Author’s response to reviews

Title: Endothelial glycocalyx in acute care surgery – what anesthesiologists need to know for clinical practice

Authors:

David Astapenko (astapenko.d@seznam.cz)
Jan Benes (benesj@fnplzen.cz)
Jiri Pouska (pouskaj@fnplzen.cz)
Christian Lehmann (chlehmann@dal.ca)
Sufia Islam (sufiaislam@gmail.com)
Vladimir Cerny (cernyvla1960@gmail.com)

Version: 1 Date: 04 Aug 2019

Author’s response to reviews:

Replies to Reviewer Comments for Manuscript BANE-D-19-00094 "Endothelial glycocalyx in acute care surgery – what anesthesiologists need to know for clinical practice"

Reviewer I:

Major points:

1. "Understanding the role of EG in these conditions is of paramount importance as further damage to the EG can contribute to clinical deterioration of the patient" does not really match up with the statement later in the same paragraph: "Currently, there is no specific intervention that could be considered as an effective directly EG protecting strategy". If there is no effective strategy to be implemented, why is such an understanding of critical importance? This is more than a pedantic academic question; I think it speaks to the need to reframe the fundamental emphasis of the paper. That is, the authors argue that targeting the EG is currently an important consideration - but offer no way of doing so. I think it would be better to argue that, first, EG degradation is ASSOCIATED with worse outcomes in various conditions; second, that this association is likely to be CAUSATIVE but that this has not been demonstrated to be true; third, that if this IS true, protecting or repairing the EG is likely to be helpful (although it would be useful to note what is known about the time course of spontaneous EG repair in this section); fourth, what interventions show promise in doing this; and fifth, what further evidence is required
before such interventions could be recommended to clinicians, and what are the barriers to gaining this evidence?

Thank you for instructive questions. We would like to keep the structure of the review as it is.

The answers to your questions are right in the text. EG is a central structure in the proper physiology of the microcirculation. It has been shown experimentally that when damaged the microcirculation becomes malfunctional. When this happens in the patient he or she deteriorates clinically. Damage to the EG has been demonstrated in commonly applied practices in critically ill patient (e.g. inadequate fluid therapy). The purpose of our review is to address these practices and to make a doctor to count with the structure of EG.

Worse outcome with degradation of EG has been shown and we cited many studies. This association is not causative as it has been demonstrated experimentally that isolated damage to the EG does not significantly impair the endothelial barrier. Damage to the EG must be understood to be in contributive to the final clinical picture and that inadequate therapy can lead to further damage. Our purpose is to show to the reader to acknowledge the EG. As there is no official (FDA approved) specific EG treatment it is more important not to further damage the EG. The key is to treat underlying cause of the critical condition with respect to the EG. As the critical condition subsides the EG recovers in a few days up to the full thickness. On the other hand, a functional layer of EG is present in a few hours so there is no need to worry about that. We have discussed all commonly used interventions and drugs in acute care surgery and lighted up those as potentially beneficial for the EG. This review did not focus on potential new EG targeted therapy but rather addressed already used practices and interventions

2. The PubMed search described on Page 7-8 must have identified many more papers than the 1089 quoted if these terms were linked by an 'OR' operator. It would be better to be specific. This description reads like a quasi-systematic review. Is it possible to be more specific about how the 125 papers were chosen for their 'relevance'? If so, it would be good to present these criteria, along with a PRISMA flow diagram.

We definitely agree that PRISMA flow diagram would be better descriptive. The reason why we did not implement this is that the review was done by specialists on microcirculation around the globe and by the time of their search no one has indicated the first number of searched items. In addition, we can presume that search of each of the authors showed a significant number of the same items so the number would be redundant. It would be now very complicated to be more specific about the PubMed search we did almost half a year ago.

3. "This approach is crucial, since we do not have specific EG regeneration therapies yet. The only exception is tranexamic acid, which showed promising results in this field and has already an established place in severe injury care.61. Reference 61 is to a study in HUVEC cells, which does indeed suggest that TxA might preserve an endothelial glycocalyx exposed to oxidative stress. However, as written, this sentence might lead an uninformed reader to think the reference states there is CLINICAL evidence showing TxA preserves the glycocalyx in severe injury, which is absolutely not the case. The "Key clinical target" recommendation of "early administration of tranexamic acid" to
preserve the glycocalyx in patients is only very thinly supported by this reference. This section should be rewritten to reflect the standard of evidence that exists.

Thank you for this note, you are right about paucity of clinical data regarding TXA protective effect. We have rewritten this section to be clear even for non-informed readers.

4. It is not clear what is meant by "Effective support of blood coagulation in order to reverse ongoing coagulopathy" in this "key clinical targets" section. The preceding section does not indicate how this should be done, other than by avoiding dilution, acidosis, hypothermia, etc. - which would be a better recommendation here. Is there evidence that these factors specifically damage the EG? If so, it would be very useful to quote relevant references. Resuscitation using different alternatives is discussed later; it would be better to defer this recommendation until this point.

Last recommendation in this section was ambiguous and more general than necessary, thank you for your remark. We have changed recommendation in more straight manner and add some additional references, as was advised.

5. Page 16, line 10: "avoiding severe hypernatremia" - this is the first mention of hypernatremia. No rationale is given for doing so.

Thank you for this point – relevant comments were added into the text.

6. Especially in the light of the willingness to employ in vitro evidence described above for TxA, the comparison between the EG effects of FFP vs. factor concentrate resuscitation is notable. The authors correctly note there is extensive preclinical evidence supporting the effectiveness of FFP in preserving the EG, which "go beyond its current indication as a source for coagulation factors", while what little evidence there is suggests this is NOT the case for factor concentrates. This is a highly topical subject given the current commercial interests advocating that clinicians replace plasma with factor concentrates in their practice. Are the implications for clinical practice of the existing evidence really "none"? If the evidence is insufficient to actually provide treatment recommendations, might it not be at least possible to note this current controversy and that the preclinical evidence supports equipoise for a randomised controlled trial?

Thanks for the comment. We have modified respective paragraph in term of adding possible role of fibrinogen in EG stabilization and added one new reference supporting the concept of the role of protective effect of fibrinogen on endotheliopathy. However, we feel we do not have enough data to change recommendation "none" for practising clinicians, despite very impressive preclinical evidence.

7. The sections that deal with the possible EG effects of choices of anaesthetic and catecholamine are very interesting and will be novel to many readers. Rather than conclude that there are simply no implications for clinical practice at present, could the authors speculate on what they consider would be the most appropriate design of a clinical trial?
We thank the reviewer for the enthusiasm and think, that clinical trials are certainly possible, at least for the choice of anesthetics. We mentioned already in the text our own study, suggesting that regional anesthesia seems to have less impact on EG compared to general anesthesia. Therefore, we changed the implication from “none” to “Consider regional anesthesia if possible”. For catecholamines the interchangeability is more limited which results in less options for clinical studies.

8. "Main indications for the administration of steroids in the acute care surgery setting include anti-edematous (traumatic brain injury, ..)" Steroids are unequivocally NOT indicated for the treatment of TBI, following the results of the CRASH study. Can the authors speculate on why this might be the case, given their mechanistic understanding of steroid effect on the EG?

We fully agree with the reviewer regarding the recommendations against steroids for the treatment of traumatic brain injury according to the findings of the CRASH trial and appreciate the comment. However, this chapter (and the whole paper) focusses on acute care surgery, which in the case of TBI sometimes represent desperate situations where one might still consider a single (high) dose of steroids. To make the acute situation clearer, we replaced the example of "traumatic brain injury" by the more general term "brain surgery", as it also applies for other neurosurgical procedures such as tumor surgery.

Minor points:

1. Of trauma: "Within the first hours, massive hemorrhage and exsanguination are the major causes of death.". Most case series find that traumatic brain injury and unsurvivable body disruption are the most common causes of death. Haemorrhage is the most common potentially preventable cause of death. The reference quoted is to the PROPPR trial; it would be better to quote an epidemiological analysis in support of this statement.

Thank you for this note. We have added one more citation oriented on epidemiology supporting our statement: ref. no 21: Sobrino J, Shafi S. Timing and causes of death after injuries. Proc (Bayl Univ Med Cent). 2013;26(2):120-123. doi:10.1080/08998280.2013.11928934

2. There are several instances of poor English expression. E.g. "Despite of extended research in this field...". "On the contrary, this microvascular reaction to trauma has its physiological meaning.". "Two potential mechanism of ATC induced by EG destruction has been identified recently". "The divergent volume effectivity of hydroxyethyl starch..".

Thank you very much for your suggestions. We revised the sentences accordingly.

Reviewer II:

Page 9 line 1-5; The concept that EG functions as a fluid reservoir is interesting. However, I'm afraid that the authors mention it too decisively. If EG degradation provide more circulating
volume, why does hypervolemia also induce EG degradation? In addition, EG degradation will facilitate fluid leakage from intravascular to interstitial space.

Thank you for a very good question. It is important to accurately understand the physiology of EG in this context which goes beyond the scope of our review. Everything is explained in cited publications for further reading. Briefly, the degradation occurs in states with dangerous impact to the human body which is already connected to fluid loss (hemorrhage or fluid redistribution). The reservoir is in this context already exhausted. In addition, if the impact it capable of degradation of EG it worsens the intravascular volume depletion. On the other hand, if iatrogenic fluid overload occurs it provokes release of the atrial natriuretic peptide which activated metalloproteinases which degrade the EG. This phenomenon is well described and cited in our review.

Page 13, line 3: Is there enough clinical/experimental evidence that early administration of TXA preserve EG?

We reflected this issue in previous response to reviewer I.

Could the authors describe more about albumin as a potential therapeutic agent for EG protection?

Thank you for this comment. Actually we have pinpointed most of the relevant features regarding positive effect of albumin on EG in the text regarding “fluid therapy” and expanded this part respectively.

On behalf of authors

Vladimir Cerny, August 3, 2019.