Review Article
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Insulin Pump Therapy: Yesterday, Today and Tomorrow

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ABSTRACT

Historically, CSII therapy counteracted the peaking and short action of a long-acting human insulin through short-acting insulin in pumps obtaining stable and steady insulin levels between meals. As better short-acting insulins became available, the efficacy of CSII improved. Recently, the availability of long-acting and "peakless" insulins reduced the need for CSII. However, with the availability of accurate sensors utilized in a closed loop algorithm in combination with CSII has resulted in resurgence of CSII use. In the future the ability to utilize glucagon or even pramlintide infusions in combination with insulin infusion may result in even better glycemic control and greater use of CSII.

Keywords: *Insulin Pumps, Long Acting Insulin, Short Acting Insulin, Compliance, Convenience, Basal Bolus Therapy*

Yesterday

In the early 1980s two major events occurred which were to revolutionize insulin therapy in the type 1 diabetic patient. The first was that animal insulin was replaced with recombinant DNA human insulin and while this solved a supply problem, we were forced to utilize insulins that were inferior. The so-called long acting human insulins were not long acting, lasted less than 24 hours and most importantly showed excessively peaking. These insulins often peaked at times when short-acting insulins given as part of basal bolus therapy (BBT) were still active resulting in an increased frequency and severity of hypoglycemia (Bell, 2007).

The second significant event in the early 1980s was the general availability of Continuous Subcutaneous Insulin Infusion (CSII) or insulin pump therapy (Tamborlane *et al*., 1979). These insulin pumps only utilized short-acting insulin and as a result were able to maintain stable insulin levels between meals and when compared with BBT, the incidence and severity of hypoglycemia was decreased.

As enthusiasts in the 1980s, we were able to accumulate a large cadre of "pump patients" who we were able to study retrospectively. We were able to confirm that severe hypoglycemia

was less frequent on CSII than on BBT and that a therapeutic HbA1c, unobtainable on BBT, could be obtained with CSII without the risk of severe hypoglycemia (Bell *et al*., 1988).

Subsequently, even better short-acting insulins than buffered human regular insulin that was the initial insulin used in CSS became available. These newer insulins (aspart and lispro) when used in CSII equally lowered the HbA1c and when compared with buffered human regular the lowering of the HbA1c was greater with both lispro and aspart. However, insulin aspart was the insulin that showed the lowest incidence of hypoglycemia and because of this became our preferred insulin for use with CSII (Bode *et al*., 2002). Subsequently, from one of our practices, we were able to show that compared with BBT, CSII utilizing lispro insulin over three years decreased the HbA1c from 8.4% to 7.7% (Bell and Ovalle, 2000). Later continuous glucose monitoring (CGM) became available which further improved the efficacy of CSII and almost "closed the loop" (Grunberger *et al*., 2018).

Today

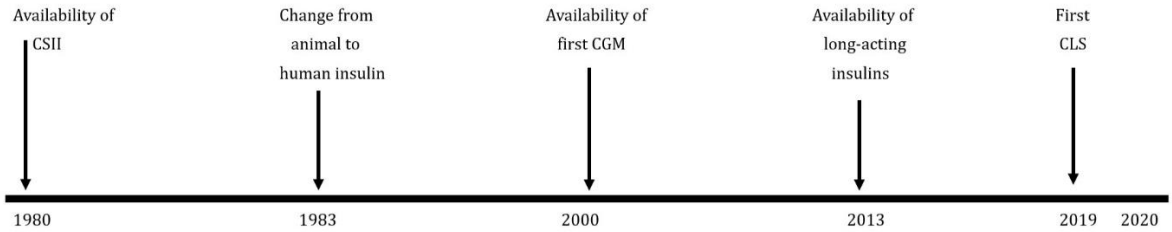
Thus, from the late 1990s, we recommended to all patients with type 1 diabetes that ideally, they should be treated with CSII, and since 2010 have advocated for the addition of CGM to CSII.

For patients who did not desire to be attached to two systems and who asked which system we would recommend we always recommended CSII with the exception of those who exercised a lot or who had manually intense occupations where we recommended CGM. This recommendation was changed with the availability of the COMISAIR study which showed that in type 1 diabetic patients the improvements in both HbA1c and the reductions in the frequency and severity of hypoglycemia was driven by CGM rather than by the route of insulin delivery (Soupal *et al*., 2016). This raised the question of whether BBT, in combination with CGM would decrease the need for the use of CSII in the type 1 diabetic subject.

In practice, we have always tried to give patients regular pump rests to preserve their ability to absorb subcutaneous insulin (Berg *et al*., 2018). Historically many have refused to participate in these pump rests and in those who did participate the vast majority returned to CSII either before or at the designated time of the completion of the pump rest. Their reasons for returning to CSII were almost invariably the deterioration in glycemic control and/or an increase in the frequency and severity of hypoglycemia that occurred with BBT.

However, with the availability of non-peaking ultra-long-acting insulins, particularly insulin degludec, with its low day-to-day variability in insulin levels, we began to see that many patients chose

not to return to CSII because during these pump rests there was no change or even a positive change in both the HbA1c and the frequency and severity of hypoglycemia (Marso *et al*., 2017; Wysham *et al*., 2017). Recently, in an in house quality audit of these pump rest patients, we documented that of the last 20 patients embarking on a "pump rest" with degludec and aspart insulins utilized in BBT only one returned to CSII even though in that patient the HbA1c was lower with no severe hypoglycemia. Prior to the pump rest severe hypoglycemia was a major problem for this patient and resulted in a loss of driving privileges (Fig. 1).



Evolution of therapy of type 1 diabetes

CSII = Continuous Subcutaneous Insulin Infusion
CGM = Continuous Glucose Monitoring
CLS = Closed loop basal insulin delivery utilizing CGM and CSII

Figure 1: Schematic representation of Evolution Therapy of Type 1 Diabetes

Of the twenty patients who did not return to CSII the average age was 50.2 years (SD ±12.9) with a range of 23 to 68 years. All had documented type 1 diabetes with an average duration 30.1 years (range 11 to 58 years, SD ±12.6). Eleven had documented asymptomatic or mildly symptomatic distal symmetrical polyneuropathy, seven had retinopathy (three proliferative), five had ischemic heart disease, three had nephropathy and three had cataracts. The HbA1c on average dropped significantly (p= 0.002) by 0.71% from 8.19% (SD ± 1.13) to 7.48% (SD ±0.75) with the majority (thirteen of the 20 patients) achieving a lower HbA1c. There was also a non-significant weight gain from 199 to 201 pounds (p= 0.37) with 12 subjects gaining weight and eight subjects losing weight. Since all subjects were on continuous glucose monitoring while on and off CSII there were very few symptomatic hypoglycemic events.

Therefore, the efficacy of the combination of continuous glucose monitoring and long acting "peakless" insulins raises the question of whether the expense of CSII is presently justified in most type 1 diabetic patients. However, due to the emergence of "smart" insulin pumps which have the capability to be combined with rapidly improving continuous glucose monitoring systems effectively closing the loop are now increasing rather than decreasing the use of CSII. These pumps operate almost autonomously and effectively "close the loop" and are increasing rather than decreasing the use of CSII.

Tomorrow and The Near Future

Currently used and soon to be widely utilized, are the hybrid closed-loop systems with automated insulin delivery driven by CGM. The prototype system which became available in 2009 combined the Paradigm Revel insulin pump with continuous glucose monitoring and management software which had the capability to predict both hyperglycemia and hypoglycemia as long as thirty minutes before an event occurred which resulted in better glycemic control compared with BBT (Slover *et al*., 2012). An extension of this therapy was the addition of the ability to suspend insulin delivery based on low glucose levels. This was assessed in the ASPIRE study where the frequency of nocturnal hypoglycemia was reduced without a significant change in the HbA1c (Weiss *et al*., 2015). The ability to suspend insulin infusion with hypoglycemia was later augmented by the ability to increase basal insulin infusion when hyperglycemia occurred utilizing the MiniMed 670G which was approved in 2017 in the USA (Messer *et al*., 2018). However, currently with this system both patients and medical personnel are frustrated by the need for three daily calibrations which usually results in a lesser time "in range" and less time in the auto mode. In addition, the accuracy of the sensor utilized by this system is inferior to Dexcom (Kravarusic and Aleppo, 2020).

A more accurate sensor (the Dexcom G6) is utilized with a hybrid closed-loop algorithm in the T-Slim x2 insulin pump. This combination results in automated corrections of basal insulin to accommodate both hypoglycemia and hyperglycemia and safely and gradually intensifies overnight glycemic control. In addition, hypoglycemia is predicted with an alarm and calibration is not necessary (Brown *et al*., 2018).

In the near future the MiniMed 780G pump will be able to provide correction boluses, adjust for missed meals and allow for lower glucose targets. This system also extends the time in range resulting in a lower HbA1c (Duffus *et al*., 2020). Newer systems also hope to incorporate automatic mealtime insulin boluses. In addition, combinations of glucagon and insulin or pramlintide and insulin in pumps combined with continuous glucose monitoring are being developed (El-Khatib *et al*., 2017; Haidar *et al*., 2020).

Conclusions

CSII revolutionized insulin therapy by utilizing only short-acting insulin so that steady basal insulin levels were maintained between meals, lessening the frequency of hypoglycemia and lowering the HbA1c to levels that could not be obtained with BBT or other insulin therapies in the type 1 diabetic patient. With shorter-acting insulins the efficacy of CSII improved due to decreases in HbA1c and rate of hypoglycemia. However, with the availability of peakless long-acting insulins the advantage of CSII over BBT diminished. There has been a resurgence in the utilization of CSII due to the availability of

systems where CSII is utilized in combination with CGM and closed loop algorithms so that hypoglycemia and hyperglycemia are corrected automatically by varying the basal insulin rate.

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