Author’s response to reviews

Title: Enhanced prehospital volume therapy does not lead to improved outcomes in severely injured patients with severe traumatic brain injury

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Dear Editors:

Our original paper (manuscript ID: EMMD-D-17-00113R1) titled: "Enhanced prehospital volume therapy does not lead to improved outcomes in severely injured patients with severe traumatic brain injury" has been completely revised according to the reviewers’ suggestions. All the changes in the text have been highlighted in yellow and were addressed as follows:

Reviewer #1:

George Shaw: "In this article entitled, "Enhanced prehospital volume therapy does not lead to improved outcomes in severely injured patient with severe traumatic brain injury (EMMD-D-17-00113_R1)," the authors present the results of a retrospective study on the relationship between pre-hospital volume and mortality with several secondary outcomes noted as well. Overall, they found no
relationship between prehospital volume administration and any change in outcome. In addition, higher volumes resulted in more significant coagulopathies.
Overall, the paper is clear, well-written and a significant study, I have a few comments as listed below.

Major Comments
1.: Page 7, Line 2: The investigators limit their study population to those patients who present primarily to the study hospitals. No transfer patients are included. This somewhat limits the generalizability of their conclusions as many trauma patients are transferred from non-trauma hospitals to trauma centers. Many of these patients therefore have received significant interventions elsewhere as a result. Some comment in the Discussion section regarding this limitation is warranted.

The reviewer’s comment is completely right. Certainly, many patients are transferred to trauma centers. As this study was particularly investigating the prehospital volume therapy in severely injured patients with traumatic brain injury, we deliberately included patients who had not received interventions in another hospital that potentially had impact on the outcome. Furthermore, the TraumaRegister DGU® does not provide information on prehospital therapies and/or the situation at the site of the accident in connection with transferred patients. Such information is only available for primarily admitted patients. A respective statement has been added to the discussion section (p. 14, lines 13-20).

2.: Table 2, Page 27, Line 25: The listed pre-hospital times are really long. This should be discussed, as should be the impact on patient outcomes. It is well-known in the trauma literature that the sooner these patients get to definitive care, the better they do.

I agree with the reviewer’s comment. Prehospital time can have a critical impact on outcome. Since a retrospective study cannot provide information why emergency treatment time was extended (and whether this had potential impact on volume administration), emergency treatment time was a matching criterion for establishing as much comparability within the population as possible. A respective statement has been added in the discussion (p. 13, lines 17-23).

Minor Comments
1.: p. 11, line 11: 'Show" should be "showed.'

The word has been corrected accordingly (p. 11, line: 11).

2.: Table 2, page 27, lines 41,42: Please observe conventions for significant digits and presumed precision of measurements. For example, claiming any precision after the decimal point for BP measurements is not plausible; a similar argument for heart rate values is also reasonable.

The reviewer’s demand in terms of better rounding is completely valid. This has been changed accordingly in the table (p. 27, lines 30-42).

3.: Finally, I think the authors understate their conclusions. This study, and others that are similar can lead a reasonable investigator to conclude that there is no role for pre-hospital volume other than blood in the resuscitation of trauma patients. In fact, the administration of colloids and crystalloids may be harmful.

It was our intention to phrase the study’s conclusion not too aggressively. It is difficult in a retrospective study to postulate definite causalities. The comments of Reviewer 3 regarding CPP must also be taken into account. This has been complemented in the discussion section (p. 12, line: 27; p. 13, lines: 1-5).
Thank you for the opportunity to review this interesting and significant paper.

Reviewer #2:

REVIEWER COMMENTS FROM REPORT: The study message is very useful. Study population is large. The authors demonstrated that the aggressive fluid administration to patients with TBI did not change the outcome

REQUESTED REVISIONS:

1.: The statistics authors used are very basic and need logistical regression analysis to interpret the results with more precision

The reviewer’s comment is correct. Higher statistical precision can possibly be achieved by means of logistical regression analysis. In a preceding study on this topic, we had already performed a logistical regression analysis that we published (Hussmann B, et al. Prehospital volume therapy as an independent risk factor after trauma. Biomed Res Int. 2015; 2015:354367). In that study, a negative effect has been shown with increasing prehospital volumes, also in patients with traumatic brain injury.

The objective of our current study was to confirm or disprove this potential negative effect of prehospital volumes (based on inclusion criteria) in a matched and restrictively defined patient population. That way, it was intended that factors influencing the administered volume (e.g. severity of head injury, initially measured blood pressure at the accident site, intubation [yes/no], age, emergency treatment time, etc.) should be identical as much as possible in order to allow the clinical outcome to be investigated with high precision, i.e. in a statistically and clinically relevant manner. We deliberately accepted a drastic reduction of the patient sample size. The significance-based statistical power is increased in small populations. Otherwise, even very small differences – that might be unimportant in clinical practice – would be significant in very large patient populations with 100000+ patients (such as the TraumaRegister DGU®). As prehospital volume administration in severe traumatic brain injury is very controversially discussed in current literature, it was important for our working group, to validate this retrospectively with another relevant statistical method. Nonetheless, a prospective randomised study for the clarification of this hypothesis would be extremely useful, but is very difficult to conduct, due the heterogeneity of patients and due to the diagnostic gap in terms of performing CT scans in patient with traumatic brain injuries in the prehospital phase. Such studies have been missing in the current literature. The Background and Methods chapters have been amended accordingly (p. 5, lines 8-12; p. 8, lines 19-24).

2.: ADDITIONAL REQUESTS/SUGGESTIONS:

The references authors used are very old (more than 10 years). They need to use current evidence Wherever possible, the literature has been checked for news, and respective amendments were implemented (p. 20-22, no. 2, 7, 11, 12, 13, 23).

Reviewer #3:

Endre Czeiter: In the present manuscript the authors investigate the potential effects of the "enhanced prehospital volume therapy" to the clinical course/outcome of the severe TBI patients. The main conclusion of the manuscript is that meanwhile the "enhanced prehospital volume therapy" not improves anyhow the outcome of the patients it has a significant negative effect to the coagulation parameters (like hemoglobin (Hb) levels and prothrombin ratio) probably due to a "dilutive effect" of excessive volume therapy.

Although the hypothesis and the aims of the manuscript are clear and well defined it has major...
limitations and raises some major and minor concerns, reviewed as follows:

1.: The authors chosen the matched-pair design for the statistical analysis. Among other parameters the 169 matched-pairs were selected according to the "Systolic blood pressure at the accident site". As the blood pressure at the accident site could be influenced by the extent of bleeding - which could determine the amount of applied volume - this method highly raise the possibility of "overmatching" which is described as the most common mistake with this statistical approach leading to potentially biased results.

The reviewer is completely right when indicating that systolic blood pressure and other factors could be influenced by active bleeding, which could have increased the amount of administered volume. Systolic blood pressure values are usually referring to the initially measured blood pressure at the accident site, generally prior to interventional measures such as volume administration. In order to minimize that potential bias, we defined very narrow matching criteria in our study design. For example, total injury severity – based on ISS and NISS – has been identical. Even associated injuries have been exactly identical from a statistical point of view (e.g. AIS abdomen, thorax). The same applies to accident causes and prehospital time. We deliberately accepted a drastic reduction of the patient sample size. Despite these strictly defined criteria, it cannot be ruled out that patients who suffered from increased bleeding were in one group or another. This cannot be conclusively clarified based on anonymised data in a retrospective study, but when considering the size of the population, a certain balance can be expected. A respective section has been added to the “Limitations” (p. 15, lines 8-18).

2.: In addition to the above the fact that beside those significant differences between group 1 and 2 described by the authors (Hb at admission to hospital; Prothrombin ratio (%) in hospital; INR; Units of fresh-frozen plasma in hospital) there were borderline significance/tendencies in such parameters as BP at accident site, Prehospital use of catecholamines, Prehospital chest tube indicating that probably those patients who received "high volume" at the prehospital stage were in worse state (probably due to the more blood loss) than those who received less volume.

In light of the above I would suggest to the authors to completely redo the analysis with a different approach (like correlation analysis between the applied prehospital volume and the in hospital coagulation parameters) especially because - as it is apparent in the "figure 1" (seemingly there were at least thousands of patients fulfilled the inclusion criteria) - the matched-pair method narrows down the number of cases in the analysis very rapidly.

As already mentioned in my response to the comment of Reviewer 2, we intentionally decided to use that statistic analysis (see Item 1 Reviewer 2). The correlation between coagulation and administered prehospital volumes is usually very strong, since both parameters are related with each other. The same would apply to the haemoglobin value and subsumed under “dilution”. This relation has been shown by Nishi et al. in their current study [Nishi K, et al. Hemodilution as a result of aggressive fluid resuscitation aggravates coagulopathy in a rat model of uncontrolled hemorrhagic shock. J Trauma Acute Care Surg. 2013;74(3):808-12]. This “diluting effect” is also considered in the European guideline [Rossaint R. et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Critical Care, 2016;20:100]. As indicated for Item 1 Reviewer 2, the script has been amended accordingly (p. 5, lines 8-12; p. 8, lines 19-24).

Beside these there are some minor comments to the manuscript:
1.: In the "background" section on the 4th page we could read the following "...no other prehospital therapeutic approaches that can improve the severity of this type of injury do exist." I would not like to utilize any kind of "therapeutic" approach which improves! the severity of the injury - probably this just should be a typo...
The respective phrase has been amended (p. 4, lines 12-14).

2.: As part of the "discussion" section in the 12th and 13th page of the manuscript the authors states the following: "Regarding a complete abandonment of volume administration, valid data is not available. Here, prospective studies are required." As the authors also admit due to the really hazardous nature to the CPP of the patients I cannot imagine an RCT for the testing of complete abandonment of prehospital volume therapy in case of severe TBI patients.

The reviewer addresses an extremely important aspect. Also in our opinion, it is difficult from an ethical perspective to conduct a prospective randomised prehospital study with patients, where one group will receive volume therapy for maintaining CPP and another group possibly does not receive volume therapy at all. Based on this fact, our study was aiming to contribute to the clarification of this question, while knowing that it was only a retrospective study, but with a strictly selected patient population. The "Discussion" section has been amended accordingly (p. 12, line: 27; p. 13, lines: 1-5).

3.: In case of "Figure 1" it would be worth to know the total amount of those patients (maybe as part of the figure legend) who fulfilled the inclusion criteria of the current study (see my major concern above about the amount of the "lost" cases for the analysis by the applied matched-pair method...)

The respective amount of patients has been specified (p. 25, line 3-5).

The reviewers’ very constructive and justified critiques were addressed accordingly in the manuscript.

Yours sincerely

Bjoern Hussmann