REVIEW

Effects of perioperative tight glycemic control on postoperative outcomes: a meta-analysis

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Abstract

Background: The optimal glycemic target during the perioperative period is still controversial. We aimed to explore the effects of tight glycemic control (TGC) on surgical mortality and morbidity.

Methods: PubMed, EMBASE and CENTRAL were searched from January 1, 1946 to February 28, 2018. Appropriate trails comparing the postoperative outcomes (mortality, hypoglycemic events, acute kidney injury, etc.) between different levels of TGC and liberal glycemic control were identified. Quality assessments were performed with the Jadad scale combined with the allocation concealment evaluation. Pooled relative risk (RR) and 95% CI were calculated using random effects models. Heterogeneity was detected by the I^2 test.

Results: Twenty-six trials involving a total of 9315 patients were included in the final analysis. The overall mortality did not differ between tight and liberal glycemic control (RR, 0.92; 95% CI, 0.78–1.07; $I^2 = 20.1\%$). Among subgroup analyses, obvious decreased risks of mortality were found in the short-term mortality, non-diabetic conditions, cardiac surgery conditions and compared to the very liberal glycemic target. Furthermore, TGC was associated with decreased risks for acute kidney injury, sepsis, surgical site infection, atrial fibrillation and increased risks of hypoglycemia and severe hypoglycemia.

Conclusions: Compared to liberal control, perioperative TGC (the upper level of glucose goal ≤150 mg/dL) was associated with significant reduction of short-term mortality, cardic surgery mortality, non-diabetic patients mortality and some postoperative complications. In spite of increased risks of hypoglycemic events, perioperative TGC will benefits patients when it is done carefully.

Key Words
- tight glycemic control
- perioperative
- surgical mortality
- surgical morbidity

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Introduction

Perioperative hyperglycemia is associated with many adverse clinical outcomes. A better management of glycemic levels during the perioperative period has been shown to improve surgical outcomes, and it was recommended by several guidelines or statements from different academic organizations (1, 2, 3, 4, 5). However, the optimal glucose target for patients undergoing surgery is still debatable (6).

Van Den Berghe and her coworkers performed and published a randomized controlled trial (RCT) in 2001, which has proved the obvious effects of intensive insulin therapy (IIT, maintain blood glucose at a level no higher than 110 mg/dL) on the reduced morbidity and mortality among critically ill patients after surgery (7). This was the first use of glucose range 80–110 mg/dL to define tight glycemic control (TGC), and then tight control of

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glycemic target became popular. Many researchers have made attempt to practice perioperative TGC with different upper level of glucose goals, which ranges from 108 mg/dL to 150 mg/dL. Despite most glucose targets being the same as those in Van Den Berghe's study, research results did not confirm conspicuous survival benefits of TGC in diverse surgical populations, and even proved that aggressive glycemic control may greatly increase the risk of hypoglycemia (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22).

To date, seven previous meta-analyses have explored the associations between TGC/IIT and postoperative complications, but two of them involved very few patients undergoing surgery (23, 24), three of them only focused on cardiac surgical patients and included few of eligible studies (25, 26, 27), one was only focused on diabetic patients and the included articles were not all RCTs (28) and one was focused on few postoperative complications (29). Moreover, many new relevant RCTs have now been published. Thus, we incorporated more data and conducted a comprehensive analysis, in which the different intensity of TGC targets were classified and more complications were well considered, to further assess the benefits and risks of tight glycemic control in surgical patients.

Methods

We reported our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (30). The review was previously registered at the international prospective register of systematic reviews (PROSPERO, http://www.crd.york.ac.uk/prospero/, registration number: CRD42018076091).

Search strategy and selection criteria

We conducted a comprehensive literature search using PubMed, EMBASE and the Cochrane Library Central Register of Controlled Trials from January 1, 1946 to February 28, 2018. The MeSH terms and key words were combined and adapted for the three electronic databases. Surgical procedures, operative, surgery, insulin, glycemic, glucose, blood glucose, mortality, death, random and RCT were carried out for search without restriction. Moreover, additional relevant studies were searched manually by checking the reference lists of identified studies or reviews. We did not search for the unpublished reports.

Two independent investigators (Z Q K and J L H) screened the correlative studies through the title or abstract. Then, the reviewers retrieved the full-text of all identified studies for further assessment. Dissenting opinions were resolved by discussion, with the involvement of a third author if necessary. Inclusion criteria were the following: (1) explored the association between perioperative glycemic control and surgical mortality and morbidity among adult patients; (2) were randomized controlled trials and published in English; (3) compared tight or liberal glucose control and set specific target of glucose control; (4) provided interrelated relative risk (RR) and 95% CI or interrelated data to calculate them. We excluded studies that provided no relevant outcome or insufficient data. If literatures were from the same study or shared an identical population, we only included the article with the longest duration of follow-up. According to the generally acceptable consensus (3, 29) about perioperative blood glucose monitoring (the upper level of glucose goal ≤150 mg/dL for tight control and ≤220 mg/dL for liberal control), studies implementing an out-of-scope glycemic target levels were excluded.

Outcomes

Outcomes were divided into two categories: postoperative mortality and morbidity. The primary outcome was mortality, which was further grouped into the short-term mortality (deaths occurred during the hospital days or within 30 days after surgery) and long-term mortality (deaths occurred more than 30 days after surgery during the follow-up days). The secondary outcomes were postoperative complications, consisting of hypoglycemia (patients with one occurrence at least of blood glucose ≤70 mg/dL), severe hypoglycemia (patients with one occurrence at least of blood glucose ≤40 mg/dL), infections (surgical site infection, sepsis, pneumonia and urinary infection), acute kidney injury, atrial fibrillation and myocardial infarction. Furthermore, tight glucose control was grouped into two intensities: very tight glucose control (upper level of perioperative glucose goal ≤110 mg/dL) and moderate tight glucose control (upper level of perioperative glucose goal 111–150 mg/dL). The intensity of liberal control was grouped into moderate liberal glucose control (upper level of perioperative glucose goal ≤180 mg/dL) and very liberal glucose control (upper level of perioperative glucose goal 181–220 mg/dL).

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Data extraction and quality assessment

Z Q K and J L H abstracted the variables from eligible studies independently using a standardized form, which included name of first author, year of publication, country of studies, blood glucose measuring method, the overall sample size, type of surgery, time of intervention, relevant outcomes, duration of follow-up, and data (sample size, mean age, proportion of male, proportion of diabetic status, target of glucose level) for treatment and control arms. We only extracted the data of postoperative patients when the studies involved both postoperative patients and medical patients in the intensive care unit. We assessed the quality of eligible studies using the Jadad score (31), which evaluated RCTs from three items (randomization, double blinding, withdrawals and dropouts), awarded three points or more was defined as high-quality study. Allow for the deficiency of the Jadad score, we evaluated the concealment of allocation as adequate, inadequate or unclear in addition (32). Disagreements were solved by consensus reached after discussion.

Statistical analysis

The effects were compared using the pooled RRs with 95% CIs. Due to the potential heterogeneity (surgery type, intervention time, blood glucose target, follow-up time, etc.) that existed among the included studies, the meta-analysis was performed with a random effects model. We used I^2 test to evaluate the magnitude of heterogeneity between studies, and the value more than 50% was defined as significant heterogeneity (33). Reasons for heterogeneity were explored through subgroup analyses or sensitivity analyses. We carried out prespecified subgroup analyses by intensity of tight glucose control, follow-up time, surgery type, different intervention time and diabetic status and different intensity of liberal control to reveal possible relationships of mortality. For the morbidities, subgroup analyses were only conducted by intensity of tight glucose control when the number of included studies was more than ten. We would perform sensitivity analysis by sequentially removing each study and rerunning the analysis (leave-one-out sensitivity analyses), if the significant heterogeneity (I^2 >50%) was detected in any outcome.

We evaluated the potential publication bias visually by inspecting funnel plots, and assess the asymmetry of the funnel plot by using Egger's or Begg's regression test, with a $P<0.05$ level indicating significance (34). All statistical analyses were performed by Stata software, version 12.

Results

Search results

Overall, 2177 studies were initially identified from the electronic databases, of which 1327 studies were excluded by reviewing the title and abstract. Eleven records were added by checking the reference lists of identified relevant studies or reviews. We retrieved the full texts of the remaining 136 studies for further assessment, 28 of them meet our inclusion criteria, and then two studies were excluded because of zero events in both groups for all outcomes. Finally, the meta-analysis included 26 eligible studies involving a total of 9315 surgical patients (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44). Figure 1 displayed the screening process.

Study characteristics

The characteristics of the 26 included RCTs were described in Table 1. Studies came from varied countries, and the majority of them were conducted in a single center. The simple size of the studies ranged from 52 to 2232 patients. 14 studies compared the very tight glucose control group vs liberal group, and the remaining 12 studies compared the moderate tight glucose control group vs liberal group. Trials varied in the intervention time of glycemic control, four trials in intraoperative period, 13 trials in postoperative period and 9 trials in both the intraoperative and postoperative periods. According to the Jadad Scale, the majority of eligible studies were evaluated as high quality varying from three to five points, eight studies acquired no more than two points (Supplementary Table 1, see section on supplementary data given at the end of this article). On the assessment of the allocation concealment, 20 studies were assessed as adequate, and 6 were unclear.

Primary outcome

Twenty-two studies providing effective data were involved in the meta-analysis for mortality, the pooled results did not show a significant difference in the overall postoperative mortality between TGC and liberal control (RR, 0.92; 95% CI, 0.78–1.07; I^2=20.1%; Fig. 2).

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Table 1 Characteristics of the 26 studies included in the meta-analysis.

Study	Country	Sample size	Surgery type	Intervention time	Measuring method
Berghe *et al.* (7)	Belgium	1548	Cardiac 63% Other 37%	Postoperative	POCT
Gery *et al.* (8)	USA	61	NA	Postoperative	PCOT
Gandhi *et al.* (9)	USA	371	Cardiac 100%	Intraoperative	POCT
Arabi *et al.* (10)	Saudi Arabia	88	NA	Postoperative	POCT
Kirdemir *et al.* (36)	Turkey	200	CABG 100%	Intra + post- operative	NA
Albacker *et al.* (35)	Canada	52	CABG 100%	Intraoperative	POCT
Bilotta *et al.* (11)	Italy	483	Neurosurgical 100%	Postoperative	CLM
Subramaniam *et al.* (37)	USA	236	Vascular 100%	Intra + post- operative	POCT
Chan *et al.* (12)	Brazil	109	Cardiac 100%	Intra + post- operative	POCT
Finfer *et al.* (13)	Australia New Zealand North America	2232	NA	Postoperative	POCT or CLM
Emam *et al.* (38)	Saudi Arabia	120	Cardiac 100%	Intra + post- operative	POCT
Cao *et al.* (14)	China	248	Gastric 100%	Postoperative	POCT or CLM
Cao *et al.* (15)	China	179	Gastric 100%	Postoperative	POCT or CLM
Lazar *et al.* (16)	USA	82	CABG 100%	Intra + post- operative	POCT
Desai *et al.* (17)	USA	189	CABG100%	Intra + postoperative	POCT
Marfella *et al.* (39)	Italy	165	PCI 100%	Postoperative	POCT
Abdelmalak *et al.* (18)	USA	381	Abdominal aortic aneurysm 16% Colectomy 30% Cystectomy 18% Other 36%	Intra + post- operative	NA
Kalfon *et al.* (20)	French	1059	Gastric or urological 35% Cardiac 19% Other 46%	Postoperative	POCT
Cinotti *et al.* (19)	French	188	Neurosurgical 100%	Postoperative	POCT
Ji *et al.* (40)	China	65	Cardiac 100%	Intraoperative	POCT
Okabayashi *et al.* (41)	Japan	447	Liver 65% Pancreatic 35%	Intra + postoperative	POCT
Umpierrez *et al.* (21)	USA	302	CABG 100%	Postoperative	POCT
Yuan *et al.* (22)	China	212	Gastric 100%	Postoperative	POCT
Zadeh *et al.* (56)	Iran	75	Cardiac 100%	Intra + postoperative	POCT
Wahby *et al.* (42)	Egypt	135	CABG 100%	Intraoperative	POCT
Wang *et al.* (43)	China	88	Neurosurgical 100%	Postoperative	NA

Subgroup analyses were conducted by intensity of TGC, follow-up time, surgery type, different intervention time, diabetic status and intensity of liberal control (Figs 2 and 3). Obvious reductions in mortality were explored in patients who received TGC when stratified by short-term mortality (RR, 0.76; 95% CI, 0.61–0.95; I^2=0%), non-diabetic patients (RR=0.59; 95% CI: 0.39–0.88; I^2=0%), cardic surgery conditions (RR, 0.61; 95% CI, 0.38–0.97; I^2=0%) and when compared to the very liberal glycemic target (RR, 0.81; 95% CI, 0.67–0.96; I^2=0%). However, we did not find significant difference in mortality when stratified by the very tight glucose control (RR, 0.92; 95% CI, 0.77–1.11; I^2=39.3%) and the moderate tight glucose control (RR, 0.70; 95% CI, 0.40–1.24; I^2=0%). Similar results existed in patients undergoing neurosurgery (RR, 0.95; 95% CI, 0.77–1.18; I^2=0%), gastric surgery (RR, 0.73; 95% CI, 0.25–2.06; I^2=0%), diabetic patients (RR, 0.70; 95% CI, 0.39–1.23; I^2=0%), long-term mortality (RR, 1.03; 95% CI, 0.88–1.21; I^2=30.1%) and when compared to the moderate liberal glycemic control (RR, 1.04; 95% CI, 0.80–1.34; I^2=38.1%). There also was no significant difference when

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Tight glucose control					Liberal glucose control							
No. of patients	Mean age (s.d.)	% Male	% Diabetes	Target level	No. of patients	Mean age (s.d.)	% Male	% Diabetes	Target level	Outcomes extracted for analyses	Follow-up	Jadad score	Allocation concealment
765	63.4 (13.6)	71	13	80–110	783	62.2 (13.9)	71	13	180–200	Mortality, AKI, sepsis, SH	Hospital days	3	Adequate
34	56 (22)	75	13	80–120	27	55 (22)	63	11	180–220	Mortality hypoglycemia	Hospital days	2	Adequate
185	63 (15)	72	20	80–100	186	63 (16)	66	19	≤200	Mortality, AF, SSI, hypoglycemia, AKI	30 days	3	Adequate
43	NA	NA	NA	80–110	45	NA	NA	NA	180–200	Mortality	Hospital days	3	Adequate
100	58 (9)	59	100	100–150	100	57 (12)	65	100	<200	Mortality, SSI, AKI, AF	Hospital days	2	Unclear
27	62 (2)	74	41	70–110	25	67 ± 2	68	40	<180	SSI, AF, MI	Hospital days	4	Adequate
241	57.3 (11.9)	63.5	9.5	80–110	242	56.9 (12.7)	51.7	10.3	<215	Mortality, sepsis, pneumonia, SSI, UI	6 months	3	Adequate
114	67 (10)	59	54	100–150	122	71 (11)	54	53	>150	Hypoglycemia, SSI, AKI, MI	Hospital days	3	Adequate
54	57 (12)	43.1	NA	80–130	55	58 (12)	56.9	NA	160–200	Mortality, SSI, AKI	30 days	3	Adequate
1111	NA	NA	NA	81–108	1121	NA	NA	NA	≤180	Mortality	90 days	3	Adequate
80	58	80	100	100–150	40	40	80	100	<200	SSI	Hospital days	1	Unclear
125	58.5 (8.1)	66.4	0	80–110	123	59.9 (7.6)	64.2	0	<200	Mortality, SH, SSI, sepsis, UI, pneumonia	28 days	3	Adequate
92	58.2 (6.3)	69.6	100	80–110	87	59.4 (7.3)	65.5	100	180–200	Mortality, SH, SSI, UI, sepsis, pneumonia	28 days	3	Adequate
40	63 (9)	80	100	90–120	42	65 (9)	61.9	100	120–180	AF, MI	30 days	2	Adequate
91	62.5 (10.2)	89	41	90–120	98	62.8 (9.5)	80	45	121–180	Mortality, SH, SSI, AF hypoglycemia, AKI, pneumonia	30 days	3	Adequate
82	NA	NA	100	80–140	83	NA	NA	100	180–200	Mortality, MI, hypoglycemia	6 months	3	Adequate
196	64 (11)	64	28	80–110	185	64 (11)	70	26	180–200	Mortality, SSI, AKI, sepsis, MI pneumonia	1 year	3	Adequate
538	NA	NA	NA	80–110	521	NA	NA	NA	<180	Mortality	90 days	3	Adequate
90	53 (16)	56	4.4	80–108	98	53 (15)	61	9.2	100–160	Mortality, SH, hypoglycemia	90 days	3	Adequate
33	44.2 (9.5)	42.4	0	80–110	32	43.1 (10.3)	46.9	0	≤200	Mortality, SSI, sepsis, AKI, hypoglycemia	30 days	4	Adequate
222	66.7 (10.1)	64	24.3	80–110	225	66.4 (10.4)	67.1	26.2	140–180	Mortality, SSI	Hospital days	2	Unclear
151	64 (9)	70	51	100–140	151	64 (10)	74	50	141–180	Mortality, pneumonia AKI, hypoglycemia	90 days	3	Adequate
106	60.5 (13.2)	43.4	100	80–110	106	61.1 (13.5)	38.7	100	<200	Mortality, SH, SI, UI AKI, pneumonia, sepsis	Hospital days	2	Unclear
38	58.2 (10.8)	44	100	100–120	37	59.2 (8.9)	35	100	≤200	Mortality, SSI, hypoglycemia, AKI	30 days	2	Unclear
67	54.9 (6.5)	73.1	100	110–149	68	56.4 (7.8)	67.7	100	150–180	Mortality, SSI, AKI, MI, AF	30 days	2	Unclear
44	46.7 (10.4)	68.2	18.2	80–110	44	45.1 (10.7)	63.6	20.5	180–200	Mortality, SSI, UI, pneumonia, Sepsis	6 months	5	Adequate

AF, atrial fibrillation; AKI, acute kidney injury; CABG, coronary artery bypass grafting; CLM, central laboratory method; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; POCT, point of care testing; SH, severe hypoglycemia; SSI, surgical site infection; UI, urinary infection.

grouped by intraoperative glucose control (RR, 0.87; 95% CI, 0.12–6.14; I^2=47.3%), postoperative glucose control (RR, 0.93; 95% CI, 0.79–1.10; I^2=34.2%), intraoperative and postoperative glucose control (RR, 0.62; 95% CI, 0.28–1.35; I^2=0%).

Secondary outcomes

We pooled the effects of the TGC on each morbidity by analyzing the eligible studies with homogeneous results. Furthermore, we performed subgroup analyses by intensity of TGC on surgical site infection and acute kidney injury, of which the number of included literatures were 17 and 12 respectively (Fig. 4).

Hypoglycemic events were regarded as the major adverse effects of TGC. Fifteen studies were involved in our meta-analysis, of which 9 studies reported the incidence of hypoglycemia and 6 studies reported the incidence of severe hypoglycemia. The risk of hypoglycemia was increased (RR, 2.14; 95% CI, 1.40–3.26; I^2=37.9%),

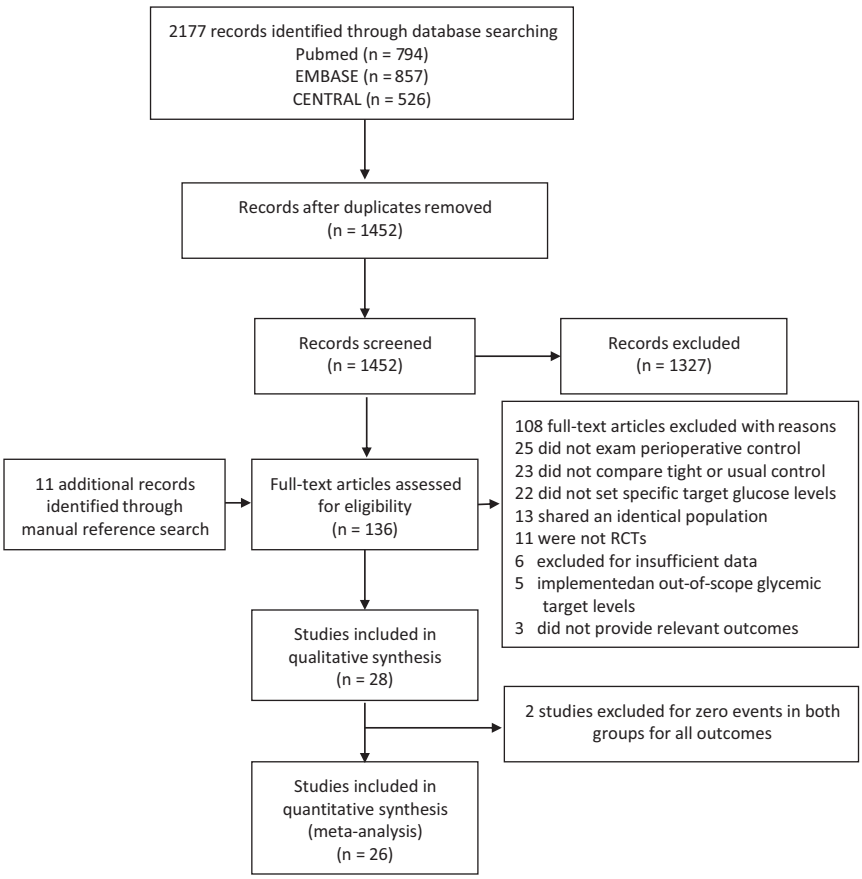

Figure 1
Flowchart of study selection.

and similarly for severe hypoglycemia (RR, 4.82; 95% CI, 2.66–8.72; I^2=0%).

Analysis results revealed the obvious decreased morbidity in the very tight glucose control group for surgical site infection (RR, 0.57; 95% CI, 0.42–0.77; I^2=0%) and acute kidney injury (RR, 0.75; 95% CI, 0.57–0.99; I^2=0%). Significant difference was also found in the overall tight glucose control group for surgical site infection (RR, 0.57; 95% CI, 0.41–0.79, I^2=43.0%) and acute kidney injury (RR, 0.79; 95% CI, 0.63–0.97; I^2=0%).

For the other adverse events, the obvious reductions of risks were founded in sepsis (RR, 0.61; 95% CI, 0.44–0.87; I^2=0%) and atrial fibrillation (RR, 0.75; 95% CI, 0.58–0.97; I^2=23.0%). We did not find significant difference in pneumonia, urinary infection and myocardial infarction (Fig. 4).

Publication bias

The shape of funnel plot did not show obvious asymmetry (Fig. 5). All the Begg's test *P* values and the majority of Egger's test *P* values were more than 0.05 (Supplementary Table 2), evidence of possible publication bias existed for surgical site infection (Begg's test, *P* for bias=0.232; Egger's test, *P* for bias=0.025).

Discussion

The results of our meta-analysis demonstrated that perioperative TGC (the upper level of glucose goal ≤150 mg/dL) was associated with a significant reduced risk of mortality in the short-term mortality subgroup, non-diabetic subgroup, cardic surgery subgroup and when compared to the very liberal glucose control. For postoperative morbidities, obvious decreased risks were found in sepsis, surgical site infection, atrial fibrillation and acute kidney injury, and no difference was found in the incidence of pneumonia, urinary infection and myocardial infarction. Furthermore, we detected increased risks of hypoglycemia and severe hypoglycemia in surgical patients receiving TGC.

Although the landmark trial revealed a significant reduction of in-hospital mortality among critically ill patients receiving postoperative TGC (7), subsequent RCTs did not show survival benefit of perioperative TGC regardless of the diabetic status. Furthermore, similar

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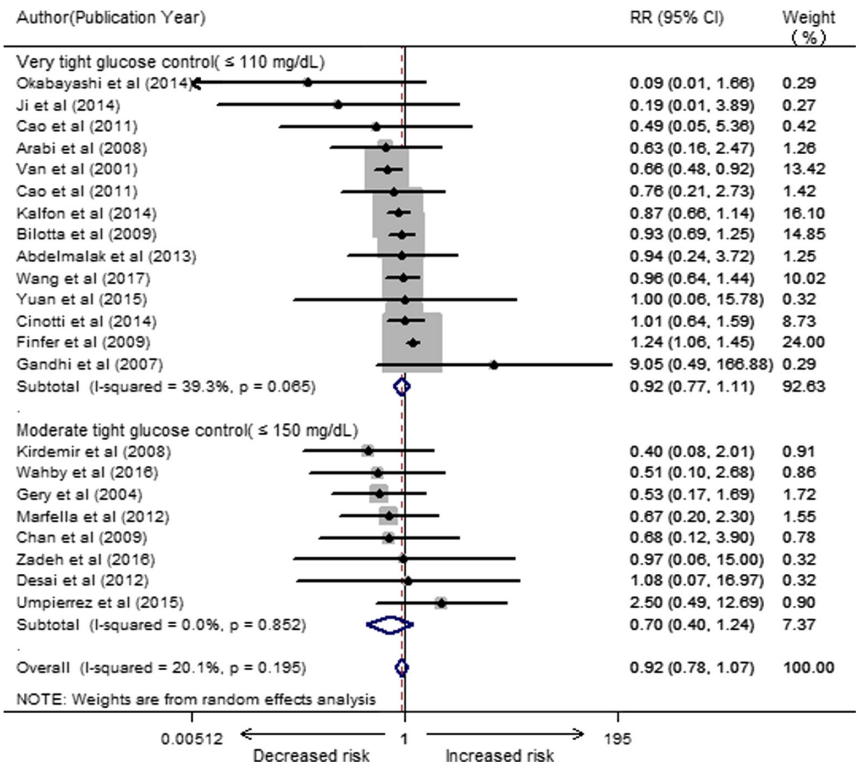

Figure 2
Random effects meta-analysis of the effect of perioperative tight glycemic control on mortality, stratified by different intensity of glucose control target.

conflicts existed among previous published meta-analyses (23, 24, 26, 27, 28). In order to ascertain the possible survival benefits in specific conditions, we performed a series of subgroup analyses for mortality. Short-term mortality was significantly lower in the tight control group. Although hypoglycemia events were more common with tight glucose control, but these were not associated with an increase in mortality. This will help researchers to dispel concerns about the mortality related to hypoglycemia. Besides, we detected a visible survival benefit of TGC in non-diabetic patients rather than patients with pre-existing diabetes, which were also confirmed

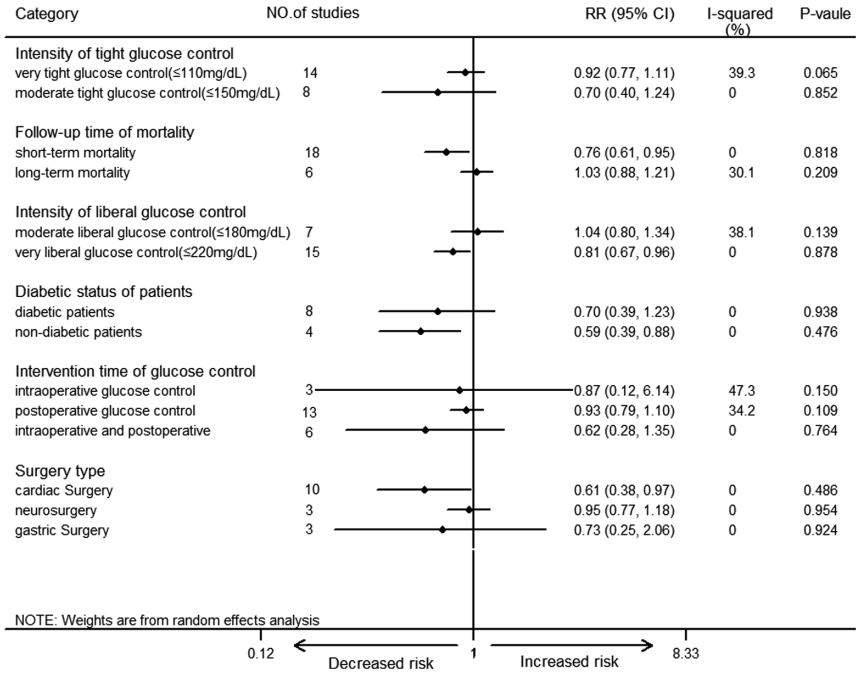

Figure 3
Forest plot of subgroup analyses for mortality.

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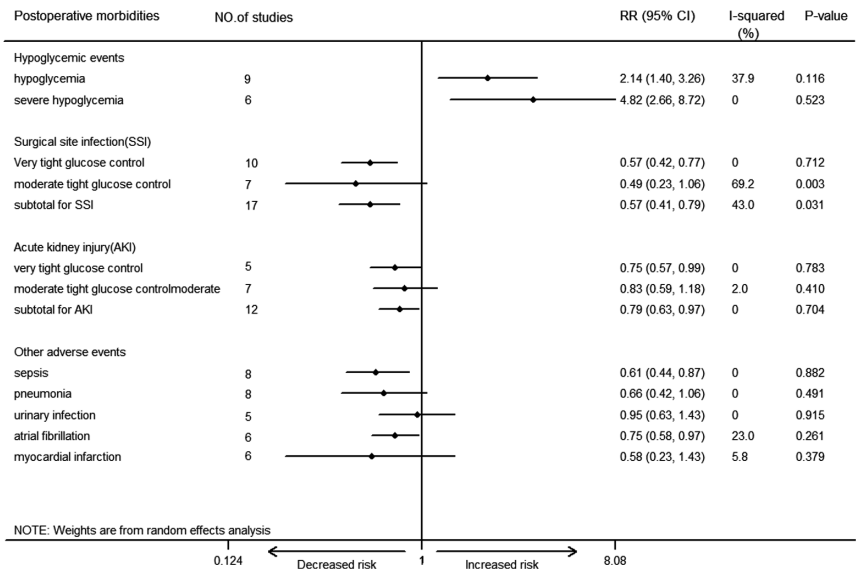

Figure 4
Comparison of postoperative morbidities between tight glycemic control and liberal control among surgical patients.

by some researchers previously (45, 46, 47). There is an increased risk that non-diabetic patients experience from perioperative hyperglycemia compared with diabetic patients; therefore, non-diabetic patients may benefit more from perioperative TGC. Some possible mechanisms may explain the findings, a decreased expression of GLUT transporters in specific cells consisted in diabetes mellitus in order to accommodate the chronic hyperglycemia status (45), and then the poor tolerance of rapid decline in blood glucose concentration (via the implementation of TGC) may evoke the counter-regulatory reaction and raise the inflammatory cytokine levels in diabetic individuals (48, 49). Another very interesting observation was the survival benefit of TGC when compared to the very liberal glucose control (181–220 mg/dL), there is likely no advantage for excessive liberal control when a greater degree of difference in glucose control existed between the tight and liberal arms. It is also in agreement with recent guidelines' recommendation that the upper glycemic target no more than 180 mg/dL when implementing perioperative glycemic control (1, 3, 50, 51).

With regard to the hypoglycemia, we used the hypoglycemia alert value (a measured blood glucose concentration ≤70 mg/dL), which was defined in the 'Standards of Medical Care in Diabetes' of the American Diabetes Association in 2018; but for the severe hypoglycemia, no specific glucose threshold was defined as glycemic criteria (52). In order to remove the potential bias among studies which reported varied standards of severe hypoglycemia, we only involved the most often used standards from the publications (a measured blood glucose concentration ≤40 mg/dL) in our analysis. The pooled results revealed increase risks of hypoglycemia and severe hypoglycemia for surgical patients using IIT, these raised various safety concerns. However, the risks of hypoglycemic events could be controlled well by using carefully monitored intravenous insulin infusion protocols in some studies, and TGC induced some beneficial effects on many efficacy outcome measures to some extent (9, 11).

For the other important surgical outcomes, we also found obvious decreased risks in sepsis, surgical site infection, atrial fibrillation and acute kidney injury. The concerns about mortality related to hypoglycemia have been one of the barriers to more widespread adoption of perioperative glucose control, but allow for the significant reduced risks of short-term mortality, sepsis, surgical site infection, atrial fibrillation and acute kidney injury, and the implementation of perioperative TGC is necessary. The researchers could implement the tight glucose control carefully in order to achieve the target level, which is helpful to avoid hypoglycemia events.

Compared to the preceding published related meta-analyses (23, 24, 25, 26, 27, 28, 29), our work has several strengths. Firstly, we involved more RCTs for analyses, especially three influential large sample RCTs with discrepant results (7, 13, 20), it was beneficial to reach a more realistic conclusion. Secondly, for the primary outcome mortality, we carried out multiple subgroup analyses to detect whether potential survival benefits existed in different intensity of TGC, short-term or long-term mortality, cardiac surgery type, different intervention time, diabetic status of participants and compared to different intensity of liberal control. Finally, we pooled the effects of more health-related complications, which can help us to evaluate the risk of TGC more comprehensively.

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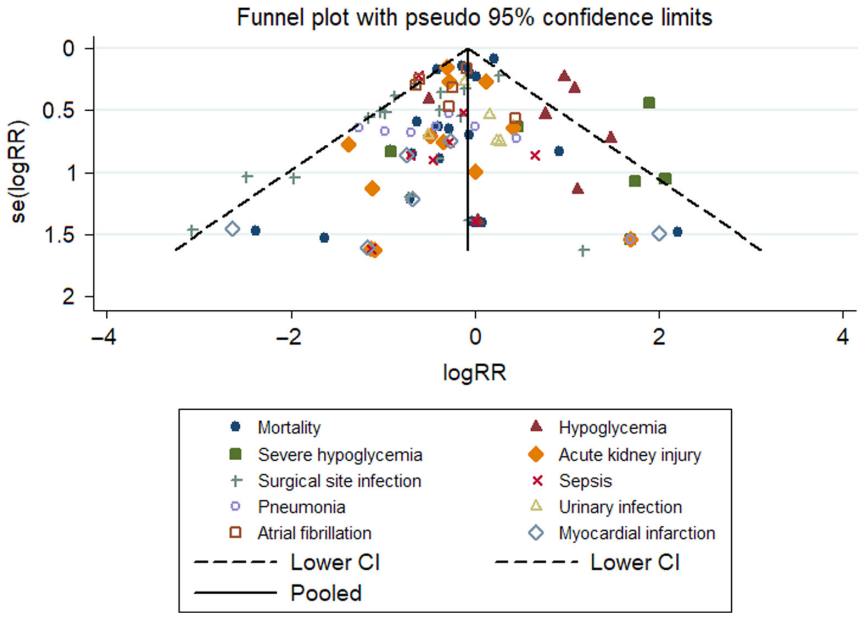

Figure 5
Begg's funnel plot with 95% confidence limits (CIs) of publication bias test.

However, several limitations existed in our work. First, we only screened the studies published in English and involved in three major electronic databases (PubMed, EMBASE and CENTRAL), potential relevant literatures unpublished or reported in other language and databases may not be involved. Second, eight studies included in the meta-analysis were regarded as low quality due to the Jadad Scale, mostly because of the unblinded design. In consideration of the nature of the intervention, the researchers should know the type and intensity of glucose control, in order to correct hypoglycemia timely, which was a crucial complication during insulin treatment. Besides, most of them used objective standards to evaluate outcomes and implemented blind to the other outcomes to minimize possible bias, so we did not exclude these studies. Third, we did not group studies based on the glucose control that was actually achieved, because most studies did not report the glucose level they actually achieved. Fourth, included studies were performed in different periods, used different research protocols and glucose control methods; these can lead to potential heterogeneity between studies. Finally, although the target levels of perioperative glycemic control recommended by current guidelines were inconsistent and controversial (1, 2, 53, 54, 55), recently a widely recognized temperate target glucose range of 140–180 mg/dL is recommended for the majority of diabetic inpatients (51). But we were incapable of comparing the surgical outcomes between this category of glucose control and other categories, because the pooled effects from the limited studies may generate unreliable results. Further RCTs evaluating the effects of perioperative glycemic control are suggested to classify the glycemic goals into more categories and measure more comprehensive surgical morbidities.

Conclusions

Perioperative TGC (the upper level of glucose goal ≤150 mg/dL) showed a statistically significant survival benefit for four specific subgroups, short-term mortality subgroup (deaths occurred during the hospital days or within 30 days after surgery), non-diabetic populations, cardiac surgery subgroup and the very liberal glycemic target (upper level of perioperative glucose goal 181–220 mg/dL). Moreover, significant decreased risks were found in sepsis, surgical site infection, atrial fibrillation and acute kidney injury for perioperative TGC. Although increased risk of hypoglycemic events related to tight control is worthy of attention, tight control was not associated with an increase in surgical mortality and morbidity. Perioperative tight glucose control will benefit patients when it is done carefully.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EC-18-0231.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Author contribution statement
Zhou-Qing Kang designed the study and performed the literature search and participated in screening, extracting and analyzing the data. She also drafted and critically revised the manuscript. Jia-Ling Huo screened the eligible articles and extracted the data. Xiao-Jie Zhai conceived the study and contributed to the revision of the manuscript.

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