Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis

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CRD summary
Tight glycaemic control with intensive insulin therapy was associated with a higher incidence of hypoglycaemia and an increased risk of death in patients who did not receive most of their calories intravenously. In general, the review was well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To determine the benefits and risks of tight glycaemic control (defined as blood glucose levels of 80 to 110mg/dL) in patients in intensive care units.

Searching
MEDLINE was searched from 2001 to August 2009 for relevant studies; search terms were reported. EMBASE and Cochrane Database of Systematic Reviews were searched. Reference lists of the retrieved studies were checked to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that compared mortality outcomes in patients randomised to intensive insulin therapy treatment to outcomes in patients who received less strict glucose control were eligible for inclusion. Trials needed to include more than 100 patients. The primary outcomes were 28-day or hospital mortality. Secondary outcomes were dialysis requirements, acquired blood stream infections and incidence of hypoglycaemia (defined as a blood glucose of <40mg/dL). Studies that used glucose-insulin-potassium infarct size limiting protocols and studies that were not conducted in intensive care units were excluded from the review.

Most studies were conducted in mixed surgical and medical intensive care units; one study was conducted in a medical intensive care unit and one in a surgical intensive care unit. APACHE II scores among the included patients ranged between nine and 23 points. The mean blood glucose level was 112mg/dL for the intensive insulin therapy group and 151mg/dL for the control group. Mean daily insulin doses were 54 units for the intensive insulin treatment group and 16 units for control groups. The proportion of patients who presented with sepsis ranged between 6% and 50%. Across the trials, 12% to 30% of the patients had diabetes mellitus. In two trials 87% of the patients' calories were provided intravenously; in the other trials 7% to 66% of nutrition was provided enterally.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
Methodological quality was assessed by two reviewers using the Jadad five-point scale of randomisation, blinding and attrition rates. Allocation concealment was evaluated. Any disagreements between reviewers were resolved by consensus.

Data extraction
Two reviewers independently extracted data to calculate odds ratios (OR) and 95% confidence intervals (CI) for the outcomes. The reviewers contacted authors of the trials for missing data. Data were recorded using intention-to-treat analyses. Any disagreements between reviewers were resolved by consensus.

Methods of synthesis
Statistical heterogeneity was assessed using the Cochran Q statistic and I². If the Q statistic was statistically significant (p≤0.10), a random-effects model was used to calculate pooled odds ratios and 95% CIs. When there was no statistical heterogeneity, pooled statistics were calculated using a fixed-effect model. Subgroup analyses were undertaken based on the results of meta-regression analyses to evaluate the relationship between treatment effects and APACHE II.
scores, mean daily glucose levels, mean daily insulin dose administration, mean daily calorific intake, percentage of calories given intravenously and percentages of patients who presented with diabetes mellitus and sepsis. The reviewers evaluated publication bias by visual appraisal of a funnel plot.

Results of the review
Seven studies (n=11,425) were included in the review. Sample sizes in the studies ranged between 504 to 6,022 patients. All studies attained a Jadad score of 3.

Significantly higher levels of hypoglycaemia were observed in the group that received intensive insulin therapy (OR 7.7, 95% CI 6.0 to 9.9).

There were no statistically significant differences reported between the group that received insulin-intensive therapy and the group that received less strict glucose control for 28-day mortality, incidence of bloodstream infections and need for renal replacement therapy.

Subgroup analyses found a trend towards beneficial treatment effects of intensive insulin therapy on 28-day mortality when 87% of calories were provided intravenously (OR 1.203, 95% CI 0.982 to 1.474). Significant negative treatment effects were found on 28-day mortality when low percentages of calorie intake were provided intravenously (OR 0.899, 95% CI 0.811 to 0.997).

The reviewers stated that there was no evidence of publication bias on visual appraisal of the funnel plot.

Authors’ conclusions
Tight glycaemic control with intensive insulin therapy was associated with a higher incidence of hypoglycaemia and an increased risk of death in patients who did not receive parenteral nutrition.

CRD commentary
The review addressed a clear question. Inclusion criteria were clearly defined. Appropriate electronic databases were searched for relevant studies. It was unclear whether language restrictions were applied. There were few attempts to identify unpublished studies, but the authors found no evidence of publication bias. Steps were taken to minimise errors and biases for most parts of the review process. The authors stated they evaluated statistical heterogeneity across the results of the trials, but did not publish data on statistical heterogeneity. However, they conducted appropriate subgroup analyses to explore sources of heterogeneity.

In general, the review was well conducted and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that intensive insulin therapy may be of benefit only in patients who received parenteral nutrition, particularly patients with a low severity of illness.

Research: The authors did not state any implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.