Severe Hypoglycaemia and Glycaemic Control in Type 1 Diabetes: Meta-Analysis of Multiple Daily Insulin Injections Compared with Continuous Subcutaneous Insulin Infusion

Pickup JC, Sutton AJ

Why is this study important?

- Continuous subcutaneous insulin infusion (CSII) is a recommended treatment for reducing severe hypoglycaemia in Type 1 diabetes. The change in hypoglycaemia compared with multiple daily injections (MDI) is unclear.
- The authors conducted a meta-analysis comparing severe hypoglycaemia and glycaemic control during CSII and MDI.

Study Highlights

- CSII produces a significant reduction in severe hypoglycaemia in type 1 diabetes. Severe hypoglycaemia was reduced during CSII compared with MDI. The reduction was greatest in those with the highest initial severe hypoglycaemia rates on MDI.
- The mean difference in A1C between insulin pump therapy and MDI was less for randomized controlled trials (RCTs) than in before/after studies, but was strongly related to the initial A1C on MDI.
- Severe hypoglycaemia during MDI was related to diabetes duration and was greater in adults than in children.

Patient Benefits

- This meta-analysis found no evidence that severe hypoglycaemia is increased during insulin pump therapy.
- Patients with the most severe hypoglycaemia on MDI and those with the longest duration of diabetes had the greatest reduction in severe hypoglycaemia.
- Glycaemic control is better during insulin pump therapy than MDI. Patients with a higher A1C on MDI had the biggest reduction in A1C when switching to insulin pump therapy.

Study Limitations

- The inclusion criteria for the studies were arbitrary.
- There was some variation among the studies in the definition of severe hypoglycaemia.
- The meta-analysis included randomized controlled trials and before/after studies. Study design was found to be an independent predictor of difference in A1C.
- The authors suggest that their study selection criteria and the use of trials from the last ten years, may lead to results that are not representative of severe hypoglycaemia rates in currently managed patients with type 1 diabetes.
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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Purpose

- To compare the frequency of severe hypoglycaemia and glycaemic control during continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDI) by conducting a meta-analysis of studies in patients with a significant initial rate of severe hypoglycaemia and adequate duration of insulin pump therapy.

Endpoints/Outcomes

- The rate of severe hypoglycaemia on MDI and the rate ratio for episodes on MDI compared with CSII.
- Overall glycaemic control using A1c.
- The mean difference in A1c on MDI compared with CSII in each trial.

Design and Methods

- MEDLINE, EMBASE and cited literature (1996-2006) were searched for randomized, controlled trials (RCTs) and before/after studies of ≥ 6 months’ duration of CSII and frequency of severe hypoglycaemia >10 episodes/100 patient years on MDI.
- RCTs and before/after studies in which patients were switched from MDI to CSII and acted as their own control were also included.
- Excluded were studies with two non-randomized groups.
- Study quality was assessed by trial design, loss to follow-up or discontinuation rate and blinding of assessment of the main outcome (hypoglycaemia). For RCTs, study quality was also assessed by the description of method of randomization and allocation concealment.

Results

- 61 studies were identified which yielded 21 studies with 22 sets of data eligible for analysis of severe hypoglycaemia.
- Four studies were identified that compared glycaemic control during MDI and CSII. However, rates of severe hypoglycaemia could not be estimated for those studies.
- There was a strong heterogeneity between the studies.

Severe hypoglycaemia during MDI

- Ten studies were in children or adolescents. Twelve studies were in adults. A total of 1414 subjects with type 1 diabetes received either MDI or CSII for a mean CSII duration of 6-48 months.
- The pooled severe hypoglycaemia event rate during MDI was 62 events/100 patient years.
- The pooled severe hypoglycaemia event rate during CSII was 14.8 events/10 patient years. (JC Pickup MD, email communication, August 20, 2008).
- Adults subjects with diabetes had a greater frequency of severe hypoglycaemia on MDI (100 events/100 patient years) than children and adolescents (36 events/100 patient years).
- There was a strong linear association between severe hypoglycaemia rate during MDI and mean diabetes duration (p=0.038).
Meta-analysis of severe hypoglycaemia rate ratio, MDI vs. CSII
- Severe hypoglycaemia was reduced during CSII compared with MDI.
- The greatest reduction in severe hypoglycaemia occurred in those subjects with the highest initial hypoglycaemia frequency.
- Mean age was a highly significant predictor of treatment effect (p=0.019). Older subjects had a significantly greater reduction in severe hypoglycaemia on CSII than those on MDI.
- There was a significant positive relationship between mean duration of diabetes and the rate ratio for severe hypoglycaemia (p=0.025).
- There was no strong evidence for a relationship between study duration or initial A1c on MDI and the severe hypoglycaemia rate ratio.

Meta-analysis of glycaemic control
- The RCTs demonstrated better glycaemic control, as measured by the mean difference in A1C, during insulin pump therapy: A1c difference 0.21% (0.13-0.30%).
- The before/after studies showed a larger difference in A1c during CSII: 0.72% (0.55-0.90%, P=0.042).
- In the meta-analysis of the 22 data sets, the mean difference in A1c was 0.62% (0.47-0.78), favoring CSII.
- There were four additional studies that assessed glycaemic control only. Those studies favored CSII. The mean difference in A1c, between glargine-MDI and CSII was 0.63% (0.10-1.16%).
- The initial A1C on MDI was significantly related to the mean difference in A1C between MDI and CSII (p=0.001). The patients that were most poorly controlled on MDI had the greatest reduction in A1C when they switched to insulin pump therapy.
- Initial A1c on MDI, study design and age were independent predictors of the difference in A1c in a multivariate model.

Authors’ Conclusion
- Severe hypoglycaemia is reduced in insulin pump therapy.
- Glycaemic control, as measured by A1C is significantly better during CSII than during MDI.