Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion

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CRD summary
This review concluded that the severe hypoglycaemia rate with type 1 diabetes was much lower while on continuous subcutaneous insulin infusion than on multiple daily injections, with the greatest reduction in patients with the most severe hypoglycaemia while on multiple daily injections. These conclusions are likely to be reliable, but the limited quality of the included studies should be considered.

Authors' objectives
To compare the outcomes of severe hypoglycaemia and glycaemic control, using continuous subcutaneous insulin infusion versus multiple daily insulin injections, for patients with type 1 diabetes.

Searching
MEDLINE and EMBASE were searched for articles from 1996 to 2006. Reference lists of relevant publications were screened and the search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared continuous subcutaneous insulin infusion versus multiple daily insulin injections, for patients with type 1 diabetes, were eligible for inclusion. Before-and-after studies where patients were switched from multiple daily insulin injections to continuous subcutaneous insulin infusion and acted as their own controls were eligible. For the evaluation of severe hypoglycaemia, only studies where patients had at least six months of continuous subcutaneous insulin infusion and where the rate of severe hypoglycaemia with multiple daily insulin injections was greater than 10 episodes or 100 patient-years of treatment, were eligible for inclusion. Trials of multiple daily injections of a long-acting insulin analogue (glargine or detemir) were included even if they had short duration or low hypoglycaemia rates. Trials of newly diagnosed type 1 diabetes and pregnant diabetic patients were excluded. The review outcomes were the incidence of severe hypoglycaemia and the change in glycated haemoglobin (HbA1c).

All the included studies used multiple daily injections of isophane- or lente-type intermediate-acting insulin, combined with regular or monomeric insulin at meals. Nearly half of them recruited children or adolescents and more than half recruited adults. Where reported, the patients' mean age ranged from 2.8 to 50 years. The patients received either multiple daily insulin injections or insulin pump therapy of continuous subcutaneous insulin infusion for a mean duration of six to 48 months. Where reported, the definitions of severe hypoglycaemia varied and the patients' mean duration of diabetes ranged from 1.3 to 33 years.

The authors did not state how many reviewers assessed studies for inclusion.

Assessment of study quality
The quality of studies was assessed using criteria for: trial design, loss to follow-up or discontinuation rate, and blinding of assessment for the primary outcome (hypoglycaemia). The quality of RCTs was assessed using additional criteria for: the description of the methods of randomisation and the allocation concealment.

The authors did not report how many reviewers assessed the validity.

Data extraction
For dichotomous outcomes, the rate ratios with 95% confidence intervals, were calculated. For continuous outcomes, means and standard errors were extracted to enable the calculation of mean differences and 95% confidence intervals. The standard errors were extracted from summary statistics, if possible, or calculated from 95% confidence intervals or, if these were not available, derived from the p-value of a paired t-test. Where necessary, the correlation between
outcomes was used to derive an approximate standard error, using a recognised method.

Two reviewers independently extracted the data, with any disagreements resolved by consensus.

Methods of synthesis
The studies were combined in a meta-analysis. The pooled rate ratios and weighted mean differences, with 95% confidence intervals, were calculated using a random-effects model. A separate analysis was performed by study design (RCT or before-and-after study). Statistical heterogeneity was assessed using the $I^2$ statistic. Random-effects meta-regression was used to explore the potential explanations for between-study heterogeneity, using a range of factors that included the patients’ mean age, the severe hypoglycaemia rate on multiple daily insulin injections, the mean duration of diabetes before the study, and the duration of continuous subcutaneous insulin infusion. Subgroup analyses for children and adults were performed. Publication bias was assessed using a funnel plot and Egger’s regression test.

Results of the review
Twenty-two studies, in 21 publications, were included (n=1,414 patients); six were RCTs and 16 were before-and-after studies. Most studies had less than 10% withdrawals or discontinuations. No studies clearly reported blinding of the assessment of the severe hypoglycaemia rate. One RCT reported satisfactory concealment of allocation and a description of the randomisation method.

Compared with multiple daily insulin injections, severe hypoglycaemia was reduced with continuous subcutaneous insulin infusion. When pooling all the studies, the rate ratio was 4.19 (95% CI 2.86 to 6.13; 22 studies); when pooling RCTs it was 2.89 (95% CI 1.45 to 5.76; six RCTs); and when pooling before-and-after studies it was 4.34 (95% 2.87 to 6.56; 16 studies). Significant heterogeneity was observed when pooling all studies ($I^2=84.2\%$).

Meta-regression revealed that the greatest reduction in severe hypoglycaemia was seen in patients with the highest initial severe hypoglycaemia rate on multiple daily insulin injections (p<0.001). It also showed that severe hypoglycaemia during multiple daily insulin injections was significantly related to the diabetes duration (p=0.038) and was significantly greater in adults than in children (p=0.036).

There was better glycaemic control with continuous infusion, than with multiple daily injections, with a mean difference in HbA$_1c$ of 0.62% (95% CI 0.47 to 0.78; 22 studies). Significant heterogeneity was observed for this outcome ($I^2=83.8\%$).

Subgroup analyses, by study design, showed that the mean difference in HbA$_1c$ was significantly larger when pooling before-and-after studies compared with pooling RCTs (p=0.04), but the pooled rate ratios of severe hypoglycaemia from RCTs and from before-and-after studies were not significantly different.

No evidence of publication bias was found.

Authors’ conclusions
The severe hypoglycaemia rate was much lower with continuous subcutaneous insulin infusion than with multiple daily insulin injections. The largest differences were in patients with the most severe hypoglycaemia while on multiple daily injections and in those with the longest duration of diabetes. The most improvement in HbA$_1c$ was in patients with the highest HbA$_1c$ while on multiple daily injections.

CRD commentary
This review’s inclusion criteria were clear and relevant databases were searched. Efforts were made to find published studies, but not unpublished studies, introducing a potential for publication bias. Publication bias was assessed and little evidence of it was found. The authors did not report whether language restrictions were applied, which makes it difficult to assess the risk of language bias. Steps were taken to minimise reviewer bias and error, by having more than one reviewer independently extract the data, but it was unclear whether study selection and quality assessment were performed in duplicate. Relevant criteria were used to assess the study quality, but the results were not fully reported. Most of the included studies had before-and-after designs. This design has limited methodological rigour, but their results for the primary outcome of severe hypoglycaemia were generally consistent with those from RCTs. Statistical
heterogeneity was assessed and appropriate methods were used to pool the results. Relevant pre-specified subgroup analyses were performed and the potential impact of a number of factors on the outcomes was explored.

Based on the evidence presented, the authors' conclusions are likely to be reliable, but the limited quality of the included studies should be considered.

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

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

*Research:* The authors stated that further studies were required to investigate the comparative frequency of severe hypoglycaemia and high HbA1c while on multiple daily injections of long-acting insulin analogues or continuous subcutaneous insulin infusion.

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