Author’s response to reviews

Title: Benefits of starting hypothermia treatment within 6 hours vs. 6-12 hours in newborns with moderate neonatal hypoxic-ischemic encephalopathy

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Author’s response to reviews:

Response to Reviewers’ comments

Dear Dr. Iughetti,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback, and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a more complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,
Reviewer #1

Background

Please add some references for the first sentence.

Response: We agree with the Reviewer. We added references [1, 2].

Methods

Please define the criteria for HIE.

Response: We thank the Reviewer for the comment. We added the criteria, as follows: "The criteria were HIE were: 1) evidence of moderate or severe clinical encephalopathy in the first 12 h of life; and 2) evidence of fetal distress, with at least one of the following: a) Apgar score at 5 min <5; b) continued need for ventilation initiated at birth for at least 10 min; or c) pH <7.00 in arterial cord blood or other sample in the first hour of life [3, 4]."

Further information about the characteristics of population are needed: US or MRI scans and the timing of these assessments and a neurological examination. Furthermore, the authors should perform a neurodevelopmental outcome.

Response: We thank the Reviewer for the comment. We now provide the MRI results in the second week after birth, as well as the rates of severe disability and death within 18 months.

Please provide the reference of Burdjalov for aEEG interpretation

Response: The reference was added [5].

Discussion

The results of the study are not correctly interpretable without neuroimaging and neurodevelopmental outcome.

Response: We agree with the Reviewer. We added the rates of neonatal death and 18-month disability, but we do not have results for longer term follow-up. Nevertheless, as added to the Results: "Table 4 presents the results of the 2-week MRI, as well as the 18-month outcomes. The results showed that the rate of normal MRI results was higher in the hypothermia group compared with the control group (P<0.01), and that in the hypothermia group, the rate of normal
MRI results was higher in the <6 h group (P<0.01). The 18-month rate of severe disability and the rate of neonatal death were lower in the hypothermia group compared with the control group (both P<0.01). There were no differences between the <6 h and 6-12 h groups."

Reviewer #2
1. A great deal of editorial (language/ grammar) is needed for better understanding of the article.

Response: We are sorry for this. The manuscript was proofread.

2. Abstracts: Abbreviations in the abstracts must be defined.

Response: The abbreviations were defined.

3. Introduction:

a. Authors should discuss why therapeutic hypothermia is more effective if started within 6 hours after delivery. What is special about 6 hours?

Response: We thank the Reviewer for the comment. The protocols actually being used are mainly based on animal data. Indeed, the 6-hour limit for hypothermia initiation comes from data suggesting that the effectiveness of hypothermia diminishes as time increases from the hypoxic ischemic event to the initiation of hypothermia, with the closing of the window occurring at 5.5-8 h after the event [6]. Nevertheless, the exact timing of the therapeutic window is mostly unknown in human newborns. The determination of the exact therapeutic window in newborns with HIE needs to be further investigated [7]. This was added to the manuscript.

b. Apart from delay presentation, what other reasons may make this golden hour impossible in your clinical setting? These will further justify this study.

Response: We thank the Reviewer for the comment. Two other reasons are frequently observed: 1) the parents are unsure and take some time to take their decision; and 2) hypothermia devices are broken or being used by other infants, leading to some delays in initiating hypothermia. These were added to the manuscript.
4. Methods:

a. Please state the exclusion criteria.

Response: We agree with the Reviewer. "The exclusion criteria were: 1) major congenital abnormalities; 2) known or suspected chromosomal abnormalities; 3) major brain malformations; or 4) aEEG abnormalities from causes other than HIE."

b. How was HIE (hypoxic-ischaemic encephalopathy) defined in this study?

Response: We thank the Reviewer for the comment. We added the criteria, as follows: "The criteria were HIE were: 1) evidence of moderate or severe clinical encephalopathy in the first 12 h of life; and 2) evidence of fetal distress, with at least one of the following: a) Apgar score at 5 min <5; b) continued need for ventilation initiated at birth for at least 10 min; or c) pH <7.00 in arterial cord blood or other sample in the first hour of life [3, 4]."

c. How was HIE classification done? What criteria were used in the classification?

Response: We thank the Reviewer for the comment. Encephalopathy was classified as mild, moderate, or severe according to a previously reported scale that focuses in the level of alertness [8, 9]. This was added to the manuscript.

d. How were the babies assigned to treatment arms? That is, what was the basis for assigning some babies into the hypothermia group and others into control group?

Response: We thank the Reviewer for the comment. The infants were grouped according to whether or not they received hypothermia treatment, which was mainly based on the parents' decision. This was clarified in the manuscript.

e. What precautions were taken while doing aEEG and NSE?

Response: Particular care was taken to place the electrodes and to be sure that they made contact with the skin. The serum samples were tested as soon as possible after separation.

5. Results: What does "5 min grade " represent? (First paragraph under Patient baseline characteristics). This should be described in the methods.
Response: We are sorry for the confusion. We meant the 5-min Apgar score. It was corrected.

6. Discussion: The first four paragraphs were merely literature review, and NOT discussion 'per se'. I think authors should re-write this section to reflect discussion of their findings.

Response: We agree with the Reviewer. We added some comparison with our own results.

7. Conclusion: The statement that "aEEG and NSE can be used as monitoring indexes for disease severity in children with HIE" is conjectural. This study did not verify that.

Response: We agree with the Reviewer. The conclusion was edited.

8. Tables:

a. Table 2 - Please indicate what F and X represent as footnotes.

Response: We thank the Reviewer for the comment. In fact, they were the values of the t test or the chi-square test. Since the P-value is much more easier to understand and is anyway reflected by the F and X values, they were removed.

b. Table 3 - It is difficult to comprehend because of too many information. I suggest that the table should be split into two. One for ΔaEEG and the other for ΔNSE.

Response: We agree with the Reviewer. The table was split.

References


