Effect of glucose-insulin-potassium infusion on mortality in critical care settings: a systematic review and meta-analysis

Puskarich MA, Runyon MS, Trzeciak S, Kline JA, Jones AE

CRD summary
This review found no differences in mortality in critically-ill patients with acute myocardial infarction, or in those who had undergone cardiovascular surgery, that received glucose-insulin-potassium infusion therapy. Further research is needed. The review was generally well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the effect of glucose-insulin-potassium infusion on mortality in critically-ill patients.

Searching
MEDLINE, EMBASE and CINAHL were searched from inception to April 2008; search terms were reported. Reference lists of included articles and relevant reviews, correspondence and editorials were screened to identify further studies. Unpublished studies were identified from searches of clinical trials websites and abstracts from annual meetings of the Society of Critical Care Medicine and the American College of Chest Physicians (1997 to 2007). Public practice guidelines for critical care (2000-2007) were also reviewed. Two experts in the field of critical care were also contacted to identify further unpublished studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of adults (aged 18 years and over) with critical illness that compared continuous infusions of glucose, insulin and potassium treatment with usual care or placebo, were eligible for inclusion. Critical illness was defined as patients enrolled in an intensive care unit or operating room, or a control group, with a mortality rate of at least 15%.

The primary outcome was mortality. Other outcomes assessed were adverse events of hypoglycaemia and hyperkalaemia.

In the included trials, the glucose-insulin-potassium infusions were given at a range of formulations ranging from 0.05U/kg/hour to 1U/kg/hour of insulin; infusion duration ranged between six to 168 hours. The interventions took place in intensive care units and operating theatres/rooms. The indications of the included patients were acute myocardial infarction, aortic valve replacements, mitral valve replacements, and coronary artery bypass grafting.

Two reviewers independently assessed the studies for inclusion, and any disagreements were resolved by conference between the reviewers. The two reviewers compared the excluded studies; the K-statistic was calculated to evaluate inter-observer agreement.

Assessment of study quality
Two reviewers independently assessed methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias in which sequence generation, allocation concealment, blinding and selective outcome reporting were evaluated on an ABC graded scale.

Data extraction
Data were extracted to permit the calculation of odds ratios (OR) with 95% confidence intervals (CI) and proportions. In the event of incomplete or missing data, the authors were contacted.

Two reviewers extracted data independently and any differences were resolved by a third reviewer and by consensus.

Methods of synthesis
The pooled odds ratios and 95% confidence intervals for the outcomes were calculated using a random-effects model. The $\chi^2$ test was used to evaluate statistical heterogeneity across the trials. The reviewers explored potential publication biases by visual appraisals of funnel plots. The $\chi^2$ test and $I^2$ test were used to evaluate statistical heterogeneity across the trials. Subgroup analyses, based on high quality trials, patients with acute myocardial infarction, and patients undergoing cardiovascular surgery, were undertaken. In addition, the authors assessed the effect of the removal from the analysis of one large trial by repeating the analysis with this trial removed.

Results of the review
Twenty-three trials (n=22,525 patients) were included in the review. The inter-observer agreement for trial selection was 98% ($K=0.79$). Four trials achieved A grades in three of four domains in the validity assessment, which met the reviewers' definition of high quality trials. Ten trials were assigned C grades for three of four domains of methodological quality. Follow-up ranged from the duration of in-hospital stay to one year following the infusion.

Mortality incidence rates ranged from 0 to 16% in the glucose-insulin-potassium infusion group and 0 to 36% in the control group.

There was no statistically significant reduction in mortality among patients in the glucose-insulin-potassium infusion and usual care or placebo groups (OR 1.02, 95% CI 0.93 to 1.11). Subgroup analysis showed similar results for: high quality trials (four RCTs; n=21,104 patients); patients with acute myocardial infarction (10 RCTs; n=21,421 patients); patients undergoing cardiovascular surgery (13 RCTs; n=1,104 patients); and removal of one large trial (22 RCTs; n=2,330 patients).

Of the six trials (n=20,633 patients) that reported the incidence of hypoglycaemia, the incidence rates were found to be 0.5% in the glucose-insulin-potassium infusion groups and 0.1% the control groups. In overall incidence of hyperkalaemia (four RCTs; n=20,313 patients) was 4.3% in the glucose-insulin-potassium infusion groups and 1.6% in the control groups.

There was no statistically significant heterogeneity reported in the analysis of the pooled results.

Authors' conclusions
There was no treatment effect of glucose-insulin-potassium infusion for critically-ill patients with acute myocardial infarction or those who had undergone cardiovascular surgery. Further research using patients with septic and other forms of circulatory shock are required to explore the potential benefits of glucose-insulin-potassium infusion in these and other critically-ill populations.

CRD commentary
The review addressed a clear question and inclusion criteria were stipulated. The search was comprehensive, and attempts were made to search for unpublished studies. There were no language biases. Steps were taken to minimise reviewer bias and error during each stage of the review process.

Sufficient study details were provided. Although there was some clinical heterogeneity, the decision of the reviewers to pool the studies appeared appropriate, as there was no evidence of statistical heterogeneity.

The review was generally well conducted and the authors’ conclusions are likely to be reliable.

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

Research: The authors stated that future studies should evaluate the use of glucose-insulin-potassium infusions for patients with septic or other forms of circulatory shock, or in other populations of critically-ill patients.

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