Author's response to reviews

Title: Randomized outcome trial of nutrient-enriched formula and neurodevelopment outcome in preterm infants

Authors:

Maria Gianni’ (maria.gianni@unimi.it)
Paola Roggero (paola.roggero@unimi.it)
Orsola Amato (orsola.amato@mangiagalli.it)
Odoardo Picciolini (odoardo.picciolini@mangiagalli.it)
Pasqua Piemontese (pasquina.piemontese@mangiagalli.it)
Nadia Liotto (nadia.liotto@unimi.it)
Francesca Taroni (francesca.taroni@unimi.it)
Fabio Mosca (fabio.mosca@unimi.it)

Version: 2 Date: 3 March 2014

Author's response to reviews: see over
Re: Randomized outcome trial of nutrient-enriched formula and neurodevelopment outcome in preterm infants

Dear Editors,
Please find enclosed a revised version of the above referenced paper for your consideration in inclusion in BMC Pediatrics as a research article.

On the following, the replies to Reviewer’s comments are listed below point-by-point as requested.

We would like to thank the Reviewers for their helpful comments, and we hope that all remarks have been clarified.

We would like to thank the Editors for their helpful comments, and we hope that all remarks have been clarified.

We thank you for your consideration,

Maria Lorella Gianni, Paola Roggero, Orsola Amato, Odoardo Picciolini, Pasqua Piemontese, Nadia Liotto, Francesca Taroni, Fabio Mosca
Editor’s comment

Copyediting: We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/authors/authorfaq/editing.

According to your suggestion, the manuscript, has been edited by a native-English speaker with scientific expertise

2. Acknowledgements: By way of a section ‘Acknowledgements’, please acknowledge anyone who contributed towards the article by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for each author, and for the manuscript preparation. Authors must describe the role of the funding body, if any, in design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. Please also acknowledge anyone who contributed materials essential for the study. If a language editor has made significant revision of the manuscript, we recommend that you acknowledge the editor by name, where possible.

The role of a scientific (medical) writer must be included in the acknowledgements section, including their source(s) of funding. We suggest wording such as ‘We thank Jane Doe who provided medical writing services on behalf of XYZ Pharmaceuticals Ltd.’

 Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

We have not provided an Acknowledgements section as there was no one to acknowledge.

Reviewer’s report
Title: Randomized Outcome Trial of Nutrient-Enriched Formula and Neurodevelopment Outcome in Preterm Infants
Version: 1 Date: 8 February 2014
Reviewer: Monique van de Lagemaat

Reviewer’s report:

The authors describe a randomized controlled trial that compared the effect of an energy- and nutrient-enriched formula and a standard term formula between term age and six months corrected age on neurodevelopmental outcome at 24 months corrected age, assessed by Griffiths Mental Developmental scale. A novel item in this study, was that the effect of such formulae was evaluated in AGA and SGA preterm infants separately. However, additional modifications and statistical clarifications are needed.
Major compulsory revisions

Introduction: The novelty of this study seems to be the comparison of the two treatment groups within AGA and SGA infants, since many other studies already evaluated the effect of nutrient-enrichment of formula after discharge in preterm infants, as also described in the discussion. I would suggest that the author would emphasize this novel idea and also provide a hypothesis regarding the primary as well as the secondary outcome of the trial.

According to your suggestion, we have emphasized this novel idea and provided a hypothesis regarding the primary as well as the secondary outcome of the trial in the introduction section.

Patients and Methods- Study design, first paragraph: What does the clinical practice on weaning implicate? Was this according to ESPGHAN and/or WHO recommendations?

Infants were weaned according to our clinical practice that complied with the recommendations of the European Society of Pediatric Gastroenterology and Nutrition. This information has been added in the patients and methods section.

Patients and Methods- Study design, second paragraph: The average daily intake of energy and protein was calculated between term age and six months corrected age. Was this calculated in kcal/d and g/d or per kg per day? It would help the reader to show these intake in the results section or one of the tables (e.g. Table 1).

The average daily intake of energy and protein was calculated per kg per day. According to your suggestion, we have added the mean protein and energy intake between term age and six months corrected age in Table 1.

Patients and Methods-Subjects, second paragraph: The paper would benefit flow chart of subject recruitment including the feeding groups and the reasons of exclusion and loss to follow-up. In addition, how many infants were eligible to participate at birth?

According to your suggestion, we have added a flow chart of the study. 402 infants were eligible to participate at birth. This information has been added in the chart.

Patients and Methods-Subjects, third paragraph: Only the definition of minor brain lesions is described, please emphasize that this was because infants with severe brain lesions were excluded (as described early as an exclusion criterium).

Done

Patients and Methods-Measurements, first paragraph: Are the mean GQ and subscale GQ described means of the total cohort or population means? Are reference values available/what is normal? Which values indicate an impairment?

The mean GQ and subscale GQ described population means. A sub-quotient <68 was classified as severe developmental delay whereas a sub-quotient from 68 to 83 indicated a mild mental retardation with regard to the domain investigated by the specific subscale. A GQ <76 was classified as severe developmental delay. A GQ from 76 to 87 indicated a mild mental retardation. These information have been added in the Patients and Methods section.
Patients and Methods-Statistics: Were the parameters normally distributed? The use of the Mann-Whitney U test implies that some parameters were not normally distributed? Why are these parameters not described as median with interquartile range?

The parameters were normally distributed. Accordingly, we have deleted the sentence stating the use of the Mann-Whitney U test as we realized we have made a mistake.

Patients and Methods-Statistics: Were analyses adjusted for gender, gestational age, abnormal MRI, maternal educational level etc.?

As no difference with regard to gender, gestational age, abnormal MRI, maternal educational level etc was present between SGA infants fed the nutrient enriched formula and SGA infants fed the term formula or between AGA infants fed the nutrient enriched formula and AGA infants fed the term formula, we decided not to correct the analyses for these parameters.

Patients and Methods-Statistics: Please provide the power analysis of this secondary outcome of the randomized controlled trial. Were sufficient infants included in the study groups?

According to your suggestion, we have provided the power analysis of this secondary outcome of the randomized controlled trial. As 30 infants in each group were needed, a sufficient number of infants were included in the study groups.

Results, first paragraph and Tables 1-3: Please provide the statistics used in a footnote en describe that no differences were found between groups (and specify between which groups). Were treatment A and treatment B compared within AGA and SGA groups or were AGA with treatment A also compared to SGA with treatment A, etc.?

We have provided the statistics used in a footnote to describe that no differences were found between groups and have specified between which groups comparison was made. Treatment A and treatment B were compared within AGA and SGA groups. This information has been added also in the text.

Results and discussion, second paragraph: what are normal GQ and subscale scores?

Normal GQ and subscales scores are indicated in the Patients and Methods section.

Results and discussion: Please provide a conclusion based on the results of this study, before the statement that further studies are needed.

According to your suggestion, we have provided a conclusion based on the results of this Study as follows: On the basis of our findings feeding preterm infants a nutrient-enriched formula after discharge appear not to affect neurodevelopment at 24 months of corrected age, both in appropriate and small for gestational age infants free form major comorbidities.

Minor essential revisions

Introduction, end of first paragraph: “intakes with the” should be “intakes and the”.

Done

Introduction, end of first paragraph: Is assume that the authors refer to the
“Mental Developmental Index scores” of the BSITD?
Yes, that is right, we have specified that we refer to the “Mental Developmental Index scores” of the BSITD

Introduction, second paragraph, second line: please rephrase “could determine” as “leads to”.
Done

Introduction, second paragraph, last sentence: please clarify the intervention period, for example “between term age and six months corrected age” and define that is were also “preterm” infants that were fed standard term formula.
Done

Patients and Methods-Study design, second paragraph: Please add “–” to “protein-to-energy ratio”.
Done

Patients and Methods-Study design, second paragraph: Was the vitamin D content of the formulae in milligram or microgram? In mg it seems quite high. The vitamin D content of the formulae is in microgram. Accordingly we have corrected the text.

Patients and Methods-Subjects, first paragraph: Please rephrase “informed written consent” to “written informed consent”.
Done

Patients and Methods-Subjects, second paragraph: “the same institution”: please name the institution.
Done

Patients and Methods-Subjects, second paragraph: The paper would benefit flow chart of subject recruitment including the feeding groups and the reasons of exclusion and loss to follow-up. In addition, how many infants were eligible to participate at birth? According to your suggestion, we have added a flow-chart of the study indicating also that 402 infants were eligible to participate at birth.

Patients and Methods-Subjects, third paragraph: “gestational age (AGA or SGA)”: being AGA or SGA does not only reflect gestational age but also birth weight. It would be better to describe this as a separate neonatal characteristic.
Done

Patients and Methods-Subjects, third paragraph: Please add “brain” to “an abnormal MRI”.
Done

Patients and Methods-Subjects, third paragraph: What is meant by “VD”? Please define this abbreviation.
VD means ventricular dilatation. Accordingly, we have defined this abbreviation in the text.

Patients and Methods-Measurements, first paragraph: What do standard
procedures mean? Or were these described previously, if so please provide a reference?
According to your suggestion, we have provided a “reference for standard procedures”

Patients and Methods-Measurements, first paragraph: Please rephrase “the same skilled examiner” as “one single skilled examiner”.
Done

Results and Discussion, third paragraph: Please specify that the PDI was part of the BSITD.
Done

Results and Discussion: Was the nutritional intake of studies mentioned in the discussion similar to the study described in the paper?
Actually it was possible to compare the nutritional intake of only one study mentioned in the discussion as in all the others the nutritional intakes were not reported. This information has been added in the text.

Results and Discussion: Are there any studies that specifically compared AGA and SGA infants and their developmental outcome? If not, I would emphasize this novelty in the discussion.
According to your suggestion, we have emphasized this novelty in the discussion as follows: “The main strengths of the present study are that the effect of a nutritional intervention on subsequent development was analyzed in subgroups of AGA and SGA preterm infants and that the actual energy and protein intakes during the intervention period were collected. Indeed, to our knowledge, studies that have investigate the effect of the consumption of high protein and energy intakes after hospital discharge in preterm infants, randomized and evaluated separately according to intrauterine growth pattern, on neurodevelopmental outcome are scarce. Agosti M. et al. [6] reported the interim results of a multicentric, randomized, controlled study on 121 very low-birth weight infants randomized at term corrected age to receive either a preterm formula (2.4 g/100 ml and 80 kcal/100 ml) or a standard term formula (1.7 g/100 ml and 70 kcal/100 ml) up to 55 weeks of corrected age. The authors focused the attention on the infants born SGA, reporting a beneficial effect of the consumption of a preterm formula in terms of higher score in the Griffiths’ Developmental Scale at 6 months of corrected age. However, the authors did not report the number of the infants born SGA that were analyzed neither their actual nutritional intakes”.

Reviewer’s report
Title: Randomized Outcome Trial of Nutrient-Enriched Formula and Neurodevelopment Outcome in Preterm Infants
Version: 1 Date: 11 February 2014
Reviewer: Harrie HN Lafeber

Reviewer’s report:
This manuscript represents the neurodevelopmental follow up at 24 months of 2 cohorts of healthy preterm infants fed a standard or a special energy and protein enriched formula as described in Pediatrics 2012;130:1215-1221.
I consider this manuscript as well written and suggest only minor revisions: I suggest to add to the discussion the aspect of the timing of the nutritional intervention. Maybe the period immediately after preterm birth is more sensitive for influences of extra protein or energy on brain development than the period after discharge from the hospital. It could therefore well be that since no
interventions in nutrition took place in that critical period no effects on the Griffith score at 24 months were observed. Of course this suggestion can only be proven by performing a randomized trial on predischarge nutrition in preterm infants. However in practice this may be considered rather unethical since such a trial may have negative influences on neurodevelopment of this vulnerable group of preterm infants.

According to your suggestion, we have added in the discussion the aspect of the timing of the nutritional intervention.