Reviewer's report

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

**Version:** 2  **Date:** 15 August 2014

**Reviewer:** Rakesh Rao

**Reviewer's report:**

The authors have attempted to answer an important clinical question regarding the incidence, risks and management of coagulopathy in newborn infants with hypoxic-ischemic injury treated with therapeutic hypothermia. They have attempted to identify cut-off points for commonly used hematological parameters used in clinical decision making for treating infants at risk of bleeding. Based on their data analyses, they make recommendations for treatment values for platelet counts/INR, aPTT and fibrinogen, and have further changed their own clinical practice based on this data. However, there are several major limitations to the data as presented, the interpretation and recommendations that would limit its use for clinical practice.

Coagulopathy as a consequence of hypoxia and acidosis are well known. There is no data on the severity of clinical encephalopathy although the laboratory data for the infants with and without bleeding show no differences.

How were the samples drawn? If they are from heparinized lines, then aPTT values are not of much use.

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?

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

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.

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 37C, not at the in vivo temperature.

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.

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

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests