Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials

Ling Y, Li X, Gao X

CRD summary
This review found that intensive glucose monitoring for critically ill patients, in the intensive care unit, did not reduce mortality and increased the risk of hypoglycaemia, compared with conventional therapy. The review was generally well conducted and these conclusions appear to be reliable.

Authors' objectives
To assess the benefits and risks of intensive, compared with conventional, glucose control in critically ill patients, in intensive care.

Searching
PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews were searched, to June 2011, for studies published in English. Search terms were reported. The reference lists of retrieved articles were checked.

Study selection
Eligible studies were randomised controlled trials (RCTs), set in adult intensive care units, which compared intensive insulin therapy to a target glucose level of under 6.1 millimoles per litre (mmol/L), versus conventional therapy to a higher target glucose level. Trials had to include at least 20 participants and to report short-term (28-day) mortality (primary outcome), 90- or 180-day mortality, hypoglycaemia, sepsis, or the new need for dialysis (secondary outcomes). Trials, in which the intervention began before or during surgery, were excluded. The outcomes were defined in the review.

The included trials were set in surgical, medical or mixed intensive care units. The mean patient age ranged from 39 to 72 years; most participants were male (range 32% to 90%); and none to all patients had diabetes. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II severity-of-disease score ranged from 16 to 23 (where reported). The indication for intensive care admission varied widely across trials, including cardiac surgery, neurosurgery, respiratory disease, and stroke. The most common target glucose level in the control group was 10 to 11.1 mmol/L, but this varied across trials, as did the mean achieved glucose level in the control group. Most trials delivered insulin to all patients by infusion.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Trial quality was evaluated using the Jadad scale, covering the adequacy of reported randomisation, double blinding, and withdrawals or dropouts. The maximum rating was five. The reviewers also assessed whether adequate allocation concealment was reported and whether intention-to-treat analysis was conducted.

Two reviewers independently conducted the assessment, resolving disagreements by discussion or with the help of a third reviewer.

Data extraction
Risk ratios and 95% confidence intervals were extracted or calculated from the differences between the groups, for each outcome, in each trial. If the 28-day mortality was not reported, data on hospital mortality (first preference) or intensive-care mortality were used.

Two reviewers independently extracted the data, resolving disagreements by discussion or with the help of a third reviewer.
Methods of synthesis

The data were combined, using a Mantel-Haenszel random-effects model, to calculate pooled risk ratios and 95% confidence intervals. Heterogeneity was assessed using $I^2$.

Subgroup analyses were conducted by type of intensive care unit and the participant’s clinical characteristics (blood glucose variables, APACHE II score, mean insulin dose in the intervention group, and the proportions of diabetic and medical patients). The medians for these variables were used the cut-off to determine the subgroups. Sensitivity analysis was conducted by excluding one trial at a time from the analysis, and by excluding trials with high weighting.

Publication bias was assessed with the Begg and Egger tests.

Results of the review

Twenty-two RCTs were included, with 13,978 participants (range 20 to 6,104). No trial used blinding. All met the three other Jadad quality criteria, apart from one which did not describe adequate randomisation methods, so only met two criteria. Adequate allocation concealment was described in 18 of the 22 trials and intention-to-treat analysis was used in 21 trials. Follow-up ranged from the hospital stay to six months.

There was no significant difference between intensive and conventional glucose control, in short-term mortality (17 RCTs; $I^2=8\%$), 90- or 180-day mortality (11 RCTs; $I^2=0$), sepsis (10 RCTs; $I^2=36\%$), and the new need for dialysis (eight RCTs; $I^2=37\%$). Hypoglycaemia was significantly more common in the intensive glucose group (RR 5.01, 95% CI 3.45 to 7.28; 18 RCTs; $I^2=61\%$). There was no evidence of significant publication bias.

In the subgroup analyses, the intensive glucose control group had significantly increased 90- or 180-day mortality, in the mixed intensive care setting (RR 1.10, 95% CI 1.02 to 1.19), but a reduced risk of sepsis in the surgical intensive care setting, when an outlying trial was excluded (RR 0.58, 95% CI 0.40 to 0.84). Other subgroup and sensitivity analyses did not change the statistical significance of the main findings.

Authors’ conclusions

Intensive glucose monitoring in critically ill patients, in the intensive care unit, did not reduce mortality and increased the risk of hypoglycaemia, compared with conventional therapy.

CRD commentary

The objectives and inclusion criteria were clear. Relevant sources were searched for trials, but the range of databases was limited. The restrictions on language and publication status meant that some trials could have been missed, but formal testing showed no evidence of significant publication bias. Steps were taken to minimise the risk of reviewer bias and error in the processes of quality assessment and data extraction, but it was unclear whether this applied to study selection. Appropriate methods were used to combine the trial data, assess statistical heterogeneity, and explore differences between the trials. As the authors noted, the included trials differed in their participant characteristics, intervention protocols, concurrent therapy, and methods of glucose monitoring, but there was little statistical heterogeneity in the main analyses.

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

Implications of the review for practice and research

Practice: The authors stated that their findings supported the guidelines, which advised a glucose range of 7.8 to 10 mmol/L for most critically ill patients, and did not recommend intensive glucose control, for these patients.

Research: The authors stated that more evidence was required to determine the optimum glucose level for critically ill patients.

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