Benefits and risks of tight glucose control in critically ill adults: a meta-analysis

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CRD summary
Tight glucose control does not significantly reduce hospital mortality among critically ill adult patients, but it does increase the risk of hypoglycaemia. The review was generally well conducted and these conclusions seem likely to be reliable.

Authors' objectives
To evaluate the benefits and risks of tight glucose control compared with usual care in critically ill adults.

Searching
MEDLINE (1950 to June 2008), the Cochrane Library (Issue 1, 2008) and multiple trial registries (in August 2007) were searched: the search terms were reported. In addition, conference proceedings of the American Thoracic Society (2001 to 2008) and the Society of Critical Care Medicine (2004 to 2008) were handsearched and the reference lists of relevant articles were checked. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared tight glucose control with usual care in critically ill adults in an intensive care unit (ICU), and reported hospital or short-term mortality (primary outcome), sepsis, new need for dialysis and/or hypoglycaemia. Tight glucose control was defined as less than 150 mg/dL obtained by insulin infusion during all or part of the stay in the ICU. Usual care was as defined in the primary study. Sepsis was defined as including sepsis, bacteraemia or positive blood cultures; hypoglycaemia as one or more blood glucose measurements below 40 mg/dL (with or without symptoms); and hospital mortality as death in hospital or within 30 days of admission. Studies where the intervention was primarily intra-operative were excluded.

Most of the included studies were conducted at single centres. Common participant diagnoses at admission were cardiac surgery, abdominal surgery, myocardial infarction, stroke, respiratory failure and sepsis. There was wide variety in mean participant age, gender distribution, the proportion with diabetes and the degree of disease severity. Studies used either insulin alone or a glucose-insulin-potassium infusion in the intervention group. Glucose goals in this group ranged from 72 to 99 mg/dL to 90 to 144 mg/dL, while achieved mean glucose ranged from 90 to 185 mg/dL. Study follow-up (where reported) ranged from 28 days to 6 months, or for the duration of hospital stay.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study validity was assessed using the Jadad scale, which measures adequacy of randomisation, blinding and management of attrition.

Two unblinded reviewers independently performed the assessment, with any discrepancies resolved by discussion.

Data extraction
The data were extracted using a standardised form. Relative risks (RRs), with 95% confidence intervals (CIs), were calculated from the numbers of events in the control and intervention groups of each study. Where ICU setting was not specified, it was categorised as mixed (medical-surgical). Investigators of unpublished studies and (if necessary) of published studies were contacted for additional data. Studies were excluded if adequate data about methodology and results could not be obtained, or if no events occurred for the outcomes of interest.

Two unblinded reviewers independently extracted the data, with any discrepancies resolved by discussion.
Methods of synthesis
The data were combined using a random-effects model to calculate a pooled RR and 95% CI. Subgroup analyses were conducted to examine the effect of ICU setting and glucose goal. Further analysis was conducted on the glucose-goal subgroup, categorising studies according to the actual mean glucose level achieved. Additional sensitivity analyses were conducted; these included an assessment of the effects of diabetes and of insulin-only infusions. Heterogeneity was assessed using the $\chi^2$ test and $I^2$ statistic, with thresholds for significant or meaningful heterogeneity of 0.10 and 50%, respectively. Where either test showed heterogeneity, the characteristics of outlying studies were reviewed. Publication bias was assessed by visual inspection of a funnel plot.

Results of the review
Twenty-nine RCTs (n=8,432) were included: 19 fully published, eight published only as abstracts and two unpublished. The sample size varied from 10 to 1,548.

No studies were blinded and all reported Jadad scores of 2 or 3. In 2 studies disease severity at baseline differed between the two groups. All RCTs had follow-up rates of at least 80%.

When studies were pooled, there was no significant difference between tight glucose control and standard care for hospital mortality (RR 0.93, 95% CI: 0.85, 1.03; 27 RCTs) or need for new dialysis (RR 0.96, 95% CI: 0.76, 1.20; 8 RCTs).

Rates of septicaemia were significantly lower in the intervention group (RR 0.76, 95% CI: 0.59, 0.97; 9 RCTs), while rates of hypoglycaemia were significantly higher (RR 5.12, 95% CI: 4.09, 6.43; 15 RCTs).

Subgroup analyses showed that the significant effect of the intervention on septicaemia rate was observed only in the surgical ICU setting and not in medical or medical-surgical ICUs, and that very tight glucose control carried a higher risk of hypoglycaemia than moderately tight control.

Most subgroup and sensitivity analyses did not materially affect the results. Heterogeneity was noted in some subgroup analyses. The funnel plot showed no indication of publication bias for hospital mortality.

Authors' conclusions
Tight glucose control does not significantly reduce hospital mortality among critically ill adult patients, but it does increase the risk of hypoglycaemia.

CRD commentary
The review objectives and inclusion criteria were clear. Relevant sources were searched, without language restrictions, for both published and unpublished studies. Steps were taken to minimise error and bias during the review process by having more than one reviewer independently undertake the validity assessment and data extraction, though it is unclear whether this also applied to the study selection stage. Relevant criteria were used to evaluate study quality, although the Jadad scale does not address allocation concealment (which has been shown to influence the risk of bias). Appropriate statistical methods were used to combine the studies and assess heterogeneity and publication bias. Potential sources of heterogeneity were thoroughly explored by pre-specified subgroup and sensitivity analyses, and distinctive features that might account for outliers were noted in the text. Other potential sources of bias, such as lack of blinding, were also discussed. The review was generally well-conducted, the findings were reasonably consistent despite marked clinical and methodological heterogeneity between the primary studies, and the authors' conclusions seem likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that guideline recommendations for tight glucose control in all critically ill patients should be reviewed pending more definitive evidence.

Research: The authors stated that large clinical trials are needed in this area as current evidence may be underpowered to show significant effects.
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