Review: Use of continuous subcutaneous insulin infusion in special populations and circumstances in patients with type 1 diabetes

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Use of continuous subcutaneous insulin infusion in special populations and circumstances in patients with type 1 diabetes

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Abstract

CSII (continuous subcutaneous insulin infusion) is a valuable therapeutic option for many patients with type 1 diabetes, specifically where hyperglycaemia or recurrent hypoglycaemia persist during MDI (multiple daily injection) therapy. Special situations under which the use of CSII requires consideration include pregnancy, surgery and exercise. There is no evidence that CSII and MDI therapy differ significantly in efficacy in relation to maternal or foetal outcomes. Accordingly, NICE (National Institute for Health and Clinical Excellence) recommends that pregnant women with insulin-treated diabetes should be offered CSII using the same criteria as the general population. While continuous intravenous insulin infusion may offer advantages over MDI in patients with diabetes undergoing surgery, the role of CSII is unclear. During sports, CSII can facilitate better glycaemic control by allowing the precise adjustment of the basal rate and the administration of small incremental doses, and this may be complemented by the use of CGM (continuous glucose monitoring). More generally, real-time CGM can substantially improve glycaemic control in poorly controlled patients and, using sensor alarms, reduce hyperglycaemia and hypoglycaemia, although the clinical role of this technology is not well defined. Further research should evaluate the potential value of CSII in other populations and clinical scenarios.

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Key words: continuous insulin infusion, diabetes mellitus, insulin, pump, pregnancy, exercise

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Abbreviations and acronyms

CGM	continuous glucose monitoring
CSII	continuous subcutaneous insulin infusion
DKA	diabetic ketoacidosis
HbA_{1c}	glycated haemoglobin
i.v.	intravenous
MDI	multiple daily injection
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
SMBG	Self-monitoring of blood glucose

Introduction

CSII is of acknowledged benefit for many patients with type 1 diabetes. The potential advantages of CSII over standard MDI insulin therapy in adults include a modest, but worthwhile improvement in long-term glycaemic control; a reduction in blood glucose variability; a reduced daily insulin requirement; a reduction in the frequency and severity of hypoglycaemic episodes; greater flexibility with regard to meals and activities; the potential to link insulin administration more closely with CGM and improved health-related well-being.[1–5] These benefits were first demonstrated versus isophane insulin by randomised studies such as the 5-Nations study in Europe.[1] Although the newer, long-acting insulin glargine and detemir analogues may have advantages over isophane insulin for MDI in some patients, they have not diminished the role of CSII.[6]

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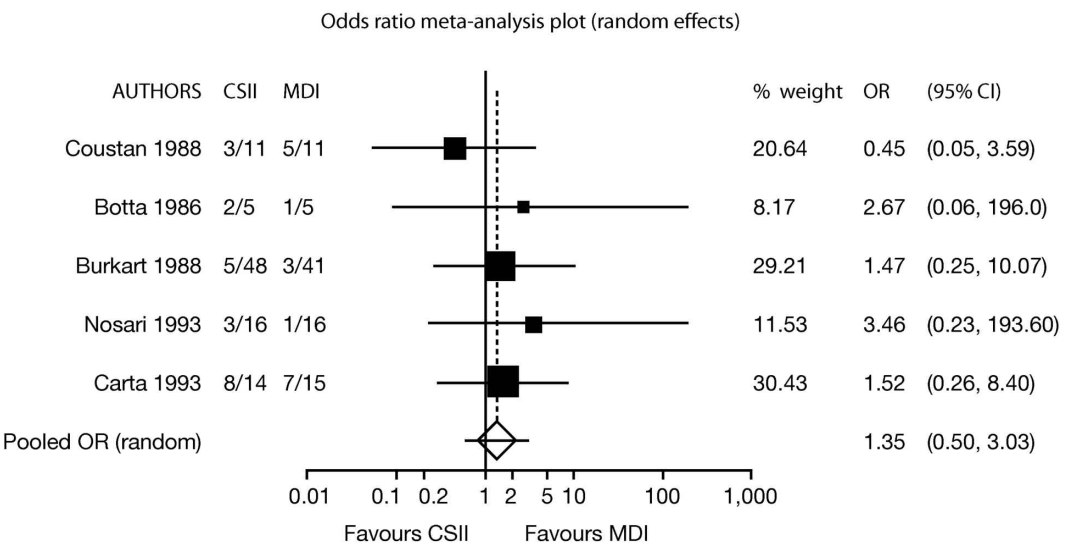
Figure 1. Odds ratio meta-analysis of studies comparing rates of hypoglycaemia when CSII or MDI was used[11]



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In the UK, NICE recommends CSII for the following:

- Adults and children aged 12 years or older with type 1 diabetes in whom MDI insulin therapy has resulted in disabling hypoglycaemia when recommended target HbA_{1c} levels have been attempted, or when HbA_{1c} remains high (≥8.5%) during MDI therapy
- Children aged under 12 years whenever the use of MDI is impractical or inappropriate.[7]

CSII is not recommended for use in patients with type 2 diabetes owing to the lack of evidence of benefit and cost-effectiveness over MDI, although it might possibly be of benefit in certain subgroups.[7] Other indications for CSII include the management of diabetes during pregnancy and certain rare situations, such as cutaneous insulin absorption problems, gastroparesis and transplantation.

This paper discusses the use of CSII with regard to pregnancy, exercise and surgery, and the potential role of CGM used in conjunction with CSII.

Pregnancy

The maintenance of good glycaemic control throughout pregnancy in women with type 1 diabetes is important to reduce the risk of miscarriage, congenital malformation, still birth and neonatal death.[8] The outcomes of pregnancies complicated by maternal diabetes have been substantially improved through the improvements in glycaemic control made possible by intensive MDI and CSII therapies and blood glucose monitoring.[9] NICE recommends that pregnant women with diabetes should aim to keep their fasting blood glucose levels between 3.5 and 5.9 mmol/L and 1-h postprandial blood glucose below 7.8 mmol/L.[8] The avoidance of hypoglycaemia and DKA is particularly important. Thus, women with insulin-treated diabetes should be offered CSII if adequate glycaemic control (HbA1c < 6.1%) is not obtained by MDI therapy without significant disabling hypoglycaemia.

According to NICE, the rapid-acting insulin analogues aspart and lispro may have advantages over conventional soluble insulin during pregnancy, while the long-acting analogue glargine is untested.[8] Data on the comparative efficacy of CSII and MDI therapy during pregnancy are limited. A recent Cochrane meta-analysis of two randomised trials of CSII and MDI involving 60 pregnant women with diabetes showed no significant differences between the two modalities in glycaemic control, maternal hypoglycaemia or hyperglycaemia, perinatal mortality or foetal abnormalities.[10] An observed increase in birth weight in infants of mothers treated with CSII was not considered clinically significant by the authors. A separate UK meta-analysis of six randomised trials also found no significant difference between CSII and MDI in terms of insulin dose, birthweight, gestational age, mode of delivery, hypoglycaemic events (figure 1), ketotic episodes, worsening retinopathy, neonatal hypoglycaemia or intrauterine foetal death.[11]

A retrospective case-control study, involving a total of 90 pregnant women, recently reported higher rates of DKA (13% versus 2%; p=0.04) and neonatal hypoglycaemia (35% versus 13%; p=0.01) with CSII than MDI.[12] However, a second prospective study reported no significant differences in maternal glycaemic control or maternal, foetal and perinatal outcomes between pregnant women with type 1 diabetes treated with either CSII or MDI (n=58).[13]

NICE has concluded that CSII and MDI do not differ significantly in efficacy or in maternal or foetal outcomes.[7] It suggests that pregnant women may benefit from CSII therapy and that the

aforementioned criteria for the general adult population should be applied when making treatment decisions. This guidance is reiterated in specific UK recommendations for management of diabetes during pregnancy. Thus, women with insulin-treated diabetes should be offered CSII if adequate glycaemic control (Hb A1c < 6.1%) is not obtained by MDI therapy without significant disabling hypoglycaemia.[8] Generally, the role of CSII should be considered within wider aspects of optimal diabetes care during pregnancy.[8,9]

During labour, it is recommended that glycaemic control in women with diabetes is controlled using i.v. infusion of dextrose and insulin. Although there is limited evidence that CSII might be at least as effective, further research is required.[8]

Surgery

Continuous i.v. insulin infusion may offer advantages over multiple injections in patients with diabetes undergoing surgery. For example, in case cohort studies, continuous i.v. insulin infusion gave significantly better perioperative glycaemic control and lower mortality than subcutaneous injections in patients undergoing coronary artery bypass grafts.[14,15] At least one randomised controlled trial has shown better postoperative glycaemic control with infusions in this group.[16] However, the role of CSII during and after surgery is unclear. Whether an individual's pump can be brought into the operating theatre should be verified with the manufacturer or healthcare provider. For example, at least one manufacturer (Animas Corporation, UK) recommends that its pump be removed from the operating theatre if X-rays or cautery are used.

Exercise

CSII can be useful in patients who regularly undertake non-contact sports, in those who engage in contact sports (using the appropriate pump and infusion set protection) and in those who perform certain other types of exercise. Some devices are sufficiently waterproof to permit their use during swimming.

In principle, CSII pumps should facilitate better glycaemic control during exercise by allowing the precise adjustment of the basal rate – to as low as 0.025 units/h for some models – according to the nature of the exercise (e.g. endurance sports versus sprint sports) and by the administration of incremental bolus doses as low, in some models, as 0.05 units. Limited evidence suggests that, in some circumstances, pumps should be deactivated during prolonged exercise and that blood glucose levels should be monitored during the hours after exercise to avoid hypoglycaemia.[17,18]

As with MDI therapy, CSII forms only one aspect of diabetes management optimised in relation to sport. Other aspects include carbohydrate counting and insulin dose adjustment calculations that take into account the raised energy intake likely in athletes. Careful blood glucose monitoring is crucial, and CGM can be of particular value in allowing patients to titrate their intake of carbohydrate during endurance exercise, according to real-time glucose trends, or to identify how carbohydrate requirements vary between different forms of exercise (e.g. between weight training and aerobic exercise).

Continuous glucose monitoring

Currently, three devices capable of providing real-time or retrospective CGM are available in the UK. These devices are of particular benefit in the following instances:

- For patients who are motivated toward self-testing
- Establishing blood glucose patterns when SMBG is unhelpful
- Exploring discrepancies between SMBG and HbA_{1c}
- Understanding overnight blood glucose profiles
- Identifying unrecognised hypoglycaemic events
- Assessing the impact of lifestyle and therapy changes
- Assessing glucose/insulin requirements during sporting activity.

Retrospective CGM has shown conflicting results, improving HbA_{1c}, but not hypoglycaemia in some studies,[19] or having the converse effects in others.[20] However, real-time CGM has given pronounced benefits in some patients with poor control: in one study, reducing HbA_{1c} by at least 1.0% over 3 months in half of poorly controlled children and adults.[21] The use of sensor alarms has reduced both hyperglycaemic and hypoglycaemic excursions.[22,23]

Real-time CGM can often be confusing to patients at first, underscoring the need for careful patient selection. Some centres begin with retrospective monitoring to familiarise users with the type of the information provided, the importance of trends over isolated results and the appropriate responses. Cost also remains a barrier to CGM use, as the devices are not reimbursed on the NHS. Typically, CGM would be expected to amount to approximately £500 a year, doubling the cost of CSII therapy over a period of 4 years.

In the future, systems that integrate CGM and CSII within a 'closed loop' may revolutionise the treatment of type 1 diabetes.[24] However, these remain experimental at present.

Conclusions

Current NICE recommendations recognise the value of CSII in many patients with type 1 diabetes, specifically where hyperglycaemia or recurrent hypoglycaemia persist during MDI therapy. Further research is necessary to establish the comparative efficacy of CSII versus long-acting insulin analogues and it is the former's impact on patient outcomes, especially those relating to patients' real-world experience of diabetes, that is of particular interest. Certainly, CSII can aid diabetes management in conjunction with exercise and might even improve performance in sports people with diabetes. Further consideration and research should be given to other populations and clinical scenarios in which CSII might improve diabetes self-management, such as the optimisation of CSII in the large 'hidden' population of middle-aged patients with type 1 diabetes who have been suboptimally maintained for decades on outdated insulin regimens, perhaps because they do not partake in invited annual review or because they have yet to be diagnosed with diabetes-related complications.

CSII is also an important option for use during pregnancy and hence the necessary resources should be available to allow patients access to this therapy. This includes the availability of specialist CSII teams capable of initiating CSII with the recommended level of education, support and monitoring. Further research into the efficacy of CSII in reducing glycaemic excursions during pregnancy is warranted.

CGM is a very useful tool that can be used to educate patients and (in the case of real-time CGM) to protect against hypoglycaemia. While individual patients often derive considerable benefit from these systems, the demonstration of population benefits has been more difficult and, as such, CGM remains a developmental technology whose role in routine management is not well defined. Nevertheless, the use of CGM is likely to increase in tandem with the anticipated increase in CSII use and as the accuracy and sensitivity of the sensors improve.

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