Treatment of the complex abdomen and acute intestinal failure

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Citation for published version (APA):
de Vries, F. E. E. (2018). Treatment of the complex abdomen and acute intestinal failure

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A SYSTEMATIC REVIEW AND META-ANALYSIS ON TARGETING LOWER PERIOPERATIVE GLUCOSE LEVELS TO REDUCE SURGICAL SITE INFECTIONS

British Journal of Surgery 2017 Jan;104:e95-e10

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ABSTRACT

Background – There is a clear association between hyperglycaemia and surgical site infection (SSI). Nonetheless, there is concern that intensive glucose control risks hypoglycaemia, in turn resulting in potentially severe complications. Studies comparing intensive glucose control protocols with conventional protocols in relation to reduction of SSI and other outcomes including hypoglycaemia, mortality, and stroke were systematically reviewed.

Methods – Pubmed, Embase, CENTRAL, CINAHL, and WHO databases from 01-01-1990 to 01-08-2015 were searched. Inclusion criteria were randomized controlled trials (RCTs) comparing intensive glucose control protocols with conventional protocols, and reporting on the incidence of SSI. Meta-analyses were performed with a random effects model and meta-regression subsequently done. Targeted blood glucose levels, achieved blood glucose levels, and important adverse events were summarized.

Results – Fifteen RCTs were included. Summary estimate showed a significant benefit of an intensive protocol over a conventional protocol in reducing SSI, OR 0·43 (95% CI 0·29-0·64) p<0·001. A significantly higher risk of hypoglycaemic events was found for the intensive group as compared to the conventional group (OR 5·55 (95% CI 2·58-11·96), without an increased risk of mortality or strokes (OR 0·74 (95% 0·45-1·23) and OR 1·37 (95% CI 0·26-7·20, respectively)). These results were consistent both in patients with and without diabetes and both in studies with moderate strict and very strict glucose control.

Conclusion – Targeting stricter and lower blood glucose levels (<150 mg/dL) using an intensive protocol in the perioperative period reduces SSI with an inherent risk of hypoglycaemic events but without a significant increase in serious adverse events.
INTRODUCTION

Surgical site infections (SSI) cause considerable morbidity, mortality, and increased health care costs worldwide. An important factor resulting in an increased risk of SSI is hyperglycaemia (see Table 1 for definitions used). Multiple mechanisms contribute to hyperglycaemia seen with major surgery. The stress response to operative trauma results in a release of catabolic hormones and inhibition of insulin function. Surgical stress influences pancreatic β-cell function resulting in lower plasma insulin levels. Altogether, this relative hypo-insulinaemia, insulin resistance, and excessive catabolism from the action of counter regulatory hormones commonly lead to hyperglycaemia.

Table 1. Explanatory table of definitions used

<table>
<thead>
<tr>
<th>Definition</th>
<th>Blood Glucose Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>&gt; 180 mg/dl / 10.0 mmol/L to &gt; 220 mg/dl / 12.2 mmol/L</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>&lt; 40 mg/dl / 2.2 mmol/L to &lt; 80 mg/dl / 4.4 mmol/L</td>
</tr>
<tr>
<td>Conventional protocol</td>
<td>More liberal and higher blood glucose target levels, generally ≤ 220 mg/dl / 12.2 mmol/L</td>
</tr>
<tr>
<td>Intensive protocol</td>
<td>Stricter and lower blood glucose target levels, generally ≤ 150 mg/dl / 8.3 mmol/L</td>
</tr>
<tr>
<td>Very strict</td>
<td>≤ 110 mg/dl / 6.1 mmol/L</td>
</tr>
<tr>
<td>Moderate strict</td>
<td>≤ 110-150 mg/dl / 6.1-8.3 mmol/L</td>
</tr>
</tbody>
</table>

Several observational studies showed an association between hyperglycaemia and SSI both in patients with and without diabetes, and in different procedures. The first large randomized controlled trial (RCT) addressing this topic, showed a significant reduction in mortality in intensive care unit (ICU) patients when using tight glucose controls, but conflicting reports have been published since then. In recent years, several systematic reviews and meta-analysis addressing this subject have not all found a clear benefit of an intensive protocol over a conventional protocol using mortality as an endpoint. Moreover, the authors expressed concerns for the risk of hypoglycaemia and the resulting adverse effects.

Recently, additional trials assessing the effect of intensive glucose control have been reported. Present aim was to evaluate the impact of intensive (with stricter and lower blood glucose target levels) vs. conventional (with more liberal and higher blood glucose target levels) glucose control protocols on the risk of SSI, through a systematic literature review. Present review also aimed to define optimal perioperative blood glucose target levels in diabetic and non-diabetic surgical patients to prevent SSI. Because of concerns regarding the risk of hypoglycaemia and the potential consequences of hypoglycaemic events, mortality, and strokes were included as outcomes in this systematic review and meta-analysis.
METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed\textsuperscript{14}.

Search strategy and selection criteria
PubMed, EMBASE (Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, and World Health Organization (WHO) global and regional databases were searched for articles published from January 1990 to August 2015 by use of the terms referring to SSI, glucose control, and surgical procedures. We have chosen not to include studies before 1990 as there have been continuous changes in other health care practices and older studies would confound conclusions. Language was restricted to English, Spanish, and French. The complete search is included in appendix A. Two authors (FdV and SG) independently screened all titles and abstracts. RCTs comparing a perioperative intensive glucose protocol (with stricter and lower blood glucose target levels) with a conventional glucose protocol (with more liberal and higher blood glucose target levels) in adult patients were included. The primary outcome was SSI (or wound infections). Secondary outcomes were hypoglycaemic events (both laboratory results or clinically relevant), stroke, and mortality. Studies comparing different protocols or a different route of administration with comparable blood glucose target levels were excluded. References of the included studies were screened for other relevant studies.

Data extraction
Study characteristics including year of publication, number of patients, types of surgical procedures, protocols for glucose control used, and outcomes were retrieved from the text and summarized in the evidence table (Table 2). Protocols, target levels, and definitions of hypoglycaemia are summarized in Appendix B. Blood glucose target levels, achieved blood glucose levels, and adverse effects for both the intensive and the conventional group are summarized in appendix D. Glucose levels are presented throughout the text as mg/dL / mmol/L.

Quality assessment
Quality of the included studies was assessed with the Cochrane Collaboration’s tool for assessing risk of bias\textsuperscript{15}. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology (GRADE Pro software\textsuperscript{16}) was used to assess the quality of the body of retrieved evidence.
Table 2. Evidence table (blood glucose = mg/dL / mmol/L)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of surgery</th>
<th>Population</th>
<th>SSI definition</th>
<th>Intervention</th>
<th>Control</th>
<th>Timing</th>
<th>Outcome (SSI/wound infections) (Hypoglycaemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmalak</td>
<td>Major non-cardiac surgery, ≥40 years, ASA ≤4</td>
<td>Diabetic and non-diabetic patients</td>
<td>Deep and organ space surgical site infections</td>
<td>Intensive: dynamic intravenous infusion with blood glucose concentrations were targeted 80-110 / 4.4-6.1</td>
<td>Conventional group: dynamic intravenous infusion with blood glucose concentrations were targeted 180-200 / 10.0 -11.1</td>
<td>Intra-operative + 2 hours post-operatively (is intraoperative in analysis)</td>
<td>Intensive group: 17/196, Conventional group 18/185 (OR 0.88, 95% CI 0.24 – 3.20, p=0.72)</td>
</tr>
<tr>
<td>Albacker</td>
<td>Cardiac surgery (CABG)</td>
<td>Diabetic and non-diabetic patients</td>
<td>Superficial wound infection</td>
<td>Intensive group: fixed high dose intravenous insulin infusion with dextrose 20% separately to maintain glucose level between 70 - 110 / 3.9-6.1 (“insulin clamp”).</td>
<td>Conventional group: Intravenous insulin infusion (sliding scale method) to maintain blood glucose &lt; 180 / 10.0</td>
<td>Intra-operative</td>
<td>Fixed high-dose insulin group 1/27 Conventional group 1/25 (p=0.99)</td>
</tr>
<tr>
<td>Bilotta</td>
<td>Emergency cerebral aneurysma clipping</td>
<td>Diabetic and non-diabetic patients</td>
<td>Wound infections as defined by National Nosocomial Infection Surveillance System (NNIS).</td>
<td>Intensive group: continuous intravenous insulin infusion maintain glucose levels 80 – 120 / 4.4-6.7</td>
<td>Conventional group: continuous intravenous insulin infusion to maintain glucose levels 80-220 / 4.4-12.2</td>
<td>Intra- and postoperative (until discharge from ICU or day 14)</td>
<td>Intensive group 1/40 Conventional group 2/38 Hypoglycaemia (&lt;80 / 4.4) occurred more in the strict group compared with the conventional group, RR 3.0 (95% CI 2.07 to 4.35)</td>
</tr>
<tr>
<td>Cao</td>
<td>Gastrectomy</td>
<td>Diabetic patients (type 2) receiving parenteral nutrition</td>
<td>Wound infection (SSI, CDC)</td>
<td>Intensive group: continuous intravenous insulin infusion target BG 80-100 / 4.4-6.7</td>
<td>Conventional group: continuous intravenous insulin infusion with target BG &lt; 200 / 11.1</td>
<td>Post-operative until oral intake</td>
<td>Intensive group 4/92 Conventional group 12/87 Severe hypoglycaemia (&lt;40 / 2.2) 6/92 strict group and 1/87 conventional group</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Surgery</td>
<td>Patients</td>
<td>Wound Infection</td>
<td>Intensive Group</td>
<td>Conventional Group</td>
<td>Postoperative until</td>
<td>Results</td>
</tr>
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</tr>
<tr>
<td>Cao 2011</td>
<td>Gastrectomy</td>
<td>Non-diabetic patients receiving parenteral nutrition</td>
<td>Wound infection (SSI, CDC)</td>
<td>Intensive group: continuous intravenous insulin infusion target BG 80-100 / 4.4-6.7</td>
<td>Conventional group: continuous intravenous insulin infusion with target BG &lt; 200 / 11.1</td>
<td>Postoperative until oral intake</td>
<td>Intensive group 5/125, Conventional group 13/123. Severe hypoglycemia (&lt;40 / 2.2) occurred in 8/125 in strict group and 1/123 conventional group.</td>
</tr>
<tr>
<td>Chan 2009</td>
<td>Cardiac surgery</td>
<td>Patients with and without diabetes</td>
<td>Wound infection (no specific definition)</td>
<td>Intensive group: targeted glucose level 80-130 / 4.4-7.2, continuous intravenous insulin infusion was initiated when glucose levels exceeded 130 / 7.2</td>
<td>Conventional: targeted glucose level 160-200 / 8.9-11.1, continuous intravenous insulin infusion was initiated only if blood glucose levels exceeded 200/11.1</td>
<td>Intra-operative and 36-hours after surgery</td>
<td>Intensive group 6/54, Control group 9/55 (p = 0.09, 95% CI 0.3-1.2). Hypoglycemia (&lt;50 / 2.8) was not significantly different in both groups p=0.67</td>
</tr>
<tr>
<td>Desai 2012</td>
<td>Cardiac surgery</td>
<td>Patients with and without diabetes</td>
<td>Deep sternal wound infection</td>
<td>Intensive group: target blood glucose level 90-120 / 5.0-6.7</td>
<td>Conventional group: target blood glucose level 121-180 / 6.7 – 10.0</td>
<td>Post-operative for a minimum 72 hours</td>
<td>Intensive: 1/91, Conventional: 0/98 (treatment difference -0.01, 95% CI -0.03 to 0.01). Hypoglycemia (&lt;60 / 3.3): 1/91, C 1/98.</td>
</tr>
<tr>
<td>Emam 2010</td>
<td>Cardiac surgery</td>
<td>All type 2 diabetic patients</td>
<td>Wound infection (superficial, deep)</td>
<td>Intensive group: intravenous insulin infusion (Braithwaite protocol) on the evening before surgery or sooner if BG ≥150 / 8.3 Target level of BG was 100-150 / 5.6-8.3.</td>
<td>Conventional group: Subcutaneous insulin per sliding scale. Target BG &lt; 200 / 11.1.</td>
<td>Intra-operative and 48 hours post-operatively</td>
<td>Intensive group 0/80, Conventional group 5/40. No patient in either group suffered a hypoglycaemic episode, either clinically or biochemically (less than 50 / 2.8).</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Study Population</td>
<td>Intensive Group</td>
<td>Conventional Group</td>
<td>Duration</td>
<td>Results</td>
<td></td>
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<tr>
<td>Gandhi 2007</td>
<td>Cardiac surgery</td>
<td>Diabetic and non-diabetic patients</td>
<td>Intensive group: continuous insulin infusion to maintain intraoperative glucose levels between 80-100 / 4.4 – 5.6</td>
<td>Conventional group: Not given insulin during surgery unless glucose levels were greater than &gt;200 / 11.1, then intravenous insulin infusion</td>
<td>Intra- and postoperative (not specified)</td>
<td>Intensive group 6/185, Conventional group 7/186. (RR 0.9 (96% CI 0.3-2.5, p = 0.79)), No significant difference when stratified by diabetic status. One patient in every group experienced intra-operative hypoglycemia (&lt; 60 / 3.3) RR 1.01 (95% CI 0.06–15.95), 8 in strict group and 14 conventional group had hypoglycemic episode during first 24 hours in ICU.</td>
<td></td>
</tr>
<tr>
<td>Grey 2004</td>
<td>Critical ill surgical patients</td>
<td>RCT, all hyperglycemic (≥ 140/7.8) adult surgical ICU patients with and without diabetes</td>
<td>Intensive group: intravenous infusion to maintain blood glucose between 80-120 / 4.4-6.7</td>
<td>Conventional group: Intravenous infusion to maintain blood glucose between 180 – 220/10.0-12.2</td>
<td>Postoperative throughout their ICU stay</td>
<td>Intensive group 2/34, Conventional group 10/34. Hypoglycemic events (&lt;60/3.3) occurred in 32% of the patients in strict protocol and 7.4% of the patients in conventional protocol (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Kirdemir 2008</td>
<td>Cardiac surgery</td>
<td>All diabetic patients</td>
<td>Intensive group: continuous insulin infusion, target glucose 100-150 / 5.6-8.3</td>
<td>Conventional group: Subcutaneous insulin, target glucose level &lt;200 / 11.1 (sliding scale)</td>
<td>Intra-operative and until third post-operative day</td>
<td>Intensive group: 1/100, Conventional group: 12/100, p=0.003 No hypoglycemic episodes</td>
<td></td>
</tr>
<tr>
<td>Lazar 2011</td>
<td>Cardiac surgery</td>
<td>All diabetic patients</td>
<td>Intensive group: continuous intravenous infusion with blood glucose target level 90-120/5.0-6.7</td>
<td>Conventional group: continuous intravenous infusion with blood glucose target level 120-180/6.7-10.0</td>
<td>Intra- and 18h postoperative</td>
<td>Intensive 0/40, Conventional 0/42 Hypoglycemic episodes (&lt; 80/4.4) intensive 30/40, conventional 4/42</td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Procedure</td>
<td>Group Description</td>
<td>Intensive Group Glucose Target</td>
<td>Conventional Group Glucose Target</td>
<td>Outcome</td>
<td>Details</td>
</tr>
<tr>
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</tr>
<tr>
<td>Okabayashi</td>
<td>2014</td>
<td>Hepato-biliary-pancreatic surgery</td>
<td>Diabetic and non-diabetic patients</td>
<td>Intensive group: intravenous insulin infusion with blood glucose target level 80-110 / 4.4-6.1</td>
<td>Conventional group: intravenous insulin infusion with blood glucose target level 140-180 / 7.8-10.0</td>
<td>Intra- and postoperative</td>
<td>Intensive group 9/222, Conventional group 22/225 (p=0.028)</td>
</tr>
<tr>
<td>Yuan</td>
<td>2015</td>
<td>Gastrectomy</td>
<td>All diabetic (type 2) patients</td>
<td>Intensive group: continuous insulin infusion with target glucose 80-110 / 4.4-6.1</td>
<td>Conventional group: subcutaneous bolus insulin with target glucose target &lt; 200 / 11.1</td>
<td>Post-operative</td>
<td>Intensive 5/106, Conventional 14/106 (p&lt;0.03)</td>
</tr>
</tbody>
</table>

No hypoglycemic (<80 / 4.4) events
Severe hypoglycemia (<40 / 2.2): intensive group 8/106, conventional 1/106, p=0.035
Hypoglycemic events: intensive group 3/50, conventional group 1/50 (NS)
Data synthesis and analysis
Meta-analyses were performed with Review Manager 5.3 with a random effect model. Studies were divided in studies with an upper limit target level < 110 mg/dL (6.1 mmol/L) in the intensive group (very strict glucose control) and studies with an upper limit target level 110-150 mg/dL (6.1-8.3 mmol/L) (moderate strict glucose control) in the intensive group for meta-analyses. Meta-regression was performed with SPSS Statistics 22.0.

RESULTS
Of the 1839 articles identified by the search, 27 articles were assessed for full review. Another 12 articles were excluded for the following reasons: five studies did not report on SSI or wound infections as a separate outcome\(^5,17-20\); two studies\(^5,17\) included medical, as well as surgical patients; five studies compared a different protocol or route of administration but with comparable blood glucose target levels\(^21-25\); one study involved trauma patients but no surgical procedure\(^26\); and one more study was not a randomized trial\(^27\). Finally, 15 RCTs were included for analysis. The flowchart of the search is depicted in Figure 1.

![Figure 1. PRISMA flow chart of the systematic review](image-url)
Study characteristics

Fifteen RCTs\(^{28-42}\) compared an intensive protocol (targeting stricter/lower blood glucose target levels) with a conventional protocol (targeting more liberal/higher) blood glucose target levels. All studies in the intensive group used intravenous insulin administration whereas three studies in the conventional group employed subcutaneous administration\(^{36,38,41}\). Some of the studies used continuous insulin administration whereas others used intermittent. One study used a fixed high dose with dextrose 20% separately ("insulin clamp")\(^{29}\). All protocols used are summarized in Appendix B.

An important variable was the duration of glucose control. Two studies\(^{28,29}\) compared only intraoperative glucose control. Eight studies\(^{30,33,35,36,38-40,42}\) investigated intraoperative and postoperative glucose control and there were five studies\(^{31,32,34,37,41}\) examining post-operative glucose control. The definition of ‘postoperative’ varied from 18 hours, “until enteral nutrition” to a maximum of 14 days. Five studies\(^{31,35,38,39,41}\) were in patients with diabetes, eight studies\(^{28-30,33,34,36,37,40}\) both in patients with and without diabetes, and two studies\(^{32,42}\) in patients without diabetes. Nine studies\(^{28,29,33-36,38,39,42}\) were performed in patients undergoing cardiac surgery and four studies\(^{31,32,40,41}\) in patients undergoing abdominal surgery, one study\(^{37}\) in critical ill surgical patients, and one other study\(^{33}\) in patients undergoing emergency cerebral aneurysm clipping. Most of these studies were performed in an ICU setting.

None of the studies had SSI or wound infections as their primary outcome, but SSI rates were reported. Most studies had a combined outcome of post-operative complications. The definition of SSI/wound infection also differed between studies. Four studies\(^{28,34,36,42}\) only mentioned deep/organ space wound infections, one study\(^{29}\) only reported superficial wound infections and the other studies either reported on both, or did not clearly describe their definitional criteria. The risk of bias in the included studies was serious as many variables were scored as unclear or even high. The risk of bias scoring is provided in Table 3. The evidence table with baseline characteristics and outcome is summarized in Table 2.
Table 3. Risk of bias

<table>
<thead>
<tr>
<th>RCT, Author, year</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Participants blinded</th>
<th>Care providers blinded</th>
<th>Outcome assessors blinded</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelmalak 2013</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH</td>
<td>LOW</td>
<td>UNCLEAR</td>
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<td>Albacker 2008</td>
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<td>UNCLEAR</td>
<td>HIGH</td>
</tr>
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<td>Bilotta 2007</td>
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<tr>
<td>Cao 2010</td>
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<td>LOW</td>
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<td>Cao 2011</td>
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<td>UNCLEAR</td>
<td>HIGH</td>
<td>HIGH</td>
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<td>Desai 2012</td>
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<td>HIGH</td>
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<td>Emam 2010</td>
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<td>Gandi 2007</td>
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<tr>
<td>Grey 2004</td>
<td>LOW</td>
<td>UNCLER</td>
<td>UNCLER</td>
<td>UNCLER</td>
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<td>Lazar 2011</td>
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<td>Okabayashi 2014</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLER</td>
<td>UNCLER</td>
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<td>Yuan 2015</td>
<td>LOW</td>
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<td>LOW</td>
<td>HIGH</td>
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<td>Zheng 2010</td>
<td>LOW</td>
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<td>UNCLER</td>
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</tbody>
</table>

Intensive protocol versus conventional protocol

Fifteen RCTs compared an intensive protocol with a conventional protocol. The meta-analysis, which had 1442 patients in the intensive group and 1394 in the control group, showed a significant benefit of an intensive protocol over a conventional protocol in reducing surgical site infections, OR 0.43 (95% CI 0.29–0.64) p<0.001 (Figure 2). Meta-analysis of eight studies\textsuperscript{28,29,31,32,36,40-42} with an upper limit target level < 110 mg/dL (6.1 mmol/L) in the intensive group showed a significant benefit of an intensive protocol pooled OR 0.50 (95% CI 0.35–0.73) and seven studies\textsuperscript{30,33-35,37-39} with an upper limit target level 110-150 mg/dl (6.1-8.3 mmol/L) showed similar effects with a pooled OR 0.27 (95% CI 0.09–0.78) (Figure 2). In meta-regression analyses, there was no evidence that the effect of intensive blood glucose control differed between studies including patients with or without diabetes (P=0.590). There was some evidence that the effect was smaller in studies that used intensive blood glucose control intra-operatively only (OR 0.88; 95% CI 0.45-1.74) compared to studies that used intensive blood glucose controls post-operatively or both intra- and post-operatively (OR 0.37; 95% CI 0.26–0.55, P=0.049 for difference between these ORs). This comparison was similar in studies with very strict and moderate strict glucose control (P=0.328).

Adverse events

Meta-analysis of adverse events showed a higher risk of hypoglycaemic events in intensive protocols vs conventional protocols (OR 5.55 (95% CI 2.58–11.96). These results were similar for studies with very strict (upper limit target level < 110 mg/dl) and moderate strict (upper limit target level 110-150 mg/dl) glucose control (OR 4.18 (95% CI 1.79–9.79) and OR 9.87 (95% CI
1.41-69.20), respectively. However, four of the 12 studies included in meta-analysis had no hypoglycaemic events and only five studies found significantly more asymptomatic hypoglycaemic events when using an intensive protocol while three other studies did not find a significant difference. For three studies the number of patients with a hypoglycaemic event were not reported and these studies were not included in meta-analysis. Meta-analyses of postoperative deaths and strokes showed no significant differences (OR 0.74 (95% 0.45-1.23) and OR 1.37 (95% CI 0.26-7.20) respectively) between intensive vs. conventional protocols. These meta-analyses are included in appendix C. Meta-regression showed no evidence for a difference in risk of adverse events between studies with very strict and those with moderate strict protocols of intensive glucose control. The risk was similar for hypoglycaemia (P=0.413), mortality (P=0.484), and stroke (P=0.511). All hypoglycaemic events are summarized in appendix D.

Figure 2. Forest plot of surgical site infection (SSI) following intensive and conventional protocols for target glucose levels. An inverse-variance random-effects model was used for meta-analysis. Odds ratios are shown with 95 per cent confidence interval.
Achieved blood glucose level

Figure 3 shows targeted blood glucose levels, mean achieved blood glucose levels, and surgical site infections. In appendix D there is an overview of the different blood glucose target levels, achieved mean blood glucose level and adverse events. The achieved blood glucose levels in the intensive group were lower than the conventional group for all studies. Four studies did not report their mean achieved blood glucose level but reported on the percentage of measurements within the target level, on minimum/maximum blood glucose levels or mentioned the fact that achieved blood glucose levels were significantly different between both groups.

![Targeted and achieved blood glucose levels and SSI](image)

Figure 3. Target and achieved blood glucose levels and surgical-site infection (SSI) or wound infection in groups undergoing an intensive and conventional protocols. Formula to calculate mmol/l from mg/dl: mmol/l = mg/dl / 18

**GRADE**

Overall evidence was qualified using GRADE. Overall, low quality of evidence shows that an intensive protocol has significant benefit in reducing SSI when compared to a conventional protocol. The level of evidence was downgraded due to serious risk of bias and indirectness. The GRADE table is included in table 4.
Table 4. GRADE table: intensive protocol with strict blood glucose target levels versus conventional protocol for perioperative glucose control to prevent surgical-site infection

An intensive protocol with strict blood glucose target levels vs. a conventional protocol for perioperative glucose control to prevent surgical site infection

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>No of participants (studies) Follow-up</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Publication bias</td>
<td>Overall quality of evidence</td>
<td>Study event rates (%)</td>
<td>Relative effect (95% CI)</td>
<td>Anticipated absolute effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical site infections</td>
<td>2836 (15 RCTs)</td>
<td>serious</td>
<td>not serious</td>
<td>serious</td>
<td>not serious</td>
<td>none</td>
<td>⬤ibaba ⬤ibaba ⬤ibaba ⬤ibaba</td>
<td>129/1394 (9.3%)</td>
<td>OR 0.43 (0.29–0.64)</td>
<td>51 fewer per 1000 (64 fewer to 31 fewer)</td>
<td></td>
</tr>
</tbody>
</table>

1. Overall, there was a great deal of unclear to high risk in blinding (especially outcome assessors), allocation concealment and incomplete outcome data
2. Most included studies investigated an intensive care population, which was mainly a cardiac population

CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial
DISCUSSION

Present systematic review and meta-analysis demonstrates that intensive protocols with stricter and lower blood glucose target levels are associated with a reduction in the number of surgical site infections, with an increased risk of hypoglycaemic events but without increased risks of stroke or mortality. This systematic review also compares achieved target levels in terms of surgical site infections and adverse events.

Meta-regression analysis showed, that the benefit of an intensive protocol over a conventional protocol was consistent both in patients with and without diabetes and begun both intra- and postoperative. A benefit of an intensive protocol in reducing surgical site infections was found both in studies with very strict glucose control (upper limit glucose level < 110 mg/dL (6.1 mmol/L)) and studies with moderate strict glucose control (upper limit between 110 and 150 mg/dL (6.1-8.3 mmol/L)). Moreover, the risk of severe adverse events (hypoglycaemia, mortality and stroke) was comparable between studies with very strict or moderate strict glucose control in the intensive group.

Since several cohort studies, in patients with and without diabetes, have shown that hyperglycaemia is associated with poorer postoperative outcome, most guidelines implemented blood glucose target levels between 140-200 mg/dl (7.8-11.1 mmol/L). Concern for the risk of hypoglycaemia has led to concerns for targeting lower levels. This is primarily based on results of the NICE-SUGAR17 study, which showed increased mortality in the intensive protocol group. Present analyses supports the notion that concerns driven by the results of the NICE-SUGAR trial (not including surgical patients) should not delay implementation of a more intensive protocol with stricter and lower blood glucose target levels. The NICE-SUGAR trial was performed in an ICU setting with critically ill patients who are at higher risk for mortality, and 21.6% of the patients were already septic at the time of randomization. Secondly, blood glucose target levels in the intensive group of the NICE-SUGAR trial are along the lowest of studies performed on this topic (81-108 mg/dl / 4.5-6.0 mmol/L). Umpierrez et al.24 showed in the RABBIT-2 trial, which studied a basal-bolus insulin protocol versus a sliding scale insulin protocol targeting blood glucose levels between 100-140 mg/dL / 5.6 - 7.8 mmol/L in a general surgical population with diabetes type 2, that a basal-bolus insulin protocol reduces postoperative complications including wound infection, pneumonia, bacteremia, and respiratory and acute renal failure (OR 3.39 (95% CI 1.50–7.65); p = 0.003). Their difference in wound infections was borderline significant (p=0.050). They found no difference in mortality and even a decrease in length of ICU stay. This study showed that targeting blood glucose levels between 100-140 mg/dL can be performed safely. Another observational study of Furnary et al.47 on cardiac surgery patients revealed that targeting blood glucose levels < 150 mg/dL (8.3 mmol/L) reduced SSIs by 66% (p<0.001) and reduced mortality.
In 2009 Kao et al.\textsuperscript{11} has performed a systematic review and meta-analysis investigating perioperative glycaemic control for the prevention of SSI. This study group has concluded that there was insufficient evidence to support intensive glucose control compared with conventional glucose control for the prevention of SSI. This conclusion is in conflict with the conclusion from the present systematic review, which can be explained by different inclusion criteria. The 2009 review has included studies with the same target levels in both groups and studies not reporting on SSI exclusively. Moreover, several new RCTs have been published since the 2009 review which are included in the present systematic review. Other systematic reviews and meta-analyses\textsuperscript{10,12,13} on perioperative glucose control focused on specific patient groups or had different endpoints.

In present meta-analyses of adverse events, the study of Gandhi et al.\textsuperscript{36} is the only study showing a significant higher number of stokes and deaths in the intensive group compared with the control group. When looking more in detail at the achieved blood glucose target levels in both groups it was found that achieved blood glucose levels were comparable after a 24-hour ICU stay (103 mg/dL / 5·7 mmol/L versus 104 mg/dL / 5·8 mmol/L, p=0·720) although they were significantly lower in the intensive protocol group during the operation and at baseline in the ICU (p<0·001). In addition, these achieved blood glucose levels are among the lowest in the included studies as we show in figure 3. This might clarify the relatively higher number of adverse events in this study. Other studies, including Ata et al.\textsuperscript{48} and Jeon et al.\textsuperscript{49}, found a clear dose-response relation between blood glucose levels and surgical site infections in favour of lower blood glucose levels.

Five studies reported significantly more hypoglycaemic measurements in the intensive group as compared to the control group. Although these events were asymptomatic (none of the studies reported clinical consequences), it remains unknown to what extend these hypoglycaemic episodes harm patients on the long term. And, even more important, if this potential harm outweighs the reduced risk of SSI. A higher odds ratio was found for hypoglycaemic events for moderate strict glucose control (OR 9.87 (95% CI 1.41-69.20) compared to very strict glucose control (OR 4.18 (95% CI 1.79-9.79)). This is probably due to the fact that only two studies were included in the meta-analysis of moderate strict groups compared to six studies in the meta-analysis of very strict group. This uncertainty is also reflected in the very wide confidence interval in the former mentioned.

Summarizing the aforementioned and considering the risk of hypoglycaemia, the evidence points out that both targeting lower stricter and lower blood glucose levels with an intensive protocol can be performed safely without the risk of a significant increase of serious adverse events. Blood glucose target levels as low as used for the NICE-SUGAR trial or Leuven-
trial (80-110 mg/dL / 4.5-6.0 mmol/L) should probably be avoided as the consequences of hypoglycaemic events remain unclear.

Several limitations should be addressed. Most of the studies used in this meta-analysis were performed in patients undergoing major cardiac or gastrointestinal surgery with a substantial part of the study population having a postoperative ICU stay. The question remains if present meta-analysis results can be extrapolated to a more general population, although observational studies outside the ICU in non-cardiac surgical patients show the same effect\textsuperscript{7,10,51,52,53} and the association of SSI and hyperglycaemia in a general surgical population is widely accepted. Moreover, the infrastructure to carry out safe intensive glucose control outside the ICU is a major concern as intensive glucose control demands skilled staff and brings higher workload and increased health care costs. However, intensive glucose control during the surgical procedure seems achievable in most settings. Probably results are primarily influenced by target or achieved blood glucose levels rather than differences in protocols or route of administration. Some studies\textsuperscript{21-23} (excluded from present review) comparing subcutaneous with intravenous administration with comparable blood glucose target levels did not show any difference in SSI, while studies\textsuperscript{25,38,41} (included in present review) comparing subcutaneous and intravenous administration did find a significant difference. Therefore, using subcutaneous insulin administration outside the operation room or ICU might also reduce the number of SSI.

There is substantial clinical heterogeneity between studies. Although all studies compared stricter and lower blood glucose target levels in the intensive group compared with more liberal and higher levels in the conventional group, there was a wide variety in protocols used, blood glucose target levels and achieved target levels. Moreover, in most studies there was a lack of information on baseline use of medication (for example antibiotics or anticoagulation) and intra-operative details such as blood loss. These factors might have influenced baseline risk of SSI and outcome.

Targeting stricter and lower blood glucose levels with an intensive perioperative glucose control protocol reduces surgical site infections without increased risks of mortality and stroke. Although the optimal target level cannot be derived from published data, the summary data of present systematic review and meta-analysis indicates that targeting glucose levels <150 mg/dL (<8.3 mmol/L) in the perioperative period can be performed safely with a minimal risk of asymptomatic hypoglycaemic events but without a significant increase in serious adverse events. Since studies with very strict and moderate strict glucose control are comparable effective in reducing SSI, and considering the risk of hypoglycaemia, targeting moderate strict glucose levels (110-150 mg/dL / 6.1-8.3 mmol/L) is preferred.
CHAPTER 8

REFERENCES


16. GRADEpro GDT.


