Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic review and meta-analysis of randomized trials


CRD summary
This well-conducted review concluded that mortality was reduced, but hypoglycaemia was increased, in surgical patients receiving perioperative insulin. Given the quality and quantity of the included data, the authors were justified in recommending that their findings be interpreted with caution and that they require confirmation in further large, well-conducted trials.

Authors' objectives
To determine the effect of perioperative insulin on morbidity and mortality in patients undergoing surgery.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched. Search terms and dates were not reported, but details of the search strategy were available from the authors on request. SciSearch and the authors' own files were searched for additional studies and topic experts were consulted. No language restrictions were applied and both published and unpublished studies were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) comparing any intravenous perioperative insulin infusion with either another insulin infusion, subcutaneous insulin or standard care in patients undergoing any form of surgery were eligible for inclusion in the review. Control insulin/other treatment groups were required to be for a glucose value higher than specified for the interventions group. Studies that randomised patients to insulin infusion after they had undergone a perioperative nonfatal myocardial infarction or a nonfatal cardiac arrest were excluded from the review. The primary outcome was total mortality, but a number of other outcomes were also included (details reported in the review).

The majority of included trials initiated insulin infusion during surgery and continued treatment postoperatively for a variable length of time. Where reported, the majority (60 per cent) of included patients were male undergoing coronary artery bypass graft (CABG) surgery. A number of the trials reported the inclusion of patients with diabetes. Interventions were either insulin or glucose-insulin-potassium (GIK); GIK was reserved for patients undergoing cardiac surgery and none of these trials reported using a specified glucose goal. In the remaining studies, the majority reported a glucose goal but this varied widely between studies. Control groups were not reported. The duration of follow-up was rarely reported in the trials. For those that reported duration of follow-up, it was usually continued until hospital discharge.

Two reviewers independently assessed the eligibility of each study for inclusion. Any disagreements were resolved through consensus.

Assessment of study quality
Two reviewers independently assessed the quality of the studies using the following criteria: adequacy of allocation concealment, blinding (patients, health care professionals and outcome assessors) and loss to follow-up. For each criterion the studies were awarded a 'yes' (fulfilled criterion), 'no' (failed to fulfil criterion) or 'NR' (not reported). Early stopping was also reported.

Data extraction
Two reviewers independently extracted the study data using a standardised form. Any disagreements were resolved through consensus. Intention-to-treat (ITT) data were extracted for all outcomes that occurred during hospitalisation or within 30 days of surgery. Study authors were contacted for missing data. Relative risks (RRs) with 99% and 95% confidence intervals (CIs) were calculated for dichotomous outcomes. The authors also report that they used RRs for continuous outcomes expressed in days. Target glycemic levels were also extracted and assumed to be insulin
supplementation if data were unavailable.

**Methods of synthesis**

Pooled RRs with CIs were calculated using the DerSimonian and Laird random effects model. Statistical heterogeneity was assessed using the $I^2$ statistic, a value of 25 per cent or less indicating a low level. Where $I^2$ values were over 25 per cent, an a priori decision was made to conduct any relevant subgroup analyses (study validity, type of surgery, treatment intervention, glycemic control goal, diabetes patients and duration of treatment). A heterogeneity-corrected optimal information size (HOIS) was also calculated for the primary outcome and the incidence of hypoglycaemia to assess the reliability of the data. The HOIS was also used to construct Lan DeMets sequential monitoring boundaries.

**Results of the review**

Thirty-four RCTs (n=5,150) were included in the review, with sample sizes ranging from 14 to 1,548 (median=34). The quality of the trials was reported as being generally low to moderate: only 16 of trials reported allocation concealment and only 12 reported blinding assessors. Most trials failed to report losses to follow-up.

Overall, a statistically significant reduction in favour of postoperative insulin in comparison with control was reported for mortality (RR 0.69; 95% CI: 0.51, 0.94; 14 RCTs, $I^2=0\%$). Postoperative insulin was also associated with a statistically significant increase in hypoglycaemia (RR 2.07; 95% CI: 1.29, 3.32; 20 RCTs, $I^2=31.5\%$). No statistically significant differences were reported for any other clinically important outcome (P>0.05). However, the meta-analyses were dominated by one trial (n=1,548) in intensive-care patients that had a number of potential limitations. Ten per cent of patients in this trial did not undergo surgery but were included in the analysis due to a lack of data. When excluded from the analyses, postoperative insulin was no longer associated with a significant beneficial reduction in mortality. Subgroup analyses failed to explain the heterogeneity where reported. Evidence from the HOIS and sequential monitoring boundaries suggested that the findings from the mortality data were inconclusive, but the hypoglycaemia data were reliable.

**Authors’ conclusions**

Evidence suggested that mortality was reduced, but hypoglycaemia was increased in surgical patients receiving perioperative insulin. The mortality conclusion required confirmation.

**CRD commentary**

This review answered a clear review question using broad criteria for participant type. Searches were conducted in a number of electronic databases and supplemented with data from other sources. Both unpublished and published studies were included and no language restrictions were applied, suggesting a low risk of publication and language bias. Rigorous review methodology was used throughout. The overall quality of the studies was low to moderate. Some studies had flaws that may affect the reliability of the data, particularly the largest and most dominant trial; the impact of this trial was assessed by sensitivity analyses. Statistical heterogeneity was also assessed and explored appropriately. Analyses were conducted to ensure that the meta-analyses were powered adequately and that the results were reliable and robust. Overall, this was a well-conducted review, but the authors were justified in advising caution when interpreting their findings given the quality and quantity of the data on which they were based.

**Implications of the review for practice and research**

Practice: the authors did not state any implications for practice.

Research: the authors stated that further large, well-conducted RCTs were required to confirm the review findings and determine the role of perioperative insulin use and tight glycaemic control. Optimal glucose controls, the duration of treatment and groups of patients at greatest risk should be identified using trials that focus on key outcomes such as mortality.

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