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, nor 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.

PALABRAS CLAVE
L-carnitina; Suplementación; Nutrición parenteral; Recién nacido pretermínio; Deficiencia.
Introduction

Carnitine (L-carnitine) is a dipeptide widely distributed in all mammal tissues, and particularly abundant in muscle tissue, which is synthesized in the liver, kidneys and brain from two essential amino acids, 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 D-isomer 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 energy. 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 formation. 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 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 formation. 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.

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 topic of our review, and written in English or Spanish. The Medical Subject Headings (MeSH) developed by the U.S. National Library of Medicine, were 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 5.

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 selected through the Jadad Scale, their scores ranged between 2 and 5, with a median score of 5 (Table 1).

All relevant data from each article were summarized in one table (Table 2); 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, dosage and time during which the supplement was administered, as well as the final conclusion of the study.

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. and Pande et al., 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., 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. (2017), 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, criteria, 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.
La primera suplementación con L-carnitina en PTNB se remonta a principios de los 80; sus conclusiones fueron que aquellos que no recibieron suplementos presentaron mayores deficiencias. Posteriormente, estudios experimentales, como el realizado por Larsson et al., demostraron una tolerabilidad superior de la suplementación con L-carnitina en sus soluciones de nutrición parenteral, lo cual dio lugar a una mejor normalización de los niveles de carnitina en plasma cuanto más temprano comenzaba la suplementación. Sin embargo, en la práctica clínica, encontramos que la suplementación con L-carnitina no mejora el crecimiento de PTNB que requieren nutrición enteral prolongada (hasta la semana 36 de gestación o hasta el alta hospitalaria). En el estudio de Shortland et al., realizado en 2005, se observó que la suplementación con L-carnitina no mejoró el crecimiento de PTNB, a pesar de que se observó una mejor normalización de los niveles de carnitina en plasma. Sin embargo, en estudios posteriores, se observó que la suplementación con L-carnitina mejoró la metabolización de ácidos grasos de cadena larga.

La tabla 1 muestra el análisis de la calidad metodológica y el riesgo de sesgo con el uso de la escala Jadad. Los resultados indican que la mayoría de los estudios cumplieron con las pautas de calidad metodológica y el riesgo de sesgo, con una puntuación entre 4 y 5. Sin embargo, se observó una falta de transparencia en el manejo de los datos y la representación de los resultados.

La figura 1 muestra el diagrama de flujo para la selección de artículos. Se eliminaron 33 referencias debido a criterios de inclusión no cumplidos, 32 artículos por no estar relacionados con el tema de estudio, 19 artículos por ser revisiones, comentarios o documentos de otro tipo, y 18 artículos por eliminación de criterios de exclusión. Finalmente, se eliminaron 14 referencias por ser consideradas de baja calidad (escala Jadad).

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

<table>
<thead>
<tr>
<th>Article</th>
<th>Study population</th>
<th>Variables measured</th>
<th>Primary endpoint</th>
<th>Dosing/Duration</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penn et al., 1980</td>
<td>20 PTNBs</td>
<td>Plasma carnitine, urinary excretion</td>
<td>To determine if PTNBs that cannot receive oral nutrition present risk to develop carnitine deficiency</td>
<td>Non-supplemented PN</td>
<td>PTNBs are not able to generate enough carnitine to cover their daily needs</td>
</tr>
<tr>
<td>Coran et al., 1985</td>
<td>12 PTNBs</td>
<td>Plasma carnitine, TG, Free FAs, KBs</td>
<td>To determine the importance of carnitine supplementation in PTNBs receiving PN with high lipid contents</td>
<td>70 μmol/kg/day (enteral administration, non-supplemented PN) 7 days Control: placebo</td>
<td>Serum carnitine levels were significantly high in the supplemented arm, though no differences were observed in serum TG and free FAs in both arms</td>
</tr>
<tr>
<td>Larsson et al., 1990</td>
<td>12 PTNBs with 27-32 GWs</td>
<td>Total carnitine, free carnitine, acylcarnitine, TG, Free FAs, βHB</td>
<td>To study the effect of carnitine supplementation in the metabolism of lipids and glucose of PTNBs receiving PN</td>
<td>10 mg/kg/day until reaching 75% of enteral nutrition. Control: non-supplemented</td>
<td>Carnitine supplementation seems to improve FA oxidation, though the effect observed in the study was temporary</td>
</tr>
<tr>
<td>Helms et al., 1990</td>
<td>43 PTNBs with 31 GWs</td>
<td>Weight gain, plasma carnitine, nitrogen balance, TG, Free FAs, KBs</td>
<td>To determine if supplementation with IV carnitine improves the nutritional parameters of NBs receiving PN</td>
<td>50 μmol/kg/day during 7 days, followed by 100 μmol/kg/day the next 7 days. Control: non-supplemented</td>
<td>Carnitine supplementation is associated with a limited weight gain and a better use of diet lipids to generate energy</td>
</tr>
<tr>
<td>Sulkers et al., 1990</td>
<td>24 PTNBs with 32 ± 2 GWs</td>
<td>Total carnitine, free carnitine, acylcarnitine, indirect calorimetry, weight gain</td>
<td>To evaluate the effect of carnitine supplementation in lipid oxidation and growth</td>
<td>48 mg/kg/day 4 days Control: non-supplemented</td>
<td>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</td>
</tr>
<tr>
<td>Bonner et al., 1995</td>
<td>43 VLWNBs &lt; 1.5 kg</td>
<td>Total carnitine in plasma and red blood cells, free carnitine, acylcarnitine, TG, βHB</td>
<td>To evaluate the effect on lipid metabolism of VLWNBs who receive IV carnitine</td>
<td>50 μmol/kg/day Until the NB tolerates &gt;50% of calories through enteral diet. Control: non-supplemented</td>
<td>VLWNBs who require PPN (&gt; 2 weeks) will develop nutritional deficiency of carnitine with ketogenesis deterioration, which seems to improve with its supplementation</td>
</tr>
<tr>
<td>Shortland et al., 1998</td>
<td>83 PTNBs with 28-34 GWs</td>
<td>Weight gain, free carnitine, acylcarnitine, hypoglycemia</td>
<td>To evaluate the effect of carnitine supplementation on growth and incidence of hypoglycemia</td>
<td>25 mg/kg/day Until reaching the 40 CW, Control: placebo</td>
<td>Carnitine addition did not improve growth or protected against hypoglycemic episodes</td>
</tr>
<tr>
<td>Meyburg et al., 2002</td>
<td>120 NBs with 22-41 GWs</td>
<td>Free carnitine, acylcarnitine</td>
<td>To measure levels in NBs to test the need to determine normal individual ranges</td>
<td>Non-supplemented PN 28 days</td>
<td>A 50% fall in levels must be considered normal in PTNBs at 14 days of life</td>
</tr>
<tr>
<td>O’Donnell et al., 2002</td>
<td>44 PTNBs &lt; 1.5 kg</td>
<td>Total plasma carnitine, apnea</td>
<td>To evaluate the role of carnitine on the idiopathic apnea in PTNBs</td>
<td>30 mg/kg/day Until reaching the 34 CW Control: placebo</td>
<td>Carnitine supplementation does not reduce apnea or dependence of mechanical ventilation</td>
</tr>
<tr>
<td>Whitfield et al., 2003</td>
<td>80 PTNBs &lt; 1.5 kg</td>
<td>Total plasma carnitine growth parameters, apnea</td>
<td>To examine the effect of carnitine supplementation on growth, apnea, and hospital stay duration</td>
<td>15 mg/kg/day Until reaching the 36 CW Control: placebo</td>
<td>Routine supplementation has not demonstrated positive effects on growth, apnea or the duration of hospital stay</td>
</tr>
<tr>
<td>Pande et al., 2005</td>
<td>63 PTNBs with &lt; 29 GWs</td>
<td>Weight gain, hospital stay</td>
<td>To confirm if carnitine administration will improve weight gain and reduce hospital stay</td>
<td>50 μmol/kg/day Until enteral diet tolerability Control: placebo</td>
<td>Supplementation causes weight gain at long-term in PTNBs</td>
</tr>
</tbody>
</table>
It is worth highlighting that O’Donnell et al.26 in 2002, and Whitfield et al.28 in 2017 included in their study designs some parameters associated with idiopathic apnea in PTNBs. Apnea of prematurity can be 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 gene-

possibility to make a transition to enteral nutrition due to their digestive immaturity.

Table 2 (cont.). Characteristics of the studies evaluated about L-carnitine supplementation in PTNBs

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<tr>
<td>Crill et al., 200626</td>
<td>29 PTNBs with 27 ± 2 GWs</td>
<td>Total carnitine in plasma and red blood cells</td>
<td>To evaluate the effect of long-term supplementation on total carnitine levels in PTNBs.</td>
<td>20 mg/kg/day 8 weeks</td>
<td>Control: placebo Supplementation causes an increase in plasma and erythrocyte carnitine levels, which improves growth and respiratory impairment.</td>
</tr>
<tr>
<td>Seong et al., 201025</td>
<td>25 LWNBs &lt; 2.5 kg</td>
<td>Free serum carnitine, TG, S-MCFAs, LCFAs, TC, HDL-c, β-HB</td>
<td>To measure the effect of carnitine supplementation on growth and lipid profile.</td>
<td>110 mg/kg/day, with parental administration 9 days</td>
<td>Control: non-supplemented Supplementation in LWNBs improves the lipid profile and carnitine serum levels, but without any effect on growth.</td>
</tr>
<tr>
<td>Clark et al., 201722</td>
<td>995 PTNBs with 23-31 GWs</td>
<td>Free carnitine, acylcarnitine</td>
<td>To describe the influence of carnitine supplementation in the metabolic profiles of PTNBs.</td>
<td>42 days (initially parenteral administration until enteral diet tolerated)</td>
<td>Control: non-supplemented Supplementation is associated with high plasma levels without any improvement in lipid profile or earlier hospital discharge.</td>
</tr>
</tbody>
</table>

β-HB: β-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 newborn; 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.

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.

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Conflict of interests
No conflict of interest.
Bibliography


