ABCD position paper on insulin pumps

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ABSTRACT

Insulin pump therapy is likely to be the most physiological form of subcutaneous insulin administration and has been shown to be of benefit particularly for type 1 diabetic patients who are unable to achieve good control of diabetes without suffering recurrent hypoglycaemic attacks. Whilst the National Institute for Clinical Excellence (NICE) estimated that such therapy should be made available to about 1% of type 1 patients (based mainly on studies done with older pumps and older insulins), experience from mainland Europe, Israel and USA suggests that 10–20% of patients are likely to benefit. Current NICE criteria also make it very difficult for children to qualify for such therapy, as they are unlikely to have tried MDI (multiple-dose insulin therapy) to justify moving to pump therapy.

The economic impact of the improved quality of life from pump therapy has also not been adequately considered, as some patients are able to return to work, or take fewer days off sick, and children may miss less time at school. There is now substantial new evidence which indicates that the availability of continuous subcutaneous insulin infusion (CSII) should be extended to a much broader group of those with type 1 diabetes than currently fulfil the NICE criteria. Furthermore, there are a number of specific indications for pump therapy where patient numbers are so small that there will never be clinical trial evidence to support the indication, but this should not preclude use of pump therapy in such circumstances where conventional treatments have failed.

This paper summarises the latest evidence regarding the benefits of CSII over MDI and gives recommendations as to the place of CSII in therapy and the service implications.

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KEY WORDS

insulin pumps; ABCD; position statement; hypoglycaemia

Background

Continuous subcutaneous insulin infusion (CSII) or insulin pump therapy is an option for delivering intensified insulin therapy, and probably gives the closest approximation to physiological insulin levels possible with subcutaneous administration of insulin. Furthermore, the delivery of insulin is more reliable and reproducible with pump therapy than with conventional subcutaneous injections.

NICE (National Institute for Clinical Excellence) Technology Appraisal Number 57 recommended insulin pump therapy as an option for those with type 1 diabetes in whom multiple-dose insulin therapy (MDI) – including, where appropriate, the use of insulin glargine – has failed, provided that those initiated on pump therapy have the commitment and competence to use it effectively.[1] Failure of MDI is defined as an inability to achieve an HbA1c no greater than 7.5%, or 6.5% in the presence of microalbuminuria, without disabling hypoglycaemia – the repeated and unpredictable occurrence of hypoglycaemia requiring third-party assistance resulting in continuing anxiety about recurrence and associated with a significant adverse effect on quality of life. NICE further recommended that pump therapy should be initiated by a specialist team, consisting of a physician with a special interest in pump therapy, a diabetes nurse specialist and a specialist dietitian.

NICE concluded that approximately 1–2% of those with type 1 diabetes would fulfil the criteria for insulin pump therapy, at odds with usage of insulin pumps in countries where the technology is well-established, including most of mainland Europe, USA and Israel, where uptake is between 10 and 20% of the population with type 1 diabetes.

NICE guidance is based primarily on the outcome of randomised controlled trials (RCTs) of CSII *versus* MDI, most of which were performed prior to 1990, using outdated pump technology and soluble human insulin. These RCTs show significant reductions in the frequency of severe hypoglycaemia for those using CSII, but marginal improvements in HbA1c, of the order of 0.25–0.5%.[2,3] However, modern pump technology and the use of rapid-acting insulin analogues improve CSII efficacy further.[4] Recent cohort and case-control studies indicate that these RCTs underestimate the potential benefits of pump therapy, with reductions of HbA1c mostly of the order of 1–1.5%.[5–7]

Thus, there is a substantial body of evidence which indicates that the availability of CSII should be extended to a much broader group of those with type 1 diabetes than currently fulfil the NICE criteria. Furthermore, there are a number of specific indications for pump therapy where patient numbers are so small that there will never be clinical trial evidence to support the indication, but this should not preclude use of pump therapy in such circumstances.

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This paper summarises the evidence regarding the benefits of CSII over MDI and gives recommendations as to the place of CSII in therapy and the service implications.

CSII and glycaemic control

The ability of CSII to significantly reduce hypoglycaemia frequency – particularly for severe episodes – whilst improving glycaemic control however modest the reduction in HbA1c, is well-proven, and forms the basis of the existing NICE recommendations.[1–3,5]

Recent evidence from a number of centres,[6–9] including the UK, has demonstrated that in normal clinical practice there is a linear relationship between pre-pump HbA1c and the reduction in HbA1c. Thus those with the highest HbA1c are able to achieve the greatest reduction. A recent publication from Guy's Hospital showed no improvement in HbA1c when insulin therapy was intensified by conversion to MDI, nor from isophane-based MDI to glargine-based MDI, but a mean reduction in HbA1c of 1.4% at six months after conversion from MDI to pump therapy.[6] The mean reduction in HbA1c in pump clinics at UK centres – including Harrogate, Bournemouth and Liverpool – following conversion from MDI to CSII is about 1.5% with the lowest HbA1c being achieved at a mean of 17 months after starting pump therapy.[7] An audit of the pump therapy service at King's College Hospital similarly showed a reduction in HbA1c of 1.3%, and a decrease in the frequency of severe hypoglycaemia from 6.45 to 0.34 per patient year, and diabetic ketoacidosis from 1.83 to 0.27 per patient year in a cohort of patients many of whom did not fulfil NICE criteria for commencing pump therapy.[8] All these data suggest there is little rationale for restricting pump therapy to those individuals who are able to achieve good glycaemic control but only at the expense of troublesome hypoglycaemia.

It has been estimated that the potential reduction in microvascular complication rates that might be achieved if pump therapy is used for optimising control irrespective of HbA1c is 25%.[6] Furthermore, this recent UK evidence supports a sustained improvement in HbA1c with pump therapy. Meta-analysis of studies comparing pump therapy and MDI has suggested that the benefits of HbA1c are most apparent when pump therapy has been used for at least one year. In these studies, with a mean duration of 52 weeks, the average HbA1c was 8.68±0.06% on MDI compared to 7.48±0.06% on pump therapy.[5]

NICE guidance suggests MDI regimens which include insulin glargine should be used before trying insulin pump therapy. There is limited evidence to compare insulin glargine MDI regimens with pump therapy. In adults and adolescents there is no evidence that glargine-based MDI regimens are any more effective than isophane-based regimens when compared to pump therapy in terms of parameters of glycaemic control.[10,11] There is no reported difference in terms of hypoglycaemia frequency between glargine-based MDI and CSII, but the number of episodes recorded is too small to draw any definite conclusion.[10,11] In routine clinical practice in 17 clinics in Sweden, conversion from isophane-based MDI to pump therapy for a median of 25 months lowered HbA1c by a mean of 0.59%, compared to 0.2% when switched to glargine-based MDI for a mean of six months.[12] However, given the limited nature of the evidence that pump therapy is superior to long-acting analogue-based MDI regimens, it would seem reasonable to have a trial of such a regimen before changing to pump therapy.

CSII and type 2 diabetes

Most studies have failed to show that CSII is superior to MDI for glycaemic control in those with type 2 diabetes, nor does it have any advantages with respect to weight control.[13,14] One recent crossover trial did demonstrate an improved HbA1c when using pump therapy compared to MDI, but this benefit was not seen in the group starting on MDI and switching to CSII.[15] Greater patient satisfaction has been reported when CSII is used rather than MDI.[13] There has also been a report of CSII usage following two weeks of intravenous insulin infusion in markedly insulin resistant individuals with marked improvement in glycaemic control.[16] However, at present, there is insufficient evidence to routinely recommend CSII for use in type 2 diabetes.

CSII and complications

There is a small amount of evidence from early studies of CSII showing a benefit in terms of reduction in progression of microvascular complications.[17] These studies have largely compared CSII with twice-daily insulin administration. In the Diabetes Control and Complications Trial (DCCT), 42% of those in the intensive arm were using pump therapy at completion of the study,[18] but whilst the benefits of intensive insulin therapy in terms of a reduction in complications were obvious the published data do not allow a comparison of CSII and MDI. Thus any potential benefit of CSII over MDI in reducing complications can only be derived from models using the reported improvements in HbA1c (see above).

There are reported benefits of CSII in alleviating symptomatic neuropathy.[17] It has been suggested that the reduction in blood glucose fluctuations when using CSII is central to the reduction in symptoms of painful and autonomic neuropathy.

There were earlier reports of deterioration in retinopathy following initiation of CSII. It has now been shown that this is temporary with no lasting visual damage.[19]

CSII and quality of life

RCT, cohort and parallel group studies using modern pump technology have frequently demonstrated that CSII users experience improved quality of life, better coping ability, greater freedom – for example, with respect to eating and sleeping – and improved general health, both mental and physical.[3,14,20–22] Pump users routinely express greater treatment satisfaction than that experienced with MDI.[3,13,23]

Cost effectiveness of CSII

Using the improvement in HbA1c demonstrated in the Pickup meta-analysis and a Markov model,

Scuffham and Carr estimated that over eight years the cost per QALY (quality adjusted life year) of pump therapy was £11 461±3656.[24] In cost-effectiveness terms, pump therapy was of least benefit to those with good glycaemic control and few episodes of severe hypoglycaemia. This in part argues against the limitations imposed by NICE. Furthermore, the cost per QALY, already well within acceptable limits, would probably be much lower using the improvement in HbA1c demonstrated in observational studies. A more recent analysis by Roze *et al.* looked at lifetime costs and, with a more generous gain in QALYs for pump therapy, produced a lifetime cost per QALY of £25 648.[25]

The improvement in glycaemic control and resulting improvement in quality of life should translate into more effective performance of pump users either in education or employment, and a reduction in severe hypoglycaemia may also reduce carer burden. These factors are difficult to account for in an economic evaluation but would clearly enhance the cost effectiveness of pump therapy.

CSII in special groups

Pregnancy

Studies of pump therapy in pregnancy are limited. Most involved only small numbers and often the women receiving pump therapy had more co-existing problems than those on multiple injections. This limited evidence suggests that the possible benefits of CSII over MDI in pregnancy are: a lower preconceptual HbA1c and better post-partum control; less blood glucose fluctuation and hypoglycaemia during pregnancy, although similar HbA1c; a reduction in neonatal hypoglycaemia and possibly other neonatal morbidity; and less maternal weight gain.[26–29] There are inconsistent findings with respect to fetal growth.[30] Pump therapy may be particularly useful in women with complicated diabetic pregnancy.[31] The reduction in preconceptual HbA1c in CSII users could translate into a greater than 50% reduction in congenital malformation rates, extrapolating from the DCCT pregnancy data.[32]

Table 1. Indications for CSII

General usage
- Adults with type 1 diabetes unable to achieve optimal glycaemic control on MDI
- Children and adolescents for intensified insulin therapy

Special situations
- Pregnancy
- Acute painful neuropathy or symptomatic autonomic neuropathy if conventional treatment has failed
- Hypoglycaemia unawareness
- Extreme insulin sensitivity
- Needle phobia
- Severe insulin resistance with poor metabolic control
- Specific quality of life issues

Children and adolescents

Pump therapy is definitely as effective as MDI for achieving improvements in glycaemic control in children and adolescents, across the spectrum of ages,[23,33] and there is an increasing body of evidence that pump therapy is as effective in children and adolescents as in adults, with pump therapy producing similar reductions in HbA1c and hypoglycaemia frequency, and improvements in quality of life when compared to MDI.[33–35] In a recent study of 32 adolescents randomised to either pump therapy or glargine-based MDI there was no significant change in HbA1c in the MDI group, but a reduction of 0.9% in the pump therapy group after 16 weeks.[11] These benefits appear to be sustained over time.[36] Pump therapy is safe in children and has been used to reduce the risk of ketoacidosis in children suffering recurrent episodes on MDI.[37] The other advantage of CSII is that it may be a suitable way of intensifying insulin therapy for children when MDI is not an option because of the impracticalities of giving insulin injections at school.

Recommendations

Table 1 lists the indications for CSII.

Main indication

Insulin pump therapy should be considered in all those with type 1 diabetes as an option for intensified insulin therapy. It will usually be initiated following a period of MDI, including use of long-acting analogues, and a course of structured education. It is of particular benefit for:

- Those who are able to achieve target HbA1c (<7.5% without complications, <6.5% with complications) but only at the expense of frequent hypoglycaemia which has an adverse effect on quality of life.
- Those who have made significant efforts to optimise control but have a high HbA1c as a result of marked fluctuation in blood glucose levels, and for whom further reduction in levels will result in unacceptable hypoglycaemia.

It is expected that adults will be self-monitoring at least four times per day and are competent at dosage adjustment for meals, physical activity and other lifestyle issues, although this may not be the case in exceptional situations.

Children and adolescents should be offered the choice of insulin pump therapy or MDI as an initial method of intensifying insulin therapy, and will be expected to self-monitor according to need and ability.

Specific indications

Women contemplating pregnancy should be offered pump therapy as an insulin delivery preconceptually, given that any improvement in control could have significant benefits for fetal and maternal outcome. Women who conceive on MDI should be offered insulin pump therapy during pregnancy if targets for glycaemic control are not achieved (HbA1c <7.0%; blood glucose 4.4–6.1mmol/L before meals, <8.6mmol/L two hours after

meals), or problematic hypoglycaemia occurs. The decision as to whether to continue pump therapy post-partum should be made on an individual basis.

A trial of pump therapy should be considered for people with diabetes suffering from acute painful neuropathy or significant symptoms related to autonomic neuropathy in whom conventional treatment has failed. In these conditions blood glucose fluctuations may play a significant role in the severity of symptoms.

In those with hypoglycaemia unawareness, pump therapy offers an option for maintaining stably higher blood glucose levels without excessively compromising overall glycaemic control.

In the rare situation of extreme insulin sensitivity, pump therapy may be the only way of achieving blood glucose control without frequent hypoglycaemia.

When needle phobia is associated with adverse metabolic consequences pump therapy may offer a solution for improving concordance and hence control.

In those with type 2 diabetes, CSII may be considered when there is severe insulin resistance with unacceptable metabolic control.

There may be specific quality of life issues which could be successfully addressed by switching to pump therapy (Table 2). The criteria for the success of CSII in these individual situations should be comprehensively defined in advance to allow objective assessment.

Contraindications

CSII therapy is contraindicated when the patient does not demonstrate the necessary commitment and competence to use such therapy effectively.

Service implications

NICE estimated the cost of insulin pump therapy at £1100–1400 per patient per year, depending on the pump used and consumable costs.[1] This may be offset by around £200 for the reduced insulin requirement and pen needles no longer required. It is possible that a national purchasing agreement could reduce costs further, and VAT costs can be defrayed by patients receiving consumables directly from the pump companies. These issues need consideration when entering into commissioning discussions with primary care trusts.

Currently, there are a few diabetes centres in the UK with significant pump experience caring for at least 50 pump users, a few centres with rapidly increasing numbers of pump users, and many centres with a handful of pump users. The remaining centres refer to local specialist centres or do not consider pump therapy as an option. The latter approach is clearly contrary to NICE guidance and cannot be sustained, whilst an expansion in pump user numbers towards 15% of those with diabetes will determine that provision of pump services should as far as possible be local. There will clearly be a period of transition where new pump services will need to rely on established centres for support, both in training health care professionals and possibly patients.

NICE has detailed the personnel needed to run a pump service: a minimum of a physician, diabetes nurse specialist and dietitian with an interest in pump therapy. It would be expected that all these personnel would have attended an accredited training course, and that a minimum of five patients per year should be initiated on pump therapy for a diabetes centre to be recognised as a centre for pump therapy. There is a need for a national system of recognition for these pump centres. Running a pump service will require additional resources, especially medical, nursing and dietetic staffing. ABCD intends to evaluate the cost and service implications in more detail with a view to developing recommendations on this issue.

If NICE guidance is to be broadened there is a need for transparent audit to ensure that those who commence pump therapy fulfil the relevant criteria and that they benefit from pump therapy. Assessment of benefit will depend on the indication, but, for the main indication, should include at least one of the following:

- Improvement in HbA_{1c}.
- Reduction in frequency of severe hypoglycaemia.
- Objective evidence of improvement in quality of life.

Evidence of benefit should be evident by six months and re-evaluated on a regular basis.

For the specific indications for pump therapy it should be defined in advance what benefit should be anticipated. Increasingly, pump centres are using contracts for pump users to define criteria for success and facilitate withdrawal of pump therapy if these criteria are not fulfilled. This policy should be made clear to the patient before starting CSII.

The evidence base for the effectiveness of pump therapy would be enhanced if pump centres were to contribute anonymised data regarding control and complications to a central database. Areas where specific research would be of value in establishing the role of pump therapy would include whether there are subgroups of those with type 2 diabetes who do benefit from pump therapy rather than MDI, and whether pump therapy has any advantages over MDI in the manage-

Table 2. Specific quality of life issues for CSII

• Excessive number of injections for optimised control
• Unacceptable number of sick days
• Pathological fear of hypoglycaemia
• Marked glycaemic excursions/dawn phenomenon
• Impaired exercise capacity
• Abnormal eating behaviour
• Shift work
• Frequent travel across time zones
• Suboptimal school performance
• Exclusion from aspects of a full school life
• Behavioural problems, e.g. meal times
• Adverse impact on family dynamics

Key points

- CSII is more effective than MDI at lowering HbA_{1c} in adults and children with type 1 diabetes, with larger falls in HbA_{1c} seen in cohort studies rather than randomised controlled trials
- CSII is associated with a lower frequency of severe hypoglycaemia than MDI despite the improvement in HbA_{1c}
- CSII is not associated with an increased risk of ketoacidosis when compared to MDI
- There is a need for intensive education for the new CSII users, although ongoing service demands are probably similar to those using MDI
- The principal indications for CSII should be:
  - Adults unable to achieve optimal glycaemic control on MDI
  - Children and adolescents for intensified insulin therapy

ment of diabetic pregnancy. There is little likelihood of an RCT being performed to establish whether pump therapy is better than MDI at reducing the risk of complications, but it may be possible to determine how effective pump therapy is in alleviating the symptoms of peripheral sensorimotor and autonomic neuropathy.

Conflict of interest statement

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