Reviewer's report

Title: Metabolic networks in a porcine model of trauma and hemorrhagic shock demonstrate different control mechanism with carbohydrate pre-feed

Version: 3
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Reviewer: Asger Granfeldt

Reviewer's report:

The study by Lusczek al investigates the effect of pre-feeding on survival following traumatic hemorrhagic shock and the effect on metabolic networks.

First of all the reviewer would like to acknowledge the work by the authors in completing a complicated experimental animal model and trying to answer an important question, how do we improve survival following trauma; however major concerns exist.

The model used is severe and highly clinical relevant.

Major Concerns:

In the study 64 animals were used. This is a very high number for a large experimental animal study. How was decided to use 32 animals in each group. Did the authors perform power calculation? It’s a large number of animals to include without any consideration of why that many pigs were included.

Since there was no effect of pre-feeding this may be related to the choice 140 mL of Karo® Syrup. How was this dose chosen? Did the authors perform any pilot studies trying to titrate to the correct dose?

The authors have recently published another study with 64 pigs using the same pre-feeding regime and traumatic animal. The pigs included in this study, are they the same pigs as in the published study? If so this should be clearly stated PLoS One. 2014 Jun 17;9(6):e100088. doi: 10.1371/journal.pone.0100088. eCollection 2014. Fed state prior to hemorrhagic shock and polytrauma in a porcine model results in altered liver transcriptomic response. Determan C Jr, Anderson R, Becker A, Witowski N, Lusczek E, Mulier K, Beilman GJ.

The reviewer is surprised by the fact that not a single hemodynamic parameter is included in the study. The first sentence in the results section implies that this is a comparative study with regards to pre-feed vs. fasting. Did feeding status have any effect on hemodynamic variables? Where the groups comparable with regards to lactate, MAP, heart rate, blood volume withdrawn, resuscitation volume, amount of blood re-transfused ect.

In the discussion the authors suddenly include venous oxygen saturation and oxygen extraction ratio however these are highly depend on cardiac output, which is not included!!

How can we compare two treatments with regards to survival when none of these
parameters are included in the study.

Since there was no effect of feeding on survival, why is it then of any importance that controlling nodes and metabolic regulatory networks differed between groups with regards to feeding group?

In sepsis cytokines and numerous of markers are elevated however therapies targeting these molecules have no effect on survival. Do the authors really believe there is a cause and effect with the markers measured which they suggest could be manipulated for therapeutic effect?

Did adenosine levels differ between groups?

Minor concerns

At what time points did animals die? A Kaplan Meier curve would be relevant. Could the size of pigs have be of any importance. Pigs at 15-20 kg are regarded as kids who may have a different metabolic profile than an adult soldier? Why did animals survive for 48 hours when the last blood sample was taken at 21 hours!

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'