Reviewer’s report

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

Version: 0 Date: 30 May 2019

Reviewer: Michael C Reade

Reviewer's report:

The manuscript is a narrative review of what is known of the structure, function, and pathophysiology of the endothelial glycocalyx, and the implications this has for treatment, particularly elements of therapy relevant to anaesthetic practice such as choice of intravenous fluid and medications.

I have several suggestions that I think, if addressed, might improve the utility of the paper:

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?

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.

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. 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.

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.

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

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?

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?

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?

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.

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..".

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons
CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal