Author’s response to reviews

Title: Intraoperative Glycemic Control in Patients Undergoing Orthotopic Liver Transplant: A Single Center Prospective Randomized Study

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Author’s response to reviews:

Anthony Bonavia (Reviewer 1): This review examines the difference in outcomes between patients undergoing conventional versus strict intraoperative glycemic control during orthotopic liver transplantation. The authors are to be commended on a well-executed randomized clinical trial in a challenging patient population.

Authors response:

We appreciate your time and efforts to review and constructive feedback in improving our manuscript. We have addressed your following comments.
- please define criteria for "graft survival" in the methods section (preferably with reference)

Graft survival is defined as death or needing re-transplant. This is the standard definition used across all transplant centers as guided by UNOS (www.unos.org). This definition has been included in the method section. (page 9, line 8-9)

- I am curious as to why patients having malignancy were excluded? I do not see the connection with glycemic control.

We agree with reviewer’s comments that there is no evidence of any association between malignancy and glycemic control. This was the protocol we agreed when the study was designed and could be considered in any additional study.
- please include the length of ICU stay following surgery in each of the comparison groups, since presumably glucose is more closely monitored (and treated) in the intensive care setting compared to the regular nursing floor.

Authors response:
We agree. Thank you. We evaluated ICU length of stay and found no difference between groups. We presented it as median with 25th and 75th percentiles, with the Wilcoxon p-value comparison between the groups within the text.
Strict group: median 3.0 (2.0 to 5.0)
Control group: median 3.0 (2.0 to 5.0)
P = 0.934
This has been added to the results section of the manuscript. (page 12, line 11-15)

-minor comments
-page 6, line 35: "hepatgenous" should be presumably changed to "hepatogenous"

Authors response: Thank you for your comments and we have corrected them. (page 6, line 13)

-page 7, line 58: there is a typo in the units of propofol that are used

Thank you for your comments and we have corrected them. (page 7, line 22)

A De Gasperi (Reviewer 2) The study tests the hypothesis that a tight control of glycemia in the perioperative period of liver transplant (LTx) could favourably impact on outcome (1y patient and graft survival rate), on postoperative complications (infections, renal, cardiac, surgical complications, etc) and late survival rate (5 y survival rate)
Too tight glycemic control was unable in Cardiac surgery to improve outcome, while broad control (<200) impacted favourably both morbidity and mortality: limits however are not well defined and still controversial. The LTx population is well known to be at risk for perioperative hyperglycemia: a retrospective study was able to demonstrate better outcomes in LTx pts with BG below 150 (not too strict, not too liberal): due to the lack of a prospective studies, the AAS are proposing a prospective randomized study comparing a conventional treatment Group (CG) with a intraop BG target of 180 - 200 (broad, with backup intervention for the control), with a study group (SG) with a specific strict BG target (80 - 120). The number of patients enrolled in the study is perhaps small (100). The study period is not reported
Main results of the study are

a. The inability of the strict BG control protocol to reach the BG targets in SG group, in spite of the strict algorithm and more episodes of hypoglycemia
   I. In general, both groups had mean intraoperative BG below 150 but above 120. "Within the conventional group the mean intraoperative BG was 143.3 mg/dL [interquartile (IQR) 123.8 mg/dL to 167.1 mg/dL] and for the strict group 130.7 mg/dL [IQR 112.2 mg/dL to 154.8 mg/dL] (p = 0.020, Table 4 and figure)"
b. The absence of difference in mortality and morbidity in the two groups (strict vs conventional intraoperative BG).

Due to points a. and b., the spontaneous questions are “worth such an effort to be done, if results are exactly the same? Better address attention to other more relevant issues in the intraop period " and “is the chosen sample too small”? Should it be the case, the study should be redone with a more appropriate number of pts

I dare ask the AAs to answer these two questions

Authors response:
The authors would like to sincerely thank the reviewer for the thorough review of our manuscript with very useful and valid comments/suggestions. The study sample size was calculated based upon the best available data at the time of design as described within the manuscript. It is possible the study was inadequately powered for the relatively small difference in glucose we detected between groups. However, our data remain meaningful and support either a more aggressive insulin regimen or a larger sample size for future studies as the reviewer suggests.

c. the power analysis for 1 y mortality is done on the Vandenberg data (ref #2) coming from ICU critically pts: totally correct for a cohort of pure surgical pts?

We agree with the reviewer’s comments but the Vandenberg’s critical care data was the best available and most closely related to our study population at the time of design.

d. the AAS performed a sensitivity analysis based on treatment threshold of the SG “to compare patients with a mean BG of ≤ 120 mg/dL and those &gt; 120 mg/dL, regardless of treatment group, to assess the response to insulin treatment or insulin resistance. The sensitivity analysis included all 100 patients. There was statistically significant improved survival for patients with a mean intraoperative BG of ≤ 120 mg/dL with a log rank p value of 0.047 (Figure 4). Blood glucose ≤ 120 mg/dL showed no significant difference in survival after adjusting for patient comorbidities, chronic preoperative steroid use, intraoperative transfusion using a multivariable Cox proportional hazard model." This passage is not clear at all, least to me

Authors response:
We have revised this in the sensitivity analysis section of the manuscript to address reviewer’s comments. (page 13, line 8-14)

i. I think it is mandatory to define the subgroup of "responders” and "survivors" with BG &lt; 120 (they should be present in both groups if I understood well)

Authors response:
The responders (&lt; 120mg/dL) included 19 from strict group (70.4%) and 8 from control group (29.6%). We have added this to the manuscript. (page 13, line 8-14)

ii. Not clear also to which kind of treatment the pts was “responders”: it should be critical to understand which kind of pts, irrespective of the treatment, did better and possibly why! I dare suggest the AAs to give an answer to this question
Authors response:
We agree with reviewer’s comments and we attempted to do this with the sensitivity analysis.
(page 13)

iii. Even if frequently reported in many other studies, I am quite concerned about the impact a single variable (BG), addressed during surgery only might have on the 5 y survival rate, particularly in the LTx setting

Authors response:
We agree with reviewer’s comments and this is demonstrated in our data by the non-significance of the 5-year survival difference between the groups.

More in details

Results (page 11 - 13)

a. Even if statistically significant, has the mean BG difference (143 vs 130.7) a clinical meaning? It seems not, to me, but also according to the reported impact on outcome and complications (see page 12). The aimed target was not reached in the SG (120 vs 130) in spite of more insulin and more frequent hypoglycemic episodes. But again, what is the clinical difference of 10 mg/dl BG with a sample of 100 pts?

Authors response:
We appreciate reviewers concerns about the magnitude of difference in the achieved glycemic control between the two groups. Although statistically significant, we agree that the clinical significance of the difference between the mean blood glucose of the strict and control groups was minor and we have conceded this as a study weakness.

b. A better glycemic control was achieved in the SG after reperfusion, a phase in which hyperglycemia is very common and treatment worth. I dare suggest the AAs to analyze the BG profiles separating the pre - (very similar) and post reperfusion phases (lines after the dashed line, very different). If a difference might be relevant, this could be from the reperfusion on.

Authors response:
We thank the reviewer for their comment. Due to the significant overlap in the standard errors shown in the graph and to avoid p-hunting with our very limited dataset, we have decided to forgo the suggested analysis. However, we agree this is noteworthy leading to the inclusion of the figure demonstrating the trajectory of glucose control.

c. Two points of the figure 2 are into my opinion of interest, at 420 mins and in the interval between 480 and 520 mins, a comment seems to be worth, particularly for the post reperfusion period, where in spite of the algorithm and the more frequent hypoglycemic episodes, the glycemic target was not reached in SG group
Authors response:
Thank you for your comments regarding this interesting finding/observation. We agree and this is very likely from insulin resistance and ongoing stress hyperglycemia.

d. It is not clear why the red line of the BG of SG group is no more present thereafter…shorter surgery? Total surgical time is not reported, please explain!

Authors response:
The data in the graph represents the length of time from anesthesia start to the indicated glucose measurement, and only extends as far as the data for the given treatment group allows; please keep in mind that case duration is longer than the surgical time. We thank the reviewer for noticing total surgical time was not included in the table, and it has been added to table 3; there was no statistically significant difference in surgical time between the groups. (updated table 3 has been included with surgical time)

e. Interesting to be underlined, according to the results shown in table 5 the absence of statistical difference in complications: however, in general complications were more represented in the SG group. In particular infections were quite high (in both groups)

We agree with the reviewer and we have addressed this in the results section on postsurgical complications.

Discussion
a. page 13: lines 18-36: quite difficult to understand why BG < 120 "in general" had a better outcome independent of the treatment. none of the proposed hypotheses are convincing (at least for me!!) …
   i. "identifying responders (----to be identified!!) or "requirements of more aggressive treatment"… please identify the treatment (more aggressive? less aggressive? Indifferent?) This point mandates a clarification page 13 lines 46-54: … why "not responders" did not respond to the aggressive strict control? Resistance could be an answer, but is very generic!! AAS should try a more convincing explanation (quality of the grafted livers?)

Authors response:
Thank for your time for an extensive review to improve our manuscript. We have addressed this in the discussion that more patients from the strict group in the < 120 mg/dL. We agree that identifying the responders who may need more aggressive treatment would certainly help. Based on the results of this study, we may consider using more aggressive algorithm for SG. This study was not designed to answer these questions. We performed sensitivity analysis in search of different thresholds for treatment. Insulin resistance is one piece of the puzzle but exogenous administration of fluids, blood products and medications do add to the problem of refractory hyperglycemia.

c. "However, most divergence in blood glucose between groups can be appreciated only after reperfusion perhaps illustrating that reliance on differences in the mean of the total
operative time to be limited." not clear to me …differences of BG profiles might be also associated with a different quality of the graft for example (which is easier to be supported). I dare suggest a separate analysis of the two periods (pre and post reperfusion, see above)

We agree with authors comments and this certainly would be better suited to be examined in a future study.

d. page 14 - line 16: according to the study results (no difference with strict vs conventional BG control) I don't think it is worth to invest resources for strict control, should I consider the conclusions! In some sense, it is quite distracting to be focused on a variable that is not able (according to the study results) to impact on clinical outcome, while other more relevant problems should be faced during LTx

Authors response:
We completely agree with reviewer’s comments.

e. pag 14 lines 49-59: "We found a statistically significant difference in patient survival if mean BG was less than 120mg/dl in the sensitivity analysis." Perhaps a new subgroup of pts including those with BG &lt; 120, independently of the treatment, should be found out and analysed in the light of the glycemic control

Authors response:
We agree with reviewer’s comments looking in to lower treatment target (120 mg/dL). We looked in to this by doing a sensitivity analysis which showed statistical significant for survival with BG &lt; 120 mg/dL.

f. page 15 - advantage of insulin treatment and disadvantage of hyperglycemia (one disadvantage, hyper fibrinolysis, relevant during OLT, has not been mentioned) are very interesting, but here the discussion has, into my opinion, only a "cultural" purpose: as a matter of fact, they are quite "out" the specific contest of the results

Authors response:
We agree with reviewer response especially in the setting of end-stage liver failure and we have included the risk of hyper fibrinolysis in the discussion. (page 15, line 17-20)

g. page 15 - premises of BG control during LTx are indeed relevant. But here the BG control was not able to impact outcome and complications. I dare suggest the AAS to try to explain why results are so different from the original hypothesis: just a matter of sample size? or perhaps sometimes less is really more?

Authors comments:
Thank you for your valid comments on this study and manuscript. The findings of the study concur with existing literature of “first do no harm”. We don’t need to have aggressive targets
but paying careful attention to glycemic control is still warranted. The study was powered to
detect a 13% difference in the mortality rate between groups at the one-year mark, while there
was an observed difference of 0%; a larger sample size would not have affected the ability to
detect a statistically significant difference here as there was no difference to detect. That being
said, we did not have the power to show statistical significance for the differences calculated
between the groups. The results may also be different due to individual response to insulin
treatment. We feel that with some evolving data that it may be time to focus on fluctuations/variability than absolute numbers. Glycemic variability has been shown to be
associated with more complications. The concept of variability is discussed in page 16 with
appropriate references. (page 17, line 4-5)

h. page 16 line 7: "is possible that patients undergoing liver transplantation share similarity
with cardiac surgical patients as signaled by the results of our sensitivity analysis:" again

AAS should analyse the subgroup with BG &lt; 120 (composed of pts with conventional and
strict BG control, as stated) to understand (if possible) why this subgroup has better

Authors response: The currently available data on LT patients suggests less aggressive approach
(&lt;200 mg/dL) is associated with better outcomes although the quality of the studies may be
questioned. We are not certain if cardiac surgical patients share similarity with LT patients but
certainly the stress response during the procedure may have similar effects on their glucose
homeostasis although we don’t have supporting data. We have added this to the manuscript.
(page 16, line 14-16)

i. page 16, lines 19-34…. sorry but the reasoning is not consequential with the results!

j. page 16, lines 47-54 - continuous BG monitoring: very expensive …according to your
data I would not recommend its use! …

Authors response:
We agree with your comments, we have addressed the page 16 (19-34) comments in the
manuscript that we author meant to say that there is not really any good evidence out there for
non-cardiac surgical patients and this analysis would certainly help design future studies. With
agree on the comment on the use of CGM and cost. We are also aware that it is not validated for
use during surgical procedures given the likely interference with electrocautery.

k. page 17 lines 1-12: the importance of a too strict control of BG has been questioned: the
AAs should provide reasons to target this aim.

Authors response:
We agree with the reviewer comments that very strict control is not recommended in the
perioperative period. We started this study during the time when the jury was still out on
glycemic control. There was no convincing data in the field of liver transplantation. We
definitely would consider different targets for treatment in future studies. This has been updated
in the manuscript under the limitation section. (page 17, line 18-20)