Author's response to reviews

**Title:** Modification of stool's water content in constipated infants: management by an adapted infant formula

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**Author's response to reviews:** see over
Reply to Dr. Underwood’s comment

Dear Dr Mark Underwood

The authors wish to sincerely thank the efforts made for the revision of our paper (the length of its report) that have made its improvement possible and hopefully will make it acceptable for publication by the Editor.

Below, please find my responses:

Concerning point 1. The abstract has been modified according to your suggestions.

Concerning points 2 to 4: We have described more comprehensively the NIRA methodology in the text, as the previous version was very poor. Below are the required details on the methodology / NIRA results:

NIRA procedure has been used in our sector for 12 years. Validity compared to other methods has been conducted by a number of different authors. We use similar methodology to them. The implementation of this procedure required a calibration that was performed in 80 stool samples for the following parameters: fat, nitrogen, water and sugar. In our country there are twelve centers using the same methodology. The device is calibrated at least once a year by the supplier.

The results that we considered as normal in our laboratory are similar to those from other hospitals in our country as well as from other subjects. Our experience and results are based on infants and children. The value found in adults are different and some of this differences may also be due to dietary factors. We agree with you that this method may lead to discrepancies when compared with other method but this is the most frequently used method in our laboratory as well as by other methodologists, mainly because of the complex and disturbing handling of feces. Below, please find the references used.


With regard to personal data relating, they have been published in a national magazine with no impact factor and a low international dissemination.


Point 5: The specification on the Bristol scale, as requested, has been added in the patients and methods paragraph.

Point 6: substantial differences in the formula used to fed infants prior to inclusion are provided in the text. We have also included in table 1, for comparison purpose, the EU regulation on infant & follow-on formulae. (See Table 1)

Regarding your pertinent suggestion to have another group of non constipated infants fed a standard formula, we did not do that. In fact the formulas used are very similar but some infants have constipation and some do not. Logically we did not expect the feces from constipated infants to have NIRA values within our normal range.

Point 7: The statistical part has been reviewed by the statistician from our hospital according to your suggestions.

Point 8: Considering the magnesium content, we are referring to EU regulation on infant & follow-on formulae to demonstrate that we are close to the maximum limits


The above references were added to the text:
In Europe, standard infant formulae usually have smaller amounts of magnesium (most about 5-7 mg/100 ml) and lactose (4-7 gr/100 ml) (See Table 1). No negative effects were observed when taking the formula. We did not conduct blood tests for the determination of magnesium. However, the formula was maintained until solid foods were introduced, without any issue related to magnesium content. Moreover, it seems that the formula is now available in dozens of country worldwide and no such side effects have been reported.

Point 9. We tried to revise as much as possible the quality of the discussion as well as the wording.

A review of the English language has been conducted by native English and some modifications have been done also following the other reviewers’ comments. New references have been introduced.

Title: Modification of stool's water content in constipated infants: management by an adapted infant formula

Reply to Dr. Chao’s comments

Dear Dr. Hsun-chin Chao

Thank you very much for your insightful comments to help improve the quality of the item if it is accepted.

Below, please find my responses:

Point 1. Novalac AE is not a new formula, it is the Spanish name of the formula designed by United Pharmaceuticals to ease constipation and commercialised in many countries under the name Novalac IT. I discovered after writing the paper, your contribution to Novalac IT. I have included it in the discussion. This responds to your question on Novalac AE/IT safety.

A review of the English language has been conducted by native English and some modifications have been done also following the other reviewers’ comments. New references have been introduced.

Title: Modification of stool's water content in constipated infants: management by an adapted infant formula

Reply to Dr. Zhaoxiang Bian’s comments

Dear Dr. Zhaoxiang Bian

Thank you very much for your insightful comments to help improve the quality of the article, should it be accepted for publication.

Below, please find my responses.
Point 1. Format: I looked at the consort statement and their check list. However, this list addresses randomized trial and does not apply to open trials (see pdf).

Point 2: The summary has been re-written and enhanced with more information. The diagnosis criteria, inclusion and exclusion criteria have been added in the abstract.

Point 3: We have deleted the following words "to increase intestinal transit" as this was not part of our work.

Point 4: We agree that the term “mild constipation” has been overused. We deleted it from the article and rather use the stools’ consistency as reported using the Bristol stools’ scale;

Point 5: We have added the name of the hospital where the work was performed.

Point 6. Painful defecation is defined, according to other authors, as related to continuous crying infants, feeling unwell, coinciding with the defecation of hard stool or the inability to deliver them.

Point 7: we clarified that these infants were examined and no physical abnormality was appreciated – their constipation was defined as functional constipation, not organic. No blood nor radiological tests were performed. All had normal birth weight and a good weight curve, without any other accompanying symptom.

Point 8: We believed that thirty patients would give us an idea on whether the formula is able or not to modify the stool’s composition. This study was performed as a preliminary evaluation and the results should be confirmed by a double blind, controlled trial.

Point 9: a diary was filled on a daily basis but only data at the start and at the end of the study have been reported.

Point 10. Rationale of the formulation: Some of the formula adjustments have been discussed in the paper (high lactose and magnesium content). They were based mainly on the breast milk composition as breast milk is associated with soft stools. Lactose is known to act as a prebiotic where as magnesium is known to be an osmotic laxative.

A review of the English language has been conducted by native English and some modifications have been done also following the other reviewers’ comments. New references have been introduced.

**Title: Modification of stool's water content in constipated infants: management by an adapted infant formula**

**Reply to Dr. Oscar Brunser’s comments**

Dear Oscar Brunser

Thank you very much for these insightful comments to help improve the quality of the article if it is accepted.

Below, please find my responses.

The study was led between February and May, in Barcelona (geographic latitude of 41.14 N-1.48 E), where during this period, the temperature is usually between 10 to 20 degrees
Celsius. Except in case of excessive sweating, it is not a common practice in such young infants (average age 4.1 weeks) to provide them with additional water - neither in our pediatric practice nor at home.

The clinic and analysis of faeces by NIRA at baseline served as control versus the clinic and new analysis of NIRA after dietary treatment with the anticonstipation formula. Results of normal values of the NIRA for infants fed standard formula (normal values in our laboratory), values at the time of inclusion in the study and after two weeks of intake the new formula are shown in Table 3.

The calcium content of the feces was not determined as it was not the subject of our study. Actually, the main parameters that have been adapted to reduce the stool's hardness (lactose, magnesium) have multiple effects (prebiotic, osmotic effect...), but there is no reason to believe that it would act on the calcium soaps which are due to malabsorption of palmitate.

However, our group also had the opportunity to study the impact of a new formula with modified fat on the calcium excretion.


Considering the magnesium and lactose content (respectively 9.1 mg and 8.1 g/100 ml or 12.8mg and 11.4g /100kcal ) : these are close to the highest levels recommended by scientific committees (European commission, Scientific Committee on Food, the ESPGHAN Committee)


Most of the standard infant formulae available in Spain have a lower amount of magnesium (generally about 5 to 7 mg/ 100 ml) and lactose (<7 g / 100 ml)

We fully agree that some newborns may have soft stools but still have "rectal dyschezia" with tears and pain. Constipated infants who cannot expel their feces, also cry and seem to suffer pain. The main difference between these two situations is that in the latter infants have hard stools and may be helped to dietary treatment.

With respect to reference 2, we clarified it as follows :

\textit{Constipation is usually defined in terms of changes in frequency, size, and consistency of the stools or defecation difficulties [1]. It is a common cause of consultation and in an observational study of 3487 infants its prevalence was 7.8\% [95 CI 6.9-8.7] [2].}
A review of the English language has been conducted by native English and some modifications have been done also following the other reviewers’ comments. New references have been introduced.