**Reviewer’s report**

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

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**Reviewer:** Andrea De Gasperi

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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:

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

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 > 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, at least to me.

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

ii. Not clear also to which kind of treatment the pts were "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.

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.

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?

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 analyse 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.

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.
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!

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)

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

b. 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?)

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)

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

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 < 120, independently of the treatment, should be found out and analysed in the light of the glycemic control

f. page 15 - advantage of insulin treatment and disadvantage of hyperglycemia (one disadvantage, hyperfibrinolysis, 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

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?

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 survival

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!…

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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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