Author’s response to reviews

Title: Point-of-Care Versus Central Testing of Hemoglobin During Large Volume Blood Transfusion

Authors:

Justin Herman (justin.b.herman@gmail.com)
Brian Park (bpark05@gmail.com)
Bharat Awsare (bharat.awsare@jefferson.edu)
Frances West (frances.west@jefferson.edu)
Denine Crittendon (denine.crittendon@jefferson.edu)
Lilah Evans (lilah.evans@jefferson.edu)
Mary Harach (mary.harach@jefferson.edu)
Julie Karp (julie.karp@jefferson.edu)
Alexis Peedin (alexis.peedin@jefferson.edu)
Marianna LaNoue (marianna.lanoue@jefferson.edu)
Barbara Goldsmith (barbara.goldsmith@jefferson.edu)
Eugene Warnick (eugene.warnick@jefferson.edu)
Michael Baram (michael.baram@jefferson.edu)

Version: 1 Date: 17 Aug 2019

Author’s response to reviews:

7/10/2019

Dear Editors,

Please review our revised manuscript for publication in your journal. Our responses to the reviewers’ questions are below. The manuscript has been resubmitted with edits marked in track changes. Additionally, the author change form has been added with e-signatures from each of our authors.
Sincerely,

Brian Park, MD

Reviewer 1:

Dear Authors,

Thank you very much for a hard work and nicely written paper. I would like you to address some concerns, which are critical from my point of view.

a) It is possible to compare two different methods for hemoglobin measurement with samples that have not been taken on the same time point. Yet, for performing this comparison, patients must be in a stable condition regarding hemoglobin values. In the case of massive transfusion, the patient's hemoglobin value may vary even within a minute due to transfusion and massive blood loss. Delta-hemoglobin levels in figure-1 demonstrates that the difference between hemoglobin values measured by two methods can reach up to 5 gr/dl in two ways. It is difficult to say that these results are not affected by the comparison of samples from different time points. It is highly controversial to use such a method in patients with unstable hemoglobin values.

This was a pragmatic paper with retrospective assessment of how well we use a tool as part of our armamentarium. It is very common to have these tests drawn not exactly at the same time, and then to compare the values. To do a prospective study would require consent from patients, which would be difficult to get during a patient’s acute resuscitation. Based on our statistician’s analysis, there appeared to be no significant difference between values that were drawn within 30 minutes of each other. Outside that window there was a statistically significant difference that could be attributed to the time differential.

b) The definition of massive transfusion protocol is stated as "the administration of at least one blood volume worth of blood, or approximately 10 units of homologous red cells for acute blood loss within a 24 hour period". How did you calculate the blood volume of a patient? What is upper and lower limits of "approximately 10 units"? This definition must be more certain since this is the main inclusion criteria.

This came from our hospital’s published policy. Blood volume is based on assumption of average size of patient. After 10 units of blood are released from the blood bank at our hospital, the massive transfusion protocol ordered is automatically placed or a physician can order it if they anticipate needing &gt;10 units of blood. This MTP order triggers the patient’s case to be included in our data set.

c) You have very well explained how conductometric measurements can be affected by different situations. In line with this, reading the reasons that disrupt your results in your study group would be enlightening, which were observed more frequently; temperature disorders, electrolyte disturbances, impaired mcv values etc?
This data was unfortunately not collected, but we know that our patient’s certainly had all of the above abnormalities given the patient population we were looking at. This would be a good idea for an additional study in the future to look at these variables.

d) how do you explain the different results in different patient groups underwent massive transfusion protocol? in your opinion, what are the reasons for the low performance of epoc in general surgery patients?

I do not have a good explanation for these differences. Many of the general surgery patients were severe trauma patients, so perhaps this difference could have been seen from differences in the rate of blood loss they were experiencing, but again this just my opinion and not based off of any data.

e) almost all reasons that affect conductometric measurements can be seen in a cardiac surgery. yet, it seems like epoc works better in cardiac surgery patients than it works in general surgery patients. i believe these results should also be discussed in discussion section.

Could be that there were more cardiac surgery patients in our population than general surgery, a coincidence, or perhaps due to the reasons discussed in (d).

Reviewer 2:
The manuscript "Point-of-Care Versus Central Testing of Hemoglobin During Large Volume Blood Transfusion" presents an interesting analysis comparing POC Hb vs. standard labs in a unique population. The study design is somehow complex and the timing for the comparison between techniques difficult to understand.

This was a pragmatic paper with retrospective assessment of how well we use a tool as part of our armamentarium. It is very common to have these tests drawn not exactly at the same time, and then to compare the values. To do a prospective study would require consent from patients, which would be difficult to get during a patient’s acute resuscitation. In order to account for the lack of standardization of time between studies we had our statistician try to find the time point at which there were statistically significant differences in hemoglobin values due to time between the blood draws. This was our way of accounting for the pragmatic nature of the study. There are also another number of issues that require the Authors' attention:

1) Was any power analysis performed?

Our statistician did not feel this was necessary for this type of study so it was not performed.

2) Was the EPOC system used for arterial gas analysis? If so please explain and specify.

The blood samples that were drawn were used for arterial gas analysis as that is part of the tests that the EPOC provides. This data was not collected as it was not felt to be relevant to our question. The hemoglobin values are all that we were looking at in this study.
3) The Authors stated that there was a time interval between standard and POC tests. In this rapidly changing clinical scenario of ongoing bleeding more than a few minutes between samples seem to make any comparison meaningless.

This was a pragmatic paper with retrospective assessment of how well we use a tool as part of our armamentarium. It is very common to have these tests drawn not exactly at the same time, and then to compare the values. To do a prospective study would require consent from patients, which would be difficult to get during a patient’s acute resuscitation. In order to account for the lack of standardization of time between studies we had our statistician try to find the time point at which there were statistically significant differences in hemoglobin values due to time between the blood draws. This was our way of accounting for the pragmatic nature of the study. We excluded time points that were >30 minutes as this was the point at which there was a statistically significant difference based on time difference.

4) I would suggest the Authors present a graphic representation of the impact of time between samples and value differences.

Figure of Hemoglobin Difference vs. Time Between Samples is included.

5) The authors should clearly separate through the paper the two concepts of "massive transfusion protocol" and "massive blood loss".

The massive transfusion protocol activation at our hospital was what was used for inclusion criteria. All of these patient’s had massive blood loss, which is what prompted MTP activation.

6) The authors should explain the transfusion protocol, if any, that was in place at their Institution in the study. Would be important to know when Hb level were measured. Was it at the discretion of the treating physician or was it part of the protocol.

Great point, added to paper. We use a 4PRBC : 4FFP : 1Plt ratio of blood products in our MTP. Blood products are released in this ratio from blood bank; however, it is up to the provider which products are actually given and when. There is no standardized timing of hemoglobin checks, and this was purely at the discretion of the provider, hence the lack of standardization and pragmatic nature of the study design.

7) Inter and intra rater variability for the EPOC system might have been relevant.

All nurses in ER, OR, and ICU received training on EPOC device utilization prior to implementation of the devices. The devices are rigorously checked, tested, and maintained by our point of care lab department.

8) A table summarizing results from previous studies and differences in techniques would be helpful to the readers.

Studies have not looked specifically at hemoglobin differences in this patient population.
9) It is not sure why the study setting would be better than the ICU as for others. How would ongoing fluid resuscitation affect the Hb measurements?

We utilize the POC lab testing in the ICU as a routine part of care. Massive transfusion replaced crystalloid fluid expansion. Crystalloid fluids would cause dilution of hemoglobin values. Potential effects of crystalloid transfusion were explained in discussion section when we discussed differences in measurement techniques between the tests.