Author’s response to reviews

Title: Postoperative Tight Glycemic Control Reduces Postoperative Infection In Patients Undergoing Surgery: A Meta-Analysis

Authors:
Yuan-yuan WANG (wayuyu@163.com)
Shuang-fei HU (hushuangfei77@sina.com)
Hui-min YING (13989356561@139.com)
Long CHEN (chenlong8420938@163.com)
Hui-li LI (lihuili1609@163.com)
Fang TIAN (fangtian212@163.com)
zhen-feng Zhou (zhenfeng9853@163.com)

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Author’s response to reviews:

Dear Ernesto Maddaloni, M.D.:

Thank you very much for your valuable recommendations. We have sincerely considered your and the reviewers’ comments. We have revised our manuscript. Thanks again for your professional suggestions! Sincerely hope our revised version will be satisfactory for publication in BMC Endocrine Disorders. Great thanks to you and the referee for the time and effort you expend on this paper.

Before we answer the comments, we are so sorry for making a major mistake of data analyses. We analyzed the data again when the Professor Ilaria Cavallari asked for reporting the overall event rates (%) and Professor Mario Luca Morieri mentioned the risk of hypoglycemia. Then we found Fang TIAN have put the wrong column (the total patients but not the patients who had not experienced the outcomes) into STATA soft for dichotomous data analyzing. We immediately asked a statistics expert named Yun-xian YU (Department of Epidemiology and Health
Statistics, School of Public Health, Zhejiang University) for the help of data analyses. We apologized for our mistake again.

Now this study found that TGC immediately after surgery significantly reduces total postoperative infection and length of ICU stay. However, the patients in the TGC group experienced a significant higher rate of postoperative hypoglycemia. TGC had a neutral effect on the risk of postoperative short-term mortality, neurological dysfunction and acute renal failure as compared to CGC.

Technical Comments:

1. the manuscript is difficult to understand due to poor English language. The whole manuscript should be extensively revised for language. Also the title should be modified to be more informative about the study design and the results achieved

Answer: Thank you very much for your comments and we are sorry to make you confused.

We have the paper edited by Elsevier Language Editing Services

We have changed the title to: Postoperative Tight Glycemic Control Reduces Postoperative Infection In Patients Undergoing Surgery: A Meta-Analysis (line 1-2, page 1), so it was more informative about the study design and the results achieved.

2. tables should be extensively revised because they are not clear. Tables are essentials for readers, in particular in meta-analysis.

Answer: Thank you very much for your advice and we are sorry to make you confused. We have extensively revised the tables, especially for Table 1. We have re-organized the table according to the review,s suggestion with the following information: first author of the study; N of patients; N of patients with diabetes; target glucose levels in the 2 arms; cardiac surgery; median FUP; primary endpoint; Jadad score.(Table 1 and Table 2).
3. there are some concerns about the methods (study selection) and power. Please use the PRISMA checklist for meta-analysis and upload it along with the revised versions of the manuscript.

Answer: We have uploaded the PRISMA checklist of meta-analysis. There was only a little regret that we have not a systematic review registration number, however, this meta-analysis was performed according to meta-analyses (PRISMA) format guidelines. We have meet the request of the remaining items, so this meta-analyse have enough power to assess any difference in the outcomes.

Best wishes.

Yours sincerely,
Dr. zhen-feng

Dear Professor Ilaria Cavallari:

Thank you very much for your valuable recommendations. We have sincerely considered your comments. Great thanks to you and the referee for the time and effort you expend on this paper.

Before we answer the comments, we are so sorry for making a major mistake of data analyses. We analyzed the data again when the Professor Ilaria Cavallari asked for reporting the overall event rates (%) and Professor Mario Luca Morieri mentioned the Risk of hypoglycemia. Then we found Fang TIAN have put the wrong column (the total patients but not the patients who had not experienced the outcomes) into STATA soft for dichotomous data analyzing. We immediately asked a statistics expert named Yun-xian YU (Department of Epidemiology and Health Statistics, School of Public Health, Zhejiang University) for the help of data analyses. We apologized for our mistake again.

Now this study found that TGC immediately after surgery significantly reduces total postoperative infection and length of ICU stay. However, the patients in the TGC group
experienced a significant higher rate of postoperative hypoglycemia. TGC had a neutral effect on the risk of postoperative short-term mortality, neurological dysfunction and acute renal failure as compared to CGC.

Major comments:

1. change the title;

Answer: Thank you very much for your valuable recommendations. We have changed the title to: Postoperative Tight Glycemic Control Reduces Postoperative Infection In Patients Undergoing Surgery: A Meta-Analysis (line 1-2, page 1), so it was more informative about the study design and the results achieved.

2. the primary outcome of the current meta-analysis was short-term mortality. All available studies published so far showed a neutral effect of the two different glycemic control strategies on mortality; of note, short-term mortality is an endpoint at low incidence. Does this meta-analysis have enough power to assess any difference in terms of mortality? Please, in the background clarify which novel information could add the present meta-analysis to the current knowledge deriving from RCTs and prior meta-analyses;

Answer: Thank you very much for your valuable recommendations. We do agree with you that mortality is an endpoint at low incidence, so we calculated the sample size and the power of this study.

(1). Sample size and power calculation:

① Sample size calculation:

When compared with a liberal target, a recent meta-analysis data showed that a moderate glycemic target was associated with reduced postoperative mortality (OR=0.48, 95% CI 0.24-0.76) (Sathya B, Davis R, Taveira T, Whitlatch H, Wu WC. Intensity of peri-operative glycemic control and postoperative outcomes in patients with diabetes: a meta-analysis. Diabetes Res Clin
A two-tailed power analysis with 0.80 power and an $\alpha$ of 0.05 was used. As compared to CGC group, assuming mortality was decrease from 6.9% to 4.7% (relative decline by 33%) with postoperative tight glycemic control (TGC). With an estimated standard deviation of 1563 patients were needed per study group. About 1709 patients per group were included in the study so as to ensure enough data to fit the analysis and to allow for comparisons among the outcomes of interest.

② Power calculation

We are planning a study with 1709 experimental subjects and 1709 control subjects. Our Prior data indicate that the mortality rate among controls is 0.026. If the relative risk of failure for experimental subjects relative to controls is 0.48 (Sathya B, Davis R, Taveira T, Whitlatch H, Wu WC. Intensity of peri-operative glycemic control and postoperative outcomes in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract. 2013. 102(1): 8-15), we will be able to reject the null hypothesis that this relative risk equals 1 with probability (power) 0.821. The Type I error probability associated with this test of this null hypothesis is .05. We will use an uncorrected chi-squared statistic to evaluate this null hypothesis.

Power calculation

(2). We have revised the background as following for clarifying the novel information to the current knowledge (red part was revised part):

Background (line 1-21, page 4)

Tight glycemic control (TGC) was found to decrease the mortality and morbidity in critically ill patients and it has therefore been recommended as the standard treatment for the duration of the perioperative intensive care unit (ICU) throughout the world. However, subsequent trials have failed to confirm the benefits of this recommendation. It should also be noted that the above mentioned studies focused on the critically ill patients, but did not include surgical patients.

Perioperative hyperglycemia is reported in approximately 20-40% of patients after general surgery and ever 80% of patients undergoing cardiac surgery. Several studies in cardiac and
general surgery patients have shown a clear association between perioperative hyperglycemia and adverse clinical outcomes including delayed wound healing, surgical site infections, and prolonged hospital stay. However, the optimal glucose target during the post-operative period is widely controversial. No significant difference was found between TGC and conventional glycemic control (CGC) when evaluating the variety of complications. However, another study including cardiac surgery patients reported a reduction of postoperative complications in TGC group. Given the conflicting results and the lack of well-powered studies that support current guideline recommendations, the present study employed meta-analysis to evaluate the current evidence and analyze the association between the strategies of immediate postoperative glycemic control and outcomes in patients undergoing elective surgery.

3. the results section should include more details on the included studies (i.e. how many patients had diabetes?; type of surgery (cardiac or not); difference cutoffs used to define tight vs. conventional glycemic control and different strategies to achieve the goals; timing of intervention). In addition, overall event rates (%) and not only RR should be reported in the figures and in the text;

Answer: Thank you very much for your valuable recommendations. We have added the details into the results section as following:

About 773 (22.5%) patients had history of diabetes; seven articles reported cardiac surgery including 1825 patients (53%). Among the included 13 articles, seven articles defined tight glycemic control and trigger blood glucose as blood glucose ≤ 110 mg/dL, two articles was ≤120 mg/dL, another two articles was ≤140 mg/dL, and the last three articles was ≤130 mg/dL, ≤150 mg/dL and ≤160 mg/dL respectively. Seven articles only control the blood glucose during postoperative period, however, another six articles were during intra and post operative period. The average Jadad Score of the studies in this meta-analyses was 2.8, only four studies have exceeded 4. (line 7-15, page 7).

We also add overall event rates (%) a in the tables and in the text (Abstract and Results part, Table 2).
4. Table 1 is rather unclear; please re-organize the table with the following information: first author of the study; N of patients; N of patients with diabetes; target glucose levels in the 2 arms; cardiac surgery; median FUP; primary endpoint; Jadad score;

Answer: Thank you very much for your advice and we are sorry to make you confused. We have extensively revised the tables, especially for Table 1. We have re-organized the table according to your suggestion with the following information: first author of the study; N of patients; N of patients with diabetes; target glucose levels in the 2 arms; cardiac surgery; median FUP; primary endpoint; Jadad score (Table 1).

5. a p value of 0.07 regarding differences in terms of post-operative hypoglycemia can not support the statement of a neutral effect, please revise; in addition, the subgroup analysis and meta-regression paragraph should be revise to improve readability.

Answer: Thank you very much for your comments and we are sorry to make you confused. We have revised this statement to “However, the patients in the TGC group experienced a significant higher rate of postoperative hypoglycemia (30.8% vs. 17.2%; RR 2.254, 95% CI 1.550 to 3.276, p < 0.001) and severe hypoglycemia (2.8% vs. 0.7%; RR 3.821, 95% CI 1.796 to 8.127, p < 0.001) as compared to CGC group.”(Abstract part, line 13-17, page 3 and Results part, line 1-7, page 9).

Subgroup analyses and meta-regression analyses were applied to detect the potential sources of heterogeneity. There was significant heterogeneity between articles only with respect to postoperative hypoglycemia, length of ICU stay and hospitalization, so we have cleared the subgroup analyses and meta-regression analyses for postoperative hypoglycemia, length of ICU stay and hospitalization to make this part readability (Results part, line 23-30, page 9, line 1-3, page 10 and line 13-19, page 10).

Minor comments:

1. improve english language in the text and check for spelling mistakes;

Answer: Thank you very much for your comments and we are sorry to make you confused.
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2. supplemental figures 4-5-6-7-9-10 could be omitted (data are already included in the text and in table 2);

Answer: We have omitted supplemental figures 4-5-6-7-9-10.

3. include a paragraph explaining the strengths of this study before the limitations.

Answer: We have included a paragraph explaining the strengths of this study before the limitations as following: “There are some strengths of this study. For the first time, the present meta-analysis was conducted to evaluate the association between postoperative glycemic control and outcomes in patients undergoing elective surgery. Second, we have included the most rigorous analysis of TGC studies to date and conducted a comprehensive meta-analysis to elevate the effect of postoperative TGC on outcomes. However, high-quality evidence to support the routine use of postoperative TGC is still lacking.” (Discussion part, line 13-17, page 13).

Dear Professor Mario Luca Morieri:

Thank you very much for your valuable recommendations. We have sincerely considered your comments. Great thanks to you and the referee for the time and effort you expend on this paper.

Before we answer the comments, we are so sorry for making a major mistake of data analyses. We analyzed the data again when the Professor Ilaria Cavallari asked for reporting the overall event rates (%) and Professor Mario Luca Morieri mentioned the Risk of hypoglycemia. Then we found Fang TIAN have put the wrong column (the total patients but not the patients who had not experienced the outcomes) into STATA soft for dichotomous data analyzing. We immediately asked a statistics expert named Yun-xian YU (Department of Epidemiology and Health Statistics, School of Public Health, Zhejiang University) for the help of data analyses. We apologized for our mistake again.
Now this study found that TGC immediately after surgery significantly reduces total postoperative infection and length of ICU stay. However, the patients in the TGC group experienced a significant higher rate of postoperative hypoglycemia. TGC had a neutral effect on the risk of postoperative short-term mortality, neurological dysfunction and acute renal failure as compared to CGC.

1) My biggest concern is for studies selection. For example, it is unclear to me why some studies, identified by the authors and cited in background or discussion (eg. Diabetes Care. 2015 Sep;38(9):1665-72) were not included in the list of studies analyzed in the meta-analysis.

Answer: Thank you very much for your advice and we are sorry to make you confused. Some studies mentioned in this study were not included after we reviewed the full-text articles. That was some consideration as following:

In the GLUCO-CABG trial (Diabetes Care. 2015 Sep;38(9):1665-72), we could not get the exactly number and rate of the outcomes. So we decided to exclude this study. It descript as following: “Figure 2A depicts the frequency of the composite and individual complications during the perioperative period. We observed a lower but not significant difference in the number of patients experiencing one or more complications in the intensive compared with the conservative group (42 vs. 52%, P = 0.08). There were no differences between groups in the frequency of individual complications, including wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury, MACE, and death. In addition, we found no differences in the number of ICU readmissions, hospital LOS, or readmissions after hospital discharge (Fig. 2A).”

The main finding of this study was that the type of patients would influent the results: “We found, however, significant differences in the effect of intensive compared with conservative insulin therapy on the rate of perioperative complications between patients with and without diabetes. In patients with a history of diabetes, there were no differences in the composite or individual complications in patients treated in the intensive or conservative group (49 vs. 48%, P = 0.87) (Fig. 2B). In contrast, we found that patients without a history of diabetes who were
treated in the intensive group experienced a lower number of perioperative complications compared with patients in the conservative group (34 vs. 55%, P = 0.008) (Fig. 2C).

GLUCO-CABG trial (Diabetes Care. 2015 Sep;38(9):1665-72)

The data analyzed in another study of Pezzella AT (Ann Thorac Surg. 2014 Oct;98(4):1281-5) were collected from patients who participated in previous study (Desai SP et al. J Thorac Cardiovasc Surg 2012;143:318–25), it was secondary analysis and subgroup analysis of Desai,s study. However, the study conducted by Desai SP has been included in this meta-analysis. So we decided to exclude those studies.

2) Early studies reporting a clear benefit of TGC in critically ill patients (also in postoperative setting) compared TGC to a "standard" treatments with glucose levels that were often higher as compared to the "conventional" glycemic control levels used in more recent trials.

a. For this reason, I think it would be very helpful to: i. Specify if studies were excluded on the basis of TGC and CGC levels.; ii. Report some measures of CGC and TGC (eg. average of CGC and TGC found across studies). In this regard, it's my opinion that table 1 is really difficult to be read and need to be simplified or edited to make it more readable. iii. Overall, I invite Authors to address this point also in discussion

Answer: Thank you very much for your advice and we are sorry to make you confused.

i. Studies were not excluded on the basis of TGC and CGC levels. EMBASE, MEDLINE, and the Cochrane Library were searched electronically by two investigators for relevant studies, and the following key words were used: “Blood Glucose” “insulin” and “Postoperative Period”. We only included randomized controlled trials (RCTs) with elective surgery patients who had received postoperative TGC. Specific eligibility criteria were as follows: (a) published in English; (b) treatment with postoperative TGC; and (c) the study documented endpoints assessed mortality (Materials and Methods part, line 14-17, page 5).
ii. We have extensively revised the tables, especially for Table 1. We have re-organized the table according to your suggestion with the following information: first author of the study; N of patients; N of patients with diabetes; target glucose levels in the 2 arms; cardiac surgery; median FUP; primary endpoint; Jadad score (Table 1).

iii. We have discussed the conflict of the results between the present meta-analysis and others according to your advice (Discussion part, line 2-25, page 12).

3) Authors have evaluated the quality of studies with the Jadad scale. However, it's not clear if studies were excluded or not on the basis of this evaluation. If not, Authors can consider doing a sensitivity analysis/subgroup analysis on the basis of this evaluation. Anyway, authors should describe and report in the text a description of the overall quality of the studies included in the meta-analyses.

Answer: Thank you very much for your suggestion and we are sorry to make you confused. Studies were not excluded on the basis of Jadad scale. We have subgroup analysis and meta-regression to evaluate the effect of the Jadad scale. The result of subgroup analyses and meta-regression identified that the Jadad scale could not identify the heterogeneity (S4 Supplemental Table 8, Table 13, Table 15 and Table 17).

We have described the overall quality of the studies included in the meta-analyses as following: “The average Jadad Score of the studies included in the meta-analyses was 2.8, only four studies were more than 4.” (Results part, line 14-15, page 7).

This study may suggest that TGC should be administrated under close glucose monitoring in patients undergoing surgery, especially in those with high postoperative infection risk. In addition, large, prospective, randomized and high quality trials on the efficacy and safety of TGC in the postoperative period are needed to investigate the ideal BG target to optimize clinical outcomes and minimize adverse events in patients undergoing surgery (Conclusions part, line 6-11, page 14).
4) Discussion and analyses: I would recommend discuss and consider the possible roles that type of treatments more than levels of glycemic controls might have on these outcomes. [see Piatti. J Clin Transl Endocrinol. 2017 Feb 11;7:47-53]

Answer: Thank you very much for your valuable recommendations. We have added Piatti,s study into the discuss part and discuss the possible roles that type of treatments as following: “A recent retrospective analysis found that the basal + premeal insulin regimen was associated with a reduced rate of postoperative infective complications than the premeal insulin alone therapy, without increasing the number of severe hypoglycemic events. These results suggest that type of treatments more than levels of glycemic controls might have on beneficial effect these outcomes.” (Discussion part, line 7-12, page 12)

5) Risk of hypoglycemia: Overall all studies shows an RR with a trend for benefit among those randomized to TGC. (RR 0.87, P=0.07). Although all studies showed RR below 1, the meta-analysis result was primarily driven by one study that showed a clear benefit RR 0.22 (0.13 to 0.36 CI).

a. However, in the discussion, PG 12 line 22 authors report that in this study the TGC group was at high risk of hypoglycemia. This is confusing. How was the RR computed? Is for TGC effect on CGC reference or the other way around?

Answer: We are sorry to make you confused. (Results part, line 2-20, page 9)

We observed a significant higher in the number of patients experiencing postoperative hypoglycemia (30.8% vs. 17.2%; RR 2.254, 95% CI 1.550 to 3.276, p < 0.001; Figure. 4) and severe hypoglycemia (2.8% vs. 0.7%; RR 3.821, 95% CI 1.796 to 8.127, p < 0.001; S3 Supplemental Figure. 5) in the TGC group as compared to the CGC group.

Sensitivity analyses revealed that there was no significant heterogeneity of postoperative hypoglycemia (I2 < 0.001 %, p = 0.980 S4 Supplemental Table 5 ) when we omitted Federico Bilotta’s study of neurosurgical patients. The result was consist with a significant higher rate of postoperative hypoglycemia in the TGC groups (16.4% vs. 6.76%; RR 2.387, 95% CI 1.842 to
3.092, p < 0.001; I² < 0.001 %, Supplemental Table 5). A funnel plot of the risk of postoperative hypoglycemia identified all studies in the 95% confidence limits (S3 Supplemental Figure. 6).

b. Please clarify and modify the text accordingly.

Answer: We are sorry to make you confused. We have the paper edited by Elsevier Language Editing Services

6) The tile appears to be unclear to me and I recommend modify it.

Answer: Thank you very much for your constructive comments and we are sorry to make you confused.

We have changed the title to: Postoperative Tight Glycemic Control Reduces Postoperative Infection In Patients Undergoing Surgery: A Meta-Analysis (line 1-2, page 1), so it was more informative about the study design and the results achieved.