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Review

Modern clinical management helps reducing the impact of type 1 diabetes in children

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ABSTRACT

Type 1 diabetes care may be very costly not only in terms of money but also in terms of psychological and therapeutic acceptance and compliance. Recently, a lot of new technologies have been introduced in the care of patients with type 1 diabetes that should allow them to achieve an improvement in glycemic control, quality of life and above all prevent long-term complications.

Combining continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion (CSII) provides a more useful tool for patients with type 1 diabetes, the sensor-augmented pump (SAP). The aim of the present review is to explore SAP efficacy and safety in young patients with type 1 diabetes. SAP demonstrated increased efficacy in lowering glycated hemoglobin when compared either to multiple daily injections or CSII alone. Its efficacy is positively associated with CGM use, baseline HbA1c and patients' age. According to currently available evidence, SAP seems sufficiently safe, effective and beneficial in improving glycemic control in pediatric patients with type 1 diabetes. Moreover, encouraging results using semi-closed loop systems are emerging, paving the way toward a fully automated artificial pancreas. As pediatric diabetologists we have the duty to offer our patients the best therapeutic option currently available, supported by evidence, to help them gain the best results with the fewest adverse effects (hypoglycemia and/or diabetic ketoacidosis), better if chomping a little piece of dark chocolate.

Contents

1. Introduction

Diabetes mellitus is one of the most common chronic diseases in the world, and continues to increase in numbers and significance [1]. Individuals with diabetes suffer from high morbidity and mortality rates due to complications that could be prevented with intensive therapy. The Diabetes Control and Complications Trial

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confirmed that tight metabolic control is regarded as crucial to prevent microvascular and macrovascular complication in type 1 diabetic patients [2].

Insulin remains the lifesaving treatment for type 1 diabetes and is also required by many patients with type 2 diabetes.

However, despite the recent advances in diabetes management, including the new long- and rapid-acting insulin analogs and insulin intensification strategies such as basal/bolus or insulin pump therapy, at least 50% of the type 1 diabetes patients in pediatric age exhibits poor glycemic control and fails to reach or maintain target glycosylated hemoglobin (HbA1c) values, putting them at increased risk for vascular complications [3].

Observational studies have clearly linked the quality of glycemic control (expressed as HbA1c) with the frequency of daily self-monitored blood glucose (SMBG) tests in insulin-treated patients [4]. Usually, type 1 diabetes patients carry out between 4 and 8 finger-prick measurements per day, or less, and rarely monitor their blood glucose level at night. This is the cause of overlooking blood glucose excursion, and possibly postprandial hyperglycemia, asymptomatic hypoglycemia, and glucose fluctuation during the night.

In the last several years, continuous glucose monitoring (CGM) has developed as a major technological help that can provide detailed information on glucose patterns and trends, thus allowing the diabetes team, and especially the patient, to manage diabetes more effectively.

Combining CGM and continuous subcutaneous insulin infusion (CSII), a now well-established way to insulin delivery [5], provides a more useful tool for patients with type 1 diabetes, the sensor-augmented pump (SAP). Adding CGM to CSII arrange for an even better insight into glycemic profiles, which can have many benefits both in patients in poor glycemic control than in those with frequent severe hypoglycemia.

The aim of the present review is to explore SAP efficacy and safety in pediatric patients with type 1 diabetes.

2. Glycemic control

The system uses a wire-type glucose sensor implanted in the subcutaneous tissue to monitor the glucose concentration of interstitial fluid in people with type 1 diabetes. Early CGM systems were first introduced in 1989, only providing data for brief periods for retrospective analysis and review of glucose traces. This allowed healthcare professionals to advice on changes in therapy. These devices were quickly followed by real-time CGM (RT-CGM) systems for personal daily use by patients at home, providing information on direction, magnitude, frequency and duration of glycemic oscillations on a moment to moment basis to aid control of diabetes by patients themselves.

Great effort has been expended over the past years to determine the effectiveness of CGM in allowing a greater proportion of type 1 diabetes patients to achieve and maintain target HbA1c levels without increasing the risk of severe hypoglycemia. Evidence from randomized controlled trials for the effectiveness of continuous glucose monitoring at improving glycemic control compared with SMBG has recently appeared. In these studies the mean reduction in HbA1c percentage with CGM vs. SMBG has ranged from about 0.1% to 0.6%, depending on age [5] and percentage of time wearing CGM, with the best HbA1c reduction when using the CGM for more than 70% of the time [6–8]. In 2006, the Guard Control Study conducted in 161 patients including 81 adults with poor metabolic control (HbA1c > 8.1%) evaluated the impact of CGM worn intermittently (3 days every 2 weeks) or continuously. Compared with the control group, the group with consistent CGM using obtained a 0.6% HbA1c decrease after 3 months, while no benefits was obtained by the group wearing sensors only intermittently [6]. In the study of Hirsh et al. [7], a sensor usage of more than 60% of the time was associated with a significant HbA1c reduction ($p = 0.046$). In 2008, the JDRF CGM controlled trial (RCT) showed that adults with type 1 diabetes had a greater reduction in HbA1c levels with use of RT-CGM and SMBG than with SMBG alone [5]. At 6 months the same study demonstrated in patients using RT-CGM system a greater HbA1c decrease (−0.53%, $p < 0.001$) when compared to controls, confirming that compliance with the device usage correlated with its effectiveness. Furthermore, after 12 months, the same study confirmed an HbA1c level reduction of −0.4% from baseline ($p < 0.001$) and a median CGM usage of 6 days or more per week [8]. The JDRF study examined also the impact of CGM in 114 children over 8–12 years and 110 adolescents 13–18 years with basal HbA1c level greater than 7%. After 6 months of use, the HbA1c reduction was modest (−0.2 to −0.3%) in children wearing the CGM when compared to the control group. Nevertheless, those who wore the CGM device 6–7 days per week during the first 6 months of the study showed a HbA1c levels decrease of 0.8% without any increase in hypoglycemia [5]. Unfortunately only 21% of the pediatric cohort maintained a frequent use of sensor for the whole study period (12 months), and those that reverted to less frequent sensor usage during the second 6 months of the study lost the HbA1c benefits observed in the first 6 months [8].

3. Sensor-augmented pump

O'Connel et al. conducted a study to assess the impact of sensor-guided pump management on glycemic control compared with standard insulin pump therapy. The study showed an improvement in HbA1c levels (−0.43%) only in the SAP group and not in the group using insulin pump only [9]. When the sensor usage was more than 70% of the time, HbA1c improvement was even higher (−0.51% vs baseline) [9]. The RealTrend study, conducted both in children and in adults, assessed the impact of CGM use in poor metabolic controlled patients (HbA1c ≥ 8%). After switching to insulin pump therapy at the start of the study, after 6-month follow-up, a significant decrease in HbA1c (−0.68%, $p < 0.001$) was observed in those patients who wore the device >70% of the time in comparison with the ones who used the sole insulin pump [10].

The largest and longest SAP RCT study to date (STAR 3 Study), confirmed the advantage when using the SAP when compared to multiple daily injections, and showed its long term beneficial effect over a 12 months study period [11]. The study involved children, adolescents and adults with type 1 diabetes. In the SAP group, pump therapy was started first and RT-CGM initiated 3–4 weeks later. After 3 months a clinically and statistically significant decline in HbA1c levels was observed in the SAP group compared to MDI group (7.5% vs. 8.1%, $p < 0.001$), with no differences among groups (children, adolescents and adults). Furthermore, the glycemic improvement observed was maintained 1 year later. The percentage of patients reaching a recommended HbA1c target <7% (American Diabetes Association), was significantly greater in the SAP group than in the MDI group (27% vs. 10%, respectively).

Hermanides et al. [12] compared the efficacy of SAP therapy compared to multiple daily injections in adult patients with poorly controlled type 1 diabetes. The study randomized 83 patients, aged 18–65 years (with HbA1c ≥ 8.2%) to 26 weeks of treatment with either SAP therapy or multiple daily injections. Mean difference in HbA1c change after 26 weeks was −1.21% (7.2% vs. 8.5%, $p < 0.001$) in favor of the SAP therapy group. Noteworthy, the glycemic improvement observed was not accompanied by an increase in the number of hypoglycemic episodes.

The Onset Study [13] evaluated the impact of initiating SAP vs. pump-only therapy at the onset of diabetes in 160 children and