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The pros and cons of continuous subcutaneous insulin infusion (CSII) therapy in the paediatric population and practical considerations when choosing and initiating CSII in children

FIONA CAMPBELL

Abstract

CSI (continuous subcutaneous insulin infusion), has the potential to improve long-term glycaemic control in many patients with type 1 diabetes. CSII may also reduce the incidence of hypoglycaemic episodes, especially in patients prone to hypoglycaemia, and may reduce glycaemic variability. A pivotal advantage of CSII over MDIs (multiple daily injection), especially in children, is its superior convenience and flexibility. Programmable basal rates are delivered automatically and with unprecedented precision, while bolus doses can easily be used to titrate insulin exposure around meals and activities and to correct hyperglycaemia. The subcutaneous cannula needs to be re-sited only once every 2–3 days. In light of these advantages, CSII is generally preferred by children and parents. Careful patient selection is crucial, however, as CSII users and their carers must be willing and able to use the equipment correctly, as well as to perform general aspects of intensive self-care. Accordingly, CSII should be initiated only by a specialist, multidisciplinary team and in conjunction with a structured, ongoing educational and monitoring programme. Factors affecting the selection of a particular pump include the size and weight of the device, ease of use, range of dose modes and increments, cost, warranty and customer services.

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Key words: continuous insulin infusion, diabetes mellitus, insulin, paediatrics, pump

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Abbreviations and acronyms

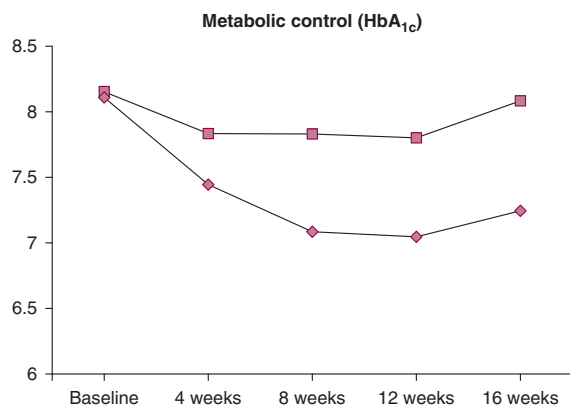
CSII	continuous subcutaneous insulin infusion
DKA	diabetic ketoacidosis
HbA _{1c}	glycated haemoglobin
MDI	multiple daily injection
NICE	National Institute for Health and Clinical Excellence

Introduction

CSII therapy for patients with type 1 diabetes is designed to mimic physiological insulin exposure by delivering a basal rate throughout the day and bolus doses around all carbohydrate intake (both snacks and major meals). CSII therapy aims to improve glycaemic control, both in terms of avoiding chronic hyperglycaemia and short-term hypoglycaemic and hyperglycaemic swings, while optimising the flexibility of therapy and improving patients' well-being.

NICE has recently updated its guidelines on CSII use, including in children with type 1 diabetes.¹ NICE now recommends CSII as a treatment option for children aged 12 years or older with type

Figure 1. HbA_{1c} levels in insulin-treated children with type 1 diabetes following randomised conversion to CSII (n=16) or MDI with insulin glargine (n=16). The difference between CSII (◆) and glargine (■) at baseline is not significant. At 16 weeks, HbA_{1c} levels in the CSII group were significantly lower than at baseline (p<0.02) and versus glargine (p<0.05)



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1 diabetes in whom MDI insulin therapy has caused disabling hypoglycaemia when a target HbA_{1c} level of 7.5% has been attempted, or when HbA_{1c} levels remain high (≥8.5%) during MDI therapy.¹ CSII is recommended in children aged under 12 years whenever the use of MDI is impractical or inappropriate.

These recommendations may help to improve paediatric access to CSII, which is at present low and variable across the UK. However, the management of type 1 diabetes in paediatric patients is subject to a variety of specific challenges that influence the selection and implementation of therapy. The paediatric population is heterogeneous in its presentation of diabetes, as well as in the physical, mental and emotional characteristics of presenting infants, children, adolescents and families. Insulin therapy, however it is delivered, is complicated by various aspects of childhood, including variable insulin sensitivity; level of self-care and parent/carer support at home, school and nursery; irregular meal intake and physical activity; susceptibility to hypoglycaemia; and communication difficulties.² Diabetes teams caring for teenage and adolescent patients must also contend with the hormonal and psychosocial changes associated with puberty.

This article discusses the advantages and disadvantages of CSII in paediatric patients, in light of the updated NICE guidelines.

Advantages of CSII in paediatric patients

Glycaemic control

Meta-analyses of randomised controlled trials have concluded that CSII is associated with better long-term glycaemic control than is MDI in patients with type 1 diabetes, as measured by HbA_{1c} level.^{3–5} Most recently, Pickup and Sutton found that CSII

was associated with a significant reduction in HbA_{1c} of 0.62% (95% confidence intervals 0.47–0.78%).⁵

In children and adolescents, short-term studies have found CSII to be more effective⁶ (figure 1) or as effective^{7–10} as MDI. Numerous 'before and after' cohort studies have provided more substantive evidence of a significant benefit when paediatric patients on MDI were converted to CSII.¹ Although these studies offer less robust data, they represent a large population in clinical practice that in some cases has been followed-up for a period of several years. For example, Weinzimer *et al.* found that HbA_{1c} levels continued to fall even 4 years after conversion to CSII in young children (mean age 4.5 years; n=65).¹¹ Moreover, significant reductions were seen in patients cared for by paid caregivers as well as those cared for by parents. Sustained benefits were also observed in older children, with a mean age of 12 years (n=42), followed-up for 4 years after the initiation of CSII.¹²

Recently, Jakisch *et al.* reported data from a large prospective study of paediatric patients initiated on CSII or MDI in Germany (n=434 matched pairs).¹³ The statistically significantly superior HbA_{1c} control achieved by CSII during the first year (7.5% versus 7.7% with MDI; p=0.006) was not maintained by the third year (8.1% versus 8.0%, respectively; p=0.99). Nonetheless, CSII was associated with statistically significant reductions in hypoglycaemic episodes, DKA episodes and insulin requirements versus MDI throughout the follow-up period: valuable outcomes in themselves.

Our own clinical experience supports a 0.5% improvement in HbA_{1c} maintained for up to 5 years when CSII is initiated in children (paper submitted) and we find a particular benefit in certain groups of children (table 1). Other evidence

Table 1. Potential indications for CSII in children with type 1 diabetes

Absolute indications	Relative indications
Children	Children
<ul style="list-style-type: none"> • Infants and small children (in whom insulin therapy is hard to manage) • Recurrent, severe hypoglycaemia • Feeding difficulties • Needle phobia 	<ul style="list-style-type: none"> • High glucose variability • Propensity for ketosis • CSII likely to improve quality of life
	Teenagers
	<ul style="list-style-type: none"> • Control has deteriorated • Insulin dose omissions are common • Control of morning glucose is troublesome • Severe hypoglycaemic events are recurrent • Presence of eating disorders

suggests that the likelihood of achievement of HbA_{1c} targets in children treated with CSII is higher in children aged 6–12 years than in those aged over 12 years, possibly owing to greater parental involvement and the lack of pubertal hormonal influences.¹⁴ More importantly, the change in HbA_{1c} upon conversion from MDI to CSII depends upon the baseline level achieved on MDI: CSII is most beneficial in the most poorly controlled patients.¹⁵ This presents a challenge worth contemplating in patients previously not considered candidates for CSII.

High HbA_{1c} levels during MDI therapy are often linked with a high degree of variation in blood glucose levels; these patients may also be prone to hypoglycaemic episodes.¹⁵ Evidence indicates that CSII can significantly reduce glucose variability or instability in adults and children.^{16,17} This may be important, as large swings in blood glucose are associated with impaired well-being and school performance in children.^{18,19}

NICE has made no recommendations with regard to the type of insulin to be used in CSII. Interestingly, Weinzimer *et al.* recently randomised almost 300 children and adolescents to 16 weeks of CSII therapy with insulin lispro or aspart.²⁰ Although a numerically greater reduction in HbA_{1c} with aspart did not reach statistical significance, more patients treated with aspart (59.7%) achieved target HbA_{1c} levels compared with patients treated with lispro (43.8%; $p=0.04$).

Hypoglycaemic episodes

Hypoglycaemic episodes remain problematic in many children treated with insulin, especially when achievement of low glycaemic targets is attempted. In principle, CSII should reduce the risk of hypoglycaemia, and indeed this has been established in some controlled studies in adults²¹ and in before-and-after studies in children.¹³ While previous meta-analyses have been inconclusive,⁴ a recent meta-analysis of 21 studies revealed that CSII was associated with a 75% lower rate of severe hypoglycaemia than MDI (rate ratio of 4.19; 95% confidence intervals 2.86–6.13).⁴ The reduction in hypoglycaemia was greatest in patients with a high hypoglycaemia rate on MDI. The three-centre, randomised, controlled INDIGO trial, due to commence in the UK in January 2009, will investigate the difference between MDI and CSII (both supported by a common educational programme) with regard to mild hypoglycaemic episodes.

Flexibility

A pivotal advantage of CSII over MDI is the greater convenience of insulin administration. Programmable basal rates are delivered automatically and with unprecedented precision (down to incremental units as little as 0.025 units/h with the Animas® 2020 pump; Animas Corporation, UK), while bolus doses can easily be used to titrate insulin exposure around meals and activities and to correct hyperglycaemia. In toddlers and younger children, the smaller basal rate of 0.025 units/h may be particularly useful to deal with the challenges of administering very small amounts of insulin that otherwise would need to be diluted. Convenience may be particularly important in children,

in whom MDI administration is often difficult to achieve with sufficient accuracy (e.g. during school or daycare time). Some CSII pumps can also help patients to calculate their carbohydrate intake, thereby facilitating the calculation of bolus dose.

CSII is also more convenient than MDI with regard to injection frequency, as the subcutaneous cannula needs to be re-sited approximately once every 2–3 days, as compared with upwards of five injections per day in patients on MDI therapy. Limited data suggest that the effectiveness of CSII in children is related to the number of cannula sites used, perhaps owing to improved absorption.¹⁴

Quality of life

CSII has been shown to improve the quality of life of adults with type 1 diabetes by reducing anxiety over hypoglycaemic episodes, enhancing flexibility (and thereby reducing the interference of the treatment with diet, lifestyle and family activities) and by increasing patient autonomy.^{1,21–23} For similar reasons, CSII also has the potential to improve the well-being of children with type 1 diabetes, together with that of their parents and carers.^{10,24–26} Treatment satisfaction appears to be higher among children randomised to CSII than to MDI.²⁷

Disadvantages of CSII in children

Competence and commitment

The safe and effective use of CSII requires high levels of self-care competence and motivation among patients and carers. However, it is important to emphasise that many of these aspects, such as the technicalities of blood glucose monitoring and carbohydrate counting, are common to intensive MDI therapy. Clearly, anyone wishing to use CSII must also be willing and able to use the equipment correctly and to maintain a sufficient stock of the necessary consumables. Accordingly, CSII should be initiated only by a specialist, multidisciplinary team and in conjunction with a structured, ongoing educational and monitoring programme.¹

Some individuals do find the technology too complex and hence the selection of prospective users is important. Even 'successful' pump users vary in their use of the technology, with some sticking to the basic functions, while most exploit the full benefit of the programmable modes (which can include multiple variable basal rates, and adjustments for exercise and menstruation). However, anecdotal evidence suggests that those who do use the full range of functions have the best glycaemic control. Patients and carers must also be able to deal with the mechanical problems that may infrequently occur, such as problems with the insulin reservoir, blockages in the infusion set tubes, and the stability or compatibility of the insulin preparation.^{28,29}

The sophistication of current CSII units also has implications for the healthcare staff who must interpret the substantial amounts of data collected by the machines and downloaded in the clinic. The presentation of these data within integrated, easily interpretable formats would be an important aid in this regard.

Safety

Some researchers have detected a small increase in DKA in paediatric patients treated with CSII, as compared with MDI, especially early after CSII initiation.³⁰ However, other studies have not confirmed this, especially in patients with good compliance and adequate family support. Indeed, a large case-control study recently reported by Jakisch *et al.*^{12,30} found that a lower baseline incidence of DKA in the CSII group was maintained throughout the 3 years of follow-up.¹³ DKA in pump users is most likely to occur when patients do not recognise that the pump is not properly delivering the correct insulin dose. Thus, the problem can be minimised by proper training and monitoring, as recommended.

It is regrettable that a recent, well-publicised, retrospective analysis of mortality in adolescents on CSII published by the US Food and Drug Administration, based on mandated industry reports in the US (totalling 13 cases over 10 years),³¹ did not place its findings in the context of the total number of patients treated with CSII, the substantial benefit provided to most users or the corresponding mortality rate in MDI users. There is no evidence that CSII is less safe than MDI and, indeed, given the safeguards built into the pumps (e.g. alarms), CSII has the potential to reduce the adverse effects of insulin therapy.

Weight and capacity

The selection of a CSII pump is influenced by a variety of factors, including the size and weight of the device, ease of use (e.g. the illumination of the screen and the simplicity of the operating system), range of dose modes and increments, presence of dose calculator, facility to use glucose sensor, link up to a blood glucose meter, cost, warranty and customer services. The issue of size involves a compromise between convenience/discreteness and reservoir capacity. Generally, the weight of any unit can be problematic for infants and toddlers, but can be ameliorated with a host of clothing solutions.

Conclusions

CSII offers the potential for improved glycaemic control in some paediatric patients with type 1 diabetes (especially those with poor control or frequent hypoglycaemic episodes) and may be preferred by patients and carers. CSII is particularly useful in younger children and, while current recommendations suggest that MDI should be tried first in older children, CSII can be instituted in the younger group without an MDI trial when the trial is deemed inappropriate or impractical.¹ Indeed, CSII should probably be considered for all paediatric patients.

Effective education and ongoing support tailored to the needs of children and parents are essential to ensure the cost-effective and safe use of CSII therapy. For the most part, this is not a unique, additional requirement of CSII. Rather, the specific education necessary for CSII use should build upon much needed improvements in the education of all patients receiving intensive therapy for type 1 diabetes.

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