Author's response to reviews

Title: Enteral nutrition in the critically ill child with shock: a prospective observational study

Authors:

Jesus Lopez-Herce (pielvi@ya.com)
Santiago Mencia (pielvi@ya.com)
Cesar Sanchez (pielvi@ya.com)
Maria J Santiago (pielvi@ya.com)
Amaya Bustinza (pielvi@ya.com)
Dolores Vigil (pielvi@ya.com)

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Author's response to reviews: see over
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Dear Sir

We enclose you the article “TRANSPYLORIC ENTERAL NUTRITION IN THE CRITICALLY ILL CHILD WITH SHOCK: A PROSPECTIVE OBSERVATIONAL STUDY” that has been reformed according to the suggestion of the reviewers. We enclose the comments to the reviewers. We hope this revised version can be published as Original Article in the Nutrition Journal.

Sincerely Yours

Dr Jesús López-Herce

Correspondence:
Prof. Dr Jesús López-Herce
Dr Castelo 47. 28009 Madrid. Spain.
Fax: 34-91-5868018  Tf: 34-91-5290327   E-mail: pielvi@ya.com
Reviewer 1

1. Reviewer 1 states that the results of our study are already known. We do not agree with this statement as, to our knowledge, there are no previously published studies that have specifically analyzed the characteristics of enteral nutrition in children with shock.

2. In a previous study [Epub ahead of publication] we have investigated the risk factors for gastrointestinal complications in the group of critically ill children with transpyloric nutrition. Shock is one of the risk factors for complications. We have added a reference to this study. In the present study, we have analyzed the characteristics of nutrition in children with shock (not just the complications), and we have compared this with the other critically ill children with transpyloric nutrition with the principal aim of evaluating whether critically ill children in shock can receive enteral nutrition.

3. An expert in medical translations, an English doctor, has revised the text to correct grammatical errors.

4. Table 1 refers to the diagnoses and not to the types of shock. The majority of patients with diagnoses of respiratory failure, other surgical interventions, and other medical diagnoses presented septic shock, although some cases were due to hypovolemic shock or septic shock. Similarly, shock in the patients in the postoperative period of cardiac surgery was sometimes due to cardiogenic shock, sometimes to septic shock and sometimes to shock of mixed septic and cardiogenic origin. Thus, despite the suggestion of the reviewer, it is not possible to clearly differentiate patients with one or other type of shock. In our opinion, it is not so important to compare tolerance between the different types of shock as a reduction in splanchnic perfusion may occur in all of them, independently of their cause, and tolerance does not depend on the type of shock. One of the most important results of our study is that children in shock can receive enteral nutrition independently of the cause of shock, although the onset of complications must be closely monitored.

5. We have shortened the discussion in accordance with the reviewer's recommendations.

Reviewer 2
1. An expert in medical translations, an English doctor, has revised the text to correct grammatical errors.

2. In a previous study [Epub ahead of publication] we have investigated the risk factors for gastrointestinal complications in the group of critically ill children with transpyloric nutrition. Shock is one of the risk factors for complications. We have added a reference to this study. In the present study, we have analyzed the characteristics of nutrition in children with shock (not just the complications), and we have compared this with the other critically ill children with transpyloric nutrition with the principal aim of evaluating whether critically ill children in shock can receive enteral nutrition.

3. Abstract: we have modified the abstract, adding the total number of patients studied and the frequency of complications in the control group.

4. Background:
   - We have modified the text on the risk of pulmonary aspiration with gastric nutrition in critically ill patients.
   - We have modified the sentence "enteral nutrition is generally not administered in patients with shock" to "enteral nutrition is not administered in many patients with shock or only a low feed volume is administered to keep the bowel active".

5. Patients and methods:
   - There is no strict, unified definition of shock as it is not possible to clearly determine the limits of shock in the critically ill child and the criteria of shock vary between studies. The criteria for the diagnosis of shock used in our study are specified on page 5. We have chosen restrictive criteria for shock in order to select the patients who clearly do not respond to volume expansion and/or the infusion of high doses of vasoactive drugs. Using this definition, it is possible that patients with a lesser degree of shock were included in the control group, which will only underline the importance of our results.
   - We did not restrict volume expansion to 20 ml/kg. Many of our patients in shock received a higher volume of fluids for expansion, but these patients in whom the hemodynamic state normalized with an expansion of less than 20 ml/kg were not included in the shock group. Furthermore, attention must be drawn to the fact that none of the patients included in the shock group required only volume expansion, but rather that they all required high doses of
vasoactive drugs. We have not used the term fluid-refractory shock, which is usually used in septic shock, as patients with cardiogenic shock due to left ventricular failure received high-dose infusions of drugs without volume expansion.

- The mean blood pressure has been used as a criterion: we have added this datum to the text.
- The moment of initiation of nutrition and the percentage of patients in whom it was started within the first 48 hours are specified in table 3.
- One of the advantages of transpyloric nutrition is the speed with which nutrition can be increased. With gastric nutrition, it is difficult to provide a sufficient calorie delivery. Although it is difficult to determine the calorie requirements of the critically ill child unless indirect calorimetry is performed, the majority of studies have found that the calorie consumption in the first days varies between 45 and 65 kcal/100 kcal metabolized per day, which is the quantity received in our study. Subsequently, and depending on the clinical state, nutrition may be increased to achieve a normocaloric feeding.
- The majority of studies which have analyzed hepatic disturbances in critically ill children (PRIMS, PELOD) use the AST and ALT to evaluate hepatocyte alterations and bilirubin to detect problems of cholestasis. Other measurements, such as the INR in children with cardiac surgery, and GGT and alkaline phosphatase, are less specific.

6. Results:
- We have removed the data that are repeated in the text and tables.
- We had not included the blood pressure values in the table as the normal reference values depend on age. The absolute figure for this variable does not therefore have any value, in contrast to what occurs in adult patients.
- Our study was a prospective, observational study. The indication for enteral or parenteral nutrition depended on the criteria of the physician responsible for the patient. For this reason, a percentage of patients received parenteral nutrition for the initial days, particularly during the first years of the study, before starting enteral nutrition.
- We have added the definition of early parenteral nutrition (first 48 hours).

7. Discussion
- We have eliminated the comment on the complications in patients with cardiac surgery.
- We agree that increasing the catecholamines sometimes does not improve and can even lead
to a deterioration in splanchnic perfusion. The response to each drug is very variable, depending on the patients, as we comment in the discussion.

- In accordance with the recommendations of the reviewer, we have eliminated the previously presented data.

8. Conclusions: we have changed the term "excessive rest" for "excessive gastric residue".

**Reviewer 3**

1. We have added the criterion of altered of conscious level.
2. The enteral nutrition protocol and the practice of aspiration is described in the patients and methods section.
3. We have included the criteria used to diagnose necrotizing enterocolitis.
4. We do not know if the calorie requirements of a child in shock differ from those of other critically ill children. Studies using indirect calorimetry are necessary, and we have not found any study that has performed this. In our study, the children in shock received a slightly lower initial calorie delivery than other critically ill patients (the difference was not significant). We have added a comment in the discussion.

**Reviewer 4**

1. We agree with the reviewer that the population is very heterogeneous, reflecting the reality of care in pediatric intensive care units but making an analysis of the data difficult. We have added this limitation in the discussion.
2. Studies that have compared the incidence of gastrointestinal complications between transpyloric nutrition and gastric nutrition in adults have not found any differences. Transpyloric administration favors a rapid increase in the nutrition, a lower number of interruptions, and a higher calorie delivery. To our knowledge, there are no data to suggest that transpyloric nutrition increases the risk in patients with intestinal ischemia.
3. Calorie delivery was adapted to the weight of the patient using the Holiday formula (100 kcal/kg for the first 10 kg, 50 kcal/kg for the following 10 kg, and 20 kcal/kg above 20 kg). In this way,
the calorie supply is contemplated per 100 kcal metabolized, making the calorie intake comparable for any age. We have added this fact in the material and methods section.

4. We have added data of the patients in shock to tables 2 and 3, with median and range instead of mean and SD.

   The drug data refers to the maximum doses received during nutrition (we have added this datum in the table footer). In accordance with the recommendations of the reviewer, we have explained the units in the table footer and have eliminated them from the column.

5. Discussion
   - We agree with the reviewer that the observation of good digestion and absorption cannot be concluded from our study and we have eliminated this sentence from the discussion.
   - We have corrected the error in the text, substituting “renal” by “acute renal failure”.

6. Abstract
   - We have eliminated the term efficacy.
   - We have added that shocked patients compared to non-shocked patients.

7. Writing
   - An expert in medical translations, an English doctor, has revised the text to correct grammatical errors.