Effect of perioperative glucose-insulin-potassium infusions on mortality and atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis

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CRD summary
This well-conducted review concluded that perioperative use of glucose-insulin infusions with/without potassium did not significantly reduce the incidence of atrial fibrillation or in-hospital mortality in patients after coronary artery bypass graft surgery. However, these findings should be interpreted bearing in mind the limitations of the included trials (their poor quality and unexplained variation).

Authors’ objectives
To determine whether the use of perioperative glucose-insulin infusions with/without potassium reduced in-hospital mortality and atrial fibrillation after coronary artery bypass graft surgery.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to June 2009. Search terms were reported; the Cochrane Collaboration randomised controlled trial (RCT) filter was applied. Reference lists of retrieved articles were screened. Topic experts contacted for further studies. No language limitations were used.

Study selection
Randomised controlled trials RCTs that compared perioperative glucose-insulin infusion with/without potassium versus placebo in patients undergoing coronary artery bypass grafting were eligible for inclusion in the review. Studies had to report in-hospital mortality and/or postoperative atrial fibrillation.

Most included trials compared intravenous glucose-insulin infusions plus potassium with placebo; the remainder mainly assessed glucose-insulin infusion without potassium cardioplegia; one trial assessed glucose-insulin infusion plus potassium cardioplegia. Where administered, glucose, insulin, and potassium differed. The mean age of included patients in the intervention groups ranged from 55.1 to 72 years and from 54.5 to 74 years in the control groups. Most trials included more men than women (where reported); three trials included only men. Over a third of trials included patients with diabetes and a third of trials did not include any diabetic patients (the remaining trials did not report data). Most trials reported adverse events in addition to mortality and atrial fibrillation.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Two reviewers assessed the methodological quality of the included trials using the Jadad scale (randomisation, blinding and adequacy of follow-up). Each trial was awarded a score between 0 and 5 points. Trials were also assessed on whether they used concealment of allocation.

Data extraction
Two reviewers independently extracted the trial data to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Discrepancies were resolved by consensus.

Methods of synthesis
Trials were grouped according to trial outcome. Pooled odds ratios with 95% confidence intervals were calculated using the DerSimonian-Laird random-effects model. Statistical heterogeneity was assessed using the Q test. The meta-analysis was stratified by the method of intervention delivery (cardioplegia solution or intravenous), type of infusion, and surgical procedure (on-pump versus off-pump). Meta-regression was performed to assess the influence of methodological and clinical factors.

Sensitivity analyses were performed to exclude trials with no outcome events in either arm, and to exclude trials where
death and/or atrial fibrillation were secondary or tertiary end points with a physiological measure as the primary endpoint.

Publication bias was assessed using funnel plots and the Begg’s test.

**Results of the review**

Twenty RCTs (n=2,943 patients) were included in the review. Five RCTs had Jadad scores of 3 out of 5; the remaining 15 RCTs scored either 1 or 2 points. Allocation concealment was only judged adequate in four RCTs.

No statistically significant differences between intervention treatments and placebo were reported for in-hospital mortality (n=2,326 patients; 16 RCTs; Q=5.6, P=0.99) or postoperative atrial fibrillation (n=1,540; 11 RCTs; Q=23.67, P=0.014; substantial heterogeneity) after coronary artery bypass graft surgery. Further analyses showed that heterogeneity could not be explained by the type of infusion, route of administration or surgical procedure. Sensitivity analyses did not alter the findings.

Fifteen trials reported data on hypoglycaemia and/or hyperglycaemia. In six of the trials reporting glycaemic abnormalities, hypoglycaemia treatment was needed. Five of the trials on glycaemic events reported more frequent hypoglycaemia among patients who received the intervention. In one of three trials that reported hyperglycaemia requiring treatment, there was more frequent hyperglycaemia among intervention patients compared with placebo patients. Other adverse event data were reported in the review.

There was no evidence of significant publication bias.

**Authors’ conclusions**

The perioperative use of glucose-insulin infusions with/without potassium did not significantly reduce atrial fibrillation or in-hospital mortality in patients who had undergone coronary artery bypass graft surgery. There was some evidence that treatment may be associated with an increase in the incidence of hypoglycaemia.

**CRD commentary**

This review answered a clearly defined research question. The literature searches were aimed at reducing the risk of both language and publication bias. Attempts were made to reduce the risk of reviewer error and bias through the use of two independent reviewers at each stage of the review process.

The methodological quality of the included trials was assessed using appropriate criteria; it was found to be limited in most cases. The trials varied in both intervention treatments and populations; there was evidence of substantial statistical heterogeneity for one outcome measure. This suggested that the pooled effect sizes may not be reliable, but was acknowledged by the authors (as were a number of other limitations in their analyses). Some attempts were made to investigate the potential effects of differences between the trials; the methodological quality of the trials was found to explain some of the observed heterogeneity. Few trials reported data on adverse events. It was unclear why one of the trials (Lolly) was included in the forest plots twice.

This was a generally well-conducted review which appeared to reflect the evidence, but should be interpreted bearing in mind the limitations of the included trials (poor quality and unexplained heterogeneity).

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

**Practice:** The authors stated that the use of infusions should be limited to investigational protocols until more evidence is available.

**Research:** The authors stated that further evidence is required before glucose-insulin infusions with/without potassium can be considered proven as an adjuvant medical treatment for patients undergoing coronary artery bypass graft surgery.

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