Author's response to reviews

Title: Thrombosis as a complication of central venous access in pediatric patients with malignancies: A 5-year single-center experience

Authors:

Verena Wiegering (Wiegering_V@ukw.de)
Sophie Schmid (sophie_schmid@web.de)
Oliver Andres (andres_O@ukw.de)
clemens Wirth (Wirth_C2@ukw.de)
Armin Wiegering (Wiegering_a@ukw.de)
Thomas Meyer (Meyer_T@ukw.de)
Beate Winkler (Winkler_B@ukw.de)
Paul G Schlegel (Schlegel_P@ukw.de)
Matthias Eyrich (Eyrich_M@ukw.de)

Version: 3 Date: 19 June 2014

Author's response to reviews: see over
Thrombosis as a complication of central venous access in pediatric patients with malignancies: A 5-year single center experience.

Dear Dr. O’Donovan,

we recently sent you the above named manuscript which provides data about thrombosis as a complication of central venous access in pediatric patients. We now send you a revised version of the manuscript following the very valuable comments of the reviewers.

Comments on the revised manuscript:

Reviewer 1

1) Population: there is some confusion in the results section. First, it should be clear that the population of interest is represented by pediatric patients with a first episode of CVC-related thrombosis. All the analyses on this group should be presented as the main analysis. Then, all the other comparisons made between these patients and those without thrombosis or with thrombosis not related to CVC should be kept separate (instead of presenting them in sparse points of the result section, eg lines 190-194, 214-218, 242-246) Moreover, the issue of recurrent CVC related-thrombosis should be better separated, ie treated in a separate subgroup analysis, otherwise data may result confusing to the reader both in the abstract (please see a comment below) and in several points in the results section.

This is a valuable comment and we apologize to remain confusing between the main analysis and the sub-analysis. We tried to reorder both, the abstract and the result section and think that the manuscript has improved through this rearrangement.

2) The issue of heparin prophylaxis is not clear in several points of the manuscript:
– line 163/164: when exactly and how long LMWH was used in patients found positive at thrombophilia screening?
This is a good point and we have clarified this issue in the manuscript: all patients with positive thrombophilia screening received during the whole period of CVC-placement LMWH, if the platelet count was above 40/nL.

- line 205-207: how long heparin was used in these patients? How many patients experienced CVC-related thrombosis while on prophylactic heparin (first episode)?
- line 352/354: how many patients received heparin and how long?

Regarding the prophylactic heparin use: the percentages of patients with CVC-associated thrombosis and prophylactic heparin use, are as follow: 43% of lymphoma patients, 35% of leukemia patients, 28% of CNS tumor patients, and 0% of solid tumor patients. The low-dose heparin therapy started minimum 7 days before the thrombosis appeared and drug monitoring (anti-Xa-levels) was performed in each patient on a regular basis. Regarding the use of low dose heparin we did not found a significant difference by comparing it with the CVC group without thrombosis.

Regarding the prophylactic heparin use in both groups we did not find a significant differences (68/269= 25% vs. 14/52= 26.9%). The duration of prophylactic heparin therapy was dependent from co-medication, therapy and the individual risk profile. We have included this information in the manuscript as highlighted.

3) Please provide the number of patients lost to follow-up.

Thank you for this comment. You are right; we did not perform a lost-of-follow-up-analysis. However, this is a retrospective analysis and we did not have defined this fact as a primary end-point. We only had a defined time-frame. We performed charge review in all patients and analyzed all data until the last visit. The last visit was the date, we calculate on duration of insertion and follow up etc.

4) lines 209-225: the issue of different time from CVC implantation to CVC-thrombosis among cancer entities, should be better addressed performing a survival analysis (i.e. Kaplan-Meier or Cox-analysis).

As you ask for, we performed a Kaplan-Meier and a Cox-analysis and studied data with a statistician. However, as the scatter range is relatively big and the number of patients is small especially in the subgroups, we did not archive statistical significance. Nevertheless, this observation fits with the clinical feeling. Therefore, we would like to leave this section in the manuscript. For sure, it should be confirmed in an adequate cohort. We tried to improve this phase as highlighted.

5) lines 242-246: when all these parameters were measured?

Sorry that we remained unclear regarding the time points – we measured/analyzed laboratory parameters twice: before catheter implantation and at the time point of thrombosis. However the parameters were within the expected normal range and did not show significant differences to the group without CVC-associated thrombosis. We have clarified this fact in the manuscript.

6) CVC entry site: on lines 238-240 you state subclavian CVCs showed the highest rate of thrombosis (by the way, please indicate if statistically different), whereas in the discussion section (lines 298-299) you say the opposite. Please clarify.

Thank you for your critical reading. We apologize for this mistake. We found indeed the highest rate of thrombosis in subclavian CVCs and corrected the discussion section.

7) Discussion: Please provide some comparison with data on the prevalence of CVC related thrombosis in children, coming from other studies

Thanks for this comment – we have included some pediatric studies.

8) Discussion, lines 343-345. This sentence is not supported by the results of the study and, also, is not supported by any other strong evidence. Please consider to remove it. 9) Conclusions: here there are some general considerations, not supported by the results of the study. Please consider to revise it.
Thank you for your advice. We tried to improve the manuscript according your instructions as highlighted in the manuscript.

Minor Essential Revisions

1.) abstracts, results paragraph: (n=52) is not clear here what you are referring to, since it is not specified. Please consider to remove it.

Thank you for this comment. We have improved this section as highlighted.

2) Figure 1. Image quality is low, it is difficult to read word/numbers

We apologize for the low image quality and have improved this figure.

3) Introduction, line 89: thromboembolism (not “thromboembolia”)

Thank you – we changed thromboembolia to thromboembolism.

4) Introduction, line 94: may be different from the adult population (not “in the adult...”)

We apologize for this mistake and have corrected it in “from the adult population”.

5) line 173/174: median time since diagnosis: please specify

Thanks, we have specified this section.

6) line 186: acronyms are used without explanations

We now have introduced the used acronyms as highlighted.

7) line 195: eight, out of?please specify. To me it should be 8 out of 17 since you are dealing with patients, not thromboses (also below, on line 200)

Thank you for these comments. We changed and clarified this section as highlighted in the manuscript.

8) line 348: it should be regimen (not regime)

Thank you – we changed regime to regimen.

9) line 356: UFH should be in bracket, not viceversa

Discretionary Revisions

Thank you, we have changed it.

10) If you collected it, please consider to add data on the incidence of post-thrombotic syndrome, if any

This is an interesting fact. Indeed, we could not observe any post-thrombotic syndrome. However, by studying the published evidence of post-thrombotic syndromes in CVC-associated thrombosis, it seems to be a rare complication in CVC-associated thrombosis and might be even lower in the pediatric cohort (for port-a-cath-thrombosis it has been estimated to be approximately 5% [Albisetti M et al. 2013]). However, it is an important fact, which should be mentioned, and we included it in the manuscript as highlighted.

Reviewer 2 as well very helpful comments to improve the presentation of our data. We will comment on them on a point-to-point basis:
We apologize that we remained unclear in the manuscript and did not show all the results properly. We tried to improve the manuscript according your suggestions as highlighted in the manuscript. We think that now the results are better exposed than before.

2. The authors also report no difference in rate of thrombosis among different types of malignant disease, but the evident lower rate in solid tumors compared to others should be emphasized. Thank you for this comment. Indeed, the rate of CVC-associated thrombosis in patients with solid tumors was lower; even if it did not reach statistical significance due to the small group. However, it seems to be an important observation and we have included it in the manuscript as you suggested. The section we added is highlighted in the manuscript.

CORRECTIONS TO BE MADE IN METHODS:
Thrombosis or vascular complications should be better defined (if inclusive of catheter occlusion) and better described in the results (site, dx imaging etc).

We apologize that we did not define thrombosis and vascular complications properly in these sections and tried to improve it as highlighted.

IN RESULTS:
2) Reported the median? time instead of mean? from CVC insertion until 173 catheter-associated thrombosis was 202 ± 32 days, and the median time (mean) since 174 diagnosis was 344 ± 53 days?.

Sorry, that we mixed median and mean times. We have uniformed it to median times in the mentioned section.

3) In Results: The Vena subclavia catheters (45/269) showed the highest incidence of thrombosis (11 patients with 45 implanted catheters; 24%),?.. In Discussion it is stated ??We confirmed that there was a lower incidence of CVC-related thrombosis with subclavian and jugular access ?.. "

Thank you again for your critical reading. As we have already mentioned to the first reviewer: We apologize for this mistake. We found indeed the highest rate of thrombosis in subclavian CVCs and corrected the discussion section.

We want to thank the reviewers explicitly for the kind revision of the manuscript. We believe the revised version of the manuscript presents our data on CVC-associated thrombosis more clearly and more completely.

We hope you may consider our data in the revised format valid for publishing in your journal.

Yours sincerely,

Dr. Verena Wiegering