Title: "Development of an invasively monitored porcine model of acetaminophen-induced acute liver failure"

Dr. Newsome and Colleagues present an experimental study to develop an invasively monitored porcine model of acetaminophen-induced acute liver failure. They show to have established a reproducible large animal model for experimental monitoring of acetaminophen-induced liver failure.

Comments: The staff is composed by expertises in the main field of clinical and biological settings. The title is suitable and the description reports an interesting and original idea; the experimental design does not contain substantial errors of fact or logic as such. The summary brings out the main points of the study design with satisfactory strengths and weakness.

Major Compulsory Revisions

1) Major criticism is related to the debate of the acetaminophen-induced ALF. The study seems to be mostly focused on the setting of an experimental monitor-model (as rightly stated in the title) for acetaminophen-induced ALF; however the ALF model as such – which is the goal of the study - needs to be supported with more exhaustive arguments in the Discussion section:

- As known, murine models have been widely adopted for the investigation of the pathophysiological characteristics of FHF since consistent hepatotoxicity has been shown in these models. However the small size of such models can cause difficulties with several aspects of experimental monitoring; then the need of large animal model. The Authors present a very interesting approach of experimental monitoring and declare that they “…produced a large animal model which reliably reproduces the syndrome of ALF observed in clinical practice”. However the model designed of acetaminophen injury should be argued in more detail in terms of 1) plasma acetaminophen levels’ correlation with the severity of changes in liver function, 2) association between acetaminophen levels and death from non-hepatic causes to sustain the effective reproducibility and dose-related injury. 3) encephalopathy and brain oedema still represents important aspects of ALF; why did the Author not perform other tests or extend the period time of monitoring to sustain their hypothesis?
2) “Animal survival” paragraph: “…two of the animals which received acetaminophen were critically unwell and were euthanased at 25 hours”; this paragraph needs to be described in more detail (what does “critically unwell” mean?)

Minor Essential Revisions.

1) Results:
   a) Authors stated that they measured Cytochrome P450 levels in homogenised liver tissue from pre-treated animal, which was significantly higher than non pre-treated animals; but it was previously (methods section) declared that all animals were pre-treated with Phenobarbital 20mL orally per day. This is confusing and needs to be rewritten to make it clearer.
   b) “Animal survival” paragraph: have microbiological tests been performed for all animals? This should be mentioned here
   c) “Cardio respiratory evaluation”: Authors stated that injured pigs developed arterial hypotension; how do they explain the p value (p=0.16) between the two groups?

3) Figures:
   a) Fig 1 is unclear
   b) Fig 2: the scores for the severity of liver and renal injury should be described in more detail (i.e. range score, percentage?); the current signs are poor informative.
   c) Fig 4: how do you explain the difference in PAOP between the two groups at time 0? This should be mentioned here
   d) Fig. 5: the legend should be corrected “….concomintant reduction in serum ALBUMIN in acetaminophen injured pigs…”

Discretionary revisions:

1) Methods: Anesthesia should be described in more detail

In conclusion, the proposed work represents a interesting and possible means in advancing and understanding within the field of acetaminophen-induced acute liver failure. The work should be re-considered for publication after revision.

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