Author’s response to reviews

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

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Author’s response to reviews:

Dear Sir/Madam,
Please find enclosed our study protocol, “NEOnatal Central-venous Line Observational study on Thrombosis (NEOCLOT): evaluation of a national guideline on management of neonatal catheter-related thrombosis” by Jeanine Sol et al., which we would like to submit for publication in BMC Pediatrics.

Evidence in literature on optimal management of neonates with central-venous line thrombosis is lacking. Only case-series and case reports are available. Therapeutic options include 1) a “wait and see” policy (an expectative policy monitored with ultrasonography), 2) anticoagulant treatment, 3) thrombolysis, and 4) thrombectomy. CVC-thrombosis may cause potential life-threatening acute and/or chronic complications. However little is known about the efficacy and safety of anticoagulant and thrombolytic agents in neonates.

The NEOCLOT working group has made a guideline based on the scarce data and expert opinion in order to standardize treatment of neonatal CVC-thrombosis nationally. In the NEOCLOT study, evaluation of this new guideline will be performed. Prospective collection of the neonates treated according to the protocol will enable evaluation of the used management strategy and generate data that can be used in follow-up treatment studies. For example, the NEOCLOT study allows investigating the natural history of specific neonatal catheter-related clots. In the current guideline “non-risky” thrombi were defined as non-obstructive thrombi in veins and thrombi filling less than 50% of the right atrium. Wait and see policy is applied to these thrombi. Results of the NEOCLOT study will show whether it will be safe to withhold anticoagulation in neonates with these thrombi.

The ethics approval was waived. We have forwarded the documentation to BMCSeriesEditorial@biomedcentral.com

This study is not externally funded by a major funding body and has therefore not undergone peer-review by a funding body.

The NEOCLOT study has started in 2014 and is still ongoing. At the moment, about 60 patients have been included. Therefore, no results of this study have been published or submitted to any journal.
We will include 150 neonates. The most important safety outcome of this prospective observational study is major bleeding. In the literature the mean prevalence of major bleeding in neonates with anticoagulants and thrombolytic agents is about 10%. With this national guideline we expect the effect on the outcome of major bleeding in all neonates, to decline from 10% to 5%. Given that we have 150 neonates, the 95% CI will be about 2.5 to 9.9%, which means that we have a large probability of a significant difference with the literature. The formula for the CI is based on the binomial distribution for independent cases. We have added this to the protocol.

Our trial was registered in the NTR on 24th of December 2013. We have corrected the trial registration note in the manuscript.

The Strobe checklist is uploaded as additional material.

No administrative permissions were required for data to be collected and used at the participating NICUs. The METC waiver of the AMC was sufficient for all sites.

All authors have approved the manuscript and agree with its submission to BMC Pediatrics.

Thank you for receiving our manuscript and considering it for review. We appreciate your time and look forward to your response.

Sincerely yours,

Heleen van Ommen, MD, PhD
Pediatric hematologist