Comparison of glucose-insulin-potassium and insulin-glucose as adjunctive therapy in acute myocardial infarction: a contemporary meta-analysis of randomised controlled trials

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CRD summary
The review found that glucose-insulin-potassium did not reduce mortality in patients with acute myocardial infarction. Limitations in the evidence on insulin infusion for glycaemic control meant that an effect on mortality could not be ruled out. The authors' conclusions reflected the limited evidence base, but should be considered tentative due to further limitations of the studies, such as clinical heterogeneity.

Authors' objectives
To assess the efficacy of a regimen focused on delivering insulin (insulin focus) and a regimen focused on tight glycaemic control (glycaemia focus) as adjunctive therapy to prevent mortality in acute myocardial infarction.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched from January 1980 to November 2009 with no language restrictions; search terms were reported. Reference lists of retrieved studies and reviews were searched.

Study selection
Eligible studies were randomised controlled trials (RCTs) that assessed glucose-insulin-potassium (GIK) (insulin focus) or insulin-glucose (glycaemia focus) as adjunctive therapy in patients with acute myocardial infarction and assessed all-cause mortality.

In the included studies, the mean age of participants ranged from 57 to 69 years and the proportion of males ranged from 62% to 100%. Most participants (67.7% to 100%) were classified as Killip I status. Baseline mean blood glucose level, where reported, ranged from 6.9 to 15.7mmol/L. Mean blood glucose 24 hours after treatment, where reported, ranged from 4.04 to 11.7mmol/L. In the insulin focus studies, mean time from onset of symptoms to treatment ranged from 2.75 to 11.4 hours. Studies either compared GIK with control or insulin-glucose with standard therapy. All participants in studies that assessed insulin-glucose had diabetes; in studies that assessed GIK the mean proportion with diabetes ranged from 6% to 24%. Studies were published between 1995 and 2007.

Two blinded reviewers independently selected studies for the review. Disagreements were resolved by consensus.

Assessment of study quality
Studies were assessed for quality using a modified Jadad score of randomisation, generation of randomisation procedure, double blinding, withdrawals and allocation concealment to a maximum score of 5. Studies with a score of at least 3 were considered high quality and those with a score of 2 or less were considered low quality.

The authors did not state how many reviewers undertook quality assessment.

Data extraction
Data were extracted on all-cause mortality on an intention-to-treat basis and relative risks (RRs) and their 95% confidence intervals (CIs) were calculated. The original authors of GIK studies were contacted for further details, where necessary.

Two reviewers independently extracted data using a standardised form. Inconsistencies were resolved through discussion until a consensus was reached.
Methods of synthesis
Studies were pooled using a Mantel-Haenszel random-effects model. Separate meta-analyses were conducted for GIK and insulin-glucose treatments. Subgroup analyses of the time of GIK administration (before or after reperfusion) were performed on the basis of a priori protocol of RCTs. Subgroup analyses of the insulin-glucose trials were performed according to whether glycaemic control was achieved.

I² was used to assess heterogeneity of the summary estimates. A value of more than 50% was considered to be evidence of significant heterogeneity. Sensitivity analysis was performed in the GIK studies to remove outliers. Post hoc sensitivity analysis was undertaken in the GIK studies by excluding the two largest studies. Publication bias was assessed using a funnel plot and the Begg rank correlation method.

Results of the review
Eight RCTs (n=22,215 participants, range 118 to 20,201) of GIK based on insulin focus and three RCTs (n=1,649, range 240 to 1253) of insulin-glucose based on glycaemia focus were included in the review. There was a discrepancy in the numbers of participants reported in the text and a table. Most studies had a Jadad score of 3 and two studies had a Jadad score of 2.

Trials using GIK (eight RCTs): There was no evidence of a reduction in mortality with use of GIK compared to control (eight trials) with considerable heterogeneity between trials (I² = 48%). In subgroup analysis, GIK before reperfusion was not associated with a reduction in mortality compared to control (five trials, I² = 24%). GIK after reperfusion was also not associated with a reduction in mortality compared to control (three trials, I² = 48.4%). Sensitivity analysis that excluded one trial that appeared to be an outlier, removed the statistical heterogeneity and did not markedly change the results.

Post hoc sensitivity analysis was undertaken to remove two trial subgroups that had greater weight in the analyses. The summary effect measure for the subgroup analysis of GIK before reperfusion was not changed markedly. However, GIK was associated with a significant increase in mortality compared to control when given after reperfusion (RR 1.78, 95% CI 1.13 to 2.80; two trials).

Trials using insulin-glucose (three RCTs): There was no evidence of a reduction in mortality with use of insulin-glucose compared to standard therapy in treatment of acute myocardial infarction with diabetes (three trials, no significant heterogeneity). Subgroup analysis according to whether glycaemic control was achieved found no evidence of a significant difference in mortality between the two groups.

There was no evidence of publication bias by inspection of a funnel plot and use of Begg correlation.

Authors’ conclusions
Glucose-insulin-potassium did not reduce mortality in patients with acute myocardial infarction. Studies of glycaemia were inconclusive and it was possible that glycaemic control was beneficial.

CRD commentary
The review addressed a clear research question. Inclusion criteria appeared mostly appropriate, but criteria for participants were not reported. Various relevant sources were searched without language restrictions. The small number of trials meant that methods to assess publication bias may not have produced reliable results. Methods for extraction of data and selection of studies were appropriate; methods were not specifically reported for quality assessment. The quality assessment tool was appropriate, but only composite scores were reported. Most studies were considered to be of high quality (3 out of a maximum of 5 points on the Jadad scale).

The authors acknowledged that the participants were clinically heterogeneous and no adjustments were made for concomitant medications. The review assessed the effects of two insulin strategies on mortality in acute myocardial infarction, but each strategy was compared with control and not compared directly with the other strategy. Synthesis of the studies in meta-analyses and the assessment of heterogeneity were appropriate. Sensitivity and subgroup analyses were used to explore the heterogeneity and stability of the results. The authors acknowledged the limited evidence on
use of insulin-glucose.

The authors’ conclusions reflected the limited evidence base, but should be considered tentative due to further limitations of the studies, such as clinical heterogeneity.

**Implications of the review for practice and research**
The authors did not state any implications for research and practice.

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