Author’s response to reviews

Title: Hypoxia and hypotension in patients intubated by physician staffed helicopter emergency medical services - a prospective observational multi-centre study

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EMMD-D-17-00009: Hypoxia and hypotension in patients intubated by physician staffed helicopter emergency medical services - a prospective observational multi-centre study

Dear Editor

Thank you for your response to our manuscript.
We wish to express our gratitude towards you and your expert reviewers for the valuable and constructive comments to the manuscript. We think these have improved the quality of the manuscript substantially.

We have revised the manuscript according to the comments, and the changes made according to the reviewers’ suggestions are written in bold in the manuscript. We have also highlighted other minor changes made within the text to increase readability.

We hope that you find the corrections acceptable.

Yours sincerely

The authors

Comments to Reviewer 1:

1. A suggestion to add "physician staffed HEMS" to the keywords.

Response: We agree with the reviewer, and have added the term "physician staffed HEMS" to the keywords.

2. Why the comparison between the heterogeneous patients groups trauma and non-trauma? Is it just to compare two groups? This needs more explanation in the introduction session.
Response: We acknowledge the reviewers point, and we see that the introduction lacked clarity regarding the reason to compare the two groups. We have rephrased the last two paragraphs in the Background section as follows (references only in manuscript):

“Pre-hospital hypoxia and hypotension are predictors of negative patient outcomes and increased in-hospital mortality in non-cardiac arrest patients, and avoidance or mitigation of hypoxia and hypotension may be considered important measures of quality of care provided by the emergency medical services (EMS). Sadly, core data on physiological responses and how they relate to pre-hospital TI are inconsistently reported. Standardised data from pre-hospital airway management could improve our knowledge about the challenges of hypoxia and hypotension in TI.

The target group of this multi-centre study were non-cardiac arrest patients requiring pre-hospital TI by physician-staffed HEMS. By excluding out-of-hospital cardiac arrests, critical trauma and non-trauma patients are the major groups to which HEMS are dispatched. Several studies describe the impact of pre-hospital hypoxia or hypotension on trauma patients but few studies compare this to the impact hypoxia and hypotension has on non-trauma patients needing pre-hospital TI. This knowledge could be important for how the two groups are handled in pre-hospital care. The primary aim of our study was to describe the incidence of pre-hospital hypoxia and hypotension in the two groups. Secondarily, we wanted to assess whether survival to hospital differed between trauma and non-trauma patients.”

3. An alternative option could be describing the whole group of pHEMS prehospital TI, with two (or more) subgroups.

Response: We thank the reviewer for this comment. We have attempted to describe the whole group better by rephrasing the Demographics section under Results. Also, we present data for “trauma, non-trauma and all patients” in the tables to better visualise this. The following sentence is included under Results:

„We included 1,265 patients requiring pre-hospital TI in the analysis. Of these, 843 were trauma patients and 422 non-trauma patients. Patients handled with bag-valve-mask ventilation (BVM), supraglottic airway devices (SAD) or continous positive airway pressure (CPAP) instead of TI
and patients with missing data relative to airway management, short-term survival status or trauma categories were excluded from the analysis (Figure 1). Patient characteristics, indication for TI and number of attempts are summarised in Table 1.”

The numbers relating to the excluded groups are presented in the flowchart. Cardiac arrests were excluded from a methodological point of view due to airway management in this group being different from trauma/non-trauma (e.g. TI during ongoing CPR) and due to the fact that the primary aim was to compare hypoxia and hypotension, which necessarily is different in this group, compared to trauma and non-trauma patients. Furthermore, we excluded patients missing key data on survival or category, and those handled with alternative airways. The number of missing data was 2%, and we believe this does not affect our results.

4. Trauma patients often have more difficult airway access. Possible C-spine injury, blood in oropharynx etc etc. This may influence the outcomes and needs explanation.

Response: We agree with the reviewer. But, in our study 92% of trauma patients were intubated on first attempt, versus 86% of the non-trauma group (Table 1). This might indicate that intubation difficulties were not predominant in the trauma group. We did not collect data on C-spine injury (or suspected injury, spinal precautions or MILS) or blood in oropharynx. Nonetheless, this is an important point, and as commented below (5) this may not be adequately monitored in the current template. We have rephrased the following sentence under Results:

„Patient characteristics, indication for TI and number of attempts are summarized in Table 1."

5. No data is presented regarding associated upper, lower airway and thoracic trauma in these (trauma) patient groups. This makes it difficult to interpret the outcomes and comparison between the groups.

Response: The reviewer is correct in pointing out that our data do not directly describe anatomical injuries to the airways or thorax. This is because the study design and data sampling
was done according to the previously published consensus template for uniform reporting of airway data (Ref: Sollid SJ, Lockey D, Lossius HM, Pre-hospital advanced airway management expert g: A consensus-based template for uniform reporting of data from pre-hospital advanced airway management. Scand J Trauma Resusc Emerg Med 2009, 17:58.). This template does include patient category (e.g. blunt trauma or penetrating trauma) and dominating indication for airway intervention (e.g. existing or impending airway obstruction). The expert group that published the original template argued that indications for airway management should include three groups: failure of airway maintenance or protection, failure of ventilation or oxygenation, and expected clinical course. We agree with the reviewer that trauma to the airways is important in the assessment of airway management (e.g. were the airways perceived as difficult, grade of visualisation, presence of blood or foreign body, etc). Although thoracic trauma (i.e: pulmonary contusions) may have no direct influence on airway management, it can result in oxygenation failure and be a cause of hypoxia in these patients. Unfortunately, data variables describing specific airway trauma were not available in the original template and therefore not collected in our study. The airway template is now under revision, and hopefully these points made by the reviewer may be included in the revised template, to improve study designs and data quality in future studies. Also, as commented above (4), a higher rate of trauma patients were intubated on first attempt, compared to the non-trauma group (Table 1), indicating that intubation difficulties were not predominant in the trauma group.

6. Hypoxemia and outcome is also associated with the time it takes to gain a secured airway. No data is presented regarding the number of attempts to secure the airway.

Response: We agree with the reviewer that the incidence of hypoxia and outcome is influenced by the time it takes to secure the patients airways, and that number of attempts may be an important variable to describe. The rate of adverse events may also increase following increasing number of intubation attempts. To clarify the number of intubation attempts in the present manuscript, we have included a distinction between one or multiple intubation attempts (two or more) for all patients and for the traume/non-trauma groups in Table-1. See also our comments above (4).

7. No emergency surgical airways are presented. According to the available literature approximately 9 ESA's could be expected in this group. This needs clarification.
Response: We thank the reviewer for this important comment. Emergency surgical airway is a potentially life-saving rescue technique. Fortunately, the high degree of advanced airway management training and skills in physician staffed HEMS today, limits the necessity of this procedure in the field. In the 1265 patients analysed in our study, an emergency surgical airway was done in only two trauma patients (and none non-trauma patients). We have included the following sentence under the results section:

“Emergency surgical airway was done in two trauma patients (0.2%), one after failed primary TI and one was a primary surgical airway."

8. In the figure the patients with a "failed airway" eg BVM and SAD are taken out of further analysis. I think this is not the correct way to treat this data. If all these patients (with probable higher incidence of hypoxemia) are for instance trauma patients this possibly influences the outcome.

Response: We acknowledge the reviewers point. Forty-eight patients (3%) who were handled by BVM (n=34, 2%) or SAD (n=14, 1%) instead of tracheal intubation were excluded from the analysis to keep the groups comparable in regards to type of airway intervention used. To check if this influenced the outcomes, we repeated the analysis. The rates of hypoxia before and after intubation for all patients were not affected by excluding these few patients. Also, all patients handled with BVM were non-trauma, creating a possible bias if we were to include these. Of fourteen patients handled with SAD, three were trauma and eleven non-trauma. We do not believe excluding these few patients have biased our results.

9. Data collection: the term survival is somewhat misleading as data is only available till hospital presentation. The term "short-term survival" would be more appropriate.

Response: We agree with the reviewer. We have rephrased the text according to the suggestion, and present now survival as “short-term survival” or “survival to hospital” in the text.
10. When survival is taken till hospital arrival, it is strange that in 15 patients the HEMS physicians did not know/noted if the patients were alive at presentation (figure). If the quality of data accusation can't make the difference between dead or alive on presentation one could question the reliably of all presented results.

Response: We agree with the reviewer that this is disappointing, but we believe that this is an expression of (expected) missing data in a clinical trial. The missing data entry rate is low for survival (1%), and as far as we can tell missing by random (MAR). This is probably due to the treating physician forgetting to fill in the item in the case reporting form. Consequently, these patients were excluded from the analysis.

11. Were the times to measure hypoxia and hypotension standardized? Or were the data collected randomly prior and after TI? This needs explanation.

Response: This comment from the reviewer is important. As commented above (5), the study design and data sampling was done according to the previously published consensus template for uniform reporting of airway data. This template includes the data variable names and definitions used. Data were not collected randomly, but according to the definitions. Regarding both hypoxia and hypotension, the definitions used were “first value recorded on scene…” and “first value recorded after finalised airway management” as time of measurement of oxygen saturation (SPO2) and systolic blood pressure (SBP). In most HEMS, monitoring equipment is set to measure vitals every few minutes. Nonetheless, acknowledging that in the prehospital setting it may not always be possible to collect data at precise time points due to challenging working conditions, we acknowledge that these definitions may be improved in the upcoming revision of the template. We have now clarified this in the Methods section (subheading Variables) and inserted the following sentence:

“SPO2 and SBP were measured as first value recorded on scene, and first value recorded after finalised airway management”.
12. Were these data collected objectively or remembered by the HEMS staff and noted afterwards, possibly adding a recollection bias?

Response: Unfortunately, automated data capture was not available in our study setting. All patients included in our study were critically ill or injured patients requiring TI in the field. All data sampling was done by the treating physician or HEMS team, with the risk of recollection bias as commented by the reviewer. We have reported this possible bias in the Limitations section.

13. The primary aim is to describe incidence of hypoxia and hypotension. Both groups receive possibly non-comparable treatment with different treatment regimes/medication. The medication and protocol in all 21 HEMS operations are not standardized. A possible variation in medication (with more hypotensive side-effect) could be a confounder. This needs attention in the discussion section.

Response: The reviewer is correct in that there are different medication regimes in different countries and different services. In our study, it was not possible to standardize the medication (or iv-fluid) protocols in the participating international centres. This is a challenge in doing international multicenter studies, when comparing other factors than medication protocols (e.g. not being able to correct for medication regimes). As commented above (5), the original template contains definitions, which were used in the data sampling based on a consensus among an international airway expert group. These include the following: 1 = Sedatives, 2 = NMBA, 3 = Analgesics/opioids, 4 = Local/topic anaesthetic or 5 = None. The template does not include generic names or doses of drugs, but we recognise that this may be improved in the future. Thus, including generic names is suggested in the upcoming revision of the template. Nonetheless, as described in the Methods section, airway management and RSI protocols were part of local standard operating procedures and we are confident the participating services all delivered high quality treatment to the included patients. As suggested by the reviewer, we have included the following sentence in the Discussion section (subheading Hypotension):

“Since it was not possible to standardise the medication or intravenous fluid protocols in the participating international centres, variation in use of these with hypotensive side effects can be possible confounders”.


14. The same could be the case for the amount of fluids that are administered prior or after intubation. Maybe local protocols limit the fluid administration in trauma because of "permissive hypotension". In non-trauma patients possibly the patients received an amount or crystalloids as "preloading" for the TI as part of local protocols.

Response: We agree with the reviewer that fluid-loading regimes may vary between patients. Unfortunately, our study with the current template was not designed to measure such differences in fluid treatments.

15. The difference in age in both groups could be an explanation for the difference found. This needs more attention in the discussion.

Response: As the reviewer commented, patient age is one of several important differences between the groups. In the current study, the non-trauma patients presented with lower mean GCS, higher mean age, and had a higher degree of comorbidity than trauma patients, and these results are to be expected from literature and clinical experience. But, as age also may be an important contributing factor we have expanded the Hypoxia subsection under Discussion with the following sentences:

“We have previously published data showing a non-linear association between the patient’s age and the TI failure risk, with the highest risk for middle-aged patients and significantly lower risk for both younger and older patients. Another study demonstrated significantly higher age among all patients experiencing desaturation during pre-hospital RSI, and also showed that the duration of hypoxia was significantly longer in non-trauma patients compared to trauma patients."

16. Survival: I think the conclusion that TI is safe and "handled adequately" cannot be drawn from this article. You can say that the majority of patients are presented at the hospital alive. Please adjust this in the conclusion or use short-term survival here.

Response: We have rephrased the section according to the reviewers comment as follows:
“We have previously shown that pre-hospital TI is safe, with few complications, in the hands of HEMS physicians. In the current study, short-term survival to hospital was not significantly different between trauma and non-trauma patients, and the majority of patients requiring pre-hospital emergency anaesthesia and TI by physician-staffed HEMS presented at the hospital alive.”

Comments to Reviewer 2:

17. As a reader, I struggled to determine the significance in the primary purpose - comparing trauma to non-trauma patients requiring airway management.

Response: We acknowledge that both the reviewers are aligned in this question. As commented above (2), we see that the introduction lacked clarity regarding the two groups. We have rephrased the two last paragraphs in the Background section as follows:

“The target group of this multi-centre study were non-cardiac arrest patients requiring pre-hospital TI by physician-staffed HEMS. By excluding out-of-hospital cardiac arrests, critical trauma and non-trauma patients are the major groups to which HEMS are dispatched. Several studies describe the impact of pre-hospital hypoxia or hypotension on trauma patients but few studies compare this to the impact hypoxia and hypotension has on non-trauma patients needing pre-hospital TI. This knowledge could be important for how the two groups are handled in pre-hospital care. The primary aim of our study was to describe the incidence of pre-hospital hypoxia and hypotension in the two groups. Secondly, we wanted to assess whether survival to hospital differed between trauma and non-trauma patients.”
18. From the purest sense, reading the outcomes for all comers in airway management was more relevant for me than the comparison, and the paper lacked an actual control group, to my eye.

Response: We agree with the reviewer that a randomised controlled trial, including a control group, would have been the preferable standard. Unfortunately, this was not feasable in our study setting. We find it difficult to design a randomized controlled trial randomising patients to prehospital intubation or not. We believe it would probably be impossible to recruit clinical centres to participate in such a study. If the treating physician on-scene believes the patient needs this intervention (TI), this would in most cases overrule a study protocol anyway. Therefore, the study is designed from a methodological and practical view as the second best thing, a prospective multicenter observational study.

19. I would also like to see a power calculation, if the theme of the paper is to remain the comparison between the two groups, so the reader is readily aware that the paper was appropriately powered to detect a difference between the groups in the areas showing no difference.

Response: We acknowledge the reviewers point. The rationale for doing a power calculation in an RCT that compares two treatments (e.g. intubation or no intubation), is that we need calculations of the study to achieve a specified level of statistical power for the primary hypothesis. When comparing treatments, this is the probability of finding a statistically significant difference between treatments. Our study was designed as an observational study, and compares the same intervention (here: pre-hospital intubation) in two groups of patients (here: trauma and non-trauma). We believe the importance of sample size calculation in observational studies depends on the context. Formal, a priori calculation of sample size may be useful when planning a new study. Such calculations may be associated with more uncertainty than implied by the single number that is generally produced. The precision obtained in the final analysis can often not be determined beforehand because it will be reduced by inclusion of confounding variables in multivariable analyses, the degree of precision with which key variables can be measured, and the exclusion of some individuals. According to the STROBE checklist for observational studies, we believe we have included these considerations in our study, and that the multicenter design and sample size may strengthen its external validity (e.g. the generalizability of the information).
20. Lines 109-111: I wasn't sure if the statement made here was regarding RSI specifically or "all airways" and whether the "in-hospital" comparison was environment specific in the referenced articles (ED, OR, etc). Please clarify in the text for better readability.

Response: We agree with the reviewer, and have rephrased the sentences as follows (references only in manuscript):

„However, TI in the pre-hospital setting may be challenging, with sub-optimal working conditions for critical care providers. Several studies report a high incidence of unanticipated difficult airways, first TI attempt failures and complications during pre-hospital advanced airway management, comparable to emergency airway management outside the operating room."

21. Lines 118-121: The end of line 118-119 requires a reference, or a combination with the following statement (which is what I recommend for better flow).

Response: We thank the reviewer for this comment, and have reprased the sentence as suggested (references only in manuscript):

„Pre-hospital hypoxia and hypotension are predictors of negative patient outcomes and increased in-hospital mortality in non-cardiac arrest patients, and avoidance or mitigation of hypoxia and hypotension may be considered important measures of quality of care provided by the emergency medical services (EMS)."

22. In the definition of hypotension, it would have been nice to also see relative hypotension included, but I understand this is more difficult to create standard data collection. I was wondering whether the data could be managed for comment on this, but understand that is likely outside the scope of this paper.
Response: This is a very interesting angle made by the reviewer, and an issue we would probably like to pursue in a later study. Unfortunately, this is beyond the scope of the current paper.