Author’s response to reviews

Title: Coagulopathy in Newborns with Hypoxic Ischemic Encephalopathy (HIE) Treated with Therapeutic Hypothermia: A Retrospective Case - Control Study

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Executive Editor
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Dear Dr. O’Donovan:

Thank you for your continued consideration of our manuscript entitled “Coagulopathy in Newborns with Hypoxic Ischemic Encephalopathy (HIE) Treated with Therapeutic Hypothermia: A Retrospective Case-Control Study”. Enclosed you will find our revised manuscript that we would like to submit for publication in BMC Pediatrics. We have performed extensive revisions and feel that we have addressed the reviewers comments from our prior submission. A detailed summary of our point-by-point response are included in this letter.

Reviewer #1:

Given the high rate of reported bleeding complications compared to the existing literature, think it would be of interest to provide more details on the nature and/or severity of the bleeding for those babies in the bleeding group (if available). Did any of these patients have significant clinical sequelae related to their bleeding events, i.e., require surgery for an abdominal bleed, increased respiratory support secondary to pulmonary hemorrhage, seizures following intracranial hemorrhage or subsequent need for neurosurgical intervention, etc.

Additional details on the clinical sequelae of bleeding events were added to the first paragraph of the Results section (line 100):

“Bleeding events were significant enough to require intervention by the clinical team; ie ventilator settings were escalated in setting of pulmonary hemorrhage, H2 blockers or proton-pump inhibitors were started for gastrointestinal bleeding, and/or coagulation products were given. However, there were no major life-threatening bleeding events requiring surgical or neurosurgical interventions.”

Also, it is not completely clear why the non-bleeding group of babies were transfused? Some comment on this in the discussion, i.e., NBG patients were transfused based on the discretion of the providers, would be helpful.

As suggested, the following comments were added to the discussion (2nd paragraph, line 148) regarding transfusion therapy in the NBG group:

“As a significant proportion of the NBG received transfusion therapy, it is presumed that this was done in response to laboratory derangements alone based on the discretion of providers. Whether this practice protected these patients from bleeding risk or whether this represents unnecessary exposure to blood products cannot be answered by the current study.”

Reviewer #2:

There is no data on the severity of clinical encephalopathy although the laboratory data for the infants with and without bleeding show no differences.
We thank the reviewer for pointing out this oversight. Data for encephalopathy grade at presentation were added to Table 2 and the following was amended in the results section (line 105):

“There were no differences in the baseline or clinical characteristics between the BG and NBG, except that more infants with severe encephalopathy were in the BG (Table 1).”

How were the samples drawn? If they are from heparinized lines, then aPTT values are not of much use. This was clarified in the methods section (line 63):

“Samples obtained from heparinized lines were treated with heparinase to neutralize the heparin effect prior to aPTT determination.”

The authors chose 4 sites of bleeding as of clinical importance (brain, GI, lungs and systemic bleeding). How did they diagnose clinically significant pulmonary bleeds?

Minor peri-intubation bleeds were excluded as described in the methods section. Clinical significance of pulmonary hemorrhage was further detailed in the Results section (line 100):

“Bleeding events were significant enough to require intervention by the clinical team; ie ventilator settings were escalated in setting of pulmonary hemorrhage…”

They have reported a much higher incidence of bleeding (54%) than that reported by the TH trials even when all these sites are included (~18%). This aspect is not clear given they have excluded the sicker infants in the first place.

We added further details on what was considered “clinically significant bleeding” in the results section (line 100), and highlighted the point that we did not only report major, life threatening hemorrhage:

“Bleeding events were significant enough to require intervention by the clinical team; ie ventilator settings were escalated in setting of pulmonary hemorrhage, H2 blockers or proton-pump inhibitors were started for gastrointestinal bleeding, and/or coagulation products were given. However, there were no major life-threatening bleeding events requiring surgical or neurosurgical interventions.”

This was then further discussed in detail in the discussion section:

“That the incidence of bleeding reported in this study (54%) exceeds the rates from published trials is likely attributable to our conservative definition of bleeding1, which was selected to encompass bleeding events felt to be of clinical significance and not confined to only major or life-threatening events. These events either required active intervention and/or had risk for independent sequelae, as in the case of intracranial hemorrhage. Variable rates of intracranial hemorrhage (8-39%) have been reported from the randomized cooling trials2,3 and it is possible that risk for hemorrhage can be impacted by variable approaches to correcting coagulopathy.”

It is also not clear why they chose the definition of significant bleeding based on deep vein thrombosis in children (ref 19).

This reference was not specific to DVT in children, but rather a consensus statement by the Perinatal and Pediatric Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, to provide a definition of clinically significant bleeding for use in pediatric trials. We added clarification in the methods section (line 66):

“Infants were stratified into two groups based on the presence or absence of clinically significant bleeding, which was defined a priori (according to the Perinatal Hemostasis Subcommittee of the International Society on Thrombosis and Hemostasis) as any observed bleeding that 1) decreased Hemoglobin (Hb) by 2g/dL in 24 hours; 2) required blood products for hemostasis; or 3) was in a critical organ system (e.g. pulmonary, gastrointestinal or intracranial hemorrhage identified on MRI performed after TH)3”
The authors excluded patients who died. This is surprising given that infants with more severe injury are more likely to be coagulopathic and have multi-organ injury. It is also likely, that bleeding alone may not have been the direct reason for mortality; including these patients with their bleeding profiles while may potentially skew the data, more importantly, including this group would likely make a stronger argument for treatment based on the ROC curves to correct the hematological disarrangements.

We agree with the reviewer that inclusion of the infants who died may have strengthened the association between laboratory derangements and bleeding, but also that this may have been open to bias. Laboratory data would be available with a variable number of observations per subject, and classification of bleeding would also be limited if infants died from non-bleeding related complications without autopsy information to identify if bleeding was also present. We felt that proceeding with analysis of only complete datasets was a more conservative approach. We expanded this rationale in the discussion section (line 184):

"Thus we used the approach of evaluating bleeding at any point during cooling/rewarming and its association with laboratory values measured over the course of TH. Due to this approach, we excluded infants who died during hypothermia as they would, by definition, have an incomplete and non-comparable observation period. As these infants were likely to have coagulopathy with more severe multi-system disease, their inclusion could have potentially skewed the data and therefore we proceeded with a more conservative approach to evaluate only complete laboratory and bleeding data from survivors."

As pointed out by the authors, the major criticism is the lack of temporal association of hematological disarrangements and bleeding. It is also not surprising that infants with bleeds have a more disarranged profile; however, the serial evolution of these profiles over time would be more useful rather than the difference in the max/min values, as presumably infants with bleeding will have worse lab values (and likely to be worse closer to the time of injury rather than following recovery from TH). As also noted by the authors, changes in lab measurements can happen just from processing at 37°C, not at the in vivo temperature.

We agree with the reviewer that the temporal association between laboratory derangements and bleeding is very important. Unfortunately, the onset of bleeding (particularly intracranial which is often silent) is often difficult to assess both prospectively and retrospectively. Thus we used the approach of looking at min/max values over a specified time period of risk to derive thresholds that are associated with bleeding. A key point is the temperature effect on PT/PTT values routinely run at 37 degrees, which would likely be further prolonged at the in vivo temperature, thus underestimating bleeding risk if routine norms are used. For this reason, these data are important as systematic evaluation of PT/aPTT values in this population have not been previously reported. We emphasized this point further in the Discussion section (line 145):

"aPTT and PT are likely to be more prolonged at 33.5°C, thus bleeding risk may be underestimated if routine norms are considered in samples that are warmed prior to determination."

Finally, to associate the hematological parameter cut-offs for treatment with outcomes, do the authors have any data to show that implementing their own recommendations would decrease the incidence of significant bleeding? If not, treatment based on cut-off values would likely increase exposure to blood products without meaningful benefit.

We agree with the reviewer that while these proposed thresholds may be derived from our data, whether active transfusion therapy decreases clinical bleeding cannot be answered by this study. We plan to continue to collect coagulation data following our change and practice and will be able to compare these rates to our historical bleeding rates reported in this study, but unfortunately do not have enough data presently. We emphasized that this is an important future direction in the last paragraph of the discussion (line 190):
“Our transfusion practice during the study period did not call for active transfusion therapy with increased laboratory surveillance when needed to maintain the goals proposed in this study. We have since adjusted our practice based on these data and plan to evaluate whether management of coagulopathy with these proposed transfusion goals reduces clinical bleeding in babies with HIE undergoing TH.”

We also adjusted our conclusion (line 197) to acknowledge this limitation: “Further study is needed to determine whether transfusion therapy according to these thresholds will reduce the incidence of clinical bleeding in babies with HIE being treated with TH.”

Other comments Not sure if this is the first study to systematically evaluate bleeding/coagulopathy- S. Sarkar et al have reported coagulation profiles before- J Perinatology 2009
While the mentioned study and others have laboratory values of interest ie: PT, aPTT, INR,and platelet count, there is no reported data on type of bleeding, rates of bleeding, or correlation of abnormal coagulopathy with bleeding events. We clarified this statement in the first paragraph of the discussion (line 123): “While some prior studies have reported platelet counts and aPTT/PT results during hypothermia,[Sarkar, 2009][Shankaran, 2008] this is the first study to systematically evaluate the relationship between laboratory and clinical evidence of coagulopathy in newborns undergoing TH.

We appreciate the thorough and thoughtful review of this paper. Please let me know if we can provide any additional information. Thank you for your continued consideration.

Sincerely,

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