Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation

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CRD summary
The authors concluded that observational studies as well as randomised controlled studies showed that continuous subcutaneous insulin infusion provides some advantages over multiple daily injections in adults and children with type I diabetes. Given the small number of varied trials and differences in findings compared with observational studies, the authors' conclusions should be interpreted with caution.

Authors' objectives
To update a previous review (see other publications of related interest) and assess the clinical and cost-effectiveness of continuous subcutaneous insulin infusion (CSII) to treat diabetes, taking into account the development of alternative therapies, in particular the long-acting analogue insulins.

Searching
An updated search in MEDLINE and EMBASE was undertaken between 2002 and June 2007 for publications in English; search terms were reported. In addition, The Cochrane Library, Science Citation Index (for meeting abstracts only), the website of the 2007 American Diabetes Association, company submissions and reference lists were also searched. Experts in the field were contacted and the National Research Register and Current Controlled Trials were searched for ongoing and recently completed trials.

Study selection
Randomised controlled trials (RCTs) that compared continuous subcutaneous insulin infusion (CSII) versus best multiple daily injections with both short and long acting analogue insulins, in patients with type I and type II diabetes mellitus, were eligible for inclusion if study duration was greater than 12 weeks. Studies of patients with type I diabetes were also eligible if they compared CSII with neutral protamine Hagedorn based multiple daily injections. Non-RCTs and observational studies were also eligible for inclusion. Outcomes of interest were glycaemic control (percentage glycated haemoglobin), blood glucose levels and variability, quality of life, hypoglycaemia, insulin dose and weight/body mass index.

Included studies were of children, adolescents and adults, including pregnant women. Where reported, most included RCTs were multicentre and conducted in the USA, Europe or Israel. CSII treatment included apart, lispro, previous insulin, while multiple daily injections included lispro and glargine, aspart or lispro and neutral protamine Hagedorn, regular insulin or humulin R and neutral protamine Hagedorn or humulin N. Treatment duration ranged from 16 weeks to 12 months in studies that compared CSII with multiple daily injections, and ranged from 16 weeks to two years in studies that compared CSII with neutral protamine Hagedorn-based multiple daily injections. Where reported, the mean baseline glycated haemoglobin levels ranged from 7.7% to 10.2% and mean body mass index ranged from 31.8 to 78kg/m2.

Data from industry submissions and perspectives of pump users were also reported, but they will not be discussed here.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
The quality of RCTs was assessed using the following criteria: randomisation, specification of eligibility criteria, similarity of groups at baseline, power calculation, robustness of outcome measurements, data analysis and description of attrition/losses to follow-up. RCTs were rated as A (all quality criteria met), B (one or more criteria only partially met) or C (one or more criteria not met). It was unclear whether quality was assessed in duplicate.

Data extraction
Two reviewers independently extracted outcome data including, where reported, statistical data and p values.
Discrepancies were resolved by discussion.

**Methods of synthesis**

Given the variability among studies, data were presented as a narrative synthesis and in tables. Where possible, results were reported separately for children, adolescents and adults.

**Results of the review**

Eight RCTs compared CSII versus multiple daily injections; five parallel and three cross-over designs. Four RCTs were of patients with type I diabetes (113 patients; range 10 to 57) and four were of patients with type II diabetes (296 patients; range 17 to 132). The quality of two RCTs was rated as A, four as B and two as C. A further eight RCTs compared CSII versus neutral protamine Hagedorn-based multiple daily injections in patients with type I diabetes (three parallel, three crossovers, one pilot study, and one not detailed). Forty eight observational studies of CSII and six studies of CSII in pregnancy were also included in the review.

**Mean glycated haemoglobin (HbA\(_1c\); eight RCTs):** Two RCTs reported a statistically significantly lower glycated haemoglobin level with continuous subcutaneous insulin infusion (CSII) compared with multiple daily injections; one in children and adolescents with type I diabetes (p<0.05) and one in adults with type II diabetes (p=0.03).

One of eight new trials comparing CSII versus NJPH-based multiple daily injections in patients with type I diabetes showed a statistically significant difference in glycated haemoglobin level in favour of CSII (p=0.002).

**Hypoglycaemia (eight RCTs):** Only one RCT, in children with type I diabetes, showed a statistically significant difference in occurrence of hypoglycaemic episodes, with children receiving CSII experiencing less severe episodes compared to multiple daily injections (p<0.05).

Most new trials comparing CSII versus neutral protamine Hagedorn-based multiple daily injections in patients with type I diabetes reported approximately half the number of severe hypoglycaemic events in patients receiving CSII.

**Quality of life (four RCTs):** Two RCTs in patients with type I diabetes showed no significant difference in quality of life between CSII and multiple daily injections. Findings were conflicting for the two RCTs of patients with type II diabetes.

No new RCTs in pregnant women were identified. Six observational studies in pregnant women, and findings from other observational studies were reported in the review.

**Cost information**

The cost of continuous subcutaneous insulin infusion includes approximately £1,800 to £2,000 per year for consumables, plus £430 to £720 per year for the pump, assuming four-year life cycle. Compared to multiple daily injections, the extra cost of continuous subcutaneous insulin infusion averages £1,700.

The cost-effectiveness review found that most studies, assuming a reduction in glycated haemoglobin level of 1.2%, found continuous subcutaneous insulin infusion to be cost-effective.

**Authors' conclusions**

The evidence base, consisting of observational studies as well as RCTs, showed that continuous subcutaneous insulin infusion provided some advantages over multiple daily injections in adults and children with type I diabetes, including better control of glucose levels, fewer occurrences of hypoglycaemia, and quality of life gains with greater flexibility of lifestyle.

**CRD commentary**

The review question and inclusion criteria were clearly stated. A number of sources were searched for relevant articles, but as this was restricted to publications in English, language bias may have been introduced. The authors acknowledged the possibility that potentially relevant studies may have been missed. The quality of RCTs was assessed using appropriate criteria. However, a substantial proportion of the evidence consisted of observational studies of unknown quality. Study selection and data extraction were performed in duplicate, but it was unclear whether this was the case for quality assessment, which meant that reviewer error and bias could not be ruled out.
Given the variability among studies, a narrative synthesis seemed appropriate. The authors acknowledged the lack of detail on educational input as part of the intervention, the influence of this on the results could not be extrapolated. The authors also acknowledged that peer reviewers had questioned the amount of weight placed on the non-randomised evidence in drawing the conclusions.

Given the small number of heterogeneous RCTs and differences in findings compared with observational studies, the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research

Practice: The authors stated that continuous subcutaneous insulin infusion was used infrequently in the UK, but more people with type 1 diabetes could benefit from its use. Wider use would mean greater expense and a need for education of patients and health-care professionals.

Research: The authors stated that larger, longer term RCTs were needed to compare continuous subcutaneous insulin infusion versus analogue multiple daily injections in adults and children and assess the effects on glycaemic control, hypoglycaemia, quality of life (in families and patients, particularly where the patients were children and using qualitative and quantitative methods of data collection) and costs (short and medium term). RCTs were also needed in pregnant women and to compare the effect of education on outcomes. The authors also noted a number of ongoing trials.

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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.