GWs	Weight gain, plasma carnitine, nitrogen balance, TG, Free FAs, KBs	To determine if supplementation with IV carnitine improves the nutritional parameters of NBs receiving TPN	50 µmol/kg/day during 7 days, followed by 100 µmol/kg/day the next 7 days. Control: non-supplemented	Carnitine supplementation is associated with a limited weight gain and a better use of diet lipids to generate energy
Sulkers <i>et al.</i> , 1990 ¹⁵	24 PTNBs with 32 ± 2 GWs	Total carnitine, free carnitine, acylcarnitine, indirect calorimetry, weight gain	To evaluate the effect of carnitine supplementation in lipid oxidation and growth gain	48 mg/kg/day 4 days Control: non-supplemented	Supplementation at this dose does not seem advisable due to the increase in metabolic rate, the increase in nitrogen excretion, and the low weight gain
Bonner <i>et al.</i> , 1995 ¹⁶	43 VLWNBs < 1.5 kg	Total carnitine in plasma and red blood cells, free carnitine, acylcarnitine, TG, β-HB	To evaluate the effect on lipid metabolism of VLWNBs who receive IV carnitine	50 µmol/kg/day Until the NB tolerates >50% of calories through enteral diet. Control: non-supplemented	VLWNBs who require PPN (> 2 weeks) will develop nutritional deficiency of carnitine with ketogenesis deterioration, which seems to improve with its supplementation
Shortland <i>et al.</i> , 1998 ¹⁷	83 PTNBs with 28-34 GWs	Weight gain, free carnitine, acylcarnitine, hypoglycemia	To evaluate the effect of carnitine supplementation on growth and incidence of hypoglycemia	25 mg/kg/day Until reaching the 40 CW. Control: placebo	Carnitine addition did not improve growth or protected against hypoglycemic episodes
Meyburg <i>et al.</i> , 2002 ⁵	120 NBs with 22-41 GWs	Free carnitine, acylcarnitine	To measure levels in NBs to test the need to determine normal individual ranges	Non-supplemented PN 28 days	A 50% fall in levels must be considered normal in PTNBs at 14 days of life
O'Donnell <i>et al.</i> , 2002 ¹⁸	44 PTNBs < 1.5 kg	Total plasma carnitine, apnea	To evaluate the role of carnitine on the idiopathic apnea in PTNBs	30 mg/kg/day Until reaching the 34 CW Control: placebo	Carnitine supplementation does not reduce apnea or dependence of mechanical ventilation
Whitfield <i>et al.</i> , 2003 ¹⁹	80 PTNBs < 1.5 kg	Total plasma carnitine growth parameters, apnea	To examine the effect of carnitine supplementation on growth, apnea, and hospital stay duration	15 mg/kg/day Until reaching the 36 CW Control: placebo	Routine supplementation has not demonstrated positive effects on growth, apnea or the duration of hospital stay
Pande <i>et al.</i> , 2005 ²⁰	63 PTNBs with < 29 GWs	Weight gain, hospital stay	To confirm if carnitine administration will improve weight gain and reduce hospital stay	50 µmol/kg/day Until enteral diet tolerability Control: placebo	Supplementation causes weight gain at long-term in PTNBs

Table 2 (cont.)

Characteristics of the studies evaluated about L-carnitine supplementation in PTNBs

Article	Study population	Variables measured	Primary endpoint	Dosing/Duration	Conclusion
Crill <i>et al.</i> , 2006 ²¹	29 PTNBs with 27 ± 2 GWs	Total carnitine in plasma and red blood cells	To evaluate the effect of long-term supplementation on total carnitine levels in PTNBs.	20 mg/kg/day 8 weeks Control: placebo	Supplementation causes an increase in plasma and erythrocyte concentrations, which improves growth and respiratory impairment.
Seong <i>et al.</i> , 2010 ²	25 LWNBs < 2.5 kg	Free serum carnitine, TG, S-MCFAs, LCFAs, TC, HDL-c, β-HB	To measure the effect of carnitine supplementation on growth and lipid profile.	110 mg/kg/day, with parenteral administration 9 days Control: non-supplemented	Supplementation in LWNBs improves the lipid profile and carnitine serum levels, but without any effect on growth.
Clark <i>et al.</i> , 2017 ²²	995 PTNBs with 23-31 GWs	Free carnitine, acylcarnitine	To describe the influence of carnitine supplementation in the metabolic profiles of PTNBs.	42 days (initially parenteral administration until enteral diet tolerated) Control: non-supplemented	Supplementation is associated with high plasma levels without any improvement in lipid profile or earlier hospital discharge.

#-HB: #-hydroxybutirate; CWs: corrected weeks; FAs: fatty acids; FTN: full-term newborn; GW: gestation weeks; IV: intravenous; KBs: ketonic bodies; LCFAs: long chain fatty acids; LWNB: low-weight newborn; NB: newborn; PN: parenteral nutrition; PPN: prolonged parenteral nutrition; PTNB: preterm new born; RDS: respiratory distress syndrome; S-MCFAs: short-medium chain fatty acids; TC: total cholesterol; TG: triglycerides; TPN: total parenteral nutrition; VLWNB: very-low-weight newborn.

The study population in different articles was very heterogeneous, though they were all PTNBs. Almost all studies coincided in the analytical variables measured (free carnitine and acylcarnitine, triglycerides, free fatty acids and ketonic bodies). Besides, some studies such as those by Whitfield *et al.*¹⁹ and Pande *et al.*²⁰, took into account other clinical variables, such as weight gain or apnea. In the majority of the studies, carnitine was added to the PN solution as long as there was tolerability to enteral administration, and at this time supplementation became oral. Only some studies had no supplements administered, such as the one by Meyburg *et al.*⁶, where only plasma levels were measured in order to compare them with those in FTNs. Supplement administration was conducted for a short term (<4 weeks), except in the study by Crill *et al.*²¹, with an 8-week duration.

Discussion

L-carnitine facilitates the entry of long-chain fatty acids into the mitochondrial matrix for their oxidation and subsequent energy generation; therefore, its lack could limit the lipid metabolism and increase triglycerides, fatty acids and ketonic bodies in plasma. Likewise, there could be a reduction in weight gain, by an increase in protein metabolism for energy generation, mostly in PTNBs, with L-carnitine levels well below usual levels, due to a lower tissue reserve and a difficult nutrient intake. However, the evidence available is still controversial in terms of the clinical relevance of low tissue levels and therefore, regarding the need for prophylactic supplementation.

The first studies on serum L-carnitine levels on PTNBs are dated in the 80s; their conclusion was that those who did not receive supplements presented major deficiencies¹¹⁻¹². Subsequent experimental studies, such as the one conducted by Larsson et al.¹³, demonstrated a higher tolerability to parenteral lipids in patients who received L-carnitine, with a positive effect on fatty acid metabolism. However, no data were collected regarding variables with higher clinical relevance, such as weight gain. In many Neonatal Intensive Care Units, prophylactic L-carnitine administration was initiated routinely as a supplement in the PN of PTNBs, based on these publications.

After this trend, the studies conducted in the 90s already started to include not only biochemical but also clinical variables among those measured, such as weight gain or hospital stay. Helms et al.¹⁴ and Sulkers et al.¹⁵ observed some limited weight gain in their studies, though their patient samples were not very large. Afterwards, and with a larger sample size, Shortland et al.¹⁷ concluded in 1998 that adding carnitine to PN did not improve PTNB growth. It was only in 2005 when Pande et al.²⁰ designed a specific study with the sole objective to demonstrate weight increase in this type of patients who received prolonged supplement administration (until Gestation Week 36 or hospital discharge) of L-carnitine; their results did not show statistically significant differences in the primary efficacy variable, weight gain: the mean weight increase in the arm receiving the supplement was 18.9 ± 4.7 grams/day vs. 18.5 ± 4.6 grams/day in the control arm ($p > 0.05$); there were no statistically significant differences found in the rest of secondary variables measured in both groups.

In accordance with this, it is worth highlighting the study conducted by Clark et al.²², including 995 very-low-weight newborns (VLWNBs), which demonstrated that adding L-carnitine to the PN solution generated an increase in plasma levels without any improvement in the lipid profile (measured as free carnitine, acylcarnitine and free fatty acids), weight gain during the first 28 days of life, or specific mortality or morbidity. During the PN stage, free carnitine levels were consistently higher in those babies who received the supplement, and the recovery in plasma levels occurred faster in those babies with higher gestational age; this was probably associated with an early initiation of enteral nutrition, supplemented with carnitine. Despite these results, carnitine supplementation did not alter the metabolism of long-chain fatty acids. This study also collected the hospital stay variable, like Whitfield et al.¹⁹ had already done in 2003; both reached the conclusion that L-carnitine supplementation does not translate into hospital stay reduction.

The study by Clark et al.²² was designed with preterm babies who did not require nutritional supplements administered parenterally for >28 days, so that plasma carnitine levels were normalized as the transition from parenteral to enteral nutrition took place (days 7-28), supplemented with L-carnitine. However, in usual clinical practice we find VLWNBs who need prolonged PN, for >1 month. Further studies would be

required to demonstrate if this patient population would benefit of a routine L-carnitine supplementation in their PN solution, as their plasma levels are highly lower than usual due to a lower tissue reserve and the impossibility to make a transition to enteral nutrition due to their digestive immaturity.

It is worth highlighting that O'Donnell et al.¹⁸ in 2002, and Whitfield et al.¹⁹ in 2003 included in their study designs some parameters associated with idiopathic apnea in PTNBs. Apnea of prematurity can be due to an alteration in the brain center which controls breathing, in the so called central apnea, or to a mechanical process, in obstructive apnea, where breathing is stopped due to a blockage in respiratory airways. Problems in other organs can also affect the respiratory control center. Apnea of prematurity is likely to have no other identifiable cause but the immaturity of the central nervous system. The potential improvement to this condition caused by carnitine can be explained by the fact that its lack causes a reduction in energy generation at muscle level. In both studies, no positive effects were observed with its supplementation in the PN solution. Subsequently, in 2006 Crill et al.²¹ published their results, and reached the conclusion that supplementation in preterm children could improve periodical breathing in this patient group, but without any statistically significant differences between patient arms in terms of the need for mechanical ventilation and duration, and incidence of bronchopulmonary dysplasia. In the study by Ozturk et al.²⁶, there was a lower incidence of bronchopulmonary incidence in the arm treated with carnitine, though there was no statistical significance. The reason for this discrepancy could lie in the different dose of carnitine used in each study: 20 mg/ kg/d in the first and 30 mg/kg/d in the second. The study designs were also different, because Ozturk et al.²⁶ intended to demonstrate the clinical benefit of carnitine supplementation in preterm babies with Respiratory Distress Syndrome (RDS). Many studies have associated the presence of low plasma carnitine levels in PTNBs with RDS²⁷. Treatment with carnitine for preterm children with RDS can reduce the duration of mechanic ventilation, the use of pulmonary surfactant and the development of bronchopulmonary dysplasia²⁶.

Although there is a high risk of carnitine deficiency, there are no standards for the administration of supplements in PTNBs receiving TPN. Practically all studies seem to confirm that the deficiency of carnitine in plasma levels at short term is not associated with clinically relevant symptoms in those patients presenting it: neither lower weight gain nor hypertriglyceridemia or shorter hospital stay. Therefore, there is no recommendation for the prophylactic supplementation of L-carnitine in PN, also because this is not free from risks. Sulkers et al.¹⁵ observed an increase in the metabolic rate and nitrogen excretion; however, it is true that they were using a dose (48 mg/kg/day) far above those currently recommended (10-20 mg/kg/day). Clark et al.²⁸ have recently published the outcomes of their study, conducted with the objective of assessment the knowledge, beliefs, and clinical practice regarding carnitine deficiency

and supplement administration among neonatologists, through an on-line survey. In total, 492 professionals participated in this survey, and only 5% determined this deficiency in preterm babies through lab tests; 40% of them administered L-carnitine supplements routinely, though 60% believed that its deficiency could have severe consequences. These outcomes showed the lack of consensus among healthcare professionals about the potential benefit of supplementation, as well as about the potential risks for PTNBs caused by its deficiency.

The limitations of this review lie in the different designs of different studies, as well as in the carnitine doses used (a range of 8 to 48 mg/kg/day), or duration of the supplementation. It would be convenient to conduct studies that are more homogeneous in terms of design, as well as to analyze the need for supplementation in those newborns requiring long-term PN.

In conclusion, and according to the bibliographic review available, almost all authors demonstrate that routine L-carnitine supplementation in the PN of PTNBs can improve plasma levels, but not reaching a significant improvement in lipid profile; and what is most important, without any increase in weight gain, reduction in morbidity and mortality, or reduction in hospital stay. Further studies will be required to demonstrate whether the systematic L-carnitine supplementation in PTNBs who require TPN over one month would offer any benefit with clinical relevance to such vulnerable patients.

Bibliography

- Gil A. Tratado de nutrición. Bases fisiológicas y bioquímicas de la nutrición. Tomo I. 2ª ed. Madrid: Editorial Médica Panamericana; 2010.
- Seong SH, Cho SC, Park Y, Cha YS. L-carnitine supplemented parenteral nutrition improves fat metabolism but fails to support compensatory growth in premature Korean infants. *Nutr Res.* 2010;30(4):233-39. DOI: 10.1016/j.nutres.2010.04.004
- Cairns PA, Stalker DJ. Carnitine supplementation of parenterally fed neonates. *Cochrane Database Syst Rev.* 2007;4:CD000950.
- Shenai JP, Borum PR. Tissue carnitine reserves of newborn infants. *Pediatr Res.* 1984;18(7):679-81. DOI: 10.1203/00006450-198407000-0002
- Penn D, Ludwigs B, Schmidt-Sommerfeld E, Pascu F. Effect of nutrition on tissue carnitine concentrations in infants of different gestational ages. *Biol Neonate.* 1985;47(3):130-5. DOI: 10.1159/000242103
- Meyburg J, Schulze A, Kohlmüller D, Pöschl J, Linderkamp O, Hoffmann GF, et al. Acylcarnitine profiles of preterm infants over the first four weeks of life. *Pediatr Res.* 2002;52(5):720-3. DOI: 10.1203/00006450-200211000-0001
- Morgan J, Young L, McGuire W. Incremento lento de los volúmenes de alimentación enteral para prevenir la enterocolitis necrosante en recién nacidos de muy bajo peso al nacer (Revisión Cochrane traducida). *Cochrane Database Syst Rev.* 2011;3:CD001241.

- Gilbertson N, Kovar IZ, Cox DJ, Crowe L, Palmer NT. Introduction of intravenous lipid administration on the first day of life in the very low birth weight neonate. *J Pediatr*. 1991;119(4):615-23.
- Long CS, Haller RG, Foster DW, McGarry JD. Kinetics of carnitine dependent fatty acid oxidation: implications for human carnitine deficiency. *Neurology*. 1982;32(6):663-6.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
- Penn D, Schmidt-Sommerfeld E, Wolf H. Carnitine deficiency in premature infants receiving total parenteral nutrition. *Early Hum Dev*. 1980;4(1):23-4.
- Coran AG, Drongowski RA, Baker PJ. The metabolic effects of oral L-carnitine administration in infants receiving total parenteral nutrition with fat. *J Pediatr Surg*. 1985;20(6):758-64.
- Larsson LE, Olegard R, Ljung L, Niklasson A, Rubensson A, Gederblad G. Parenteral nutrition in preterm neonates with and without carnitine supplementation. *Acta Anaesthesiol Scand*. 1990;34(6):501-5.
- Helms RA, Mauer EC, Hay WW, Christensen ML, Storm MC. Effect of intravenous L-carnitine on growth parameters and fat metabolism during parenteral nutrition in neonates. *JPEN J Parenter Enteral Nutr*. 1990;14(5):448-53. DOI: 10.1177/0148607190014005448
- Sulkers EJ, Lafeber HN, Degenhart HJ, Przyrembel H, Schlotzer E, Sauer PJJ. Effects of high carnitine supplementation on substrate utilization in low-birth-weight infants receiving total parenteral nutrition. *Am J Clin Nutr*. 1990;52(5):889-94.
- Bonner CM, DeBrie KL, Hug G, Landrigan E, Taylor BJ. Effects of parenteral L-carnitine supplementation on fat metabolism and nutrition in premature neonates. *J Pediatr*. 1995;126(2):287-92.
- Shortland GJ, Walter JH, Stroud C, Fleming PJ, Speidel BD, Marlow N. Randomised controlled trial of L-carnitine as a nutritional supplement in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1998;78(3):F185-8.
- O'Donnell J, Finer NN, Rich W, Barshop BA, Barrington KJ. Role of L-carnitine in apnea of prematurity; a randomized, controlled trial. *Pediatrics*. 2002;109(4):622-6.
- Whitfield J, Smith T, Sollohub H, Sweetman L, Roe CR. Clinical effects of L-carnitine supplementation on apnea and growth in very low birth weight infants. *Pediatrics*. 2003;111(3):477-82.
- Pande S, Brion LP, Campbell DE, Gayle Y, Esteban-Cruciani NV. Lack of effect of L-carnitine supplementation on weight gain in very preterm infants. *J Perinatol*. 2005;25(7):470-7. DOI: 10.1038/sj.jp.7211334
- Crill CM, Storm MC, Christensen ML, Hankins CT, Jenkins MB, Helms RA. Carnitine supplementation in premature neonates: effect on plasma and red blood cell total carnitine concentrations, nutrition parameters and morbidity. *Clin Nutr*. 2006;25(6):886-96. DOI: 10.1016/j.clnu.2006.05.002
- Clark RH, Chace DH, Spitzer AR. Impact of L-carnitine supplementation on metabolic profiles in premature infants. *J Perinatol*. 2017;37(5):566-71. DOI: 10.1038/jp.2016.253

- Schmidt-Sommerfeld E, Penn D, Wolf H. Carnitine deficiency in premature infants receiving total parenteral nutrition: effect of L-carnitine supplementation. *J Pediatr*. 1983;102(6):931-5.
- Honzík T, Chrastina P, Hansíková H, Böhm M, Martincová O, Plavka R, et al. Carnitine concentrations in term and preterm newborns at birth and during the first days of life. *Prague Med Rep*. 2005;106(3):297-306.
- Winther B, Jackson D, Mulroy C, MacKay M. Evaluation of serum carnitine levels for pediatric patients receiving carnitine-free and carnitine-supplemented parenteral nutrition. *Hosp Pharm*. 2014;49(6):549-53. DOI: 10.1310/hpj4906-549
- Ozturk MA, Kardas Z, Kardas F, Gunes T, Kurtoglu S. Effects of L-carnitine supplementation on respiratory distress syndrome development and prognosis in premature infants: a single blind randomized controlled trial. *Exp Ther Med*. 2016;11(3):1123-7. DOI: 10.3892/etm.2015.2964
- Korkmaz A, Tekinalp G, Coskun T, Yigit S, Yurdakok M. Plasma carnitine levels in preterm infants with respiratory distress syndrome. *Pediatr Int*. 2005; 47(1):49-52. DOI: 10.1111/j.1442-200x.2005.01998.x
- Clark MA, Stein REK, Silver EJ, Khalid S, Fuloria M, Esteban-Cruciani NV. Carnitine deficiency in preterm infants: A national survey of knowledge and practices. *J Neonatal Perinatal Med*. 2017;10(4):381-6. DOI: 10.3233/NPM-16146

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Conflict of interest declaration

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