Tight glycemic control reduces infection and improves neurological outcome in critically ill neurosurgical and neurological patients

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CRD summary
This review concluded that intensive insulin therapy and tight glycaemic control reduced infection risk and improved neurological outcome, but increased rates of hypoglycaemic events in critically-ill neurosurgical and neurological patients. Limitations in the search strategy, reporting of review methods and the analysis mean that these conclusions should be interpreted cautiously.

Authors' objectives
To compare the effects of intensive insulin therapy versus conventional insulin therapy on infection and neurological outcomes in critically-ill neurosurgical and neurological patients.

Searching
PubMed and SCOPUS were searched from January 1997 to December 2010; search terms were reported. Searches were restricted to articles in English. Bibliographies of retrieved articles were screened for additional studies.

Study selection
Prospective and retrospective studies of critically-ill neurosurgical or neurological patients who were receiving insulin for hyperglycaemia were eligible for inclusion, regardless of insulin protocol. Included studies had to compare conventional glycaemic control (conventional insulin therapy) with tight glycaemic control (intensive insulin therapy). Included studies were required to report outcomes on blood glucose levels. Studies of general intensive care unit patients that reported data for neurological or neurosurgical patients were also included.

Five of the nine included studies were conducted in surgical patients, one study included only medical patients, one included a mixed population, and the remainder were unspecified. The primary diagnosis of study participants varied including traumatic brain injury, aneurysmal subarachnoid haemorrhage, and neurovascular disease. The mean age of participants ranged from 35 to 64 years in the conventional insulin therapy group and from 46 to 63 years in the intensive insulin therapy group. The included studies had a similar proportion of men and women, where reported. Most studies did not exclude patients with diabetes mellitus, where reported; one study excluded patients with type I diabetes. Admission blood glucose was similar across the two groups and mean admission blood glucose ranged from 130 to 185mg/dL, where reported. The method and frequency of blood glucose monitoring varied across studies (details were reported in the article).

The authors did not state how studies were assessed for inclusion.

Assessment of study quality
The methodological quality of included studies was assessed using the 5-item Jadad scale including randomisation, blinding and handling of withdrawals (maximum score 5).

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Data were extracted on the rates of infection, hyperglycaemia (as defined in the primary studies) and mortality in each intervention group, during the acute hospitalisation period (not defined). Data were also extracted on neurological outcome at six or 12 months using the Glasgow Outcome Scale, Rankin Scale, or extended Glasgow Outcome Scale. Odds ratios with 95% confidence intervals were calculated for each outcome measure reported.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled estimates of odds ratios, with 95% confidence intervals, were calculated using a fixed-effect model.

Subgroup analyses and meta-regression were used to explore the effects of the target glucose range for tight glycaemic control and to compare neurosurgical patients versus the whole population.

**Results of the review**

Nine studies (1,459 patients, range 47 to 483) were included in the review. Most of the included studies (six out of nine) were randomised controlled trials (RCTs); the remaining three were non-randomised, comparative studies, which appeared to be mainly retrospective. The Jadad score for all included studies ranged from 0 to 4.

Intensive insulin therapy and tight glycaemic control was associated with a lower risk of infection (OR 0.59, 95% CI 0.47 to 0.76) and better neurological outcomes (OR 1.72, 95% CI 1.36 to 2.16) than conventional insulin therapy. Infection rates were correlated with tighter limits of glycaemic control, but good neurological outcome was not.

The risk of severe hypoglycaemia was greater with intensive insulin therapy than with conventional insulin therapy (OR 8.04, 95% CI 4.85 to 13.31), but risk was not correlated with the target limits of glycaemic control.

There was no significant difference in mortality between the two treatment groups.

There was no evidence of statistically significant heterogeneity for any outcome measure.

**Authors' conclusions**

Intensive insulin therapy and tight glycaemic control reduced infection risk and improved neurological outcome, but increased rates of hypoglycaemic events. An optimum target for serum glucose concentration could not be determined.

**CRD commentary**

The reporting of the research objective was somewhat unclear; a limited definition of some inclusion criteria was provided. Only two databases were searched for relevant studies and the restriction to articles in English increased the likelihood that relevant studies could have been missed.

The authors did not report any measures to minimise error and/or bias in the review process. The methodological quality of the included studies was assessed using the Jadad scale, but the Jadad scale is intended for the assessment of RCTs and three of the included studies were not RCTs. Therefore, it was not possible to fully assess the potential effects of the quality of included studies or review methods upon the reported results.

The meta-analytic methods used were broadly appropriate and included some attempts to explore potential sources of clinical heterogeneity. However, the validity of pooling studies with different outcome definitions (hypoglycaemia and neurological outcomes differed and the definition of infection was unclear) was questionable.

Limitations in the search strategy, reporting of review methods and analysis mean that the authors' conclusions should be interpreted cautiously.

**Implications of the review for practice and research**

**Practice:** The authors did not specify any recommendations for clinical practice.

**Research:** The authors stated that a large, multi-centre randomised controlled trial was needed to determine how tightly blood glucose concentrations should be controlled in neurosurgical patients in intensive care.

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