Author’s response to reviews

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

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To whom it may concern

Dear editor

thanks for the chance to revise our manuscript. We would like to thanks all reviewers for their comments, they definitely improved our manuscript. Please, find below your comments or queries and our respective answers.

P.S. Figure 1 remains the same from previous version of manuscript, other figures are attached/uploaded again due to their new order and numbering as well.

On behalf of all authors

prof. Vladimir Cerny, MD, PhD, FCCM

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

2nd query:

The authors have not addressed this point satisfactorily. In their reply, they state their opinion that the association between endothelial glycocalyx degradation and worse outcome is "not
causative”. If this is so, there can be no rationale for targeting any intervention at preserving or restoring the glycocalyx.

Dear reviewer, thank you for your comments. We have deleted the sentence “Currently, there is no specific intervention that could be considered as an effective directly EG protecting strategy” from that paragraph as it is supposed only to briefly introduce the role of EG in the complex pathophysiology of the microcirculation.

The association between EG degradation and worse outcome has been demonstrated and cited in many studies in our manuscript. The cause of the critical condition (e.g. bacterial sepsis) leads to both the outcomes. Damage to the EG has so far not been described to be the isolated cause of critical condition. There is no animal model of EG damage although might be feasible by injecting specific EG degradation enzymes directly into the blood stream. This experimental strategy would on the other hand never happen in real life.

In our review we defend the idea that by clinical appreciation of EG and avoidance of already described damaging conditions (e.g. hypernatremia, hypervolemia, oxidative stress) we can speed up the EG recovery which goes in hand with positive clinical outcome and in all the areas in our review we try to give the best advice to do so. The association between these conditions (e.g. hypernatremia, hypervolemia, oxidative stress) has been demonstrated to be CAUSATIVE.

As for the specific treatment of EG recovery, there are some candidates in experimental research and clinical research (e.g. sulodexide, hyaluronan). With these substances there are only limited experiences and these specific studies has been cited and summarized in table 1 at the end of our manuscript.

We believe we have sufficiently explained and uncovered the message in our manuscript. We decided to write it in its manner because we hear many questions from our colleges, and we wanted to give them answers.

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.

2nd query:
This is a reasonable explanation of how the papers came to be selected. However, the methodology described in the paper for the literature review will not match the results obtained by a reader if they attempt to replicate this search. The question of how papers were selected for 'relevance' has not been addressed.

Thank you kindly for your comment. We have rewritten the methods section and inserted modified PRISMA flow diagram. We hope now it will be described sufficiently.

Revised paragraphs:

The PubMed was searched for words: glycocalyx, acute care, trauma, surgery, damage control, anaesthetics, sevoflurane, desflurane, isoflurane, propofol, opioids, fentanyl, morphine, rocuronium, vecuronium, atracurium, pancuronium, catecholamines, phenylephrine, ephedrine, noradrenaline, norepinephrine, adrenaline, epinephrine, insulin, hydrocortisone, antibiotics, cephalosporin, penicillin, quinolones, doxycycline, blood transfusion, transfusion, fresh frozen plasma, plasma transfusion, erythrocytes, blood products, platelets, thrombocytopenia, cryoprecipitate, albumin, coagulation factors, immunoglobulin, sepsis, septic shock. We identified 2715 records. After duplicates removal 1089 papers were screened for relevance and 130 papers were included into the review (figure 2). Inclusion criteria were original papers and reviews, English language, topic concerning glycocalyx in clinical and experimental research, publication from 1966 till January 2019.

3. This point has been satisfactorily addressed.

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.

It is difficult to tell what has been changed without marked-up version of the manuscript or specific notation in the text. However, the only additional text I can find that has been added that seems to relate to this comment is "A possible protective effect of iso-oncotic albumin solution has been reported by Jacob et al. in two laboratory studies with isolated heart but didn’t seem to be clinically reproducible 83,84.". This is not an adequate response to the query.

After reconsideration of this part, we do agree with your point and omit this target from the text. In fact, the effect of reversing coagulopathy on EG are indirect and has never been proven in literature.
5. This point has been satisfactorily addressed on page 15. It would have made the re-review of this paper considerably easier if the authors could have noted specifically in their reply, or in a marked-up version of the manuscript, how it had been altered in the revised version.

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.

2nd query:
This response misses the point. While I agree that the preclinical and very limited clinical evidence is insufficient to justify practice recommendations, simply making this point would be a valuable summary of the current state of knowledge. Many believe there is sufficient evidence to support the use of fibrinogen concentrate over alternatives, and have modified their practice accordingly whereas, as the authors not, this really is not the case.

Thank you kindly for your comment. Honestly (and we do apologize for that), we are little bit confused now how to change this paragraph to make you satisfied. Our previous modification reflected insufficient evidence to state any general recommendation for using fibrinogen as an EG protecting agent.

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.

2nd query:

'Consider regional anesthesia if possible'. That isn't really what I was intending as the modification. If there is insufficient evidence to support this, this should not be the recommendation. Rather, if there is equipoise for a trial, this should be the recommendation. Clinical trials don't just happen - a rationale must be built, typically by papers such as this making a case that investigators use in support of their applications for funding etc. This would be a very useful recommendation.

We apologize for the misunderstanding – our enthusiasm might be a bias here and we do agree, that more studies are needed before regional anesthesia can be recommended as preferred method rather than general anesthetics. Our wording: “Consider regional anesthesia if possible” was not supposed to give the impression that this is already the preferred method of anesthesia to protect the EG. It was more meant to give a recommendation based on our and some other clinical studies but should not exclude more clinical studies. We are happy to change the recommendation to: “Clinical trials needed to confirm potential benefits of regional versus general anesthesia”.

Revised paragraphs:

According to the results of our own studies, regional anesthesia seems to have less impact on EG compared to general anesthesia, however, such preliminary results must be robustly confirmed by adequately powered clinical trials before any recommendation for particular anesthesia technique to modulate EG can be made 108.

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) focuses 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 to 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.

No additional comments from the reviewer.
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

2nd query:

The manuscript still does not state that these are the major causes of preventable death. The reference that has been added is a review that quotes several primary evidence papers which found that the most common cause of immediate death was brain injury, not haemorrhage.

Dear reviewer, we have modified the statement according to your original suggestion. Thank you very much for your comment.

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.

This point has been satisfactorily addressed.

Reviewer II: The authors answered all the questions and revised the manuscript accordingly.

Thank you.