Reviewer's report

Title: NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related thrombosis

Version: 1 Date: 22 Jun 2017

Reviewer: Leonardo R Brandão

Reviewer's report:

Dear authors,

I have read with great interest the manuscript BPED-D-16-00696R1, entitled "Neonatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related thrombosis". Given the high frequency of venous thrombotic complications in neonates in comparison to other age ranges throughout childhood, I congratulate the authors for organizing this national project gathering two of the main clinical stakeholders involved on the management of neonates/infants with venous pediatric thrombosis, pediatric hematologists sub-specialized on the management of children with thrombotic complications and neonatal intensive care specialists. Secondly, the protocol focuses on the most prevalent type of venous occlusion leading to deep vein thrombosis (DVT) in neonates and in children, namely, central venous catheter (CVC)-related thrombosis.

In brief, the manuscript shares the research protocol of the project entitled NEOCLOT, originated in 2014. The study plans to recruit 150 neonates diagnosed with CVC-related DVT. A protocol proposing a treatment algorithm according to a thrombus risk stratification created by consensus is the basis of the entire project. The study's primary outcome will be the efficacy and safety of this proposed protocol; secondary outcomes will include the evaluation of CVC-related DVT risk factors, adherence to the guideline, and chronic complications within at least 1 year of clinical follow up. The study inclusion period suggested is of at least 5 years, meaning that the initial results can be anticipated for 2020 if all goes as planned.

From a manuscript review point, the paper is very well written and merits very minor comments, if any. On the other hand, the review may still be beneficial in case some of the suggestions listed can be considered for the future study publications.
Comments from this reviewer:

Study design and setting:

1) 150 neonates will be recruited over a 5 year period (i.e. 150/5 years = 30 patients per year/10 NICU = 3 patients with CVC-related DVT per NICU per year).

Looking at these numbers, this reviewer suspects that a different recruitment rate will occur between NICUs according to team awareness, study engagement, and overall patient disease severity. The study will report the efficacy and safety of the proposed consensus-based management of CVC-related DVT in neonates, stating that "violations to the protocol" will be noted and that neonates and infants without a signed consent will be excluded. Therefore, a potential for patient selection bias may hamper the study findings if, for example, only NICUs with the sickest patients, where DVTs are more likely, include patients. Conversely, because mothers from severely ill neonates may also be still hospitalized, maybe such patients would be less likely to be included if a consent cannot be obtained. With these examples, this reviewer suggests that the authors consider reporting the population included according to disease severity (examples: PELOD, NEOMOD), which may address some of the points raised herein. Secondly, it would also be important to report the rates of thrombosis (clinically noted), bleeding, and death in the population of patients excluded, to improve the interpretation of the study findings and address the study's generalizability (i.e. intracranial bleeds in anticoagulated vs. non-anticoagulated subjects).

2) Diagnosis of CVC-related thrombosis: a) the clinical recognition of DVT relies on experience. Because the body of nurses working in NICUs rotates, the authors may consider having a horizontal person per NICU to review the patients included to ensure that some type of "clinical adjudication" exists; b) the same applies to imaging (i.e. imaging adjudication vs. imaging performed could be reviewed by local expert in vascular imaging in neonates and infants).

Outcome measures:

1) On the topic of DVT recurrence: a) the DVT-risk stratification of NEOCLCOT encompasses either a vein within the deep venous system or the right atrium. A third potential category of CVC-related thrombotic events that may also be considered separately in the neonatal population would be the portal vein.

2) Some of the DVTs detected in neonates are identified when the thrombus is already in a sub-acute/chronic state and this has not been taken into consideration in the risk stratification algorithm (i.e. calcification). This will be important, particularly in the "wait and see" patient category.
3) For DVT recurrence and lab. monitoring, the anti-Xa kit used amongst the 10 NICUs may differ; this may need to be addressed in the evaluation of the DVT recurrence results, particularly if the recurrence rates differ amongst the NICUs.

4) For DVT risk factors and DIC, I would bring to the authors' attention that ISTH has DIC criteria available, which they may consider as an alternative to the one provided.

5) Regarding bleeding, while ISTH has a standardized criteria for bleeding secondary to anticoagulation in children, there may be additional bleeding scores that could be seen as more suitable for patients in an intensive care unit setting. For example, the authors may consider the one published in the Arch Dis Child Fetal Neonatal Ed. 2013 May;98(3):F260-3. doi: 10.1136/archdischild-2012-302443. Epub 2012 Nov 9.

6) For post-thrombotic syndrome (PTS): neonates and infants will be followed for at least 1 year. It is very likely that at the time of their PTS evaluation, the report will only be feasible by proxy. Currently, both pediatric PTS tools, the modified Villalta and the Manco-Johnson Scale, have limitations particularly in this age range. Hence, the authors may consider using a scale already validated, when obtained by proxy.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Unable to assess
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organisation that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license ([http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)). I understand that any comments
which I do not wish to be included in my named report can be included as confidential comments
to the editors, which will not be published.

I agree to the open peer review policy of the journal