

Peer Review File

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Reviewer A: The authors present a manuscript on 365 neonates and infants undergoing cardiopulmonary bypass for the repair of congenital heart defects, measuring pre and post-bypass fibrinogen levels with attempted correlations to the use of blood products, bleeding, and peri-operative ICU findings (ventilation, length of stay, etc.). while the limitations of such a retrospective study are explained and understandable, the presentation is confusing, the correlations hard to understand or really cleanly believe, and are influenced by many intra-operative variables (as acknowledged by the authors), which are not measured. my concerns:

Comment 1: page 4, line 91: congenital heart operation is listed as single, as if there was only one type of defect and/or repair was done; which operations, and for which defects? why were the surgeries performed at 20-28 degrees, which is a degree of hypothermia currently abandoned by many centers around the world, specifically because it has such a strong influence on blood components and therefore bleeding and need for products? also, 20 degrees has a much stronger effect on hemostasis compared to 28 degrees - your population, your operations, and even your temperature strategies are not homogenous, and therefore your results skewed.

Reply 1: Thank you for your comment. I agreed your opinion, and I checked the temperature for hypothermia. I figured it out wrong, and corrected from 20-28 degrees to 28-30 degrees. (Page 8, line 13)

Although congenital heart operation is not listed, I divided it into simple, and complex congenital heart disease (CHD) because the operation is also decided by that classification. I presented it in the Results (paragraph 4), and wrote the definition in the Materials and Methods. (Page 8, line 4-6)

Comment 2: page 4, lines 102-104: this way of presenting allows for tremendous variation; how anesthesia and perfusion react to compensate for bleeding during and at the end of a bypass case are subject to tremendous variation.

Reply 2: Thank you for your comment. I agree your opinion. However, many operating physician and the anaesthesiologist who don't have any system for POCT of coagulation decide transfusion by clinically significant bleeding.

Comment 3: page 7, line 177: no definition of simple versus complex congenital heart defect is ever given anywhere in the manuscript.

Reply 3: Thank you for your comment. I added the definition in the Materials and Methods. (Page 8, line 4-6)

Comment 4: page 9, lines 262-264: this is not valid.

Reply 4: Thank you for your comment. I removed it.

Comment 5: page 9, lines 264-265: you should have included this parameter.

Reply 5: Thank you for your comment. I agree your opinion. However, it's not possible to evaluate correct intraoperative bleeding volumes because the blood circulates in the CPB circuits. The blood from cell saver or pump was transfused only after transferring the patient to the ICU.

Comment 6: page 9, lines 265-268: this statement invalidates all of your findings.

Reply 6: Thank you for your comment. I agree your opinion. However, this study was conceived because some institutions do not have the system of POCT such as TEG, or ROTEM. I think it might be worthy. Please consider it.

Comment 7: page 10: your limitations paragraph is quite humbling; it basically destroys all of your findings.

Reply 7: Thank you for your comment. I agree your opinion. However, this study was conceived because some institutions do not have the system of POCT such as TEG, or ROTEM. I think it might be worthy. Please consider it.

Comment 8: page 10, conclusions: "pre-emptive PLT transfusion can help management.". this is not supported by your data and is pure contention.

Reply 8: Thank you for your comment. I removed the statement about pre-emptive platelet transfusion in Abstract, and conclusion. I also corrected the conclusion. (Page 3, line 22/ Page 16, line 1-3)

Comment 9: In summary, I find the manuscript has many deficiencies in its structure, the variable included, but mostly all of the factors which will influence the results which are NT included, which invalidate not only the results, but also the message your are trying to convey. i would not recommend publication in this form, and ask the authors if they could account for the many missing variables, or somehow limit the inclusion group to a more homogenous intra-operative scenario.

Reply 9: Thank you for your comment. I tried to check, and correct this article according to your comments.

Reviewer B

Comment 1: The authors describe a single institution retrospective study of the influence of the pre and post op fibrinogen levels and its affect on bleeding and blood transfusion requirements after pediatric cardiac surgery. I have the following questions and comments:

1)375 newborns and infants were included in the study. However, the authors do no disclose what operations and what the diagnosis for these patients were. A detailed table listing the diagnosis and operation performed must be included. This has a huge bearing on this study as the readers need to know if the patients

had cyanotic vs acyanotic / single ventricle vs 2 ventricle pathology

Reply 1: Thank you for your comment. I already added the definition of simple versus complex CHD in the Materials and Methods. (Page 8, line 4-6)

Comment 2: The authors compare simple vs complex heart surgery but do not explain what types of surgeries are under each category. Please define the terms simple and complex with the types of surgery included under each diagnosis

Reply 2: Thank you for your comment. I already added the definition of simple versus complex CHD in the Materials and Methods. (Page 8, line 4-6)

Comment 3: The authors state under clinical practice that procedures were performed between 20-28 degrees hypothermia. What was such deep hypothermia performed in these children? Again, what types of operations were performed? What was the need for such deep hypothermia?

Reply 3: Thank you for your comment. I agreed your opinion, and I checked the temperature for hypothermia. I figured it out wrong, and corrected from 20-28 degrees to 28-30 degrees. (Page 8, line 13)

Comment 4: What percentage of kids had circulatory arrest performed for surgery?

Reply 4: Thank you for your comment. There was no surgery performed under circulatory arrest.

Comment 5: What was the reexploration rate for bleeding? How many of the patients in this study had to be taken back to the OR for exploration?

Reply 5: Thank you for your comment. There was no patient who was taken back into the OR for exploration.

Comment 6: How many of these patients had to have temporary sternal closure performed for coagulopathy?

Reply 6: Thank you for your comment. Unfortunately, there's no patient who experienced temporary sternal closure for coagulopathy. Temporary sternal closure in our institution is performed for unstable hemodynamics.

Comment 7: As demonstrated in table 1, only 13.2% of patients with low fibrinogen required platelet transfusion. The majority still did not require a platelet transfusion. It should be cautioned that based on this data preemptive platelet transfusions even in the patients with low fibrinogen must not be performed as the majority of these patients did not require it. The statement about pre-emptive platelet transfusion must be eliminated.

Reply 7: Thank you for your comment. I removed the statement about pre-emptive platelet transfusion in Abstract, and conclusion. I also corrected the conclusion. (Page 3, line 22/ Page 16, line 1-3)

Reviewer C: The manuscript studies the relationship between preoperative and postoperative level of fibrinogen on amount of bleeding in postoperative period in neonates and infants with congenital heart defects. As well as on amount of blood transfusion.

I would like congratulate authors on the study. However, I believe that the article need to be revised.

I have numerous minor and major comments on the article. Please see below.

Comment 1: Please provide list of abbreviations when they are used for the first time all around the text of the article.

Reply 1: Thank you for your comment. I provided the list of abbreviations. (Page 5, line 1-12)

Comment 2: Introduction. The second paragraph, lines 65-66. The sentence is written as if fibrinogen is acting to aggregate the platelets which is not wrong but to me it is the phrase taken from the context. Please rephrase sentence so I would be clear of the function of fibrinogen in coagulation and promoting aggregation of platelets ...

Reply 2: Thank you for your comment. I corrected the sentence. (Page 6, line 12)

Comment 3: Lines 70-76 on the same page. These sentences contradict each other. First you are saying that fibrinogen has been studied widely in both pediatric and adults. Then you are emphasizing that it is unclear in pediatric cardiac surgery? Please clarify rationale for the study clearly. Please elaborate on the studies with small volume of participants. Any reference?

Reply 3: Thank you for your comment. I tried to emphasize that there is small volume of study for identifying the relationship of plasma fibrinogen levels with the bleeding and transfusion amount in pediatric cardiac surgery. I corrected this sentence. (Page 6, line 21, 22) The references for pediatric patient are 17, 19.

Comment 4: Materials and methods. Please replace end point with outcomes. Again, abbreviations all around the text without explanations when they are mentioned for the first time.

Reply 4: Thank you for your comment. I replaced end point with outcomes. (Page 9, line 5, 7) I checked the abbreviations.

Comment 5: Line 112-113. Please remove moreover and future...

Reply 5: Thank you for your comment. I removed line 112-113.

Comment 6: Statistical analysis. Please identify whether you have tested the samples for normality of distribution and what kind of tests therefore were used for normally and non-normally distributed data. Authors listed and used correlation tests Spearman's and Pearson's test. The first is for nonparametric data

and the second is for parametric. Both can't be used simultaneously for the same samples of data. Also please add regression analyses and ROC curve in the statistical methods. These were used in table 6.

Reply 6: Thank you for your comment. I added the detailed contents of statistical analysis according to your comments. (Page 8, line 13, 16, 18-20) I also corrected Table 5.

Comment 7: Please provide demographics of the patients in a separate table.

Reply 7: Thank you for your comment. I think it's more appropriate that the demographics of the patients are written in Table 1-3 for the comparison.

Comment 8: Please define what is complex and what simple CHD is. I am not aware of this classification. I suggest authors to use RACH-1 classification to analyze data appropriately.

Reply 8: Thank you for your comment. I already added the definition of simple versus complex CHD in the Materials and Methods. (Page 8, line 4-6)

Comment 9: It is clear from table 4 that duration of bypass, bleeding, transfusion amount, fibrinogen and etc. were different statistically significant (assuming the right statistical test was used). Therefore comparing patients with different complexity of surgery based on fibrinogen level brings bias to the study, as apples can not be compared to oranges. In order to identify correlation and impact of fibrinogen concentration on outcomes the base line parameters have to be similar (RACHS-1, demographics, etc.). Also authors provided the rationale how patients were divided based on fibrinogen level... my question is why these numbers were chosen. Would it be more reasonable to find the value (fibrinogen concentration pre or post op) associated with the largest blood product requirements instead and use that as a due point for clinical practise in future... Just a thought.

Reply 9: Thank you for your comment. I agree your comment, and the surgical procedure is usually more complex in the complex CHD, and simpler in the simple CHD. Therefore, this might be more intuitive for the readers.

Normal fibrinogen levels range from 150–400 mg/dL; further, the reference PreCPB value was set at 150 mg/dL. Moreover, the reference PostFib value was set at

100 mg/dL since 100 mg/dL was considered a required threshold concentration for

adequate haemostasis in patients with congenital fibrinogen deficiency.

Comment 10: It is absolutely unclear what policy for blood priming for the population is. It seems that patients with "simple" had way less blood primes as a result diluted fibrinogen after coming off bypass... this has to be defined and analyzed accordingly. Is plasma used for priming along with red cells? This information alone could change all analyzes of the data in my opinion.

Reply 10: Thank you for your comment. In every cases of pediatric cardiac surgery under CPB, blood priming (except for FFP) was used, and I think it did not affect the analysis in this study.

Comment 11: It would be nice to know of intraoperative bleeding volumes as well as cell saver or any other blood conservation strategies were used.

Reply 11: Thank you for your comment. It's not possible to evaluate correct intraoperative bleeding volumes because the blood circulates in the CPB circuits. The blood from cell saver or pump was transfused only after transferring the patient to the ICU.

Reviewer D

Major concerns:

Comment 1: There is data available that fibrinogen levels in cardiac surgery in general should be targeted to be above 150mg/dl postbypass (some even suggesting this should be above 200mg/dl). It is therefore not surprising that the authors see an increased amount of bleeding in those patients. Furthermore, I do not agree with the rationale to state that if fibrinogen levels are low, one should give platelets (certainly not preemptively). What about replacing fibrinogen, either with concentrate (though not widely available) or using cryoprecipitate? Also why not institute a coagulation protocol, for example getting a TEG, fibrinogen level, and PLTs when rewarming (or a similar algorithm using Rotem(R))?

Reply 1: Thank you for your comment. This study was conceived because some institutions do not have the system of POCT such as TEG, or ROTEM.

Comment 2: How can you assure that the difference is not merely due to to the impact of complex versus simple CHD (rather than high or low pre/post fibrinogen)?

It appears that the major take home point of the study is that in that dataset, if fibrinogen was low, providers gave more PLTs to correct this (successfully so, given that there was no difference in bleeding).

Reply 2: Thank you for your comment. I removed the statement about pre-emptive platelet transfusion in Abstract, and conclusion. I also corrected the conclusion. (Page 3, line 22/ Page 16, line 1-3)

Minor concerns:

Comment 3: This is a retrospective study, which by definition, does not allow for the evaluation of a causal relationship between two factors. I would caution against making strong recommendations based on this data set. Especially one that will expose patients to multiple donors.

Reply 3: Thank you for your comment. . I removed the statement about pre-emptive platelet transfusion in Abstract, and conclusion. I also corrected the conclusion. (Page 3, line 22/ Page 16, line 1-3)

Comment 4: Introduction, there are many more factors related to increased bleeding risk in peds cardiac surgery. They should be mentioned in more detail.

Reply 4: Thank you for your comment. I tried to add factors related to increased bleeding risk in pediatric cardiac surgery in more detail. (Page 6, line 6-8)

Comment 5: I think the most interesting point here is the concept of fibrinogen dysfunction. This should be explored in more depth, including references.

Reply 5: Thank you for your comment. I explored in more depth, including references according to your comment. (Page 3, line 22/ Page 16, line 1-3)

Comment 6: Methods, it is stated under Clinical practice that "the operation was performed under deep hypothermia", while under study design it is stated that patients had "simple and complex heart anomalies" - I take it that not everybody underwent deep hypothermia for that?

Reply 6: Thank you for your comment. I agreed your opinion, and I checked the temperature for hypothermia. I figured it out wrong, and corrected from 20-28 degrees to 28-30 degrees. (Page 8, line 13)

Comment 7: How is coagulation corrected post bypass? Is there a standard protocol or is everyone doing their own thing? If so how many different providers (surgeons and anesthesiologists) are there?

Reply 7: Thank you for your comment. Upon CPB weaning after completing the main procedure, heparin was reversed using protamine sulphate (1 mg/heparin 100 unit. Protamine sulfate (0.5-1 mg/kg) was additionally administered to maintain a baseline ACT of < 110%. (Page 8, line 17-19)