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Peri-operative glycaemic control regimens for preventing surgical site infections in adults

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Abstract

Background—Surgical site infections (SSIs) are associated with significant morbidity, mortality, and resource utilization and are potentially preventable. Peri-operative hyperglycaemia has been associated with increased SSIs and previous recommendations have been to treat glucose levels above 200 mg/dL. However, recent studies have questioned the optimal glycaemic control

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Authors' conclusions

There is insufficient evidence to support strict glycaemic control versus conventional management (maintenance of glucose < 200 mg/dL) for the prevention of SSIs. No trials were found that evaluated strict glycaemic control in the immediate pre-operative period or outside the setting of an intensive care unit. The trials were limited by small sample size, inconsistencies in the definitions of the outcome measures and methodological quality. Further large randomised trials are required to address this question and may be most appropriately performed in patients at high risk for SSIs.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support strict glycaemic control in the intra- and post-operative period among surgical patients for the prevention of SSIs. There are no randomised trials evaluating immediate pre-operative glycaemic control in any setting or intra-/post-operative glycaemic control in non-ICU patients. High quality evidence for strict glycaemic control in the intra- and/or post-operative period among surgical ICU patients, cardiac and non-cardiac, to reduce SSIs, independent of other potential benefits, is also lacking.

Implications for research

Further large, adequately-powered, well-designed randomised trials are necessary to identify the ideal target for peri-operative glycaemic control in patients at high risk for SSIs. Future trials should report all nosocomial infections as well as SSIs. Given the heterogeneity seen in the included trials, it would appear that trials should be targeted at very specific populations and attempts to draw broader conclusions should not be made.

CONTRIBUTIONS OF AUTHORS

Kao: Conception and design of study, analysis and interpretation of data, drafting the review, final approval of the document to be published

Meeks: Analysis and interpretation of data, drafting the review, commenting on the review critically for intellectual content, final approval of the document to be published.

Moyer: Design of study, analysis and interpretation of data, commenting on the review critically for intellectual content, final approval of the document to be published.

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Contributions of editorial base:

Nicky Cullum: edited the review, advised on methodology, interpretation and review content. Approved the final review prior to submission.

Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited and copy edited the review.

Ruth Foxlee: designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

None.

regimen to prevent SSIs. Whether the benefits of strict or intensive glycaemic control with insulin infusion as compared to conventional management outweigh the risks remains controversial.

Objectives—To summarise the evidence for the impact of glycaemic control in the peri-operative period on the incidence of surgical site infections, hypoglycaemia, level of glycaemic control, all-cause and infection-related mortality, and hospital length of stay and to investigate for differences of effect between different levels of glycaemic control.

Search strategy—A search strategy was developed to search the following databases: Cochrane Wounds Group Specialised Register (searched 25 March 2009), The Cochrane Central Register of Controlled Trials, The Cochrane Library 2009, Issue 1; Ovid MEDLINE (1950 to March Week 2 2009); Ovid EMBASE (1980 to 2009 Week 12) and EBSCO CINAHL (1982 to March Week 3 2009). The search was not limited by language or publication status.

Selection criteria—Randomised controlled trials (RCTs) were eligible for inclusion if they evaluated two (or more) glycaemic control regimens in the peri-operative period (within one week pre-, intra-, and/or post-operative) and reported surgical site infections as an outcome.

Data collection and analysis—The standard method for conducting a systematic review in accordance with the Cochrane Wounds Group was used. Two review authors independently reviewed the results from the database searches and identified relevant studies. Two review authors extracted study data and outcomes from each study and reviewed each study for methodological quality. Any disagreement was resolved by discussion or by referral to a third review author.

Main results—Five RCTs met the pre-specified inclusion criteria for this review. No trials evaluated strict glycaemic control in the immediate pre-operative period or outside the intensive care unit. Due to heterogeneity in patient populations, peri-operative period, glycaemic target, route of insulin administration, and definitions of outcome measures, combination of the results of the five included trials into a meta-analysis was not appropriate. The methodological quality of the trials was variable. In terms of outcomes, only one trial demonstrated a significant reduction in SSIs with strict glycaemic control, but the quality of this trial was difficult to assess as a result of poor reporting; furthermore the baseline rate of SSIs was high (30%). The other trials were either underpowered to detect a difference in SSIs, due to a low baseline rate (less than or equal to 5%), or did not report SSIs as a single outcome but as part of a composite. Of the three trials reporting hypoglycaemia (which was not consistently defined) all had a higher rate in the strict glycaemic control group but none attributed significant morbidity to the hypoglycaemia. Adequacy of glucose control between groups was measured differently among studies. Studies could not be compared due to differences in target ranges, and were susceptible to measurement bias due to differences in frequency of measurement and lack of blinding by the providers following the glycaemic protocols. Infection-related mortality was not reported in any of the trials, and no trials demonstrated a significant difference in all-cause mortality. Length of hospital stay was significantly reduced in the strict glycaemic control groups in only one trial.

Medical Subject Headings (MeSH)

Hyperglycemia [complications; *prevention & control]; Hypoglycemic Agents [therapeutic use]; Insulin [therapeutic use]; Intraoperative Complications [prevention & control]; Perioperative Care; Postoperative Complications [prevention & control]; Randomized Controlled Trials as Topic; Surgical Wound Infection [etiology; *prevention & control]

MeSH check words

Adult; Humans

PLAIN LANGUAGE SUMMARY

Strict control compared with conventional glycaemic control for preventing surgical site infections in adults

Wound-related infections that complicate operations (“surgical site infections”) result in worse patient outcomes. Previous studies have suggested that decreasing blood glucose levels to within a low, narrow range (strict control) around the time of surgery may decrease infections and improve outcome. However, concerns about side effects from low glucose levels, such as seizures and increased risk of death, have prevented widespread use of this strategy. There are only five trials comparing strict control strategies with the conventional strategy of treating blood glucose levels only when they become high. These trials differ significantly in patient characteristics, glucose targets, medications and methods used to lower glucose levels, as well as the outcomes measured. Furthermore, the individual studies, which are small and/or flawed, do not demonstrate a significant decrease in surgical site infections. There are insufficient data to support the routine adoption of strict blood glucose control around the time of operation to prevent surgical site infections.

BACKGROUND

Surgical site infections (SSIs) can result in death, increased length of hospital stay, and increased resource utilization (Kirkland 1999). SSIs range from simple wound infections involving the skin and subcutaneous tissues, to deep soft-tissue infections, or infections of the space or organ manipulated during the surgical procedure. Depending on the location, depth, and severity of the infection, an SSI can cost up to tens of thousands of dollars (US \$) per case (Fry 2002). Both pre-existing patient diseases (such as diabetes) and modifiable risk factors (such as failure to use sterile precautions or to administer appropriate antibiotics prior to surgery) contribute to the development of these infections. One potentially modifiable risk factor associated with SSIs is peri-operative hyperglycaemia or elevated blood glucose levels around the time of surgery (Estrada 2003; Pomposelli 1998; Trick 2000). While normal glucose levels in non-diabetic non-stressed patients range from 70 to 110 mg/dL, glucose levels between 110 and 200 mg/dL have not traditionally been treated in the peri-operative period. Published guidelines from the Centers for Disease Control recommend treatment of hyperglycaemia in surgical patients with diabetes to achieve levels below 200 mg/dL peri-operatively (Mangram 1999). This recommendation, however, has been challenged by studies suggesting that more aggressive treatment of elevated glucose levels with insulin, even in non-diabetic patients, reduces infectious complications (Furnary 2004; Grey 2004; Van den Berghe 2001). The optimal glucose level is unknown, particularly since hypoglycaemia (variably defined as glucose levels less than 40 to 60 mg/dL) - which can result in seizures, hypotension and death - becomes of increasing concern with a lower glucose target (Bhatia 2006). A large amount of the available data evaluating the effect of different degrees of glycaemic control on SSIs are limited to cardiac surgery patients, which raises questions about the generalisability of this information to other surgical patients (Furnary 2004; Van den Berghe 2001).

Hyperglycaemia occurs after surgical stress - even after uncomplicated elective surgery - and may increase the risk of infectious complications (Ljungqvist 2005). Hyperglycaemia stimulates the release of pro-inflammatory mediators and depresses the immune system, thus increasing susceptibility to bacterial infections (Cavaillon 2001; Delamaire 1997; Stephan 2002). In critically-ill patients who require intensive care, there is evidence that treatment of hyperglycaemia with intravenous insulin infusions results in fewer infections and improves outcome. The largest randomised controlled trial (RCT) of more than 1500 patients of strict glycaemic control to maintain glucose levels less than 110 mg/dL compared with less than 200 mg/dL in critically-ill patients (the Leuven trial) demonstrated reduced bloodstream

infections and improved mortality in patients receiving strict glycaemic control (Van den Bergh 2001). Although the majority of patients were cardiac surgery patients, SSIs were not measured as an outcome. Strict glycaemic control has not been uniformly adopted in surgical patients, however, because both the reproducibility of the results of the Leuven trial and the generalisability to other patient groups have been challenged (Brunkhorst 2008; Devos 2007).

In addition to RCTs in critically-ill patients, several studies - largely published in the cardiothoracic surgery literature - have reported an association between peri-operative glucose levels and post-operative infection rates (Estrada 2003; Furnary 2004; Latham 2001; Trick 2000; Zerr 1997). A large proportion of these data were derived from retrospective and prospective cohort studies, which were subject to methodological flaws such as confounding by temporal changes. Additionally, the timing of glucose control (pre-, intra-, or post-operative) and the target levels vary between studies. Many of these studies utilize a threshold of 200 mg/dL to define hyperglycaemia, which may still confer an increased risk for SSIs and mortality in critically-ill cardiac-surgery patients; the risks and benefits of a lower threshold remain to be clarified. Additionally, the question of whether cardiac-surgery patients differ from other surgical patients has been raised (Kennedy 1994). Therefore, the benefits of using a lower glycaemic target may be more profound amongst cardiothoracic surgery patients, particularly those with diabetes, than in general surgical patients.

This review will consider the evidence for the impact of glycaemic control (target blood glucose below the conventional target of 200 mg/dL) in the peri-operative period for prevention of surgical site infections. This review will evaluate whether the evidence supports the use of strict glycaemic control to normalize glucose levels to 110 mg/dL in both cardiac and general surgical patients without increasing harm due to hypoglycaemia. Furthermore, differences in outcome with other glycaemic targets between 110 and 200 mg/dL will be evaluated.

OBJECTIVES

To summarize the evidence for the impact of strict glycaemic control in the peri-operative period on the incidence of surgical site infections, hypoglycaemia, level of glycaemic control, all-cause and infection-related mortality, and length of hospital stay and to investigate for differences of effect between different levels of glycaemic control.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials (RCTs) in which patients were assigned to different glucose control regimens pre-, intra-, or post-operatively will be included.

Types of participants—Studies involving people aged 18 years of age or older, regardless of diabetes status, who underwent a surgical procedure, (i.e. an operation in which a skin incision is made).

Types of interventions—One glycaemic control regimen compared with at least one other glycaemic control regimen pre-, intra-, and/or post-operatively. Since conventional therapy is to treat glucose levels above 200 mg/dL, comparison was made between conventional treatment (of glucose values above ~200 mg/dL) and lower targets (with maximum of less than 200 mg/dL) or between two regimens evaluating glycaemic targets both below 200 mg/dL. Only glycaemic control regimens using medications to lower glucose levels (oral, subcutaneous, and/or intravenous) were included. A subgroup analysis

was planned of studies using intravenous insulin as the lower targets for glycaemic control are not achievable in hyperglycaemic patients with oral medications or subcutaneous insulin alone, and insulin infusions have a higher theoretical risk of hypoglycaemia. Pre-operative glycaemic control will be limited to within one week before surgery as the effects of long-term glucose control on outcome is a separate question.

Types of outcome measures

Primary outcomes—The incidence of surgical site infections as defined by the study authors.

Secondary outcomes—When reported, the following secondary outcomes were to be recorded:

- incidence and severity of hypoglycaemia (defined as blood glucose concentration of less than 60 mg/dL, which is the level at which most clinicians would treat with exogenous glucose);
- level of glycaemic control (percentage of measurements within the target range or mean glucose level);
- all-cause and infection-related mortality;
- length of hospital stay.

Search methods for identification of studies

Electronic searches—We searched the following databases:

- Cochrane Wounds Group Specialised Register (Searched 25 March 2009)
- The Cochrane Central Register of Controlled Trials (CENTRAL) - *The Cochrane Library* Issue 1 2009
- Ovid MEDLINE - 1950 to March Week 2 2009
- Ovid EMBASE - 1980 to 2009 Week 12
- EBSCO CINAHL - 1982 to March Week 3 2009

The following search strategy was used in CENTRAL:

- #1 MeSH descriptor Blood Glucose explode all trees
- #2 MeSH descriptor Hypoglycemic Agents explode all trees
- #3 MeSH descriptor Hyperglycemia explode all trees
- #4 MeSH descriptor Hypoglycemia explode all trees
- #5 MeSH descriptor Insulin explode all trees
- #6 blood glucose:ti,ab,kw
- #7 (hypoglycaemi* or hypoglycemi*) NEXT (agent* or drug*):ti,ab,kw
- #8 (glucose or glyceic or glycemic) NEXT control*:ti,ab,kw
- #9 oral NEXT (hypoglycaemi* or hypoglycemi*):ti,ab,kw
- #10 glucose NEXT target:ti,ab,kw
- #11 insulin:ti,ab,kw
- #12 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)

#13 MeSH descriptor Surgical Wound Infection explode all trees

#14 infection*:ti,ab,kw

#15 MeSH descriptor Infection Control, this term only

#16 (#13 OR #14 OR #15)

#17 (#12 AND #16)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 1, Appendix 2 and Appendix 3 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2008). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2009). The search was not limited by language or publication status.

Searching other resources—The reference lists of all eligible trials, key textbooks, and relevant systematic reviews were hand searched for additional trials. Additionally, relevant conference proceedings from the past meetings from 1998 to 2008 (Surgical Infection Society, European Surgical Infection Society, American College of Surgeons, Society of Critical Care Medicine, Society of Cardiac Surgeons) were hand searched. ClinicalTrials.gov was searched for relevant ongoing studies, and authors were contacted to identify any additional published or unpublished data.

Data collection and analysis—The standard method for conducting a systematic review, as described in the Cochrane Handbook for Systematic Reviews of Interventions, version 5, was used for this review (Higgins 2008).

Selection of studies—Two review authors independently reviewed the results from the database searches and identified relevant studies. These studies were obtained in full and independently scrutinised by two review authors.

Data extraction and management—Details of the studies were independently abstracted by two review authors. Trial authors were contacted when possible to provide missing information. The following information were included on the data extraction form:

1. Publication details.
2. Study design (inclusion/exclusion criteria, method of allocation, sample size calculations).
3. Patient population (age, diabetes status -- insulin-dependent and non insulin-dependent, pre-operative glucose level, type of surgical procedure(s), number of patients, pre-operative risk stratification for SSI using the National Nosocomial Infection Surveillance System or NNIS score, use of standard preventive measures (sterile precautions, antibiotic administration)).
4. Setting of treatment (including country).
5. Duration of treatment and follow-up.
6. Details of intervention and control or comparison strategy (timing of treatment: pre-, intra-, or post-operatively) insulin or oral hypoglycaemics, glucose target range).

7. Outcome measures (surgical site infections, hospital length of stay, all-cause and infection-related mortality, hypoglycaemia less than 60 mg/dL or otherwise defined, level of glycaemic control or percentage of glucose values in range).
8. Adverse effects (for example hypoglycaemia).
9. Withdrawals (per group with numbers and reasons).

Assessment of risk of bias in included studies—The risk of bias of the individual trials was assessed independently by all review authors. Any disagreement was resolved by discussion. The risk of bias domains assessed were the generation of the randomisation sequence, allocation concealment, masking, incomplete outcome data and intention-to-treat analysis.

Randomisation was assessed as follows:

- A = Adequate sequence generation was reported using random number tables, computerized random number generation, coin tossing, or shuffling.
- B = Did not specify one of the adequate methods, but mentioned randomisation.
- C = Other method of allocation that may not be random.

Allocation concealment was assessed as follows:

- A = Adequate randomisation methods was described that would not allow an investigator/participant to know or influence intervention selection prior to enrolment (central randomisation, serially numbered, opaque, sealed envelopes, etc).
- B = Trial stated as being randomised, but no information was provided on the method used or is not clearly adequate.
- C = Inadequate method of randomisation used or information available to study investigators/participants allowing influence in the intervention group selection.

Blinding was assessed using the following questions in a yes/no/not reported fashion. Blinding of investigators and participants may not have been possible due to the differences in the glycaemic targets and algorithms (i.e. frequency of glucose checks may have been higher in the strict glycaemic control arms). However, the outcome assessors and data analysts should have been able to be blinded.

- Blinding of investigators.
- Blinding of participants.
- Blinding of outcome assessor.
- Blinding of data analyst.

Intention-to-treat (ITT) was assessed as follows:

- A = Specifically reported by authors that ITT was undertaken and this was confirmed on study assessment; or not stated, but evident on study analysis that ITT was undertaken.
- B = Described as ITT analysis, but unable to confirm on study assessment or not reported and unable to confirm.
- C = Lack of ITT confirmed on study assessment regardless of whether ITT was reported.

Incomplete outcome data was evaluated based on:

- All randomised patients were accounted for in the analysis, including attrition and exclusions from analysis.
- Reasons for exclusions from analysis were described.
- If incomplete follow-up was obtained, the attrition rate was less than 20% (outcomes for >80% of randomised patients were reported).

Measures of treatment effect—Dichotomous outcomes (SSIs and mortality) were reported as risk ratios (RR) with 95% confidence intervals (CIs). Continuous outcomes (length of stay, glucose levels) were reported as means and standard deviations (SDs) or standard errors of the mean (SEMs).

Assessment of heterogeneity—If appropriate, statistical heterogeneity was to be assessed using the chi-squared statistic ($p < 0.1$) and the I^2 statistic (Higgins 2003). The latter examines the percentage of total variation across studies due to heterogeneity rather than to chance. Values of I^2 over 75% indicate a high level of heterogeneity.

Data synthesis—If a meta-analysis was possible, the data were to be pooled using the RR, given that the incidence of SSIs may have been so low such that the RD may have been very small. Additionally, given the variation in baseline risk for SSIs, RRs may have been more consistent across studies. If the data were insufficient to conduct a meta-analysis, we had planned to present the results narratively.

Subgroup analysis and investigation of heterogeneity—If present, possible sources of heterogeneity were to be explored using subgroup analyses. Possible sources could have included: use of insulin infusion versus subcutaneous insulin or oral medication, type of surgical procedure -- in particular, cardiothoracic versus general surgical procedures, diabetic versus non-diabetic patients, and timing of glycaemic control (pre-, intra-, or post-operative). If the subgroup analyses did not reveal a source of heterogeneity, we had planned to perform a meta-regression evaluating the different glycaemic targets between 110 and 200 mg/dL.

Sensitivity analysis—Sensitivity analyses were planned if a single large trial appeared to be driving the results of the meta-analysis. Also, sensitivity analysis were planned - including all studies and then excluding those of poor quality.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search—The search strategy identified 658 citations. The bibliographies of citations that were reviews or guidelines were searched for further potential RCTs. The majority of studies were not considered eligible for further consideration because they did not address the proposed question. 15 studies addressing the question of interest were ineligible because they were observational studies. Ten studies were retrieved in full. A total of 5 trials did not meet the inclusion criteria and are detailed in the Characteristics of excluded studies. Two trials were excluded because they were in critically-ill, nonsurgical patients (He 2008; Wang 2006). One RCT was excluded that compared glucose-insulin-potassium infusion (GIK) to 5% dextrose, because the glucose range maintained intra-

operatively was between 180 and 270 mg/dL for both groups (Quinn 2006). Bilotta 2008 performed an RCT in neurologically injured patients, 41% received an intracranial pressure monitor as the sole procedure. De La Rosa 2008 performed an RCT in a mixed medical and surgical intensive care unit but the number of operations was not recorded, the percentage of surgical patients differed between groups, and surgical site infections were not measured.

Four further citations are being retrieved and at present are awaiting assessment (Arabi 2008; Barcellos 2007; Bilotta 2009; He 2007).

Included studies—Five eligible trials were included with a total of 773 patients randomised. Three trials randomised people having cardiac surgery to two different peri-operative glycaemic control regimens (Gandhi 2007; Lazar 2004; Li 2006). Two trials enrolled only people with diabetes and compared an intravenous insulin infusion to a subcutaneous insulin regimen (Lazar 2004; Li 2006), but only Lazar 2004 compared two different glucose target ranges. Gandhi 2007 compared strict with conventional glycaemic protocols, both using insulin infusions.

The other two trials enrolled patients undergoing emergency cerebral aneurysm clipping (Bilotta 2007) and critically ill surgical patients (Grey 2004). Both compared a strict to a conventional glycaemic control regimen using insulin infusions.

Risk of bias in included studies

The details of individual trials are included in the Characteristics of included studies table and Risk of Bias information summarized in Figure 1 and Figure 2.

Adequacy of the randomisation process—All five trials were reported to be randomised. However, only three out of five trials reported an adequate method of sequence generation; Bilotta 2007 and Gandhi 2007 used computer-generated random sequences and Grey 2004 used a coin toss to assign treatment. Neither Lazar 2004 nor Li 2006 reported a method of sequence generation.

Adequacy of allocation concealment—Only Bilotta 2007 and Gandhi 2007 described a method of allocation concealment - sealed envelopes. None of the remaining trials described the method of allocation.

Blinding—None of the trials reported blinding of patients or healthcare providers to the treatment assignment. Given the differences in protocols between treatment arms in the trials, blinding of healthcare providers would have been difficult. Glucose levels or degree of glucose control was an outcome measure in two trials (Grey 2004; Li 2006) and was reported in all five trials. Lack of blinding of healthcare providers could have biased these results if glucose measurements were not obtained according to a strict protocol. In particular, Grey 2004 allowed for glucose measurements based on clinical judgment in addition to prespecified times in the algorithm.

Bilotta 2007 and Gandhi 2007 reported that outcome assessment was performed by trained, blinded personnel. The other three trials did not report blinding of outcome assessors. Outcomes such as mortality (Lazar 2004; Li 2006) were unlikely to have been affected by lack of blinding. However, assessment of other outcomes such as wound complications or infections (Grey 2004; Lazar 2004; Li 2006) could potentially have been influenced by knowledge of treatment group.

Use of intention-to treat analysis—Although Grey 2004 and Lazar 2004 did not state that they performed an ITT analysis, they also did not report any losses to follow up,

withdrawals, or cross-overs. Bilotta 2007 and Gandhi 2007 both specified an ITT analysis. However, Gandhi excluded 15 patients from the analysis due to lack of intra-operative hyperglycaemia. The decision to exclude these patients was based on a pre-defined objective criterion, lack of intra-operative hyperglycaemia ≥ 100 mg/dL, and exclusion could not have been identified pre-operatively. Patients were excluded equally between groups. There is insufficient data to determine whether the excluded patients were significantly different from those included. The authors enrolled extra patients in each group in anticipation of this problem so as to maintain adequate power to detect a difference. Li 2006 had 7 patients cross over from one arm to the other during the study; all of these patients were excluded from the analysis. All 7 patients were in the subcutaneous insulin group originally and were dropped from the study by their primary physicians due to lack of adequate glucose control. Thus, their exclusion likely resulted in an underestimation of the benefits of continuous insulin infusion in obtaining glucose control and possibly in infection rates. Furthermore, although the overall mortality rate was low and would have been unlikely to have been significantly different amongst those 7 patients (the authors estimated that 2,842 patients would have been required to identify a difference in mortality), their mortality is nonetheless unreported.

Extent of loss of follow-up—Three trials (Bilotta 2007; Grey 2004; Li 2006) reported no loss to follow up. Lazar 2004 reported no loss to follow-up in terms of the 30-day mortality and in-hospital outcomes but there was loss to follow-up for the 5-year outcome measure, for which they had data for 60/72 (83%) and 60/69 (87%) in the two groups. No data are provided regarding the similarity of those lost to follow up with those patients remaining in the study. Gandhi 2007 excluded 8 patients who were lost to follow-up after hospital discharge, in addition to 21 patients excluded after randomisation (15 non-hyperglycaemic patients and 6 patients whose surgery was cancelled). The 8 patients lost to follow-up were significantly younger than the other patients but otherwise did not differ in baseline characteristics. Gandhi also had missing 24 hour glucose data. The authors substituted 20-hour glucose data and demonstrated no difference in 20 and 24 hour glucose levels among patients with both data points.

Effects of interventions

Comparison 1: Intra-operative strict versus conventional glycaemic control using intravenous insulin (1 RCT, 400 participants)—Gandhi 2007 randomised 400 people stratified by the presence of diabetes who were undergoing on-pump cardiac surgery to receive continuous insulin infusion to maintain glucose levels between 80 to 100 mg/dL (strict glycaemic control, n=199) or to insulin push/infusion to maintain glucose < 200 mg/dL (conventional glycaemic control, n=201) intra-operatively. The same strict glycaemic protocol was used post-bypass for 24 hours post-operatively in all patients.

Primary outcome—The primary outcome of SSIs was reported as deep sternal infections, based on a standardised definition from the Society of Thoracic Surgeons. There was no significant difference between the groups. Overall, 6/185 (3%) deep sternal infections occurred in the strict glycaemic control group compared with 7/186 (4%) deep sternal infections occurred in the conventional glycaemic control group, RR 0.86 (95% CI 0.30 to 2.52)(Analysis 1.1). There was no significant difference in deep sternal wound infection rate between groups when stratified by diabetic status. Superficial wound infections in any location were not reported. This trial with adequate sequence generation, concealed allocation and blinded outcome assessment was at low risk of bias.

Secondary outcomes

Hypoglycaemia: Only one patient in each treatment group experienced intra-operative hypoglycaemia, defined as glucose level < 60 mg/dL, RR 1.01 (95% CI 0.06 to 15.95) (Analysis 1.2). The number of patients who experienced post-operative hypoglycaemia in the ICU was 14 (8%) in the strict insulin group compared with 8 (4%) in the conventional insulin group, RR 1.76 (95% CI 0.76 to 4.09) (Analysis 1.3). All of the episodes of hypoglycaemia were reported to be mild without adverse consequences.

Adequacy of blood glucose control: Both groups had similar baseline glucose levels. Mean post-cardiopulmonary bypass glucose levels and mean glucose levels on arrival and after 24 hours in the ICU were recorded. There was a significant difference in both. Mean post-cardiopulmonary bypass glucose levels were 123 mg/dL (SD 24) in the strict insulin group compared with 148 mg/dL (SD 35) in the conventional group, $p < 0.001$. Mean glucose levels on arrival in the ICU were 114 mg/dL (SD 29) in the strict insulin group compared with 157 mg/dL (SD 42) in the conventional group, $p < 0.001$. There was no significant difference in the 24 hour ICU glucose levels between groups [103 mg/dL (SD 17) for the strict group and 104 mg/dL (SD 22) for the conventional group]. There were missing data at 24 hours, for which 20 hour glucose values were substituted. In patients for whom both 20 and 24 hour glucose data were available, the comparison showed no significant difference between treatment groups.

Subgroup analyses of people with and without diabetes yielded similar results. The strict insulin group had lower post-cardiopulmonary and initial ICU glucose levels than the conventional management group. No differences were seen at 24 hours.

Mortality: All-cause mortality was recorded. Four patients (2%) in the strict group died and no patients in the conventional group died, RR 9.05, (95% CI 0.49 to 167) (Analysis 1.4).

Length of hospital stay: There was no difference in hospital or ICU length of stay between groups. The median hospital length of stay was 6 (interquartile range 5 to 8) days and the median ICU length of stay 1 (IQR 1 to 2) days for both groups. Diabetic status did not affect the results.

Comparison 2: Intra- and post-operative strict versus conventional glycaemic control using intravenous insulin (1 RCT, 78 patients)—Bilotta 2007 randomised 78 patients undergoing emergency cerebral aneurysm clipping to receive intra- and post-operative insulin infusions at either a conventional rate to maintain glucose levels 80 to 220 mg/dL ($n=38$) or at an intensive rate to maintain glucose levels 80 to 120 mg/dL ($n=40$). Insulin infusions were continued until discharge from the ICU or until post-operative day 14.

Primary outcome—The primary outcome variable of the study was infection, including pneumonia, sepsis, urinary, and wound infections as defined by the National Nosocomial Infection Surveillance System (NNIS). Overall, there were fewer infections in the strict glycaemic control group (11/40 or 27%) compared with the conventional glycaemic control group (16/38 or 42%), RR 0.65 (95% CI 0.35 to 1.22) but this difference was not statistically significant (Analysis 2.1). Wound infections represented 11% of the total infections in the strict group and 13% in the conventional group, RR 0.47 (95% CI 0.04 to 5.03) (Analysis 2.2). This trial with adequate sequence generation, concealed allocation, blinded outcome assessment and no missing outcome data was at low risk of bias.

Secondary outcomes

Hypoglycaemia: Hypoglycaemia was reported by the authors as the percentage of occasions that blood glucose concentration was lower than 80 mg/dL. Blood glucose concentrations were more frequently lower than 80 mg/dL in the strict control group compared with the conventional control group, RR 3.0 (95% CI 2.07 to 4.35). No major complications were attributed to hypoglycaemia. Specifically, neurologic status at 6-month follow-up was no different amongst patients who had experienced peri-operative hypoglycaemia.

Adequacy of blood glucose control: The percentage of glucose values in the target range was 69% (80 to 120 mg/dL) for the strict insulin group and 83% (80 to 220 mg/dL) in the conventional insulin group. The authors do not report the percentage of patients in the strict control group with values greater than 220 mg/dL, nor do they report mean blood glucose concentrations for each group. Thus, given that the ranges overlap, between group comparison of glucose control is difficult.

Mortality: All-cause mortality at six months was similar between the two groups; 6/40 (15%) in the strict glycaemic control group and 7/38 (18%) in the conventional glycaemic control group, RR 0.81, (95% 0.3 to 2.20)(Analysis 2.3).

Length of hospital stay: Length of hospital stay was not reported.

Comparison 3: Intra- and post-operative strict glycaemic control with intravenous glucose-insulin-potassium infusion (GIK) versus conventional glycaemic control using subcutaneous insulin (1 RCT, 141 participants)—

Lazar 2004 studied 141 people with diabetes undergoing coronary artery bypass grafting. Patients were randomised to either strict glycaemic control with glucose-insulin-potassium (GIK) infusion to maintain glucose levels of 125 to 200 mg/dL (n=72) or to conventional glycaemic control with subcutaneous insulin to maintain blood glucose concentration at less than 250 mg/dL (n=68). Glycaemic control was initiated before anesthesia induction and continued for 12 hours post-operatively. Subsequently, patients resumed their pre-operative diabetic regimen, titrated to maintain glucose levels at less than 200 mg/dL.

Primary outcome—Wound infection was reported along with the rate of pneumonia. There was a statistically significantly lower rate of pneumonia and wound infections in the strict glycaemic control group, RR 0.05 (95% CI 0 to 0.84)(Analysis 3.1). Poor reporting meant that this trial was potentially at high risk of bias with unclear sequence generation, unclear allocation concealment, unclear blinded outcome assessment and incomplete follow up data.

Secondary outcomes

Hypoglycaemia: Frequency of hypoglycaemia was not reported.

Adequacy of blood glucose control: Mean blood glucose concentrations were measured before cardiopulmonary bypass and after 12 hours in the ICU. Both groups had comparable baseline mean glucose levels. The GIK group had a lower mean blood glucose concentration before cardiopulmonary bypass [169 mg/dL (SEM 4.9) versus 209 mg/dL (SEM 5.3), $p<0.0001$] and after 12 hours in the ICU [134 mg/dL (SEM 3.7) versus 267 mg/dL (SEM 6.3), $p<0.0001$]. Percentages within range were not reported.

Mortality: There were no deaths at 30 days in either group. Kaplan-Meier curves demonstrated a significant increase in 2-year survival in the strict control group ($p=0.04$, Hazard Ratios not reported). After five years, with 85% overall follow-up, there was 1 death

(1/60 or 2%) in the GIK group and 6 deaths (6/60 or 10%) in the conventional group. All of the deaths were secondary to cardiac or vascular complications. There were no infection-related deaths reported.

Length of hospital stay: The mean duration of post-operative hospital stay was reported to be shorter in the GIK group than in the conventional group at 6.5 days (SEM 0.1) compared with 9.2 days (SEM 0.3), $p=0.003$.

Comparison 4: Post-operative strict versus conventional glycaemic control with intravenous insulin infusion. (1 RCT, 61 participants)—Grey 2004 randomised 61 hyperglycaemic (≥ 140 mg/dL) adult surgical ICU patients, both with and without diabetes, to either strict glycaemic control (blood glucose between 80 to 120 mg/dL) ($n=34$) or conventional glycaemic control (blood glucose between 180 to 220 mg/dL) ($n=34$) with intravenous insulin infusions throughout their ICU stay.

Primary outcome—The primary outcome of SSIs was encompassed in a broader category of nosocomial infections, although the percentage of patients developing SSIs was also reported. Nosocomial infections were defined using CDC criteria and included intravascular device infections, bloodstream infections, SSIs, pneumonias, and urinary tract infections. Taken from the figure, 30% of people in the conventional glycaemic control group developed an SSI compared with 7% in the strict glycaemic control group.

Although the authors state that the data were presented as infection rate per 1,000 patient-ICU days, the overall effect was reported narratively. Quantitative data were presented in a figure as percentage of patients. There were more nosocomial infections in the conventional glycaemic control group overall, as well as increases in specific types of infection. These increases were all statistically significant ($p<0.05$) except for rates of UTIs and pneumonia. The authors reported a 4-fold increase in intravascular device infections and bloodstream infections in the conventional glycaemic control group. They also observed a 3.5 fold increase in intravascular device-related bloodstream infections and SSIs. Specific point estimates and confidence intervals were not provided. The authors state that they adjusted for the variable durations of stay of individual patients and presented as an infection rate per 1,000 patient ICU days, but these data are not reported in the study publication. The only report is a figure labelled percentage of patients. This trial was at moderate risk of bias with adequate sequence generation and no missing data but lacked reporting with respect to allocation concealment and blinding of the outcome assessor.

Secondary outcomes were

Hypoglycaemia: Hypoglycaemia was defined as blood glucose concentrations of < 60 mg/dL. Thirty-two percent of patients had an episode of hypoglycaemia in the strict glycaemic control group compared with 7.4% in the conventional glycaemic control group ($p<0.001$). The frequency of blood glucose concentration at < 60 mg/dL were 0.8% and 0.1% in the strict versus conventional control groups respectively, ($p<0.001$). None of the episodes of hypoglycaemia were associated with major morbidity.

Adequacy of blood glucose control (mean glucose level): The group mean blood glucose concentration was lower with strict glycaemic control (125 mg/dL (SD 36)) compared with conventional glycaemic control (179 mg/dL (SD 61)), $p<0.001$. Additionally, the mean daily glucose concentration was significantly lower in the strict glycaemic control group for all days. Percentage of glucose levels in range was not reported.

Mortality: All-cause hospital mortality was not significantly different between the groups; 11% with strict glycaemic control versus 21% for the conventional glycaemic control group, $p=0.50$.

Length of hospital stay: The mean length of ICU stay was not significantly different between the two groups; 33.4 days (SD 68.3) versus 24.5 days (SD 19.4) for the strict and conventional glycaemic control groups respectively, $p=0.52$.

Comparison 5: Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin (1 RCT, 93 participants)—Li 2006 randomised 100 diabetic patients undergoing coronary artery bypass grafting to either intravenous insulin infusion ($n=51$) or subcutaneous insulin ($n=49$) for 2 days post-operatively to maintain glucose levels between 150 and 200 mg/dL in both groups.

Primary outcome—The primary outcome of surgical site infections was reported separately as sternal wound and leg wound infections. Both superficial and deep sternal wound infections were recorded and confirmed by microbiological culture. Specific criteria for identifying sternal or leg wound infections were not reported. There were two sternal wound infections in each group, RR 0.82, (95% CI 0.12 to 5.60)(Analysis 5.1). There was one leg wound infection reported in the insulin infusion group compared with none in the subcutaneous insulin group, RR 2.48 (95% CI 0.1 to 59.4)(Analysis 5.2). This trial was at high risk of bias having unclear sequence generation, unclear allocation concealment, no blinding of outcome assessment and no ITT analysis.

Secondary outcomes were

Hypoglycaemia: Frequency of hypoglycaemia was not recorded.

Adequacy of blood glucose control (mean glucose level, percentage in range): Results were reported as percentage of patients achieving mean blood glucose concentration (average of mean daily glucose levels for 5 post-operative days) less than 200 mg/dL; 33/51 (61%) of patients achieved the target in the intravenous insulin group and 12/41 (29%) in the subcutaneous insulin group, $p<0.001$. Daily mean glucose concentration were also recorded, and the difference between groups was most pronounced for the first two post-operative days, both in terms of percentage in range (mean glucose < 200 mg/dL) and mean daily glucose levels. For post-operative days 3 through 5, there was no statistically significant difference between groups in adequacy of blood glucose control.

Mortality: There was no significant difference in operative mortality (length of follow-up not specified) between the two groups; 2/51 (3.9%) in the intravenous infusion group and 1/42 (2.4%) in the subcutaneous insulin group, RR 1.65 (95% CI 0.15 to 17.54)(Analysis 5.3).

Length of hospital stay: Only the length of intensive care unit (ICU) stay was recorded. There was no significant difference in the mean length of ICU stay: mean length of stay was 5.7 days, median 4 days for the insulin infusion group compared with 6.3 days, median 5 days for the subcutaneous insulin group, $p=0.75$. (No standard deviations or ranges were reported).

DISCUSSION

Despite biological plausibility and some evidence from observational cohort studies for an association between reduced surgical site infections and strict glycaemic control (usually

defined as treatment of glucose levels greater than 200 mg/dL), only five randomised controlled trials were identified that addressed the question of peri-operative glycaemic control and SSIs. These trials were all very different although all patients had an initial postoperative stay in the intensive care unit. There was significant heterogeneity in the patient populations studied, in particular with regard to diabetes status, type of surgery and mortality risk. The glycaemic control regimens also differed significantly in terms of timing (intra-operative versus intra- and post-operative), duration of the study protocol post-operatively (12 hours to end of ICU stay), route of administration (continuous insulin infusion versus intravenous insulin infusion and push versus subcutaneous insulin), and target glucose ranges (maximum and minimum glucose levels, width of acceptable target range, and degree of overlap between study arms). Due to the heterogeneity, a meta-analysis was not deemed appropriate.

All five RCTs reported infection as an outcome measure however not all trials reported the rates of SSIs or only reported a subgroup of SSIs (such as deep sternal wound infections after cardiac surgery). Of the trials reporting SSIs, three had a baseline rate in the conventional glycaemic control group of less than or equal to 5%. None of these trials were individually powered to identify a difference with such a low baseline rate, likely accounting for the use of composite outcomes. The trials were too heterogeneous to combine. The other two trials that reported a difference in infection rates had much higher baseline infection rates and/or used a composite outcome. Grey 2004 had a baseline SSI rate of 30%, which likely reflects the severity of illness of the patients (as evidenced by the fact that 44% of patients in the standard group and 50% of patients in the strict glucose control group required vasopressors). Lazar 2004 also had a higher baseline rate of infection in the conventional therapy group, but did not specify how many of the infections were either pneumonia or SSI. Additionally, the higher baseline infection rate in the control arm may be due to a higher than conventionally acceptable mean glucose concentration in that group (above 200 mg/dL). Both studies had (at least) moderate risk of bias.

In addition to the differences in the glycaemic control regimens used, post-operative nutrition protocols were either not described in detail or not described at all. Both baseline nutritional status and post-operative nutrition may have been potential confounders. Malnutrition as well as obesity are risk factors for infectious complications. No serum markers or anthropomorphic measurements of baseline nutritional status were reported. However, three studies (Grey 2004; Li 2006; Gandhi 2007) reported baseline Body Mass Indices (BMIs) for the randomised patients. The mean BMIs in all three studies were in the overweight range (25 to 30 kg/m²). Additionally, post-operative nutrition can also affect outcome in that enteral nutrition is associated with fewer infectious complications and a shorter length of stay than parenteral nutrition (Mazaki 2008). Two of the studies reported following standardized nutrition guidelines post-operatively, but did not describe the details (Grey 2004; Bilotta 2007). The other three studies were all in cardiac surgery patients; the composition of the post-operative diets were not described in detail, or whether differences existed based on diabetes status.

This review is unable to confirm the findings from observational cohort studies, most notably the Diabetic Portland Project. Furnary 2004 which demonstrated a reduction in sternal wound infections, mortality, and hospital length of stay with progressive lowering of the target glucose range among diabetic cardiac surgery patients over time. One potential reason for the lack of effect of strict glycaemic control in the RCTs of cardiac surgery patients may be that the glycaemic control in the conventional group may have been lower than that in the historical cohorts in the observational studies. In the Gandhi 2007 trial, which was the largest of the 5 trials reviewed and at low risk of bias, the mean 24 hour postoperative glucose level was less than 110 mg/dL in both groups. In the Furnary 2004

study, maintenance of post-operative glucose levels in the 100 to 150 mg/dL range for 3 days improved outcome. Thus, both groups in the Gandhi trial were within the target range proposed by the Portland Project and demonstrated low sternal infection and mortality rates. Because of data from observational cohort studies, use of higher glycaemic targets in the conventional treatment arm (above 200 mg/dL), such as in the Lazar 2004 trial, may no longer be accepted.

Although not a primary outcome measure listed in the review protocol, theoretically, the same rationale for reduction in SSIs with strict glycaemic control should apply to other nosocomial infections. Because of differences in the infections recorded, data from the trials cannot be combined. Bilotta 2007 reported a composite infection outcome that included urinary tract infections, pneumonia and SSI, as a primary outcome measure and identified a large difference in infection rates between treatment arms. The generalisability of this trial may be limited however given that only patients undergoing emergent cerebral aneurysm clipping were enrolled and all patients received steroids. Thus, given the biologic plausibility and the difficulty of powering future trials on SSI rate alone, future trials should consider evaluating nosocomial infections as a primary outcome measure.

Hypoglycaemia rates and adequacy of glucose control are difficult to compare between studies for several reasons. The strict and conventional glycaemic control regimens not only differed in target ranges between the groups (except for Li 2006 which used the same target range for both groups) but also in the frequency of glucose measurements. The strict control groups received more blood glucose measurements than the conventional control groups, potentially resulting in a measurement bias, particularly when reported as percentage of hyper- or hypoglycaemic levels of the total. Additionally, studies differed in the reporting of hyper- and hypoglycaemia, using either the percentage of patients who experienced at least one episode of hyper/hypoglycaemia versus the percentage of glucose measurements greater or less than the cut-off value. Of the three studies that measured hypoglycaemia, all reported a higher rate of hypoglycaemia in the strict glycaemic control group, with Grey 2004 reporting 32% of patients having at least one episode of hypoglycaemia. None of the studies reported adverse outcomes secondary to hypoglycaemia.

In the Leuven trial of strict versus conventional insulin therapy in surgical ICU patients, Van den Berghe 2001 identified a mortality reduction of 32% with intensive insulin therapy (or strict glycaemic control). The major reduction was in deaths due to a septic focus and multi-organ failure amongst patients receiving intensive insulin therapy for five or more days. None of the 5 RCTs included in this review included infection-related mortality as an outcome measure. Short-term all-cause mortality was not significantly different between treatment arms in any of the studies, although baseline risk factors were different due to very heterogeneous populations between studies. Whilst the all-cause mortality rate was twice as high in the conventional glycaemic control arm compared with the strict control arm in the Grey 2004 trial, this difference was not statistically significant, possibly due to lack of power. In the Lazar 2004 trial, there was no difference in 30-day mortality, but there was an increase in 2-year mortality in the no-GIK group due to cardiovascular complications. The death rate in the study by Gandhi 2007 was too low to detect a difference (only four deaths overall). Future trials must consider the potential harms as well as benefits of strict glycaemic control.

The length of stay was shorter associated with strict glycaemic control in only one study (Lazar 2004) there being no difference in the remaining studies, although they are likely underpowered. Bilotta 2007, Gandhi 2007, Lazar 2004, and Li 2006) did not show a difference in mortality and, although not statistically significant, Grey 2004 reported more deaths in the conventional glycaemic control group.

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RWJ Physician Faculty Scholars Award

CHARACTERISTICS OF STUDIES

DATA AND ANALYSES

APPENDICES

Appendix 1. Ovid MEDLINE search strategy

1. exp Blood Glucose/
2. exp Hypoglycemic Agents/
3. exp Hyperglycemia/
4. exp Hypoglycemia/
5. exp Insulin/
6. blood glucose.ti,ab.
7. ((hypoglycaemi\$ or hypoglycemi\$) adj (agent\$ or drug\$)).ti,ab.
8. ((glucose or glycaemic\$ or glycemic\$) adj control\$).ti,ab.
9. (oral adj (hypoglycaemi\$ or hypoglycemi\$)).ti,ab.
10. glucose target.ti,ab.
11. insulin.ti,ab.
12. or/1-11
13. exp Surgical Wound Infection/
14. exp Surgical Wound Dehiscence/
15. infection\$.ti,ab.
16. Infection Control/
17. or/13-16

18. 12 and 17

Appendix 2. Ovid EMBASE search strategy

1. exp Glucose Blood Level/
2. exp Antidiabetic Agent/
3. exp Hyperglycemia/
4. exp Hypoglycemia/
5. exp Insulin/
6. blood glucose.ti,ab.
7. ((hypoglycaemi\$ or hypoglycemi\$) adj (agent\$ or drug\$)).ti,ab.
8. ((glucose or glycaemic\$ or glycemc\$) adj control\$).ti,ab.
9. (oral adj (hypoglycaemi\$ or hypoglycemi\$)).ti,ab.
10. glucose target.ti,ab.
11. insulin.ti,ab.
12. or/1-11
13. exp Surgical Infection/
14. exp Wound Dehiscence/
15. infection\$.ti,ab.
16. Infection Control/
17. or/13-16
18. 12 and 17

Appendix 3. EBSCO CINAHL search strategy

S18 S13 and S17
 S17 S14 or S15 or S16 or S17 or S18
 S16 (MH "Infection Control+")
 S15 TI infection* or AB infection*
 S14 (MH "Surgical Wound Dehiscence")
 S13 (MH "Surgical Wound Infection")
 S12 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
 S11 TI insulin or AB insulin
 S10 TI glucose target* or AB glucose target*
 S9 TI (oral N1 hypoglycaemi* or oral N1 hypoglycemi*) or AB (oral N1 hypoglycaemi* or oral N1 hypoglycemi*)
 S8 TI (glucose control or glycaemic control or glycemc control) or AB (glucose control or glycaemic control or glycemc control)

S7 TI (hypoglycaemi* N1 drug* or hypoglycemi* N1 drug* or hypoglycaemi* N1 drug* or hypoglycaemi* N1 agent*) or AB (hypoglycaemi* N1 drug* or hypoglycemi* N1 drug* or hypoglycaemi* N1 drug* or hypoglycaemi* N1 agent*)

S6 TI blood glucose or AB blood glucose

S5 (MH "Insulin+")

S4 (MH "Hypoglycemia+")

S3 (MH "Hyperglycemia+")

S2 (MH "Hypoglycemic Agents+")

S1 (MH "Blood Glucose")

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 3, 2009

15 April 2008	Amended	Converted to new review format.
13 December 2007	New citation required and conclusions have changed	Substantive amendment

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Figure 1.
Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?
Bilotta 2007	+	+	+	+
Gandhi 2007	+	+	+	?
Grey 2004	+	?	?	+
Lazar 2004	?	?	?	-
Li 2006	?	?	-	?

Figure 2.
Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

Characteristics of included studies [ordered by study ID]

Bilotta 2007	
Methods	Randomised controlled trial
Participants	Patients with subarachnoid haemorrhage undergoing emergency cerebral aneurysm clipping. Inclusion criteria: Prehospital Rankin score 1 to 7 and not endotracheally intubated
Interventions	Intra- and post-operatively until discharge from the ICU or upon postoperative day 14. Conventional: insulin infusion, target range 80 to 220 mg/dL Strict: insulin infusion, target range 80 to 120 mg/dL. Insulin - Actrapid HM, NovoNordisk, Copenhagen, Denmark. No intravenous dextrose was administered in the first 24 hours. Subsequently, a parenteral/enteral nutrition per protocol was administered.
Outcomes	Primary outcome: infection (pneumonia, sepsis, urinary, wound infections) as defined by NNIS. Secondary outcomes: Vasospasm, neurologic outcome, 6-month mortality.
Notes	

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random sequence, stratified by Hunt-Hess score (classifies patients with subarachnoid haemorrhage).
Allocation concealment?	Yes	Sealed envelopes, not reported whether or not they were sequentially numbered or opaque. Randomisation and allocation concealment appeared adequate. Important baseline characteristics such as body mass index and diabetes were similar between the groups.
Blinding? All outcomes	Yes	Outcome assessment of infection and neurologic outcome were assessed by blinded personnel. Blinding of caregivers was not specified, but is unlikely given different insulin algorithms. The outcomes are unlikely to have been influenced by lack of blinding of the caregivers, although no standardized protocol for initiating a workup for infection was detailed.
Incomplete outcome data addressed? All outcomes	Yes	Follow-up was 100%. No missing outcome data reported.

Gandhi 2007	
Methods	Randomised controlled trial
Participants	Adults with and without diabetes undergoing elective cardiac surgery who had intra-operative hyperglycaemia defined as glucose levels ≥ 100 mg/dL. Patients undergoing off-pump cardiopulmonary bypass procedures were excluded. Mean age of patients was 63 years. 69% male. ~20% of patients had diabetes, among whom the mean Hemoglobin A1c was 7 (SD 2).
Interventions	Intraoperatively followed by strict (intensive)glycaemic control post-operatively for 24 hours then individualized recommendations by the hospital diabetes consulting service. Conventional: regular insulin IV bolus/infusion, target range < 200 mg/dL. Strict: regular insulin infusion, target range 80 to 100 mg/dL.
Outcomes	Primary outcome: Composite of death, sternal wound infections, prolonged pulmonary ventilation, cardiac arrhythmias, stroke, and acute renal failure within 30 days after surgery. Secondary outcomes: length of stay in the ICU and hospital.
Notes	

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated, permuted blocks of 4, stratified by surgeon, surgical procedure, and diabetes.
Allocation concealment?	Yes	Sequential, opaque, sealed, tamper-proof envelopes. Randomisation and allocation concealment appear adequate - baseline characteristics appear similar between groups.
Blinding? All outcomes	Yes	Outcome assessment was performed by trained study personnel, blinded to treatment assignment, using confirmable objective criteria based on the Society of Thoracic Surgeons database. Nurses not associated with the study performed the insulin titration per assigned protocols.
Incomplete outcome data addressed? All outcomes	Unclear	A per protocol analysis was performed in that patients who did not have intra-operative hyperglycaemia ≥ 100 mg/dL were excluded from analysis. A total of 15 patients were excluded, evenly distributed between the groups. Three patients in each group were excluded due to cancellation of surgery. No intention to treat analysis was performed. Eight patients were lost to follow-up.

Grey 2004	
Methods	Randomised controlled trial.
Participants	Critically ill surgery patients. Patients predicted to have a brief stay or not expected to survive beyond 48 hours were excluded from the study. Also excluded: patients with active infections, disseminated cancer, or receiving chemotherapy, radiation, or corticosteroids. Mean age ~55-56 years. 69% of patients male. 11% diabetic. 25% received corticosteroids and 54% received vasopressors.
Interventions	Post-operatively, throughout their ICU stay. Conventional: regular insulin infusion, target range 180 to 220. Strict: regular insulin infusion, target range 80 to 120. Nutritional support was managed by a critical care nutritional support team using standardized guidelines (not described in detail).
Outcomes	Serum glucose values and nosocomial infections (intravascular device infection, pneumonia, urinary tract infection per 1,000 ICU days) as defined by the Centers for Disease Control.
Notes	

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Coin toss.
Allocation concealment?	Unclear	Allocation concealment not described.
Blinding? All outcomes	Unclear	Assessment of outcomes was not stated to have been performed by blinded personnel.
Incomplete outcome data addressed? All outcomes	Yes	Did not report on missing data.

Lazar 2004	
Methods	Randomised controlled trial.
Participants	Adults with diabetes undergoing primary or reoperative coronary artery bypass surgery. Mean age ~ 63 years. 62% male.
Interventions	Intra- and post-operatively (for 12 hours), patients were randomised to GIK (glucose-insulin-potassium) or no-GIK groups. GIK: IV regular insulin bolus/insulin infusion (with glucose and potassium), target range 126 to 200 mg/dL. No GIK: Subcutaneous regular insulin, target range 80 to 249 mg/dL.
Outcomes	Mortality, ischemic events, and wound complications.
Notes	

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	The method of sequence generation was not described.
Allocation concealment?	Unclear	No method of allocation concealment was described. Although neither the method of sequence generation or allocation concealment were described, important baseline variables such as age, sex, type of diabetes, or urgency of surgery were comparable between groups per the authors.
Blinding? All outcomes	Unclear	Assessment of outcomes was not stated to have been performed by blinded personnel.
Incomplete outcome data addressed? All outcomes	No	30-day and in hospital data appeared to be complete. Follow-up data (over 5 years) was only available for 60/72 (83%) of the GIK group and 60/69 (87%) of the no-GIK group. No method was discussed for addressing the incomplete data.

Li 2006	
Methods	Randomised controlled trial, but method not stated.
Participants	Diabetic adults undergoing coronary artery bypass grafting. Mean age ~ 63 years. 62% male. Mean Body Mass Index ~ 27 kg/m ² .
Interventions	Post-operatively, the target glucose ranges were the same in both arms, but the route and duration differed. Conventional: Subcutaneous insulin (Humulin® R, Eli Lilly and Company, Indianapolis, Indiana) for 5 days, target range 150 to 200 mg/dL. Strict: intravenous insulin for 2 days, target range 150 to 200 mg/dL. Post-operative nutritional support not described.
Outcomes	The primary outcomes were operative mortality and sternal wound infections. The secondary outcome was adequacy of glucose control as calculated by the composite average of daily mean glucose levels through the 5th post-operative day.
Notes	

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	The method of sequence generation was not described.
Allocation concealment?	Unclear	The method of allocation concealment was not described. Although neither the method of sequence generation or allocation concealment were described, important baseline variables such as age, sex, or underlying diseases were comparable between groups per the authors.
Blinding? All outcomes	No	The study was not blinded. Seven patients randomised to subcutaneous insulin were dropped from the treatment protocol due to physicians' concerns about their high glucose levels.
Incomplete outcome data addressed? All outcomes	Unclear	No missing data were reported. An intention to treat analysis was not performed.

Characteristics of excluded studies *[ordered by study ID]*

Bilotta 2008	No surgical procedures were performed.
De La Rosa 2008	The RCT included both medical and surgical patients; randomisation was not stratified by type of patient. Surgical site infections were not measured.
He 2008	No surgical patients were included.
Quinn 2006	Both groups had intra-operative glycaemic control targeted between 180 to 270 mg/dL. Neither arm had strict glycaemic control.
Wang 2006	No surgical patients were included.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Arabi 2008	
Methods	
Participants	
Interventions	
Outcomes	
Notes	study being retrieved in full for evaluation.

Barcellos 2007	
Methods	
Participants	
Interventions	
Outcomes	
Notes	study being retrieved in full for evaluation.

Bilotta 2009	
Methods	
Participants	
Interventions	
Outcomes	
Notes	study being retrieved in full for evaluation.

He 2007	
Methods	
Participants	
Interventions	
Outcomes	
Notes	study being retrieved in full for evaluation.

Comparison 1

Intra-operative strict vs. conventional glycaemic control with insulin infusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deep wound infection	1	371	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.30, 2.52]
2 Percentage of patients with intra-operative hypoglycemia below 60 mg/dL	1	371	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 15.95]
3 Percentage of post-operative patients with hypoglycemia below 60 mg/dL	1	371	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.76, 4.09]
4 Mortality	1	371	Risk Ratio (M-H, Fixed, 95% CI)	9.05 [0.49, 166.88]

Comparison 2

intra- and post-operative strict versus conventional glycaemic control with intravenous insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Infection (pneumonia, sepsis, urinary, wound infection)	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.35, 1.22]
2 Wound infection	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.04, 5.03]
3 Mortality	1	78	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.30, 2.20]

Comparison 3

Intra- and post-operative strict glycaemic control with intravenous glucose-insulin-potassium infusion (GIK) versus conventional glycaemic control with subcutaneous insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pneumonia and wound infections	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.84]

Comparison 5

Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sternal wound infection	1	93	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.12, 5.60]
2 Leg wound infection	1	93	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.10, 59.36]
3 Mortality	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.15, 17.54]

Analysis 1.1

Comparison 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion, Outcome 1 Deep wound infection

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion Outcome: 1 Deep wound infection

Analysis 1.2
Comparison 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion, Outcome 2 Percentage of patients with intra-operative hypoglycemia below 60 mg/dL

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults
 Comparison: 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion Outcome: 2 Percentage of patients with intra-operative hypoglycemia below 60 mg/dL

Analysis 1.3
Comparison 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion, Outcome 3 Percentage of post-operative patients with hypoglycemia below 60 mg/dL

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion Outcome: 3

Percentage of post-operative patients with hypoglycemia below 60 mg/dL

Analysis 1.4

Comparison 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion, Outcome 4 Mortality

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 1 Intra-operative strict vs. conventional glycaemic control with insulin infusion Outcome: 4 Mortality

Analysis 2.1
Comparison 2 intra- and post-operative strict versus conventional glycaemic control with intravenous insulin, Outcome 1 Infection (pneumonia, sepsis, urinary, wound infection)

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 2 intra- and post-operative strict versus conventional glycaemic control with intravenous insulin

Outcome: 1 Infection (pneumonia, sepsis, urinary, wound infection)

Analysis 2.2

Comparison 2 intra- and post-operative strict versus conventional glycaemic control with intravenous insulin, Outcome 2 Wound infection

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 2 intra- and post-operative strict versus conventional glycaemic control with intravenous insulin

Outcome: 2 Wound infection

Analysis 2.3

Comparison 2 intra- and post-operative strict versus conventional glycaemic control with intravenous insulin, Outcome 3 Mortality

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 2 intra- and post-operative strict versus conventional glycaemic control with intravenous insulin

Outcome: 3 Mortality

Analysis 3.1
Comparison 3 Intra- and post-operative strict glycaemic control with intravenous glucose-insulin-potassium infusion (GIK) versus conventional glycaemic control with subcutaneous insulin, Outcome 1 Pneumonia and wound infections

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 3 Intra- and post-operative strict glycaemic control with intravenous glucose-insulin-potassium infusion (GIK) versus conventional glycaemic control with subcutaneous insulin Outcome: 1 Pneumonia and wound infections

Analysis 5.1

Comparison 5 Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin, Outcome 1 Sternal wound infection

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 5 Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin

Outcome: 1 Sternal wound infection

Analysis 5.2

Comparison 5 Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin, Outcome 2 Leg wound infection

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 5 Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin

Outcome: 2 Leg wound infection

Analysis 5.3

Comparison 5 Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin, Outcome 3 Mortality

Review: Peri-operative glycaemic control regimens for preventing surgical site infections in adults

Comparison: 5 Post-operative glycaemic control with intravenous insulin infusion versus subcutaneous insulin

Outcome: 3 Mortality