

Continuous vs. Intermittent Insulin Delivery in Children and Adolescents with Type 1 Diabetes Mellitus

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SUMMARY

This multicenter, open label, parallel group, randomized controlled trial was conducted to compare the efficacy, safety, and cost utility of continuous subcutaneous insulin infusion (CSII) with multiple daily injection (MDI) regimens during the first year following diagnosis of type 1 diabetes mellitus (T1DM) in children and adolescents (7 mo – 15 y) in UK. A total of 294 participants with a new diagnosis of T1DM were randomized, stratified by age and treating center, to start treatment with CSII ($n=145$) or MDI ($n=149$) within 14 days of diagnosis. Primary outcome was glycemic control, as measured by glycated hemoglobin (HbA1c), at 12 months. At 12 months, mean HbA1c was comparable with clinically unimportant differences between CSII and MDI participants (60.9 mmol/mol vs 58.5 mmol/mol; mean difference 2.4 mmol/mol; 95% CI -0.4 to 5.3; $P=0.09$). Achievement of HbA1c lower than 58 mmol/mol was low among the two groups (66/143 (46%) CSII participants vs. 78/142 (55%) MDI participants (RR 0.84; 95% CI 0.67 to 1.06). Parents (but not children) reported superior pediatric quality of life inventory scores for those patients treated with CSII compared to those treated with MDI. The authors concluded that during the first year following diagnosis of T1DM, no clinical benefit of CSII over MDI was identified in children and young people in the UK setting, and treatment with either regimen was suboptimal in achieving HbA1c thresholds. CSII was not cost-effective.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Blair, *et al.* [1] recently published the data from a pragmatic randomized controlled trial (RCT) comparing the efficacy, safety and cost-effectiveness of insulin therapy delivered over a period of one year, either as continuous infusion (through a pump) or multiple daily injections, in children with newly diagnosed type 1

diabetes mellitus (T1DM). The rationale for this study was the significant rising burden of T1DM in European countries, considerable economic as well as non-economic consequences of managing T1DM in young people, and the availability of multiple methods of insulin delivery to achieve glycemic control. Limited available data suggested that superior glycemic control (and its consequent clinical, social and economic benefits) could be possible by using insulin pumps designed for continuous (rather than intermittent) insulin delivery [2]. However, the limited evidence pool is based on small clinical trials with inherent biases, thereby making it difficult to draw a robust conclusion. This trial [1] is a value addition against this backdrop of scientific uncertainty. **Table I** summarizes the broad outline of the trial [1].

Critical appraisal: **Table II** outlines the methodological aspects of the trial.

This RCT [1] has a published protocol [3], although the trial was started nearly 4 years prior to the protocol being made public. Nevertheless, it is heartening that there are no deviations from the protocol.

The trial was conducted as a pragmatic RCT. Pragmatic trials are generally designed to examine the ‘effectiveness’ of interventions in real-world clinical settings, rather than ‘efficacy’ in highly controlled research settings. The latter trials are designated explanatory trials these days [4]. Pragmatic trials are especially useful to estimate the external validity and hence generalizability of findings for interventions determined to be efficacious through explanatory trials with high internal validity. However, in real-life many trials including this one has elements of both types of trials.

Analysis of this trial [1] using the PRECIS tool [5,6] suggests that it is not a completely pragmatic trial. A strictly pragmatic trial is designed to mimic the real-

TABLE I OUTLINE OF THE TRIAL COMPARING CONTINUOUS AND INTERMITTENT INSULIN DELIVERY

<i>Characteristic</i>	<i>Comments</i>
Clinical question	Although the authors did not state a clinical question in the PICOT format, it could be expressed as: “What is the efficacy, safety and cost (<i>O=Outcomes</i>) of insulin therapy delivered by continuous infusion (<i>I=Intervention</i>) compared to multiple, intermittent injection (<i>C=Comparison</i>) in children with newly diagnosed T1DM (<i>P=Population</i>) over a period of one year (<i>T=Time frame</i>)?”
Study design	Pragmatic, randomized controlled trial with individual participants
Study setting	Clinical centers based in 15 cities in the United Kingdom with expertise in managing pediatric diabetes
Study duration	May 2011 to January 2017
Inclusion criteria	Children and adolescents (7 mo to 15 y) with newly diagnosed T1DM based on (undefined) standard clinical practice. The trial protocol also mentioned an additional inclusion criterion <i>viz</i> children aged >8 y able to adhere to the treatment and study protocols; although, it was unclear how this was ascertained.
Exclusion criteria	A number of exclusion criteria were laid down; notably, prior treatment for T1DM, hemoglobinopathy, unspecified co-morbidities that could impact glycemic control, psychological or psychiatric disorders, known allergy to any component of insulin as part or insulin glargine, intake of unspecified medication(s) that could impact glycemic control, thyroid disorder, and poorly controlled celiac disease .
Intervention and Comparison groups	All participants underwent pre-trial analysis of blood glucose, HbA1c level, pH, thyroid function, anti-islet cell and anti-glutamic acid decarboxylase antibodies, and antibodies for coeliac disease. They were provided formal education using the syllabus prescribed by the International Society for Paediatric and Adolescent Diabetes. Children/caregivers were trained to deliver insulin, and record blood glucose by glucometers. The intervention arm received training to use infusion pumps as well. The total insulin dosage per day was calculated as 0.5 U/kg/d (in pre-pubertal children) or 0.7 U/kg/d in pubertal children. Those in the Comparison arm received half of the total insulin dosage as long-acting insulin glargine or detemir once a day, and the other half as short-acting insulin as part delivered thrice daily before meals. Additional insulin as part was delivered when >10 g carbohydrate was consumed. The Intervention arm received half the daily dose as insulin as part infused at a continuous basal rate, and the other half as boluses before meals. Additional insulin as part was delivered when >5 g carbohydrate was consumed. Correction doses for hyperglycemia were calculated for both groups.
Outcomes	<p><i>Primary:</i> HbA1c measured 12 months after the start of therapy</p> <p><i>Secondary:</i></p> <ul style="list-style-type: none"> • Proportion of children achieving the national target range HbA1c. • Frequency of severe hypoglycemia (ie associated with altered sensorium). • Frequency of diabetic ketoacidosis (DKA). • Change in height z score • Change in BMI z score • Insulin requirement per day. • Partial remission rate • QoL score at 6 and 12 months • Serious adverse events • Adverse event rate • Incremental cost per quality adjusted life year (QALY) gained
Follow-up protocol	Children were followed-up with formal study visits every 3 months after enrolment. During these visits, HbA1c, adverse events, anthropometry measurements, usage of insulin, records from glucometers and insulin pumps, treatment diaries etc were examined. In order to

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Characteristic	Comments
	determine access of health care services outside the study, local hospital databases were also examined.
Sample size	<i>A priori</i> sample size calculation was performed for a superiority trial, to detect 0.5% (5.46 mmol/mol) difference in HbA1c at the end of 12 months as this difference is considered to be clinically significant.
Data analysis	Intention-to-treat (ITT) analysis was performed, analyzing participants in the groups to which they were randomized. Additional per protocol analyses were also performed.
Comparison of groups at baseline	The groups were comparable at baseline with respect to age, gender, ethnicity, socio-economic deprivation, body mass index, height, HbA1c, blood glucose, and pH.
Summary of results (Intervention vs Comparison groups)	<p>Primary outcome:</p> <ul style="list-style-type: none"> HbA1c (ITT) at 12 months (mmol/mol): 60.9 (58.5, 63.3) vs 58.5 (56.1, 60.9). HbA1c (per protocol) at 12 months (mmol/mol): 60.2 (56.4, 63.9) vs 59.3 (55.3, 63.2). <p>Secondary outcomes:</p> <ul style="list-style-type: none"> Proportion of children achieving the national target range HbA1c. <ul style="list-style-type: none"> <58 mmol/mol: 46.2% vs 54.9% <48 mmol/mol: 15.4% vs 20.4% Frequency of severe hypoglycaemia (%): 4.2 vs 1.3 Frequency of DKA (%): 1.4 vs 0.0 Change in height z score: -0.1 vs 0.0 Change in BMI z score: 0.6 vs 0.5 Insulin requirement (U/kg/day): 0.7 vs 0.6 Partial remission rate (%): 24.4 vs 32.8 QoL score at 6 and 12 months: <ul style="list-style-type: none"> Statistically insignificant difference in child-reported QoL scores. Statistically significant but clinically insignificant difference in parent-reported QoL score. Serious adverse events (incidence density rate): 1.4 vs 0.0 Adverse event rate (incidence density rate): 1.4 vs 0.0 Incremental cost per quality adjusted life year (QALY) gained: GBP 1863 (1620, 2137) <p>The investigators undertook additional analysis of the primary outcome based on baseline HbA1c and socio-economic deprivation. They did not observe any difference in efficacy between the groups.</p>

T1DM: Type 1 diabetes mellitus; QoL: Quality of Life; HbA1c: Glycated hemoglobin; GBP: Great Britain Pounds.

world setting as closely as possible. Thus, it may not have rigid inclusion or exclusion criteria, and clinicians are not often constrained by guidelines on how to apply the experimental intervention. Further, the intervention can be applied by clinicians with all levels of expertise. There may not be formal scheduled follow-up visits but data are collected as participants report for follow-up. Mechanisms to ensure compliance to the trial protocol and strategies to enhance adherence to prescribed treatment are also not generally included. Understandably, an extremely pragmatic trial could compromise internal validity considerably.

The title of this study [1] suggests that continuous infusion of insulin was compared against multiple daily injections. However, both groups received 50% of the total daily insulin dose as three bolus injections prior to meals. Only the remaining 50% was delivered either as a continuous infusion or a single bolus injection. Thus, in effect, there was only one injection less (per day) in the intervention group. Although this distinction is obvious to clinicians managing pediatric T1DM, it may not be immediately understood by parents of children newly diagnosed with the condition, who are offered either option.

TABLE II CRITICAL APPRAISAL OF TRIAL METHODOLOGY

<i>Criteria</i>	<i>Conclusion</i>	<i>Comments</i>
Generation of random sequence	Adequate	Internet-based randomization using variable block sizes was done by a statistician. Participant were also stratified by age bands (7 months to <5 years, 5 years to <12 years, ≥12 years) and by treating center.
Allocation concealment	Unclear	The process has not been mentioned either in the protocol or the study report.
Blinding	Inadequate	There was no blinding of participants or outcome assessors.
Completeness of reporting	Adequate	All randomized participants were included in the primary intention-to-treat analysis. The required sample size was nearly fulfilled for this. Detailed description of participants who dropped out have been provided. Adverse events were analyzed on the basis of actual intervention received rather than group to which randomized.
Selectiveness of outcome reporting	Adequate	All clinically relevant outcomes were included.
Overall impression	Moderate risk of bias	Well designed trial; although, allocation concealment should have been clearly specified.

The trial [1] had numerous methodological refinements. The study centers were carefully selected based on the presence of personnel with expertise in pediatric T1DM and insulin pump therapy. Children enrolled in the trial underwent an educational program structured as per international guidelines. A noteworthy feature of this trial is that potential beneficiaries appear to have been included in designing the trial protocol, participation and outcomes to be measured. The trial management committee and the trial steering committee included parents of children with T1DM and children themselves. However, the details of these and the impact thereof (positive or negative) are not mentioned. The investigators reported that the study results and clinical significance were discussed with the families of enrolled children. This suggests a high degree of stakeholder involvement. This stakeholder involvement is further evident as children/parents were offered a choice of either intervention, and those who had fixed preferences were not included in the study. It appears that even during the course of the study, there was room to switch interventions. These actions mimic the real-world scenario to a large extent.

In terms of methodology, the investigators chose a large set of clinically meaningful outcomes reflecting efficacy and safety of the intervention. Additionally, costing data were included to assess value for money. It is difficult to confirm whether the efficacy data in this study represent effectiveness in the real world. The proportion of children with adequate glycemic control appears to be fairly low in both groups. On the other

hand, episodes representing poor control such as severe hypoglycemia, DKA, and unscheduled medical visits were also infrequent. In this regard, it is laudable that the investigators did not solely rely on parental report of additional medical care, but examined local hospital and clinic databases as well.

A recent systematic review [7] suggested that continuous subcutaneous insulin infusion had a marginal but statistically significant benefit (in terms of reduction in HbA1c) over multiple daily injections, in adults as well as children. However, there were no meaningful differences in terms of severity and duration of hypoglycemic episodes.

Extendibility: This trial showed that (50% of the daily) insulin dosage in children with T1DM, was comparable in terms of efficacy and safety, whether delivered as a continuous infusion (using a pump) or a single bolus injection. However, the pump-based therapy was significantly more expensive – mostly due to the cost of the pump, associated consumables and unscheduled hospital admission.

Conclusion: The findings in this well-conducted RCT suggest that there is no pressing need to consider insulin pump-based therapy in T1DM.

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Pediatric Endocrinologist's Viewpoint

Even a century after the discovery of insulin, the quest for a treatment regimen that could achieve an optimal glycemic control (HbA1c <7.5%) for a majority of patients with type 1 diabetes mellitus (T1DM), is a never-ending search. Continuous subcutaneous insulin infusion (CSII) using pumps have shown some promise in small short-term trials, but even this costly therapy has not been able to achieve optimal glycemic control in a majority of patients with T1DM.

This trial comparing CSII with multiple daily injections (MDI) of insulin has some notable differences from previous trials [1]. First, the patients were enrolled, and CSII (intervention) was started within 15 days of onset of T1DM. Second, the duration of intervention was fairly longer (1 year) when compared to previous trials. Third, the enrolment spanned over 7 years at 15 different centers in the UK. Most of the RCTs assessing the efficacy of CSII have shown conflicting results. The index trial has shown no superior efficacy of insulin pumps (CSII) over MDI over 1-year study period in children aged between 7 months and 15 years. The study reported improved Quality of Life (QoL) scores

(reported by parents) among insulin pump users compared to those treated with MDI. Further, the authors reported that CSII was not cost effective for UK or NHS standards.

The results of this trial are in slight contradiction to previous meta-analysis comparing CSII with MDI, where a modest efficacy of CSII was shown. Most of the previous RCTs and meta-analysis (as discussed in this article as well) are more than a decade old. Most of the RCTs included in this meta-analysis have been of 6 months duration and conducted on children with T1DM on long-term follow-up who were randomized to either CSII or MDI. Outside the stringent trial settings, most of the retrospective or prospective observational data analysis from various registries of children with T1DM from the developed world has shown that more than 50% of children with T1DM are on CSII, and have better glycemic control compared to children on MDI [2-5].

Even the paper published on the detailed methodology of this trial has not mentioned the type of insulin pumps used in the study [6]. As technology is evolving very fast, newer versions of insulin pumps with advanced functions have come up over the duration of this study, and after the study enrolment was done. Insulin pumps with low (and predictive low) glucose suspend have more likelihood of achieving time in range for target glucose. Further, the study has not compared the sensor-augmented insulin pump therapy, which has been associated with better glycemic control in previous studies comparing the MDI with CSII treatment regimens. Another limitation of the study is a failure to have the consent of more than 50% eligible children for enrolment in the study. This could compromise the validity of the results as it may not be a real reflection of the target population. Moreover, the first 6 months of diagnosis of T1DM may not be the ideal time to start a patient on the insulin pump as patients and parents are still adjusting to the diagnosis (mentally and physically), and acquiring knowledge on various aspects of home care of T1DM. It may be an extra burden to learn and manage insulin pump therapy on top of other day-to-day stringent regimens, which they are still trying to cope with. Effective Insulin pump therapy needs a highly motivated patient and family willing to give their best of efforts.

Another important component of this study was cost-effectiveness analysis, which is more relevant to policymakers rather than individual patients. Cost-effectiveness may not have much relevance as long as an individual patient seeking CSII pays from his/her (or parent's) pocket as is the status in India. However, for

physicians working in poor or developing economies, it is even more important to understand the efficacy of such a costly therapy. Simultaneously, we also need to understand that there are several aspects of the management of T1DM in children, and cost is just one of the aspects that need consideration. The physicians, especially Pediatric Endocrinologists, who manage children and adolescents with T1DM on daily basis can understand the plight of these children and families who have to follow a very stringent treatment regimen of at least 8 needle pricks (4 for self-monitoring of blood glucose and 4 needle pricks for insulin injections) per day along with meticulous measure of amount of meals and activity. Any intervention that could make the life of these families and kids easy even by a small fraction will be most welcome. CSII with insulin pumps reduces the number of insulin injection pricks, and has shown to improve quality of life across all the studies among all ages. Improvement of HbA1c, even if modest, is a bonus.

This study is relevant to the Indian context because of the sheer number of children and adolescent with T1DM in India. Prevalence of T1DM among children and adolescents (<15 years) in India is estimated at 1,28,000 (nearly 6 times the prevalence in the UK) as per IDF Atlas, 2017 [7]. However, experts believe that actual numbers may be far more than these estimates as there is no registry or formal reporting of T1DM in India.

In India, where providing optimal insulin therapy for children with T1DM could be a challenge for most of the families, CSII is a far-fetched and unrealistic option for the majority at present. However, with the widening gap between rich and poor in India, we do get parents who can easily afford CSII for their children. It may not be ethically correct not to offer a form of therapy which a patient (parent) can afford. CSII is definitely a more convenient (could be subjective) and physiological way of replacing insulin in T1DM, but it has only shown modest efficacy in improving glycemic control compared to MDI with insulin analogues. Especially for the Indian setting, it is important to understand that this modest short-term improvement in glycemic control comes at an exorbitant cost of CSII. For obvious reasons, there are no RCTs on this subject from Indian children with T1DM. There are few anecdotal reports of small series of patients followed after they were shifted from MDI to CSII, where glycemic control improved significantly [8].

In my personal experience (unpublished data) of 20 children (8 months to 15 years) on CSII, there was a significant improvement of glycemic control in a majority of the patients after changing from MDI to

CSII. Most of the parents who sought insulin pump for their children belonged to literate working-class getting reimbursement of expenses on treatment of their kids from the employer.

To summarize, CSII should be discussed, as one of the modes of giving insulin, with all patients with T1DM. As per the existing evidence on the efficacy of CSII, the main indication for starting CSII in children has to be patient's or parent's convenience/preference rather than glycemic improvement. The recent ISPAD guidelines [9], recommend CSII as the preferred (over MDI) mode of insulin treatment for children less than 7 years, as it is practically impossible to cover multiple small meals and snacks with as many insulin injections (6-9 meals/snacks requiring an equal number of insulin bolus injections). Further, all affording patients with poor glycemic control on MDI may be offered CSII.

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Pediatrician's Viewpoint

Intensive management is the key for improved long-term outcome in diabetes [1]. Maintaining an optimal glycemic control (as measured by HbA1c targets) especially in preschoolers and adolescents remains a challenge worldwide.

In this randomized controlled trial and economic evaluation of infants, children and young people in the first year of Type 1 diabetes mellitus (T1DM) diagnosis, glycemic control was suboptimal in both MDI and CSII arms. Moreover, CSII was neither more clinically effective nor more cost-effective than MDI. The only benefit of using CSII over MDI was a superior Quality of Life score by the parents [2].

Insulin pumps provide superior metabolic control when compared to 1-2 injection/day regimens. The latest ISPAD 2018 guidelines recommend that if available, insulin pumps should be used in preschoolers and certain other conditions [3]. Studies done to document any benefit of CSII vs MDI have shown variable results. Most of these studies have shown CSII to be superior to MDI in achieving better glycemic control, superior health related quality of life/patient satisfaction and lower insulin requirements [4,5]. Even in those studies where HbA1c was comparable, a higher treatment satisfaction was noted in pump users and many of them continued pump usage having no benefit in HbA1C levels [6,7]. CSII have become the preferred insulin delivery system in countries with high pump penetration; *e.g.*, USA, Australia and many European nations. These centers are starting many of their T1DM pediatric patients, particularly preschoolers, on CSII right from the onset of disease.

Though HbA1c is the standard tool for checking glycemic control, it has its own limitations such as lack

of information regarding acute glycemic excursions, hypo/hyper-glycemia, intra/inter-day variability, and false low values in anemia and hemoglobinopathies. Advances in diabetes care and technology have now shifted the clinical target focus from HbA1c to more meaningful metrics of "Time in Range" (time in range defined as blood glucose levels between 70-180 mg/dL) [8]. In this SCIP study, HbA1c was comparable between the two arms but it was not designed to compare the time in range and glycemic variability between the two arms of the trial. Despite having comparable HbA1c, there might have been difference in the time in range between the two groups (which signifies a better glycemic control). Similar multicenter, longer term studies with the objective to determine time in range are needed to ascertain which of the two modalities is better.

Due to lack of affordability of insulin pumps, multiple daily injections still remain the standard of care of T1DM in India. Affordable Insulin regimen, extensive diabetes education of the patient/parents and coupled psychological support system remain the cornerstone for achieving good glycemic control during crucial first year of diagnosis of T1DM.

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