Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections

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CRD summary
This review concluded that continuous subcutaneous insulin infusion slightly improved glycaemic control in adults with type 1 diabetes compared with multiple daily injections, but glycaemic control was similar for both delivery systems in adults with type 2 diabetes. The authors’ conclusions reflected the evidence presented but, given the poor quality of the included trials, the evidence may not be reliable.

Authors’ objectives
To compare the effects of continuous subcutaneous insulin infusion and multiple daily injection of insulin on the control of glycaemia and hypoglycaemia.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 2002 to March 2008, using reported search terms. There were no language restrictions. Bibliographies of retrieved articles were examined for further reports. Unpublished articles were searched for in Clinicaltrials.gov and by contacting insulin pump manufacturers (Deltec, Animas, OmniPod).

Study selection
Randomised controlled trials (RCTs) of intensive insulin therapy delivered as continuous subcutaneous insulin infusion or multiple daily injection in adults or children with diabetes (type 1 or type 2) were eligible for inclusion. Trials of critical illness or pregnancy were excluded. The outcomes reported were mild, severe and nocturnal hypoglycaemia (definitions provided) and glycosylated haemoglobin (HbA1c).

Hypoglycaemia was measured by various techniques which relied predominantly on self reporting. The majority of included trials were of patients with type 1 diabetes. The mean age of patients ranged from 3.6 to 66 years. Trials varied according to the patients experience and training with an insulin pump, the type of insulin pump and the type of insulin. In some trials, patients with severe hypoglycaemia or hypoglycaemic unawareness were excluded.

Two reviewers independently selected studies, there were no disagreements.

Assessment of study quality
Allocation concealment, blinding, loss to follow-up and funding sources were used to assess quality.

Study quality was assessed independently and in duplicate by four reviewers, disagreements were resolved by a fifth.

Data extraction
Means and standard deviations were extracted for levels of HbA1c and for the number of episodes of hypoglycaemia. Data were also extracted in order to calculate odds ratios (OR) and 95% confidence intervals (CI) for the number of episodes of hypoglycaemia.

Three reviewers independently, and in duplicate, extracted the data using electronic extraction forms.

Methods of synthesis
A DerSimonian-Laird random-effects model was used to perform meta-analysis and obtain a pooled odds ratio and 95% confidence interval for hypoglycaemic events or pooled weighted mean difference (WMD) and 95% confidence interval for levels of HbA1c.
interval for HbA1c. The Becker-Balagtas marginal was used to estimate odds ratios for cross-over trials and inverse variance was used to pool cross-over and parallel trials. Heterogeneity was assessed using $I^2$ statistics. Trials of type 1 and 2 diabetes were pooled separately. Sensitivity and subgroup analysis were used to test for the influence of age, type of diabetes, insulin type, training and support, and trial length on the analysis.

Results of the review

Fifteen RCTs (n=906 patients) were included in the review. Duration of follow-up ranged from five to 52 weeks. There was adequate allocation concealment, loss to follow-up was substantial (mean=8.5%) and nine trials reported financial ties with pump manufacturers.

Glycaemic control: For patients with type 1 diabetes, there was statistically significant improved glycaemic control (measured by levels of glycosylated haemoglobin HbA1c) in those who received continuous subcutaneous insulin infusion compared to those who received multiple daily injection (WMD:-0.18, 95% CI -0.27 to -0.10; 13 RCTs). However, for patients with type 2 diabetes (two RCTs), there was no statistically significant difference in glycaemic control between patients who received continuous subcutaneous insulin infusion compared with those who received multiple daily injection.

Hypoglycaemia: For patients with type 1 diabetes and for patients with type 2 diabetes, there was no significant difference in the risk of severe hypoglycaemic events or nocturnal hypoglycaemic events for those who received continuous subcutaneous insulin infusion compared with those who received multiple daily injections.

Multiple daily injection was found to significantly improve minor hypoglycaemia in parallel studies (WMD 0.68, 95% CI 0.16 to 1.2; three RCTs; n=89 patients) but in cross-over trials minor hypoglycaemia was unaffected. Subgroup analysis did not find any significant results.

Authors' conclusions

In comparison to multiple daily injections, continuous subcutaneous insulin infusion slightly reduced glycosylated haemoglobin HbA1c in adults with type 1 diabetes and had an unclear impact on hypoglycaemia. In type 2 diabetes, continuous subcutaneous insulin infusion and multiple daily injections had similar outcomes. The effect of hypoglycaemia unawareness or recurrent severe hypoglycaemia on patients remained to be determined.

CRD commentary

The review addressed a clear research question and had clearly stated inclusion criteria. A number of relevant databases were searched for studies. There were no language restrictions and attempts were made to locate unpublished studies. Publication bias was unlikely, but was not formally tested. Quality was assessed using appropriate criteria. It was unclear how HbA1c data was measured or extracted for analysis. The use of independent reviewers at all stages of the review reduced error and bias. The data synthesis was appropriate and there was little or no statistical heterogeneity between trials. Subgroup analysis was used to explore differences such as patient age, trial design and insulin type. The authors' conclusions reflected the evidence presented in this well-conducted review, but given the poor quality of the included trials, the evidence may not be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that the reporting of hypoglycaemia and its outcomes should be standardised and occur promptly. Trialists should report the number of patients experiencing no, few, several, and many episodes of severe or nocturnal hypoglycaemia. Larger and longer trials are needed to elucidate the role of continuous subcutaneous insulin infusion in the management of patients with type II diabetes.

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