Abstract
In the years since continuous subcutaneous insulin infusion (CSII) was invented, modern insulin injection therapy has evolved to include multiple daily injections (MDI), education, dietary advice, frequent blood glucose self-monitoring and insulin dosage adjustment. As MDI can produce strict glycaemic control in many type 1 diabetic patients, we should consider whether or not CSII is still needed. Recent meta-analyses have shown that HbA1c is significantly lower on CSII than on MDI, but the difference is greatest in patients on MDI who achieve the worst control. Severe hypoglycaemia frequency is about 4 times less on CSII than on MDI, but the reduction is also greatest in the most severely affected patients on MDI. Current evidence indicates that MDI based on long-acting insulin analogues and MDI which includes a structured patient education programme do not match the strict control and low hypoglycaemia frequency of CSII. It can be concluded that, at least for the substantial percentage of patients who fail to achieve satisfactory control on MDI, CSII is still needed.

Keywords: continuous subcutaneous insulin infusion, type 1 diabetes mellitus, insulin, hypoglycaemia, HbA1c.

Introduction
Continuous subcutaneous insulin infusion (CSII) was invented some 30 years ago, in almost a bygone era of insulin treatment for type 1 diabetes. Insulin of animal origin was injected by a syringe (which was glass, at least in the UK) and needle (which had to be sterilized by the patient), and injected only once or twice daily. Blood glucose concentrations were used to monitor metabolic control only in hospital. Insulin dosages for meals of any size and composition were usually fixed, though most physicians realised that this lacked any rationale.

Many advances in management have occurred since, including the introduction of human insulin made by recombinant DNA technology, shorter-acting monomeric and long-acting insulin analogues, frequent blood self-glucose monitoring at home, insulin pens and disposable plastic syringes and fine needles, multiple daily insulin injections and the concept of basal bolus regimens, continuous glucose monitoring, and structured patient education programmes such as DTTP and DAFNE and, with them, the re-introduction of carbohydrate counting. There is good evidence that at least some of these measures have substantially improved diabetes control and/or patient satisfaction, and reduced the risk of tissue complications. It is timely to ask, then, if CSII is still needed in the modern era of diabetes treatment.

Has MDI produced good control that matches that of CSII?
MDI should be considered as a package of measures, including multiple injections in a basal-bolus mode, blood glucose self-monitoring with insulin dosage adjustments, education, dietary advice and frequent access to health care professionals. Such a package was used to good effect in the Diabetes Control and Complications Trial, where the mean HbA1c for those patients receiving MDI was about 7.0%. Therefore, it is reasonable to ask whether CSII can achieve this same impressive level of strict control.

A first meta-analysis that we performed of randomised controlled trials comparing glycaemic control during MDI and CSII concerned only trials from 1982 to 2000 and, therefore, older, less-reliable pumps and mostly non-monomeric pump insulin were used. We found that HbA1c was significantly lower than during MDI, the difference being 0.5%. But this result does not tell the
whole story because the trials were conducted in volunteers without particular clinical problems and not in whom we would now regard as the most appropriate clinical target groups of patients with problems such as severe hypoglycaemia. Indeed, an audit of hypoglycaemia-prone type 1 diabetic patients in the Insulin Pump Clinic at Guy’s Hospital in London, who were referred because of failure to achieve satisfactory control on injection therapy, indicated that the change in HbA$_1c$ on switching patients from MDI to CSII was approximately three-fold higher than expected, at about 1.5%.\textsuperscript{14}

We therefore performed a second meta-analysis in which we selected only trials published in the last decade (i.e. modern pumps and insulins), with a duration of pump therapy ≥6 months and in which the initial frequency of severe hypoglycaemia on MDI was significant, i.e. in the main target group (J.C. Pickup and A.J. Sutton, unpublished data). Whilst the overall mean difference in HbA$_1c$ at 0.6% was similar to that of the previous meta-analysis, we found that the change in control was highly dependent on the initial HbA$_1c$ on MDI – those patients on MDI with an HbA$_1c$ of, say, 10% experienced a fall of about 1.5% on switching to CSII. The conclusion that insulin pump therapy works best in the worst controlled patients was also reported by us, in individual subjects from our insulin pump clinic\textsuperscript{15} (figure 1), and by other workers in a pooled analysis of different trials.\textsuperscript{16}

Thus, we can see that MDI is only likely to match the control achievable by CSII in type 1 diabetic patients who are already reasonably well controlled during MDI. In poorly controlled subjects on MDI, the glycaemic control will be expected to be substantially improved.

**Is the frequency of hypoglycaemia the same on MDI and CSII?**

In the years following the publication of the DCCT,\textsuperscript{12} a significant concern was that attempts to improve the glycaemic control of patients by means of more intensive insulin regimens would lead to an increase in the frequency of severe hypoglycaemia. Indeed, some were of the opinion that hypoglycaemia is an inevitable consequence of intensive insulin regimens such as MDI and CSII, and that such treatments are contraindicated in those with frequent hypoglycaemia.\textsuperscript{17}

In our recent meta-analysis, we found that the mean rate of severe hypoglycaemia was about four times lower during pump therapy than during MDI (rate ratio 4.2), and that (as with HbA$_1c$) the greatest improvement occurred in those worst controlled on MDI; in this case, the most marked reduction in hypoglycaemia occurred in those with the most severe hypoglycaemia on MDI.

The frequency of lesser degrees of hypoglycaemia not resulting in coma or needing assistance from a third party is also lower on CSII. We found that the percentage of self-monitored blood glucose readings that were <3.5 mmol/l was reduced by about 75% after switching from MDI to CSII.\textsuperscript{14}

**Blood glucose variability on MDI and CSII**

There has been a resurgence of interest in blood glucose variability in diabetes in recent years, partly because of the emerging possible links between variability and microvascular disease\textsuperscript{18} and partly because postprandial blood glucose excursions may be a risk factor for macrovascular disease.\textsuperscript{19} Unpredictability of glycaemic control is also a major frustration for patients and physicians trying to make logical changes in insulin dosages to improve control. We found that both within- and between- day blood glucose variability are significant determinants of the level of HbA$_1c$, that can be achieved during MDI,\textsuperscript{15} presumably because those with wide swings in blood glucose concentrations resist attempts to tighten control by increasing insulin dosages since they fear that hypoglycaemia will develop.
When we assessed the within-day or between-day blood glucose variability on the basis of the standard deviation or the interquartile range of the self-monitored blood glucose tests, we found that it was significantly reduced on CSII compared to MDI (figure 2). This may be because of the lower variability of insulin absorption associated with CSII, but it undoubtedly contributes to the ability of pump therapy to improve both HbA1c and hypoglycaemia frequency in patients.

**Does MDI with insulin analogues match the efficacy of CSII?**

In our clinic, we have found that the patients who were poorly controlled on MDI based on isophane insulin nearly always remained poorly controlled on MDI based on long-acting insulin analogues such as glargine, yet subsequently enjoyed a substantial improvement in HbA1c when changed to CSII. A meta-analysis of four studies comparing glargine-MDI with CSII indicates that the mean difference in HbA1c between the two treatments (0.6%) is similar to that when pumps are compared to isophane-MDI (J.C. Pickup and A.J. Sutton, unpublished data).

Severe hypoglycaemia has not been adequately studied in head-to-head trials of long-acting insulin analogue-based MDI and CSII, for example, because the studies have been of too short a duration for hypoglycaemia to be assessed reliably. However, several trials comparing isophane-MDI with glargine- or detemir-MDI have shown that neither HbA1c nor severe hypoglycaemia frequency were significantly different between the regimens.

One must realise that subgroups of people with type 1 diabetes can be just as well managed by analogue-based MDI as by CSII. In our clinic, we always enter patients into a pre-pump assessment programme in which we attempt to optimise control again on MDI, paying attention to education, insulin injection technique and the avoidance of lipohypertrophy, switching to glargine or detemir insulin if currently on isophane- or lente-based MDI, instituting carbohydrate counting and so on. About 10% of referred subjects can be improved during the programme and are therefore not offered a trial of pump therapy. This percentage is small for the Insulin Pump Clinic which sees patients who have been selected as having continued severe hypoglycaemia, elevated MDI and glycaemic variability during MDI, but larger numbers are, of course, effectively managed by analogue MDI in the general type 1 diabetes population.

**Does including structured patient education as part of the MDI regimen match the efficacy of CSII?**

One has often heard the criticism or comment over the years that much of the apparent power of CSII to improve control is due to the higher level of attention and education given to the patients. If this were offered to MDI-treated patients, would not control be equally improved?

The most cogent counter to this argument is an observation going back to the first paper on CSII: improvement in control occurs in many cases within a day or so of starting pump therapy and in the absence of any special education (which was not given at that time). This suggests that the main advantage of CSII over usual management lies in the physiological insulin delivery – when one gives insulin in a manner that mimics non-diabetic insulin delivery (basal and meal boluses), glycaemic control is rapidly brought towards near-normoglycaemia.

But let us leave this argument aside and focus on the power of modern diabetes education. One of the most...
discussed and programmed is the 5-day DAFNE course,\textsuperscript{11} modelled on the education provided and developed by Michael Berger in Düsseldorf, Germany. A key component is teaching patients to adjust insulin on a meal-by-meal basis, according to carbohydrate content. In a randomised controlled trial comparing the outcomes in type 1 diabetic patients trained in DAFNE to those of subjects managed without this education programme, the mean HbA\textsubscript{1c} was 8.4% and severe hypoglycaemia was unchanged. This indicates that neither glycaemic control nor control of hypoglycaemia were matched by that of CSII.

**Conclusions**

At least for those type 1 diabetic patients who fail to achieve satisfactory glycaemic control on MDI because of frequent unpredictable severe hypoglycaemia or an elevated HbA\textsubscript{1c} (often accompanied by glycaemic variability), switching to CSII offers improved control. I have estimated elsewhere\textsuperscript{29} that about 15% to 20% of people with type 1 diabetes will clearly fall into this category, a percentage similar to the number already receiving CSII in the USA and some other countries.

There is increasing evidence that quality of life is better on CSII than on MDI\textsuperscript{30,31} and we must expect a debate in the coming years about whether patients can simply choose CSII as their form of intensive insulin therapy on the basis of preference and quality of life. However, if we just confine our conclusions to the present evidence on clinical factors, we must consider that CSII is still needed.

**Practical considerations**

- Recent meta-analyses have shown that HbA\textsubscript{1c} is significantly lower on CSII than on MDI, but the difference is greatest in those worst controlled on MDI.
- Severe hypoglycaemia frequency is about 4 times less on CSII than MDI, but the reduction is also greatest in those worst affected on MDI.
- At least for the substantial percentage of patients who fail to achieve satisfactory control on MDI, CSII is still needed.

---

**References**

The need for CSII. J.C. Pickup


