A meta-analysis of tight versus conventional glycemic control in critically ill brain injured adults

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CRD summary
The review concluded that compared with conventional glycaemic control, tight glycaemic control was not associated with improvement in overall mortality or neurological impairment, but was associated with a greater prevalence of hypoglycaemic events. Differences between trials in terms of participants and the measurement of outcomes mean that the authors’ conclusions may not be reliable.

Authors' objectives
To determine the efficacy of tight glycaemic control versus conventional glycaemic control in critically ill adults with brain injury.

Searching
Several databases including PubMed, EMBASE, Science Direct, Chongqing Weipu (CQVIP) were searched without language restriction up to December 2011. Search terms were reported. The references of key articles were also manually searched for additional trials.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared tight glycaemic control with conventional glycaemic control in adults with a diagnosis of brain injured neurological or neurosurgical disorder, and that reported at least one relevant outcome. Trials were required to be within a critical care or intensive care setting. Tight glycaemic control was defined as blood glucose of 8.0mmol/L or less. Trials in which participants’ diagnoses were mixed with disorders of other organs that could not be separated, and trials in which participants were enrolled in another trial were excluded.

The primary outcome measures selected were in-hospital and overall mortality. Secondary outcomes included hypoglycaemia (defined as any blood measurement less than 4.4mmol/L) episodes, infection rates, intensive care unit length of stay, and good neurological severity score (Glasgow outcome score of 4 to 5 or as defined by the author).

Baseline mean blood glucose ranged from >6.50mmol/L to 16.80mmol/L and hypoglycaemic thresholds ranged from 2.20 to 5mmol/L (where reported). The mean neurological severity score ranged from 3.0 to 14.3 on the Glasgow Coma Scale (16 studies), the remaining studies used six different scales. Most participants were classified as having traumatic brain injury or stroke; other conditions included subarachnoid haemorrhage and mixed brain injury. Mean age ranged from 35 years to 75 years and most participants were male. In trials that reported the proportion of participants with diabetes mellitus, this ranged from zero to 91%. Almost half the trials were conducted in China.

Two reviewers independently selected trials for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed the quality of the included trials using the five-point Jadad scale, which considered reported randomisation, blinding and withdrawals/drop-outs. Disagreements were resolved by group discussion.

Data extraction
Two reviewers independently extracted odds ratios for all dichotomous outcomes of interest and mean differences for all continuous outcomes of interest, along with their associated 95% confidence intervals. Where additional information was required, the authors of primary trials were contacted. Disagreements were resolved by group discussion.

Methods of synthesis
Pooled odds ratios and weighted mean differences, with associated 95% confidence intervals, were calculated using a
fixed-effect model or a random-effects model if significant statistical heterogeneity was found. Heterogeneity was investigated using the Cochran's Q statistic and the $I^2$ statistic ($Q$ statistic $p<0.10$ or $I^2 >30\%$ were deemed significant). Subgroup analyses were planned where significant heterogeneity was found (no further details reported). Sensitivity analyses were performed by removing trials with low Jadad scores (below 3). Publication bias was assessed visually with a funnel plot for the primary outcome late mortality.

Results of the review
Twenty-six RCTs (3,759 participants) were included in the review. Jadad scores ranged from 1 to 4 (17 trials received a score of 3 or more).

No significant between group difference was found for overall mortality but a statistically significant difference was found for in-hospital mortality in favour of tight glycaemic control compared with conventional glycaemic control (OR 0.76, 95% CI 0.58 to 0.99; twelve RCTs). No statistically significant heterogeneity was found.

A statistically significant difference in favour of conventional glycaemic control was found for occurrence of hypoglycaemia using two different methods: number of patients experiencing at least one hypoglycaemic episode (Peto OR 6.24, 95% CI 4.83 to 8.07; fourteen RCTs), and numbers of hypoglycaemic episodes by total measurement (Peto OR 2.73, 95% CI 2.56 to 2.91; five RCTs). A significant difference was also found, in favour of tight glycaemic control, for infection rate (Peto OR 0.51, 95% CI 0.42 to 0.62; eleven RCTs) and length of intensive care unit hospital stay (WMD -2.37, 95% CI -2.99 to -1.74; six RCTs). No significant between group difference was found for long-term neurological severity score. No statistically significant heterogeneity was found in these analyses.

Removal of low quality trials did not significantly alter the main findings. Publication bias was assessed as low.

Authors' conclusions
In critically ill brain injured adults, tight glycaemic control was not associated with improvement in overall mortality or neurological impairment but was associated with a greater prevalence of hypoglycaemic events.

CRD commentary
The review was supported by clearly defined inclusion criteria and several electronic sources were searched without language restriction for relevant literature. No attempt appeared to have been made to identify unpublished trials, but publication bias was assessed as low. The review process was likely to have minimised error or bias in the selection of trials, extraction of data and assessment of trial quality. Whilst assessment of trial quality considered a number of appropriate criteria, allocation concealment was not included and only summary scores were reported.

Meta-analysis was used to synthesise the trials and statistical heterogeneity assessed, however, there were differences across the trials in terms of population (injury, admitting blood glucose level, neurological severity, age, and proportion with diabetes) which may have meant that pooling estimates was not appropriate. In addition, the threshold used for measuring hypoglycaemia varied between studies from 2.2 to 5mmol/L, and the outcome "long term neurological severity" appeared to have used data from different scales, so the authors' conclusions may not be reliable.

Implications of the review for practice and research

Research: The authors state that further research was needed to provide a more robust conclusion.

Practice: The authors suggest that as tight glycaemic control showed insignificant benefits but increased risk of hypoglycaemic episodes it should not be considered for use in critically ill brain injured patients.

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