

Dear editor,

The authors would like to thank the reviewers for all useful and helpful comments on our manuscript. All comments have been taken into account and the paper has been revised accordingly.

Further to the revisions made in the manuscript, the authors believe that the whole paper has been improved and we are happy to forward it back to you for your consideration and for the publication of manuscript to the “World Journal of Clinical Pediatrics”.

Please find attached a revised version of our manuscript, as well as a rebuttal letter with an itemized, point-by-point response to the editor’s and reviewers’ comments

Sincerely yours,

Miglena Georgieva

Miglena Georgieva, MD, PhD
Associate Professor
Second Pediatric Clinic,
University Hospital “St. Marine”,
1 Christo Smirnenki Avenue
Varna, 9000, Bulgaria
Tel. +359 899 07 42 68
E-mail: mgeorgieva7@yahoo.com

Reviewer 1 (00646336):

The paper is well done and presented. All the criteria for a correct presentation were respected. The research was conducted randomized, partly double blind with informed consent and with the acceptance of ethical committee.

Reply: The authors would like to thank the reviewer for the positive feedback on our manuscript.

The lack of a control Group is justified by the goal of the paper that is reported on page n 21 (my suggestion is to report it in the abstract and in the introduction).

Reply: As suggested by the reviewer the phrase “No control group receiving standard formula was included in the study” was added in the revised manuscript (Page 3, Lines 7-8).

Reading the results I feel a little bit confused from the data (56 pts - 4 - 6 = 46 total) that are more clarified from the figure 1. I suggest to ameliorate the exposition and to erase from line 353 to 358 in which discussed data are not reported in the study.

Reply: As suggested the text between lines 353 and 358 was erased by the revised version of the manuscript. Furthermore, as also pointed by the reviewer the first paragraph in the “Results” section (Page 14, Lines 246-259) was revised to present the data more thoroughly clearly? to the reader. Furthermore, a small revision was also made in figure 1, so as to reflect more accurately the revised text in the “Results” section.

Last suggestion to add the comment that numbers are little and a further implementation is going on.

Reply: As suggested a relevant comment was added in the “Discussion” section of the revised manuscript (Page 19, Lines 378-382).

My best compliments to the Authors for the correctness and completeness in the presentation

Reviewer 2 (00646232):

Lengthy article, the results were repeated in the discussion section. Need to be more crispy. What was the power of the work?

Reply: The discussion section was revised throughout to avoid repetitions with the results section. As a result the length of the article is reduced, and it is more “crispy” (as suggested by the reviewer). Regarding the power of this work, to our knowledge this is the first study examining the efficacy of formulas containing cold versus hot soluble CBG galactomannans at different concentrations on infants’ reflux and tolerance indices. In this regard the findings of the present study regarding the greater effectiveness of Formula A are novel and have been highlighted in the conclusions of the abstract (Page 4, Lines 33-35) and the discussion section (Page 19, Lines 390-392).

Reviewer 3 (00646241):

In their work, "Effects of carob-bean gum thickened formulas on infants' reflux and tolerance indices", the authors Georgieva et al. present a very clear and well conducted, controlled randomized study analysing the effects of three different anti-reflux formulas for infants with gastro-esophageal reflux (excluding complicated cases). The study included not too many, but a sufficient number of patients, it was performed for a relatively short period of time, but probably just sufficient. It is well described, and the results are conclusive and helpful.

Some additional information should be given:

- what is the chemical basis of cold or hot soluble forms of galactomannans, as basis of the formulas?

Reply: The cold soluble form of CBG galactomannans is heated during production to be pre-gelatinised and gets gelatinised when dissolved in lukewarm water. The hot soluble form of CBG galactomannans is only minimally heated during production and needs to be dissolved in water temperature of 90°C to be gelatinised. This information has been added in the "Methods" section of the revised manuscript (Page 8, Lines 120-124).

- the inclusion criteria should be highlighted more clearly.

Reply: As suggested the methods section was revised to present inclusion criteria more thoroughly and consistently (Page 8, Lines 103-112).

Some aspects would have been helpful for future studies, but cannot be included in this study:

- are there methods to assess whether the babies liked the food?

- was there any influence on the gastrointestinal flora - which may be of great relevance for feeding difficulties as much as for weight gains?

Since some effects on gastrointestinal flora may take some time, the given observation time might be too short to answer these questions.

Reply: The authors agree with the reviewer that it would have indeed been helpful for future studies if the liking of the formulas by infants and the effect of the intervention on gastrointestinal flora could also be examined in the present study.

Regarding the degree up to which infants liked the formulas, this aspect could probably have been rated by mothers/caregivers and possibly the researchers using a standardised rating scale. Regarding the potential influence of the formulas on infants' gastrointestinal micro flora, collection of faeces samples from infants at baseline and follow-up and subsequent microbiological analyses of the collected samples could have provided this information.

Nevertheless, although very interesting, the examination of these two research questions was not within the scope of the present study. In addition and as also pointed by the reviewer the duration of the current intervention was also not adequate to answer these research questions-especially the questions regarding the influence of the intervention on the gastrointestinal microbiome

Finally, it may also be asked, if the infants were in fact healthy, which benefit introducing such a formula really has; i.e., in which cases gastroesophageal reflux really requires a dietary intervention. These questions should be discussed more in detail in the discussion.

Reply: Infants participating in the present study were diagnosed with GER (based on a score > 7 in the GER Orenstein questionnaire) and as such required an intervention treatment. In this kind of disorders the intervention of choice is usually a dietary one, by providing baby formulas that contain anti-reflux thickening agents. In order to avoid confusion to the reader the term “healthy infants” was erased from the methods and discussion section of the revised manuscript.

Minor points: line 448: instead of “In this study infants were provided with the thickened formula after been fed with a standard formula for two weeks”. better write “In this study infants were provided with the thickened formula after having been fed with a standard formula for two weeks”.

Reply: The sentence was revised as suggested by the reviewer (Page 16, Lines 312-314).