

# Why Pumps? Continuous Subcutaneous Insulin Infusion for Children and Adolescents with Type 1 Diabetes

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The goals of intensive management of type 1 diabetes were established in 1993 following publication of the Diabetes Control and Complication Trial, a 9 year study of 1,441 youths with type 1 diabetes. The results demonstrated that tight metabolic control with intensive insulin therapy was superior to conventional treatment for reducing the risk of long-term microvascular complications. These effects, however, were associated with an increased risk of severe hypoglycemia and a corresponding weight gain [1].

Both these complications have particular significance in children and adolescents, who tend to have erratic eating behaviors [2], worry about their body image [3], and find it difficult to comply with regular insulin injections, frequent blood glucose monitoring, and regular meals [2]. Indeed, the adolescent group in that trial had higher glycosylated hemoglobin levels than the adults, and a higher rate of severe hypoglycemic events [4]. At the same time, the prepubertal and pubertal years seem to have a major impact on microvascular complications in diabetes [5,6], making tight metabolic control during this period of major importance. This consideration prompted the development of mechanical infusion systems that better mimic beta-cell function.

## History of insulin pumps

The first continuous insulin delivery device was fashioned in 1960, but it was large, cumbersome and impractical [7]. About 15 years later, research groups [8] suggested that in patients with type 1 diabetes the best method to improve metabolic control was to administer insulin in a manner that simulates the physiologic patterns of insulin secretion, that is, continuous 24 hour "basal" delivery with superimposed prandial-related boosts or "boluses." Although this could be achieved with multiple daily injections, controlled insulin infusion by portable pump appeared to be more flexible and precise. In several countries, early trials using variable rates of intravenous insulin delivery [7,8] noted improved blood glucose control compared to traditional methods. However, the clinical application of an intravenous infusion system was limited by risks of infection, thrombosis, phlebitis, insulin precipitation and aggregation, as well as difficulties in maintaining arm vein patency. As a result, new efforts were invested in developing portable delivery systems for continuous subcutaneous insulin infusion. The first report was published by Pickup et al. [9] in 1978. Soon after,

Tamborlane and co-workers [10] demonstrated that CSII, when combined with self-monitoring of blood glucose ("intensive insulin therapy"), yielded HbA1c values in the near-normal range. The metabolic improvement in patients using the pump was at least as good as with the intravenous route.

In view of these early successful results, several prototypes of smaller, lighter, electronically programmable pumps, with different kinds of open-loop systems, were introduced. Modern pump modifications that improve function and ease of use include electronic memory, multiple basal rate programming, bolus options, and suspension or temporary rate preprogramming of insulin for set times throughout the day. In addition, pumps now come in a variety of colors and the information screen is easier to read. The infusion sets have softened catheters that obviate the need for the insertion needle to be left in place, and "quick-release" options that permit the pump user to easily disconnect from the infusion tubing during activities such as showering, swimming, and sexual intimacy. Some of the pumps have a safety lockout feature, a remote control, and alarms that signal the user to recharge the battery, fill the syringe, etc. Newer tapes have been developed that better secure the needle or catheter on the skin while causing less local skin irritation. The use of local anesthetic cream makes catheter insertion nearly painless.

## Advantages of CSII therapy

The secretory responses of insulin to physiologic stimuli are complex and difficult to duplicate. At present, CSII appears to offer the most physiologic means of insulin delivery, by combining predetermined basal rates of insulin to meet non-prandial requirements (between meals and during sleeping hours) and bolus doses at mealtimes. The basal rate is set to the minimum insulin needed to suppress gluconeogenesis and ketogenesis, while keeping blood glucose levels within the normal range without inducing hypoglycemia. The mealtime boluses are calculated by an algorithm and depend on the caloric and nutritive composition of the meal, the capillary glucose concentration before the meal, and the anticipated level of physical activity after the meal. For better prandial and postprandial glycemic control, according to the type of

CSII = continuous subcutaneous insulin infusion  
HbA1c = glycosylated hemoglobin

food ingested and duration of the meal, current pump technology offers several bolus options: normal, where the programmed bolus is given immediately before the meal; square-wave, where the bolus is distributed over a chosen time; and dual-wave, which combines these two methods in a suitable ratio selected by the patient. The rate of basal insulin infusion can vary during the day to accommodate diurnal changes in insulin needs. The ability to set different basal profiles throughout the day and thereby decrease or increase the insulin infusion rate also prevents the dawn phenomenon; that is, the basal rate can be increased in the early morning hours without inducing nocturnal hypoglycemia [11]. This advantage is even more important during the pubertal years, when the extent of the increase in early morning insulin requirements is maximal [12]. The ability to change the basal rate also decreases the risk of exercise-induced hypoglycemia [11].

Studies have shown that the use of only short-acting (regular) insulin significantly decreases the variation in subcutaneous absorption of insulin compared to intermediate-acting insulin (~ 3% vs. ~30 to 50% difference) [13]. In addition, placement of the catheter in the same area for a few days overcomes the large difference in subcutaneous insulin absorption from different injection sites, so that blood glucose profiles are more consistent, with smaller fluctuations compared to multiple daily injections [14]. The introduction of rapid-acting insulin analogues with their faster subcutaneous absorption further improved diabetic control and glucose profiles by insulin pumps [15].

Thus, by using CSII, patients are spared both the need for multiple daily injections of insulin by syringe or pen and the peak-action profile that characterizes intermediate- or long-acting insulin preparations, allowing them more flexibility with meals and daily activity.

Recent technological advances have made the pump less liable to mechanical failure and more user-friendly [16]. The pumps of the 1980s were large and heavy and often had a negative impact on body image [17]. Today, pumps are pager-size, easy to carry and, in our era of cellular phones, much more socially acceptable. The development of electronic memory, several basal profiles, enhanced safety alarms, a soft cannula, remote control, and waterproof materials have dramatically improved the day-to-day use of insulin pump therapy [16].

### Disadvantages of CSII

As CSII has grown in popularity, patients and physicians have begun to recognize some of its limitations. The lack of a subcutaneous depot of intermediate- or long-acting insulin and the short half-life of serum insulin during CSII [12] increase patient susceptibility to diabetic ketoacidosis secondary to dislodgement or occlusion of the infusion set or pump failure [18]. Since the currently available device alarms do not warn of leakage or dislodgement, frequent SMBG is needed, with rapid, appropriate action to correct high glucose levels.

Another disadvantage is the high risk of infection at the infusion-set site [18]. In addition, some patients show local allergic reactions

to components of the infusion system [19]. These local complications can be prevented by meticulous management of the insertion site: changing the insulin delivery catheter every 2–3 days, changing components of the infusion system, and applying local antibiotic cream, as necessary.

It is also noteworthy that despite the technological improvements in design and convenience, the pump remains a complex, sophisticated instrument, and its handling requires cognitive abilities, technical expertise, good understanding and familiarity with the device, environmental support, and careful follow-up by the healthcare provider [16,20]. In addition, some patients still feel burdened by the need to carry the pump and to leave the cannula in the subcutaneous tissue 24 hours a day [20].

### Patient selection

Suitable patients for pump therapy must fulfill several important criteria: very high motivation with strong familial support, readiness to perform between four and seven SMBG tests per day, and close cooperation with the attending medical staff. In addition, either the family or the patient should have sufficient cognitive and technical skills to use the pump device. Up to age 8 years, children are totally dependent for treatment on their parents; from age 8 to 12 they can undertake some of the tasks; after age 12, they can operate the pump alone, provided there is high parental involvement in the procedure. In our experience, both patients with eating disorders and mildly retarded patients can benefit from the pump so long as they have strong parental support [16]. To ensure good results, pump use in these age groups should be accompanied by 24 hour online support from the medical staff.

### Transition from MDI to CSII

Choosing CSII as the mode of intensive therapy requires appropriate education and adjustment to the new therapeutic modality. Before switching to CSII, patients are taught carbohydrate counting and insulin bolus dosing based on the insulin-to-carbohydrate ratio.

Pump therapy is usually used only with the rapid-acting insulin analogues, humalog (Lispro<sup>®</sup>, Lilly, USA) or aspart (NovoRapid<sup>®</sup>, Novo Nordisk, Denmark). Studies have shown that diabetic control during CSII therapy is slightly but significantly better (-0.26% in HbA1c levels) and patient satisfaction greater with rapid-acting insulin analogues than with regular insulins [21]. However, other researchers reported similar glycemic control and blood glucose profiles with regular insulins [22]. As CSII usually requires less insulin than MDI to achieve similar glycemic targets [20,23], the transition from MDI is achieved by decreasing the average total insulin dosage per day by about 20%, calculated on the basis of the dose used over the preceding 2 weeks. Of the total new daily dose, 50% is given as basal insulin and 50% as pre-meal boluses.

The initial starting insulin dose should correspond to patient age and physical activity. Conrad et al. [24] recently showed that switching from MDI to CSII was associated with the need to decrease the insulin dose by 18% in pubertal patients but by only

SMBG = self-monitoring of blood glucose

MDI = multiple daily infusion injections

1.7% in prepubertal children. They therefore suggested that clinicians consider a smaller dose change during transition from MDI to CSII in prepubertal children. They also demonstrated that the maximal basal rate occurred from 3 a.m. to 9 a.m. and from 9 p.m. to 12 a.m. in pubertal patients, and from 9 p.m. to 12 a.m. in prepubertal patients [24].

At our center [20,23], to calculate the starting bolus insulin dose, we use 1 U of insulin per 10–20 g of carbohydrate in the anticipated meal. Patients are asked to perform frequent SBGM (before meals, after meals, and during the night). The target glycemic range for children and adolescents is 80–150 mg/dl before meals and at midnight and 120–180 mg/dl 2 hours after meals. According to the post-meal SBGM and food diary, additional insulin is added to the regimen to cover for elevated blood glucose levels, as necessary. In addition, elevated blood glucose levels are corrected with additional insulin, 1 U for every 30–100 mg/dl above 150 mg/dl. This, of course, can be done without the need for additional needle pricks. Most clinicians ask their patients to change the infusion site every 3 days in regular circumstances, and earlier if blood glucose is >300 mg/dl and the urine is positive for ketones, if blood glucose is >300 mg/dl and fails to respond to corrective insulin doses, or in the presence of signs of infection at the insertion site.

### CSII vs. MDI in type 1 diabetics

Studies comparing glycemic control and adverse events in CSII and MDI have shown contradictory results. However, most used a non-controlled, non-randomized, or non-crossover design. Some used a retrospective paired-comparison design where the same individuals were assessed before and after initiation of CSII, and others included patients who had been treated by both conventional and intensive insulin therapy with MDI before CSII. Furthermore, the vast majority of studies was done in the adult population. A recent meta-analysis [25] of 12 randomized control trials comparing CSII with MDI in adults with type 1 diabetes found that CSII was associated with a decrease of ~1 mmol/L in mean blood glucose concentration, a decrease of ~0.5% in HbA1c, and a decrease of ~14% in insulin dose. A second meta-analysis [26] of 52 studies – 41 paired studies and 11 parallel studies – of patients of all ages, reported slightly better mean blood glucose levels and HbA1c with CSII. The main finding was the impact of the duration of CSII therapy on the improvement in glycemic control. Specifically, a significant improvement in glycohemoglobin (mean  $\pm$  SD,  $8.68 \pm 0.06$  before vs.  $7.48 \pm 0.22$  after,  $P < 0.001$ ) was noted in the patients who used pump therapy for at least 1 year, but not in those who did so for less time ( $9.4 \pm 0.23$  vs.  $9.2 \pm 0.01$ ,  $P = 0.3$ ). Besides the faulty methodology used in most of the studies reviewed, both meta-analyses failed to compare the rate of adverse events, and the descriptive data were equivocal with regard to the rates of diabetic ketoacidosis, severe hypoglycemia and catheter-site infections, as well as psychosocial functioning.

In contrast to the adult population with type 1 diabetes, data on CSII in children and adolescents are still sparse. The few studies already conducted were mostly small and non-randomized, with a short duration of CSII use [27]. Studies comparing conventional

therapy with CSII (one or two injections per day and infrequent SBGM) generally showed better glycemic control with CSII [28,29], but those comparing MDI to CSII had contradictory results [16,30–34]. Boland and colleagues [31], in a parallel non-randomized study of 1 year duration, noted significantly better glycemic control and a decreased rate of severe hypoglycemia in adolescents using CSII, similar to the results of Kaufman et al. [32] who performed a short-term randomized crossover study using pumps only during the night. However, in a paired longitudinal study, Kaufman et al. [16] reported similar glycemic control in the CSII and MDI-treated patients, though with a decreased rate of severe hypoglycemia in the former. Maniatis et al. [33] and Raile et al. [34] failed to show any significant differences between the groups.

These discrepancies, combined with the lack of appropriate studies comparing the two modes of intensive therapy in young patients and the growing interest of patients and their families in pump therapy, prompted our group to conduct two open, randomized, crossover trials in children [20] and adolescents [23]. We evaluated CSII and MDI for glycemic control, incidence of hypoglycemia and hyperglycemia, dose requirements, weight gain, quality of life, and satisfaction. In the children, glycemic control and the rate of adverse events were similar for the two modalities. However, body mass index increased during MDI and did not change during CSII, and treatment satisfaction was greater with CSII. Comparing glycemic patterns by mode of therapy using the Continuous Subcutaneous Glucose Sensor (CGMS, MiniMed, Sylmar, CA, USA) in the same group of patients, we found that CSII use was associated with a smaller nocturnal area under the curve in the hypoglycemic range and a longer duration of within-target glucose tracings, with similar glycemic control to MDI [35]. In the adolescents [23], HbA1c decreased by 0.43% during CSII and increased by 0.1% during MDI; this difference did not reach statistical significance owing to the small number of subjects. Again, treatment satisfaction was greater with CSII. The rate of severe hypoglycemia was slightly lower during CSII for similar levels of glycemic control. Despite the increased rate of ketonuric events associated with CSII in both studies, diabetic ketoacidosis developed in only one adolescent subject during CSII therapy.

Studies have shown that most patients are highly satisfied with the pump because it affords them greater lifestyle flexibility and spares them the need for frequent injections [20,23,31]. Indeed, the rate of continuation with pump therapy in the pediatric population is 75–90% [16,20,23]. In our center, of the 200 children started on pump therapy 75% opted to continue with this mode (unpublished data).

Recently, glargine, a new longer-acting, peakless insulin analogue, was introduced as a basal insulin for MDI [36]. However, the results of comparisons between MDI with glargine and CSII were unclear. In one paired study of adults with type 1 diabetes, Lepore and associates [37] demonstrated that both CSII with Lispro and MDI with Lispro plus glargine equally improved metabolic control and reduced severe hypoglycemia compared to MDI with neutral protamine hagedorn (NPH) as the basal insulin. However, Boland et al. [38], using a randomized parallel design and a pediatric study

group, found significantly better improvement in glycemic control during CSII with the rapid analogue insulin, aspart, than during MDI with glargine and aspart.

### CSII for younger age groups

CSII has been shown to be a safe and effective mode of therapy also for toddlers and young children with type 1 diabetes [39], and even for infants with congenital diabetes. It is our impression, too, that infants, toddlers and very young children who have motivated and adherent parents benefit from CSII therapy. Their blood glucose profiles are smoother, parental fear of hypoglycemia is decreased, and management of sick days is easier. Clinicians should be careful to define different target glycemic ranges for infants (150–250 mg/dl), toddlers (120–200 mg/dl) and young children (100–180 mg/dl) compared to prepubertal and pubertal children, and the insulin dose should be adjusted accordingly.

### Cost-benefit

In most countries the cost of the pump itself and the monthly supplies is higher than the cost of conventional or MDI therapy. Therefore, health insurance to cover pump costs is essential for most diabetic patients. In our era of budget limitations and decreased health resources, this issue must be addressed by healthcare providers. Larger analyses of the long-term cost-benefits of CSII compared to other modalities of intensive control of both type 1 and type 2 diabetes in different age groups are still needed.

### Closing the loop

Current insulin pumps are based on an open-loop infusion system, where the rate of insulin infusion is not automatically adjusted to blood glucose levels. The patient has to decide on the basal infusion rate at different hours of the day and the amount of bolus insulin that should be given before each meal. In the future, with the development of accurate and fast-acting glucose sensors, we expect that the system will change to a closed-loop system. Efforts to connect the CSII device with a real-time glucose sensor have already been made in animal models and even in some human trials [40]. Operating together, the glucose sensors and insulin pumps will in effect serve as an artificial pancreas, mimicking the role of the pancreatic beta-cells and freeing the patient from the need for frequent daily SBGM and constant daily calculations.

### Summary

CSII is a feasible, safe and well-accepted mode of therapy for many children with type 1 diabetes. For a significant number of patients and parents, it serves as a much easier means of coping with the huge daily burden of diabetes. Therefore, we believe that both CSII and MDI should be made available to the diabetic team and the patients to better tailor therapy, improve satisfaction and decrease the fear of hypoglycemia.

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