Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled trials
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CRD summary
This review examined the effect of insulin therapy initiated during hospitalisation on mortality in adult patients with a critical illness. The authors concluded that insulin therapy reduces short-term mortality in different clinical settings. Given some methodological problems, and the mixed results of the individual studies, the conclusions should be interpreted with caution.

Authors' objectives
To determine the effect of insulin therapy initiated during hospitalisation on mortality in adult patients with a critical illness.

Searching
MEDLINE (January 1966 to April 2003) and the Cochrane Controlled Trials Register (Issue 2, 2003) were searched; the search terms were reported. The bibliographies of all relevant retrieved articles, relevant review articles, monographs, personal reference lists and meeting proceedings were also manually searched for further studies. Only studies published in the English language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), including original clinical trial data, were eligible for inclusion.

Specific interventions included in the review
Studies of insulin therapy during hospitalisation were eligible for inclusion. Some included studies used a glucose-insulin-potassium (GIK) infusion; in others insulin was administered intravenously or subcutaneously.

Participants included in the review
Studies on adult patients hospitalised for acute myocardial infarction, stroke, coronary artery bypass grafting, or an illness requiring admission to the intensive care unit, were included in the review. Studies including pregnant women and children were excluded.

Outcomes assessed in the review
Studies with mortality outcomes (in hospital or within 30 days after discharge) reported in relation to insulin therapy were included. Reported adverse events were also recorded.

How were decisions on the relevance of primary studies made?
Two independent reviewers screened abstracts. Full-text articles were obtained and reviewed if a decision on inclusion could not be made based on the abstract.

Assessment of study quality
Quality was assessed on the basis of allocation generation (proper randomisation), allocation concealment, placebo-controlled status, blinding and intention-to-treat analysis. The authors did not state how many reviewers performed the quality assessment.

Data extraction
The authors did not state explicitly how the data were extracted for the review, or how many reviewers performed the data extraction. Mortality outcomes (number and causes of death) and adverse events were extracted for each intervention or control arm, and a relative risk (RR) of mortality reduction was calculated for each trial. For trials with duplicate publications, the most complete or updated publication was used.

**Methods of synthesis**

**How were the studies combined?**

The RRs were combined using a random-effects model, weighting studies by the inverse of the within-study and between-study variances. The pooled RR and 95% confidence interval (CI) were reported.

**How were differences between studies investigated?**

Subgroup analyses were performed for studies that differed in terms of methodological quality, maintenance of euglycaemia as the target of insulin therapy, inclusion of patients with diabetes mellitus, clinical condition or hospital setting, method of insulin administration (GIK versus non-GIK), and use of reperfusion therapy in studies of acute myocardial infarction.

**Results of the review**

Thirty-five RCTs (n=8,478) were included in the review.

The method of allocation generation was clearly reported and considered appropriate in 13 studies. Blinding was reported in 10 studies, 5 of which were double-blind. Only 2 studies met strict criteria such as appropriate randomisation, double-blind status and clearly stated statistical methods.

Based on all 35 trials, patients receiving insulin therapy showed a statistically significant 15% reduction in mortality compared with controls (RR 0.85, 95% CI: 0.75, 0.97).

In studies in which the goal was to achieve glucose control, patients receiving insulin showed a 29% reduction in mortality relative to the controls (RR 0.71, 95% CI: 0.54, 0.93). Studies in which insulin was administered without aiming to achieve glucose control found no benefit of insulin on mortality.

Studies that included patients with diabetes mellitus showed a significant benefit of insulin on mortality (RR 0.73, 95% CI: 0.58, 0.90). In studies that excluded patients with insulin-requiring diabetes mellitus, the benefit of insulin was smaller, while in trials that excluded patients with a history of diabetes mellitus, there was no benefit.

Studies in which insulin was administered as a GIK solution showed no statistically significant benefit of insulin on mortality. Studies that administered insulin in a way other than GIK (n=5) showed a statistically significant 27% reduction in mortality in patients receiving insulin compared with controls (RR 0.73, 95% CI: 0.56, 0.95).

Patients who received insulin when admitted for acute myocardial infarction or cardiac surgery showed no statistically significant benefit of insulin therapy. One large trial showed that patients receiving insulin on a surgical intensive care unit had a significant 42% reduction in mortality. Studies of patients with myocardial infarction who were not treated with reperfusion showed a reduction in mortality for insulin treatment (pooled RR 0.84, 95% CI: 0.71, 1.00), but no significant benefit was found in the studies where reperfusion was used.

Based on 10 studies, patients receiving insulin were three times more likely to develop hypoglycaemia than controls (RR 3.4, 95% CI: 1.9, 6.3).

**Authors' conclusions**

Insulin therapy initiated in the hospital in critically ill patients was found to have a beneficial effect on short-term mortality in the surgical intensive care unit, in patients with diabetes mellitus, and in patients with myocardial infarction who were not treated with reperfusion therapy.
CRD commentary
The authors set out a clear objective at the beginning of the review and the inclusion criteria were clearly defined. Appropriate sources were searched, and an effort was made to avoid publication bias by searching for meeting proceedings. However, studies were restricted to those published in English, which might have introduced language bias, and relevant studies might have been missed. Two independent reviewers screened abstracts, which helps reduce the risk of bias. However, it was unclear how many reviewers extracted the data or assessed quality. Quality was assessed using appropriate criteria.

Adequate details of the studies were presented. Given that the included studies were of mixed quality, had different clinical populations and settings, and that statistical heterogeneity was not reported, the pooling of all studies might not have been appropriate. However, subgroup analyses were used to investigate these differences. The authors’ conclusions were generally in line with the data they presented, although it should be noted that the conclusion regarding the surgical intensive care unit was based on one study only. In addition, the conclusions regarding both diabetes mellitus patients and reperfusion were based on a body of evidence with mixed results which are only in favour of the intervention as pooled results. Given these limitations, the conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that their results did not support the use of insulin, as administered in these trials, for decreasing mortality in the peri-operative setting for open heart surgery.

Research: The authors stated that it had not yet been determined whether insulin therapy was beneficial in other clinical settings, such as stroke, or other patient groups, such as the medical intensive care unit or general surgical or medical ward.

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