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

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Executive summary

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Executive summary

Background

Continuous subcutaneous insulin infusion (CSII) is a way of giving insulin. A small programmable pump with a reservoir of short-acting insulin is connected to a cannula under the skin by a narrow tube. The pump is set to deliver insulin at slow rates appropriate to the time of day, and can be adjusted by the user to accommodate reduced insulin needs during and after exercise, and to deliver a higher infusion rate to cover food intake. The rate can be changed at any time by the user. For example, mealtime doses are delivered by activation of a booster dose by the user.

Continuous subcutaneous insulin infusion provides a form of intensified insulin therapy, and is part of a system of self-care that also includes home testing of blood glucose, self-adjustment of insulin dose, and care with diet. It is an alternative to multiple daily injection (MDI) of a combination of long- and short-acting insulins, usually involving four or more injections per day.

In 2002, the National Institute for Health and Clinical Excellence (NICE) issued guidance on the use of CSII, recommending restricted use in people with type 1 diabetes mellitus (T1DM) who could not achieve good control on MDI without problems with severe hypoglycaemia. So the population of interest is people already on MDI, whose diabetes is not sufficiently well controlled – for whom control refers not only to lowering high blood glucose, but also to achieving that without blood glucose becoming too low.

It was not recommended in type 2 diabetes mellitus (T2DM). At that time, there were no randomised trials in children or in adults with T2DM. There was little evidence in diabetic pregnancies, and that which there was showed little difference from MDI. The guidance expected that only 1–2% of people with T1DM would become insulin pump users.

Continuous subcutaneous insulin infusion is used in around 1% of people with T1DM in the UK, much less than the 10–20% in comparable countries in Europe or North America.

The aim of this report was to update the previous assessment report by reviewing evidence that has emerged since the last appraisal, and to take account of developments in alternative therapies, in particular the long-acting analogue insulins, which cause fewer problems with hypoglycaemia. We also have increasingly tight glycaemic targets, and an increasingly educated patient population that wants to achieve these.

Methods

A systematic review of the literature and an economic evaluation were carried out. The bibliographic databases used were MEDLINE and EMBASE, from 2002 to June 2007. Earlier studies had been included in the assessment report for the previous NICE appraisal of CSII. The Cochrane Library (all sections), the Science Citation Index (for meeting abstracts only) and the website of the 2007 American Diabetes Association were also searched.

The primary focus in T1DM was on comparison of CSII with MDI, based on the newer insulin analogues, but, for completeness, trials of NPH-based MDI that had been published since the last assessment were identified and described in brief. In T2DM, all trials of MDI versus CSII were included, whether the long-acting insulin was analogue or not, because there was no evidence that analogue-based MDI was better than NPH-based MDI in T2DM.

Trials shorter than 12 weeks were excluded.

Some recent observational studies were reviewed for data on longer-term results, discontinuation rates and adverse events. Studies on quality of life were also included. Previous studies of the cost-effectiveness of CSII were reviewed.

Information on the patient's perspective was obtained from four sources: the submission from the pump users group – Insulin Pump Therapy (INPUT); interviews with parents of young children who were members of INPUT, in order to get an impression of the problems of CSII in these very

young children, in whom the use of CSII seemed to be increasing; some recent studies; and from a summary of findings from the previous assessment report.

Economic modelling used the Center for Outcomes Research (CORE) model, through an arrangement with NICE and the pump manufacturers, whose submission also used the CORE model.

Results

Number of studies

A total of 922 studies was found in literature searches, of which 557 were excluded from the abstracts alone, followed by another 291 after reading the full text. The 74 studies retained for analysis included eight randomised controlled trials (RCTs) of CSII versus analogue-based MDI in either T1DM or T2DM, eight new (since last NICE appraisal) RCTs of CSII versus NPH-based MDI in T1DM, 48 observational studies of CSII, six studies of CSII in pregnancy, and four systematic reviews.

In the last guidance, NICE commented on the absence of trials of CSII against analogue-based MDI in T1DM. Unfortunately, only four such trials have been carried out since then, and only two have been published in full, of which one was only a pilot. The trial in children had 32 participants, and those in adults had 10, 14 and 57 recruits, giving a total of 81 adults. They lasted from 16 weeks to 6 months, which is too short. They were too dissimilar for a meta-analysis to be carried out.

For the comparison of CSII versus MDI in T2DM, we found four studies with 296 patients. There were eight new trials of older forms of MDI against CSII in T1DM, with 500 patients, although over half came from one trial. There are many observational studies, mainly case series.

Clinical effectiveness

As reported in the previous assessment report, the benefits of CSII can include:

- Better control of blood glucose levels, as reflected in glycated haemoglobin (HbA_{1c}), by reduction in swings in blood glucose levels, and in problems due to the dawn phenomenon.
- Fewer problems with hypoglycaemic episodes, of which severe incapacitating hypoglycaemia is most important.
- A reduction in insulin dose per day, thereby partly off-setting the cost of CSII.
- Quality of life, including a reduction in the chronic fear of severe hypoglycaemia.
- More flexibility of lifestyle – no need to eat at fixed intervals, more freedom of lifestyle, and easier to participate in social and physical activity.

These are dealt with, in turn, below.

Control of blood glucose

CSII versus analogue-based MDI in T1DM

- The one study in children and adolescents reported that HbA_{1c} was reduced by 1% ($p < 0.05$). The usual minimum difference regarded as clinically significant is 0.5%.
- The studies in adults found no difference in HbA_{1c}.
- The studies were of short duration, ranging from 16 weeks to 6 months.

CSII versus MDI in T2DM

- In T2DM, there was little evidence that CSII was better than analogue-based MDI. There was only one trial, in which there was no clinically significant difference in HbA_{1c}.
- Three trials compared CSII with NPH-based MDI. One found no difference in HbA_{1c}. The other reported reductions of 0.5% (clinically useful but not statistically significant in this study) and 0.9% ($p < 0.03$).

CSII versus NPH-based MDI in T1DM – new trials

- Of the eight new trials, three showed no difference in HbA_{1c}; four showed differences which were not statistically significant (although one showed a clinically significant difference of 0.5%), and the last showed a larger and statistically significant difference of 0.84%. Some had very small numbers of patients. The largest trial had 272 patients; this was more than all the other trials put together.

Observational studies

There are far more observational studies available now than there were at the last review. They need to be interpreted with caution due to the greater risk of bias. In general, they report greater improvements in HbA_{1c} than reported in the trials.

- In all 18 studies in adults, there were reductions in HbA_{1c} in adults and mixed age groups, ranging from 0.2% to 1.4%.

- In total, 20 of 23 studies in older children and adolescents showed reductions, ranging from 0.2% to 1.2%, and in 13 studies the reductions were statistically significant.
- The five studies in young children (under 7 years) reported decreases of 0.2–1.6%, with these being statistically significant in all but one small study (only 14 patients – reduction 0.2%).

Hypoglycaemia

CSII versus analogue-based MDI in T1DM

- The trials in adults had too few patients, too short durations and too few severe hypoglycaemic episodes to be conclusive, but reported no significant differences in the frequency of severe hypoglycaemia.
- The trial in children reported a statistically significant drop in severe hypoglycaemia, but based on five episodes on MDI versus two on CSII.

CSII in T2DM

- None of the four trials reported a significant difference in hypoglycaemic episodes.

CSII versus NPH-based MDI in T1DM – new trials

Again, most trials had small numbers. Five trials had < 30 patients.

- The trials that reported the number of severe hypoglycaemic events usually found about half the rate with CSII than with MDI.
- The biggest trial (which had more patients than all the rest put together) reported annual rates of severe hypoglycaemia of 0.2 per patient-year on CSII and 0.5 on MDI.

Observational studies

These reported considerable reductions in severe hypoglycaemia. This may reflect selection for CSII of people having particular problems with hypoglycaemia, but that would make them more applicable to routine care. Of 26 studies reporting comparable before/after data:

- 15 showed a statistically significant decrease in severe hypoglycaemic episodes
- five reported a statistically non-significant decrease
- three reported a decrease in episodes, but did not report significance levels
- three did not report any episodes.

Patient evidence

This came from the submission from INPUT, or from individual testimonies provided to NICE. Several patients reported that they had found that the onset of hypoglycaemia was much slower on CSII than MDI, giving them more time to take preventative action and avoid severe hypoglycaemic events.

Reduction in insulin dose

CSII versus analogue-based MDI in T1DM

The study in children reported a reduction, from 0.7 units/kg per day on CSII to 0.6 units/kg per day on MDI, but this was not statistically significant.

The only published trial in adults reported a significant drop by 24 weeks in the CSII group, from 0.7 units/kg per day before CSII to 0.4 units/kg per day after 24 weeks. The MDI group showed an insignificant rise, from 0.7 to 0.8 units/kg per day.

The studies available only as abstracts gave no details.

CSII in T2DM

No persisting differences in insulin dose were found.

Observational studies

Eight studies in adults, 11 in older children and adolescents, and two in younger children, reported comparable data. Six out of the eight adults studies reported a decrease in insulin dose, ranging from 2% to 27%. Of the 11 studies in older children and adolescents, 10 showed decreases varying in size from 3% to 32%, with most being statistically significant.

There were no significant changes in two studies in the youngest children.

Quality of life

CSII versus analogue-based MDI in T1DM

The two studies that reported quality of life outcomes found no differences, but had only 14 patients, followed up for 24 weeks, and 32 patients, followed up for 16 weeks.

CSII in T2DM

Of four RCTs, one study reported no difference and one reported a significant improvement in treatment satisfaction on CSII.

Observational studies

Bias in observational studies is more of a problem with questionnaire-based results than with biochemical ones such as HbA_{1c}, and all results must be treated with caution. Of 48 observational studies, only nine reported on quality of life aspects. Study numbers were small, with at most 35 patients.

One study in adult patients reported that they preferred CSII – another reported gains in quality of life.

In older children and adolescents, three out of four studies reported gains in various measures such as less worry, patient satisfaction, sleep quality, flexibility of mealtimes, better moods in children, and reduced impact of diabetes. But some reported initial worry, difficulties calculating insulin dose, and that it took from 6 weeks to 9 months to feel confident.

In children under 7 years, most families preferred CSII. In one study, parents reported quality of life gains; in another, children did not, but both had small numbers (15 and 14 children).

Other outcomes

Fifteen observational studies reported the frequency of diabetic ketoacidosis (DKA). None reported a statistically significant increase, but three reported statistically significant decreases.

The trials reported no difference in weight gain between CSII and MDI. Most of the observational studies reported no significant weight change before and after CSII.

Pregnancy

There were no new trials. Observational studies in general showed that CSII achieved similar glycaemic control to MDI. Maternal and fetal outcomes were similar. One study reported more DKA with CSII. A recently published Cochrane review noted that there was a dearth of good evidence.

Industry submission

The pump manufacturers submitted a joint submission. It used the CORE diabetes model. Three HbA_{1c} scenarios were assessed, all for T1DM:

- a baseline HbA_{1c} based on an unpublished meta-analysis of results from trials, with a reduction in CSII of 0.62%
- a higher baseline thought to be more representative of levels in the UK, with a reduction of 1.3%
- an intermediate scenario with a reduction of 0.95%.

All of these scenarios assumed a severe hypoglycaemic episode rate of 15 per 100 person-years.

The submission concluded that CSII in T1DM was cost-effective if the drop in the level of HbA_{1c} was 0.9% or more. Some assumptions favoured CSII, including the cost of hypoglycaemic episodes and the size of the reduction in insulin dose. The model also assumes that reductions in HbA_{1c} levels with CSII are sustained. In other ways the industry submission may have underestimated the benefits, for example by not including hypoglycaemic mortality and not allowing for all the quality of life gains. However, some of the omissions are understandable, given that some gains, for example in flexibility of lifestyle or happiness of children, are not easily measurable, and do not fit easily into cost per quality-adjusted life-year (QALY) estimations.

There are only occasional deaths from hypoglycaemia, but because they often occur in young people the number of life-years lost can be considerable.

The industry submission did not examine the economics of CSII in T2DM. In practice, CSII would be considered only in people with T2DM who had progressed to intensive insulin therapy, and would have a β-cell failure status not far off those with T1DM. Treatment group is more relevant than type of diabetes.

Perspective of pump users

The submission from INPUT emphasised the quality of life gains from CSII, as well as improved control and fewer hypoglycaemic episodes.

We carried out a small study by interviewing parents of 10 children aged 5–8 years. The following findings were included:

- They often had problems getting pumps, and some had to travel to distant clinics.

- They often found out about CSII from sources other than their local diabetes service.
- The benefits reported were much wider than the outcomes studied in trials, and included improvements in behaviour and parental quality of life.
- There seem to be problems with diabetes care in schools, with MDI regimens being difficult to implement.

There is a marked discrepancy between the improvement in social quality of life reported by successful pump users, and the lack of convincing health-related quality of life gains reported in the trials. The quality of life gains are not just to pump users, but to their families. Several parents reported that it was difficult to be in employment when looking after primary school children with diabetes.

Costs

The main cost of CSII is for consumables, such as tubing and cannulas – about £1800–2000 per year. The cost of the pump, assuming 4-year life, adds another £430–720 per annum. The extra cost compared with analogue-based MDI averages £1700.

Cost-effectiveness

A review of existing studies found three full papers and eight abstracts examining the cost-effectiveness of CSII compared with MDI. Most use the CORE model, and most found CSII to be cost-effective. They assumed a reduction in HbA_{1c} level of 1.2%; if CSII resulted in an improvement of only 0.5% then its cost-effectiveness was much poorer.

Modelling was carried out with varying assumptions about improvement in HbA_{1c} level, and reduction in severe hypoglycaemic episodes. With an improvement in HbA_{1c} level of 0.9%, and a reduction in severe hypoglycaemic episodes of 50% (from a relatively low baseline severe hypoglycaemic event rate of 19 per 100 patient-years), the cost per QALY is about £38,000. If higher-baseline severe hypoglycaemia rates are used, the cost per QALY falls but only to about £36,500 because the CORE model is driven more by HbA_{1c} level than by hypoglycaemia, and because the quality of life decrement from each hypoglycaemic event is of short duration.

The base case assumes an average age of 40 years at baseline. If we assume a younger starting age, of say 30 years, the cost per QALY falls to £34,000. The CORE model was not designed to run with children and so the results of CSII started in childhood have not been modelled.

If the reduction in level of HbA_{1c} is assumed to be only 0.6% then the incremental cost-effectiveness ratio (ICER) rises to over £50,000. Conversely, if the reduction in HbA_{1c} level is 1.4% then the cost per QALY falls to around £25,000.

A reduction in severe hypoglycaemic events can produce benefits in three ways. First, the immediate disbenefits at the time of the episode are avoided. Second, the chronic fear of a recurrence is reduced or relieved. Third, reduction in the fear of severe hypoglycaemia may allow more intensive therapy and lower HbA_{1c} level, hence reducing future complications. The second aspect has major implications for the cost per QALY, which has not been factored into any of the above estimates. An annual quality of life increment of as little as 0.01 from reduced fear of hypoglycaemia would, because of the number of years of benefit, reduce the base-case cost per QALY to about £29,000. An annual increment of 0.03 would reduce it to about £21,000 per QALY.

Patient selection

Continuous subcutaneous insulin infusion is a form of intensive insulin treatment that requires commitment from patients, and is part of package of care and self-care, along with structured education, home self-testing of blood glucose, adjustment of insulin dose, and attention to diet and physical activity.

Diabetes clinics that provide a specialist CSII service have developed ways of selecting patients who would be most suitable for CSII.

Implementation

If CSII were to be made more widely available, education would have to be provided not only for patients (perhaps involving a course such as DAFNE – Dose Adjustment For Normal Eating), but also for health-care professionals in centres that do not currently provide a pumps service.

Uncertainties

Some gains and losses in utility remain uncertain, or have not been quantified. These include:

- The fear of severe hypoglycaemia.
- The possibility of cognitive impairment due to severe hypoglycaemia in some children who become diabetic when very young.
- The non-health related benefits of CSII, such as greater flexibility of lifestyle, easier participation in social activities or school events/trips, happier children, less disruption to family routines, and, in mothers of young children with diabetes, less interrupted employment.

The costs per QALY in children have not been estimated.

Many of the trials are of short duration. It takes time to get the full benefit from CSII, for example by trying out different basal rate combinations, and so short trials may underestimate benefit.

Research needs

- The need identified by NICE at the first appraisal of CSII for adequate trials of CSII against analogue-based MDI has not been met. We need further trials, with larger numbers and longer durations, comparing CSII and optimised MDI in adults, adolescents and children. Duration is important because the maximum benefit from CSII may not be obtained for many months. Conversely, we need to know if initial benefits in HbA_{1c} level are sustained.
- There should be a trial of CSII versus MDI with similar provision of structured education, such as the DAFNE package, in both arms. Without such trials, we cannot be sure whether the benefits observed with CSII are due to the CSII itself, or to increased understanding of diabetes resulting from increased patient education.
- Automated systems for monitoring blood glucose levels are entering clinical practice, and there is potential to link with the insulin pumps.
- There is a need for a large trial involving pregnancy in women with pre-existing diabetes, which, in order to allow for using CSII to best effect, should start before conception.
- There should be a survey of difficulties of management of diabetes in schools.
- The present economic model assumes an adult population, and we need a model that would assess use in children to be developed.

Conclusions

Based on the totality of evidence, using observational studies to supplement the limited data from randomised trials against best MDI, CSII provides some advantages over MDI in T1DM. For both children and adults, these are:

1. Better control of glucose levels as reflected by HbA_{1c} level, with the size of improvement depending on the level before starting CSII.
2. Fewer problems with hypoglycaemia.
3. Quality of life gains, such as greater flexibility of lifestyle.

There are benefits for families. However, the benefits of CSII come at an extra cost of about £1700 per annum. There is no evidence that CSII is better than analogue-based MDI in T2DM, or in pregnancy. The amount of weight that we placed on the non-randomised evidence in drawing the above conclusions was questioned in the peer-review process.

Publication

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