Glucose-insulin-potassium in cardiac surgery: a meta-analysis
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CRD summary
The review assessed glucose-insulin-potassium treatment after cardiac surgery. The authors concluded that glucose-insulin-potassium therapy may improve recovery of contractile function and reduce the incidence of atrial fibrillation after surgery. There are too many uncertainties about the review methods to be confident that the conclusion is reliable.

Authors' objectives
To assess the effect of glucose-insulin-potassium (GIK) therapy on the recovery of contractile function following cardiac surgery.

Searching
MEDLINE was searched; the search terms were reported. The search extended at least as far back as 1970. The reference lists of the included studies and reviews of GIK were checked for additional studies. Only studies published in the English language were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of GIK therapy were eligible for inclusion. Studies in which other substances were given in addition to GIK were excluded. In the included studies GIK was administered either pre-operatively, peri-operatively, post-operatively or peri- and post-operatively. The duration of treatment ranged from a few seconds to around 18 hours. The total amounts of glucose, insulin and potassium administered differed greatly between studies. The control intervention appeared to be placebo.

Participants included in the review
Studies in cardiac surgery patients were eligible for inclusion. The patients in the included studies underwent coronary artery bypass grafting or heart valve replacement. A few studies specifically excluded patients with diabetes whereas one study included only patients with diabetes. Some studies included both patients with preserved and impaired ventricular function, while some included only those with preserved ventricular function. Five studies excluded patients on the basis of ejection fraction (EF), specifying a cut-off of less than 20, 40 or 50%. Two studies used age as an exclusion criterion, over 70 years and over 80 years, respectively. One study excluded women.

Outcomes assessed in the review
Studies that used recovery of contractile function as a primary outcome were eligible for inclusion. The measurements used in the included studies to assess recovery of function were cardiac index, dp/dt max and EF. Other outcomes reported included post-operative atrial fibrillation (AF) and post-operative requirement for inotropic support.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The main outcome data extracted were the mean and standard deviation for pre-operative and post-operative cardiac index values, and the number of post-operative AF events, in each treatment and control group. Mean and standard deviation values for dp/dt max and EF were extracted from the studies that did not report cardiac index. To facilitate comparison between studies, the first pre-operative measurements and the post-operative measurements closest to the time point of 4 hours were extracted. It appeared that p-values reported in the individual studies were extracted where available. Data on the post-operative use of catecholamines were also extracted to estimate the need for inotropic drugs (the actual data extracted were unclear). The requirement for inotropic drugs was expressed as an index of control/GIK greater, equal to, or less than 1.

Methods of synthesis
How were the studies combined?
The overall effect of GIK on post-operative recovery of cardiac function was estimated by first calculating the relative difference in the pre-operative cardiac index versus the post-operative value for each treatment and control (placebo) group within each study. The percentage difference between the control group and the GIK group in each study was then calculated. The sum of these values was then calculated, weighted by the number of cases in each study. The dp/dt max and EF data were added to the combined analysis to assess the effect this had on the overall estimate of recovery of function. The overall impact of GIK on post-operative AF was estimated by calculating the pooled weighted average of the incidence of post-operative AF in the treatment and control groups over all trials. The method of weighting was unclear. The effect of GIK on preventing AF was tested using the Mantel-Haenszel statistic (p<0.05 indicated statistical significance).

How were differences between studies investigated?
Differences in study characteristics were highlighted in the text and tables. A subgroup analysis of recovery of function was undertaken based on whether GIK was given peri-operatively or peri- and post-operatively; all measurements of recovery of function (cardiac index, dp/dt max and EF) were included. The subgroup analysis did not appear to be pre-specified.

Results of the review
Eleven studies, including 468 patients, were included.

Seven trials showed better post-operative recovery of contractile function in GIK patients compared with controls, three trials found no difference, and a p-value was not available for one trial.

The overall mean relative improvement in post-operative recovery of cardiac index was 11.4% for GIK patients compared with controls, based on six trials. The inclusion of data from the trial that reported EF reduced the overall relative improvement to 11.2%, whereas the inclusion of data from the trial that reported dp/dt max increased it to 26%. Data were not available to determine if the difference was statistically significant.

The subgroup estimates of relative improvement were 6.1% by peri-operative GIK (five trials, 284 patients) and 19.5% by peri- and post-operative GIK (three trials).

The overall incidence of post-operative AF in five trials was 36 out of 86 in the GIK groups and 20 out of 86 in the controls. The difference was statistically significant (p=0.009).

Nine trials provided data on the requirement for inotropic drugs. Five trials had an index of 1, while four trials had a lower requirement in the GIK group.

Authors' conclusions
GIK may improve post-operative recovery of contractile function and reduce the incidence of atrial arrhythmias after...
cardiac surgery.

**CRD commentary**
The review addressed a clear question and stipulated the inclusion criteria. Relevant studies might have been missed because few sources were searched, whilst the restriction to studies published in English raises concern about the potential influence of publication and language bias on the results. In addition, there was no mention of methods used to minimise reviewer bias in the selection of studies for inclusion. The lack of reporting of review methods gives no reassurance that bias and errors in the data extraction were minimised. The reliability of the individual study results was uncertain because the quality of the studies was not assessed. Furthermore, the methods of analysis raise doubt about the validity of the pooled estimates of effect. Although the characteristics of the included studies were fairly well described (with the notable exception of the control intervention) and the marked heterogeneity was acknowledged, this was not taken into account in the analysis. The reliability of the conclusions is questionable.

**Implications of the review for practice and research**
Practice: In relation to the surgical treatment of cardiac patients, the authors stated that the results from older studies included in the review may not be transferable to current practice (the publication dates of the included studies ranged from 1984 to 2001).

Research: The authors stated that large multicentre RCTs are needed to assess the effectiveness of GIK in cardiac surgery.

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contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.