Author's response to reviews

Title: Thromboelastometry guided blood transfusion: an alternative and efficient approach to manage acute fatty liver of pregnancy. A case report.

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Author's response to reviews: see over
LETTER TO JOURNAL OF MEDICAL CASE REPORTS

Thromboelastometry guided blood transfusion: an alternative and efficient approach to manage acute fatty liver of pregnancy. A case report (MS: 4700376871683747).

Dear Editor

A point-by-point response to the reviewers' comments follows. Changes are marked in green in the manuscript.

Reviewer 1: Tae-Yun Sung

1. Was written informed consent to publish this case obtained?: No
   Response: As stated on page 8 of the submitted manuscript, written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is attached in the end of this letter.

2. Authors reported the experience of the thromboelastometry guided blood transfusion in patient who has AFLP. While I do not doubt the effectiveness of thromboelastometry in critically ill surgical patients, I would like to see a more developed discussion. Unlike prophylactic transfusion of blood product, is prophylactic correction of thromboelastometry results using fibrinogen concentrate and prothrombin complex concentrate justified? Especially, in pregnant women, and is that totally safe in mother and fetus? I think authors should state about this problems in discussion.
   Response: We acknowledge the reviewer for addressing this important issue. As pointed out by the other reviewer (see below), the appropriate choice of haemostatic therapy has not been resolved yet in patients with AFLP. The rarity and the severity of
this disease makes the prospective assessment and comparison of different hemostatic therapy approaches a challenge. From the other hand, observational studies have been suggesting an association between low plasma fibrinogen levels and the risk and the severity of postpartum haemorrhage [1,2]. Thus, the increased bleeding risk in this population of patients might overcome the potential risk of adverse reactions associated with fibrinogen concentrate / prothrombin complex concentrate administration.

The outcomes and safety of fibrinogen replacement in obstetric patients were recently evaluated in an observational study including 77 patients with major obstetric hemorrhage [3]. Thirty-four patients were randomized to receive cryoprecipitate (n=14) or fibrinogen concentrate (n=20). The mean (±SEM) administered dose of cryoprecipitate was 2.2±0.35 pools and mean (±SEM) dose of fibrinogen was 4.0 ± 0.8 g. Estimated blood loss, need of red blood cell transfusion and rate of adverse reactions or thrombotic complications did not differ between cryoprecipitate and fibrinogen groups [3].

More recently, in a multicenter randomized controlled trial, 249 adult women with early postpartum hemorrhage (i.e., bleeding from uterus and/or birth canal within 24 hours after delivery) were randomized to receive a single dose of 2.0 g of fibrinogen concentrate or placebo (normal saline) [4]. The authors reported no significant differences between the groups regarding the need of blood transfusion and on the incidence of adverse events [4].

As suggested by the reviewer, we have included one sentence in the discussion section addressing the safety concerns related to prophylactic transfusion of fibrinogen concentrate or prothrombin complex concentrate in pregnant women (page 8 lines 5-9): “Observational studies have been suggesting an association between low fibrinogen levels and the risk and severity of postpartum haemorrhage [21]. Therefore, the increased bleeding risk in this population of patients might overcome the potential risk of adverse reactions associated with fibrinogen concentrate administration.”

References


3. Introduction There are many overlapped sentences in introduction and discussion section page3 line 18 “Moreover~and jaundice”, line 21"the most ~of coagulopathy”
Response: The introduction section was rewritten to avoid overlapped sentences. Now the first paragraph of introduction reads as follows (page 3 lines 4-10): “The clinical picture of AFLP is nonspecific and comprises headache, fatigue, anorexia, nausea, vomiting, abdominal pain, fever and jaundice [1]. However, the most severe spectrum of the AFLP is characterized by an early multiorgan involvement [1]. Liver failure is the landmark of the AFLP and may be accompanied by encephalopathy, gastrointestinal bleeding, acute kidney injury and different degrees of coagulopathy, which intensify the risk of obstetric hemorrhage and death [2].”

4. Please present the patient’s history of allergies to medicines, foods, or other substances.
Response: The patient’s history of allergies to medicines, foods or other substances was added to the CASE PRESENTATION section of the revised manuscript (Line 11 page 4).

5. Temperature was 35: is that core temperature or skin temperature?
Response: We reported skin (axillary) temperature. This was added to the revised manuscript (Line 14 page 4).

6. P5 L4 : please, present the estimated blood loss (EBL) and fluid input and output during operation.
Response: The fluid input (crystalloids) and output during operation were, respectively 2000 ml and 200 ml. These data were added to the CASE PRESENTATION section (line 1 page 5 of the revised manuscript). Unfortunately, the estimated blood loss during the surgery was recorded as a qualitative data ("small bleeding") instead of as a continuous data (in mL).

7. Discussion P6 L27 “.. disorders within 5min in…” : To my knowledge, it takes 10 to 15 min, minimally to obtain valuable data.
Response: A thromboelastometry assay (ROTEM) takes up to 60 minutes to be completed. However, the amplitude of clot strength can be assessed 5 (Amplitude 5 min), 10 (Amplitude 10 min), 15 (Amplitude 15 min), and 20 minutes (Amplitude 20 min) after the CT until the maximum amplitude (MCF) is reached (1). Furthermore, it has been demonstrated that thromboelastometry amplitude at 5 min is effective in early detect critically low platelets and fibrinogen in hypocoagulable patients undergoing liver transplantation (2).

This issue was acknowledged in the revised version of manuscript (page 6 line 23): “Thromboelastometry enables a contemporary detection of several hemostatic disorders within 5 min (amplitude at 5 minutes) after CT EXTEM, INTEM and FIBTEM in patients with severe coagulopathy [15,16].”

References

**Reviewer 2: Cristina Solomon**

If any information is missing from the reporting, please detail it here: Dosing of the drugs used.
Response: The amount of administered fibrinogen concentrate was 4.0 g (Haemocomplettan® P, CSL Behring, Marburg, Germany) and the administered amount of prothrombin complex concentrate was 1000 UI (Beriplex® PN/500 UI, CSL Behring, Marburg, Germany), both administered at the beginning of the cesarean section. This information was added (line 31 page 4 and line 10 page 12) to the revised manuscript.

1. Title: Consider amending the title to: “Thromboelastometry-guided hemostatic therapy: an efficacious approach to manage bleeding risk in acute fatty liver of pregnancy. A case report.”
Response: We thank you the reviewer for her suggestion. We changed the article title as proposed by the reviewer.

2. Abstract, Case Presentation: the authors may want to rethink the term “brown”. It is not commonly used. Perhaps Afro-Brazilian?
Response: We agree. The term “brown” was replaced by “Afro-Brazilian” in Abstract (line 13 page 2) and on case presentation section (line 9 page 4).

3. Abstract, Case Presentation: consider adding actual values to the text (e.g. INR values, fibrinogen concentration values).
Response: We agree. This sentence of the introduction section now reads as follows (line 16 page 2): “The laboratory exams revealed metabolic acidosis, acute kidney injury (serum creatinine = 3.4 mg/dL), platelets 97 x 10^3/mm^3, serum fibrinogen 98 mg/dL and increased International Nationalized Ratio (INR = 6.9) without acute bleeding.”

4. Abstract, Case Presentation: it would be helpful to indicate in the text that the EXTEM and FIBTEM tests were used. e.g. "Based on the results of the thromboelastometric tests EXTEM and FIBTEM…
Response: We modified this sentence of the introduction section accordingly the reviewer suggestion. Now, this sentence reads as follows (line 19 page 2): “Based on the results of the thromboelastometric tests EXTEM and FIBTEM, prothrombin complex concentrate and fibrinogen concentrate were administered at the beginning of the cesarean section…”

5. Abstract, Conclusion: as the study did not investigate the impact on thromboelastometry in a large sample size, the Conclusion may be overreaching. Please amend slightly: e.g. “with the potential advantage of helping avoid transfusion in these patients”.
Response: We modified this sentence of the introduction section accordingly the reviewer suggestion. Now, this sentence reads as follows (line 25 page 2): “Thromboelastometry may be considered a useful, feasible and safe tool to monitor and manage coagulopathy in obstetric patients with acute fatty liver of pregnancy, with the potential advantage of helping avoid unnecessary transfusion in such patients.”

6. Introduction, page 4, line 1: please correct “it represents” to “they represent”
Response: Changed accordingly (page 3 line 31 of the revised manuscript).
7. Introduction, page 4, line 3: please replace “Therefore, thromboelastometry guided blood transfusion could be considered” with “Therefore, thromboelastometry guided hemostatic therapy could be considered.“
Response: Replaced accordingly (Page 3 line 33 of the revised manuscript).

8. Introduction, page 4, line 6: please replace the word “blood with “hemostatic therapy”, because this is the point of the case.
Response: Replaced accordingly (Page 4 line 2 of the revised manuscript).

9. Introduction, page 5, paragraph 1: please add the specific triggers (e.g. EXTEM CT, FIBTEM MCF) and the values used as triggers to the text, so that the readers do not have to go back and forth to the table. Please add the information on the fibrinogen and PCC dose to the text.
Response: The ROTEM values used as triggers and the doses of fibrinogen and PCC were added to the revised manuscript (page 4, lines 31-34).

10. Discussion, page 6, paragraph 2: The correct term is “thrombelastography” – not “thromboelastography” (4 times to be corrected in this paragraph)
Response: We apologize by our mistake. The correct term “thrombelastography” was used in the revised manuscript: Key-words (Page 2 line 30), Discussion (Page 6 lines 7,8,11,12 and 18).

11. Discussion, page 6, paragraph 3: with regards to thromboelastometry, a few years ago the term “rotation” has been deleted from the nomenclature of the method. Please delete the word “rotation” (2 times to be corrected in this paragraph)
Response: The term “rotation” has been deleted from lines 16 and 18 of page 6.
13. Discussion, page 7, paragraph 2: Please add that prolongation of CT may also be observed when not enough substrate is available for the fibrin and platelet clot. This finding is supported by the fact that CT shortening has been observed in experimental and clinical work following fibrinogen correction (Bolliger et al 2009 BJA, “finding the optimal concentration...”, Grottke 2015 Anesthesiology “Prothrombin complex concentrates...” – with considerations on the limitations of CT when fibrin is decreased; Solomon et al 2013, BJA, “Haemostatic effects...”.

Response: We thank you the reviewer for addressing this issue. The following sentence was added to the DISCUSSION section of the revised manuscript (Page 7, line 6):

“Furthermore, it has been demonstrated that CT prolongation may also occur when not enough fibrinogen is available for clot formation [17–19].”


Please add a paragraph on the limitations of CT in guiding PCC (i.e. fibrin clot quality should be corrected first, and a new CT value should be obtained to understand whether there is a thrombin generation deficit which requires correction. In this case, however, the coagulation defect was very profound, and the CT prolongation was so severe, that it is likely that it was cause by both fibrin deficit and thrombin generation deficit. Nevertheless, a step-wise approach for coagulation testing and hemostatic therapy may be preferable.
Response: We agree with the reviewer. The following paragraph was added to discussion (page 7 Lines 7-11): “Therefore, a stepwise approach for hemostatic therapy is advisable. When CT is prolonged, fibrinogen should be replaced first and then, if CT remains
prolonged, coagulation factors deficiency should be corrected with FFP or prothrombin complex concentrate administration.”

14. Discussion, page 7, paragraph 2: please delete “The CFT is more strongly influenced by clot polymerisation disorders than by the MCF. A prolonged CFT, with a normal MCF, thus indicates a polymerization disorder, whereas a reduced MCF with a normal CFT indicates a deficiency of clottable substrate (fibrinogen and / or platelets).” These statements are not correct. CFT is comparably influenced by fibrin and platelets.
Response: We agree with the reviewer. This sentence was removed from the manuscript.

15. Discussion, page 7, paragraph 3 and page 8, paragraph: please replace “dysfibrinogenemia” with “hypofibrinogenemia”
Response: The term “dysfibrinogenemia” was replaced by “hypofibrinogenemia” (Page 7 line 24 of the revised manuscript).

16. Discussion, page 7, paragraph 3: please use “administering” instead of replacing
Response: The term “replacing” was modified by “administering” (Page 7 line 26 of the revised manuscript).

17. Discussion, page 7, paragraph 3: the last sentence appears incomplete. Please consider correcting to “More importantly, this was possible with…”
Response: This sentence was rewritten as follows (line 9 page 8 of revised manuscript): “More importantly, it was possible to correct the hypofibrinogenemia by replacing 4.0 g of fibrinogen concentrate.”
18. Table 1 and figure 1: the figure presents a set of ROTEM images obtained post therapy, but it would be useful to have the actual values also in the table i.e. between 0 hrs and 3 hrs in the table.

Response: We modified the figure 1 accordingly the reviewer suggestion. Now, figure 1 (below) depicts the thromboelastometry analysis performed at the beginning of the cesarean section (Time 0; panels A-C) and a second thromboelastometry analysis performed after 4.0 g of fibrinogen concentrate (Haemocomplettan® P, CSL Behring, Marburg, Germany) and 1000 UI of prothrombin complex concentrate (Beriplex® P/N 500 UI, CSL Behring, Marburg, Germany) administration (Time 3 hours; panels D-F). Unfortunately, no additional thromboelastometry analysis was performed between times 0 and 3 hours. Thus, table 1 was not modified as suggested by the reviewer.
INTENSIVE CARE UNIT - HOSPITAL ISRAELITA ALBERT EINSTEIN
SÃO PAULO - BRAZIL

INFORMED CONSENT:

Name of Article: THROMBOELASTOMETRY GUIDED BLOOD TRANSFUSION: AN ALTERNATIVE AND EFFICIENT APPROACH TO MANAGE THE ACUTE FATTY LIVER OF PREGNANCY. CASE REPORT.

Author: Tomaz Crochemore Date: March 20, 2015

I give my consent to this material to be published by Dr. Tomaz Crochemore - Hospital Israelita Albert Einstein - SP / Brazil in the journal and associated publications that is best suited for scientific research purposes in medicine.

I understand that my name will not be included in the published article, and that every effort will be made to keep my identity anonymous in the text and in any images. However, I understand that complete anonymity cannot be guaranteed, and it could be possible for someone who knows me to identify me from the published article.

I understand that the published article will be freely available via the internet, and that the article may be reproduced on other websites or in print. I have been offered the opportunity to read the article.

Informed consent was obtained from the patient for publication of this case report and accompanying images.

[Signature]

Name

[Signature]

Date

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