Long-term Benefits in Emergency Admissions, Hospitalization and Metabolic Control of an Integrated Continuous Glucose Monitoring and Insulin Pump System in a Cohort of Diabetic Patients

Miguel Augusto O´Meara
Compensar Salud: Compensar EPS  https://orcid.org/0000-0002-8345-6155

Juan Camilo Mateus (✉ jcmatteus@gmail.com )
Fundacion Cardi infantil Instituto de Cardiologia  https://orcid.org/0000-0001-6645-5022

Andrea Uribe
Compensar Salud: Compensar EPS

Research Article

Keywords: automated insulin delivery, continuous glucose monitoring, glycemic control, hypoglycemia, sensor-augmented insulin pump, type 1 diabetes

Posted Date: September 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1688540/v2

License: ☺  This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: There is evidence in the literature that the use of sensor-augmented insulin pumps in patients with type 1 diabetes improves metabolic control. However, there is no long-term information on clinical outcomes such as hospitalization or admission to the emergency room.

Our paper describes the outcomes of metabolic control, incidence of hospitalizations and emergency room visits in a Colombian population using this technology.

Methods: A retrospective cohort study was carried out in patients with diabetes previously treated with an intensive insulin regimen at a specialized diabetes treatment center in Bogotá, Colombia, who required sensor-augmented insulin pumps due to poor metabolic control despite optimization of medical management. Glycated hemoglobin, severe hypoglycemic episodes, non-severe hypoglycemic episodes, perception of hypoglycemia, and the incidence of emergency room visits and hospitalizations before and after treatment were evaluated.

Results: Sixty-four patients with a median age of 36 years (interquartile range 27-46) were included in the study. We found statistical reduction of glycated hemoglobin (8.35% vs. 7%), non-severe hypoglycemic episodes (95.9% vs. 87.7%), emergency room visits (57.5% to 6.45%) and hospitalization (50% vs. 13.79%) in patients using CSII.

Conclusions: The use of sensor-augmented insulin pumps coupled with a strict follow-up program for patients with type 1 diabetes leads to a significant and sustained reduction in glycated hemoglobin and hypoglycemic episodes, as well as in the rate of emergency room visits and hospitalizations. These results encourage the adoption of this technology in patients who do not achieve metabolic control with optimal management of type 1 diabetes.

Background:

An estimated 537 million people worldwide have diabetes, and it is projected that by 2045, more than 783 million people will have the disease (a prevalence of 12.2%) [1]. Consequently, the incidence and prevalence of type 1 diabetes (T1D) are growing every year. The management of this condition has been a challenge due to the complete lack of insulin leading to high glucose fluctuations. To have adequate care for this condition, patients require education on diabetes, dietary advice, knowledge on counting carbohydrates, application of multiple daily insulin injections (MDIs), including dosage adjustment. At times, the use of sensor-augmented insulin pump (SAP) therapy, combines continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) is fundamental to achieve glucose targets.

The current American Diabetes Association (ADA) and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend the therapeutic objectives of glycated hemoglobin (A1C) < 7% in most patients or < 7.5% or < 8% depending on the risk of hypoglycemia, access to technology or ability to
manage their condition [2, 3]. In addition, there is already ample evidence of the limitations of using A1C as the only guide for managing diabetes. The lack of information regarding intra- and inter-daily glycemic excursions and the complications derived from hyper- and hypoglycemia are some of the reasons for considering other tools for managing diabetes [4–6].

With recent advances over the last few years, such as better safety profiles in insulin pharmacokinetics and new diabetes devices, the risk of hypoglycemia has been reduced, and better A1C goals have been reached [7–12]. Thus, the knowledge and adjustment of treatment based on continuous glucose monitoring metrics (time in range, time below range, time above range and coefficient of variation) have led to their widespread use and have allowed better metabolic control in patients, reducing hypoglycemic episodes [13–17].

As a result, the quality of the programs is vitally important, both for the care and management of these patients, to achieve adequate metabolic control, to prevent micro- and macrovascular complications, as well as hypoglycemic episodes, emergency room visits and hospitalizations.

Although there is evidence of the benefit of CSII therapy in glycemic control [18–20] and the reduction of hypoglycemia [14, 21], other studies have not demonstrated the usefulness of this type of therapy [22, 23], and there is scant evidence of their long-term benefit in reducing emergency room visits and hospitalizations [24].

The objective of our study was to evaluate the long-term effects of SAP therapy in patients at a specialized diabetes care center who use this type of technology. we present a retrospective longitudinal study with a median four-year follow-up.

**Materials And Methods:**

**Design and participants:** This was an analytical, retrospective observational study designed to evaluate the long-term effect of the use of SAP on clinical outcomes and metabolic control after the admission of diabetic patients to a specialized care program using this type of technology at a healthcare insurance company in Bogotá, Colombia. The study was approved by the local ethics committee.

The inclusion criteria were patients over the age of 18 years with a diagnosis of type 1, type 2, or another type of diabetes, in basal-bolus insulin regime, referred by endocrinology due to poor metabolic control (A1C > 7% and hypoglycemia values < 70 mg/dl) despite optimal treatment and diabetes Self-Management Education and Support (DSMES), which was defined as adequate use in: insulin self-titration, frequent glucose monitoring (at least 4 a day), self-management of hypoglycemic episodes and education in carbohydrate counting based on international and local guidelines for T1D management[25–27].

All patients prior to SAP therapy were using insulin analogs (long-acting insulin glargine U100/mL and fast-acting insulin (lispro, aspart or glulisine) and after 2017 second-generation basal insulin (insulin
The patients used SAP from the time of their admission to the program following the consensus statement of insulin pump management task force [28, 29]. The data was collected from that point and recruited from 2013 until November 2020. No patients were excluded, given the specific focus of the program in which they participated.

The primary outcome of the study was to evaluate the clinical and glycemic control, including changes in glycemic control, severe hypoglycemic episodes (SH), non-severe hypoglycemic episodes (NSH), and number of hospitalizations or emergency room visits prior to beginning the program and during follow-up in the insulin pump program.

All the study participants used an insulin pump (Paradigm VEO, Medtronic MiniMed 640G and 670G, Inc., Northridge, CA) and real-time continuous glucose monitoring (Enlite or Guardian Link 3, Medtronic, Northridge, CA). They were encouraged to perform SMBG at least six times per day and sensor calibration 3–4 times per day. The patients were re-educated in carbohydrate counting, management of hypo-hyperglycemic episodes and infusion set changes every three days.

The data were obtained from a chart review, the insurance company’s database with their affiliated hospitals, and direct patient surveys. The assessment of adherence to treatment and the measurement of variables related to insulin pump use were reviewed through the Care-Link Medtronic system software. We used the Gold scale as an assessment tool for hypoglycemia, with lower values indicating a greater perception of hypoglycemia and higher values reflecting a total loss of its perception [30].

To minimize bias, the data were independently reviewed by one of the authors to assess biologically implausible or lost data.

**Statistical analysis:**

The categorical variables were analyzed through absolute and relative frequencies. The Kolmogorov-Smirnov test was used to evaluate the normality of numerical variables. Parametric data are expressed as the mean and standard deviation, while nonparametric data are reported as medians and interquartile range (IQR).

Changes in variables over time were evaluated with Student’s T test for paired data or the McNemar test for categorical variables. The Wilcoxon test for paired data and Friedman’s test were used for nonparametric data.

**Results:**

**Patient characteristics:**
Seventy-four patients using SAP were analyzed between January 2013 and August 2020. There were no losses to follow-up, and all the patients were included in the data analysis.

The median age was 36 years (IQR 27–46). The body mass index (BMI) was 24.3 (IQR 22.7-27.19). Of the total population, 41 (55%) were female, and most had a diagnosis of T1D (71; 95%), with 20 years since diagnosis (IQR 14–33). The median number of years of follow-up using the SAP was four years (IQR 2–7). Altogether, 85.1% of the patients had poor metabolic control, with a median A1C of 8.35% (IQR 7.3–9.8.) The baseline demographic and clinical characteristics are shown in Table 1.

The hospitalization and emergency room visit rates prior to SAP therapy were 0.5 events per patient-year (IQR 0.5-1.0) and 1.0 events per patient-year (IQR 0.5-2.0), respectively. All had a history of hypoglycemic episodes with an NSH rate of 20 events per patient-year (IQR 11–35) and an SH rate of 1.5 events per patient-year (IQ 1–6), with a Gold score of 4 (IQR 2–4) and the mean total daily insulin dose was 52.5 ± 21.9 international units (IU) prior to treatment.
Table 1
Baseline patient characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>31 (45%)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (55%)</td>
</tr>
<tr>
<td>BMI, Median (IQR)</td>
<td>25 (22.7–27.2)</td>
</tr>
<tr>
<td>Age in years, Median (IQR)</td>
<td>36 (27–46)</td>
</tr>
<tr>
<td>T1D, n (%)</td>
<td>71 (95%)</td>
</tr>
<tr>
<td>T2D, n (%)</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Diabetes, other, n (%)</td>
<td>1 (1.35%)</td>
</tr>
<tr>
<td>Diabetes years, median</td>
<td>20 (14–33)</td>
</tr>
<tr>
<td>Total daily insulin doses, Mean (SD)</td>
<td>52.5 ± 21.9 IU</td>
</tr>
<tr>
<td>Type of pump:*</td>
<td></td>
</tr>
<tr>
<td>Paradigm VEO</td>
<td>6 (8.82%)</td>
</tr>
<tr>
<td>Minimed 640</td>
<td>36 (52.96%)</td>
</tr>
<tr>
<td>Minimed 670</td>
<td>26 (34.24%)</td>
</tr>
<tr>
<td>A1c, Mean (SD)</td>
<td>8.8% (2.7)</td>
</tr>
<tr>
<td>A1c, Median (IQR)</td>
<td>8.35% (7.3–9.8)</td>
</tr>
<tr>
<td>Gold, Median (IQR) +</td>
<td>4 (2–4)</td>
</tr>
<tr>
<td>Non-severe hypoglycemic episodes, EPY</td>
<td>20 (11–35)</td>
</tr>
<tr>
<td>Severe hypoglycemic episodes</td>
<td>1.5 (1–6)</td>
</tr>
<tr>
<td>Hospitalization rate, EPY</td>
<td>0.5 (0.5-1.0)</td>
</tr>
<tr>
<td>Emergency room visit rate, EPY</td>
<td>1.0 (0.5-2.0)</td>
</tr>
</tbody>
</table>

A1C, glycated hemoglobin; BMI, body mass index; IQR, interquartile range; EPY, events per patient-year; T1D, type 1 diabetes; T2D, type 2 diabetes; IU, international units; SD, standard deviation.

* Type of pump initiated from the follow-up.

+ Gold scale, assessment tool for hypoglycemia

**Metabolic control**

At the established cut-off point for analysis, A1C decreased to 7.0% (IQR 6.5–7.4) compared with the initial figure of 8.35% (p = 0.0001). The percentage of patients with A1C less than 7% prior to treatment
was 14.5%, and at the end of follow-up, it increased to 40.6%, \( p = 0.0001 \).

At the end of follow-up, the median time in range (TIR) was 75.5% (IQR 70-80.5), with 21% time above 180 (TIR > 180) (IQR 15–29%) and 3% time below 70 (TIR < 70) (IQR 1–3).

**Hypoglycemic episodes**

There was a statistically significant decrease both in the rate of NSH episodes as well as in the percentage of patients with at least one episode in the last year, going from 20 episodes per patient-year (IQR 11–20) to four episodes per patient-year (IQR 2–7) \( p = 0.001 \) and from 95.9–87.7%, \( p = 0.0142 \), respectively (\( OR = 0.91 \ [95\% \ CI \ 0.083–0.99] \)).

Severe hypoglycemia, expressed in rates and percentage of episodes in the last year, decreased from 1.5 episodes per patient-year (IQR 1–6) to 0.5 (IQR 0.31–0.5), \( p = 0.137 \), and from 28.3–14.3%, \( p = 0.14 \), respectively, but without statistical significance.

An assessment of the Gold scale changes before and after beginning SAP therapy showed a score reduction from 4 (IQR 2–4) to 2 (IQR 1–3), \( p = 0.0001 \). Likewise, the percentage of patients with a score of 4 or less prior to using this technology increased from 75–87% (\( p = 0.0001 \)).

**Emergency room visits and hospitalization**

Significant differences were found before and after the use of SAP therapy in terms of reduced hospitalizations, with an initial rate of 0.5 events per person year (IQR 0.5-1) decreasing to 0.266 events per patient-year (IQR 0.16–0.667), \( p = 0.004 \). The percentage of patients requiring hospitalization (during the last two years) was 50% prior to and 13.79% after beginning therapy (\( p = 0.0001 \) (\( OR = 0.23 \ [95\% \ CI \ 0.001–0.58] \)).

Likewise, prior to beginning SAP therapy, 57.5% of the patients had to be admitted to the emergency room, and at the end of the study, 6.45% of them had to be admitted, \( p = 0.0001 \) (\( OR = 0.11 \ [95\% \ CI \ 0.01–0.83] \)). Emergency room visits went from one event per person year to 0.5 events per person year, \( p = 0.0022 \). Table 2.
Table 2
Follow-up of the variables related to glycemic control

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of followup</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%) SD</td>
<td>8.35</td>
<td>7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>28.3</td>
<td>14.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-severe hypoglycemia</td>
<td>95.9</td>
<td>87.7</td>
<td>0.0142</td>
</tr>
<tr>
<td>Gold +</td>
<td>4</td>
<td>2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>57.5</td>
<td>6.45</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>50</td>
<td>13.79</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

A1C, glycated hemoglobin

+ Gold scale, assessment tool for hypoglycemia

**Discussion:**

The most relevant result of this study is the long-term (four-year) benefit of a reduction in hospitalizations and emergency room visits, in addition to better metabolic control, with the use of SAP. Many publications [19, 20, 24, 31–33] have shown that SAP therapy has clinical and glycemic benefits in patients not controlled with a basal-bolus regimen. Prior studies, such as Gómez et al. [21], have shown A1C reductions with SAP from 8.8% +/- 1.9–7.5% +/- 1.0% at five months (mean difference − 1.3%; 95% CI -1.09 to -1.50; p < 0.001) and 7.1% +/- 0.8% (mean difference − 1.7%; 95% CI -1.59 to -1.90; p < 0.001) after 47 months of follow-up. Likewise, the incidence of SH decreased significantly from 66.6–2.7% (p < 0.0001). Ramirez-Rincon et al. [24] in addition to A1C reduction (from 8.7% +/- 1.7–7.4% +/- 0.8% [p < 0.05]), found a decline in hospitalizations from 16.5–6.0% (p < 0.05), as well as a reduction in the incidence of SH from 32–7.1% at one year of follow-up.

However, there are some studies that show no benefit in metabolic control with the use of this type of technology. Blair et al. [23] found no A1C reduction or cost effectiveness in using CSII compared with MDI (CSII, 7.72% [95% CI 7.5–7.94%]; MDI, 7.5% [95% CI 7.28 to 7.72%]. However, this study evaluated the results of patients from 7 months to 15 years old. The outcomes were examined at patients with a de novo T1D diagnosis and analyzed within the first year of the disease. This protocol makes it difficult to observe the benefit or difference between therapies due to complex glycemic control and known limitations in the pediatric population [34]. The glycemic and pathophysiological behavior of T1D in this age group, especially in the first year after diagnosis [35, 36], may have masked the differences that could be seen in patients with a medium- to long-term duration of the disease. Bolli et al. [22] found no differences between the use of MDI or CSII. The mean A1C reduction was similar in both groups: CSII − 0.7 +/- 0.7%; MDI − 0.6 +/- 0.8%, with an adjusted difference of 0.1% (95% CI 0.5–0.3). However, the patients had previously used NPH insulin and were randomized to the glargine insulin regimen or CSII.
The design of this study limits the ability to find differences between the groups, as long-acting insulin should be the standard treatment today, not a comparative alternative to CSII. The indication to initiate CSII should be in patients with untargeted glycemic control or persistent hypoglycemic events after using a basal-bolus regime with second-generation and rapid-acting insulin [28, 29, 37].

It should be noted that only a fraction (but an ever-growing fraction) of patients with T1D will require devices for measuring interstitial glucose and/or administering insulin in addition to the standard MDI + SMBG management to achieve metabolic control and avoid hypoglycemic episodes [38, 39].

In our study, the patients had been diagnosed with T1D for an average of 20 years and had poor metabolic control with MDI despite having complete diabetes training, including the technique for applying and self-titrating insulin, carbohydrate counting, management of hypoglycemia and the use of second-generation insulin analogues, as a recommendation of T1D international and local guidelines management [25–27]. This is vitally important because in our population, SAPs are used as a step-up treatment only when the metabolic control goals are not met despite interdisciplinary and specialized management and not as an alternative treatment in patients who will potentially be controlled through optimized management with education and training in disease management.

One of the advantages of our study is that the majority of the patients used recent insulin pump models, which in other publications have been shown to be beneficial in reducing hypoglycemic episodes and A1C [40, 41]. Bolli et al.’s study [22] was performed using the MiniMed 508 model, which did not have technologies such as the bolus wizard. The latter is useful for estimating the bolus dose using a calculation of the insulin-to-carbohydrate ratio, the insulin sensitivity factor, the target blood glucose and active insulin. The most recent devices allow more stringent targets to be pursued, reducing the risk of hypoglycemia and the coefficient of variation [42].

The main limitation of this study is its retrospective character. Several data were taken from the chart review and the insurance company’s database and others from patient surveys, which may lead to various types of bias.

Another limitation of our study is the lack of a control group without SAP therapy. However, given the type of population to which we had access in this program, it was not possible to include patients without this technology and carry out long-term follow-up.

Conclusion:

This study is the first to evaluate the safety, clinical and glucose benefits of using SAP therapy in a population with T1D, with real-life data and long-term follow-up. The use of this technology for an average of four years led to a significant A1C reduction and achievement of A1C goals and a lower number of NSH episodes, emergency room visits and hospitalizations. These results promote the adoption of this technology in patients who do not achieve metabolic control with optimal care of T1D. It should be noted that its efficacy requires a multidisciplinary team with experience in the use of this...
technology and close patient support. Finally, we recommend carrying out experimental studies to compare this technology with other therapies.

**Abbreviations:**

(SAP) sensor-augmented insulin pump, (A1C) glycated hemoglobin, (SH) severe hypoglycemia, (NSH) non-severe hypoglycemia, (T1D) type 1 diabetes, (T2D) type 2 diabetes, (IQR) interquartile range, (MDI) multiple daily insulin injections, (CSII) continuous subcutaneous insulin infusion, (CGM) continuous glucose monitoring, (ADA) American Diabetes Association, (ISPAD) International Society for Pediatric and Adolescent Diabetes, (BMI) body mass index, (TIR) time in range from 70 – 180 mg/dl, (TIR > 180) time above 180 mg/dl, (TIR < 70) time below 70 mg/dl, (SMBG) self-monitoring of blood glucose.

**Declarations:**

**Ethics approval and consent to participate:** This study was approved by the ethical committee of Fundacion Cardioinfantil – Instituto Cardiologia.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** This paper was supported by the Asociación Colombiana de Endocrinología [Colombian Association of Endocrinology].

**Authors’ contributions:** Concept and design: MO and JCM. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: MO and JCM Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: MO. Supervision: AU. All authors read and approved the final manuscript.

**Acknowledgements:**

To Nora Londoño, administrator of the specialized health service; Hercy Lopez and Natalia Gelvez, nurses in the Compensar EPS high-complexity diabetes program; and Luz Adriana Quintero, Compensar EPS care model professional.

Special thanks to Jorge Cárdenas M. D, MSc for his advice in drafting the study protocol.

We would like to thank Fundación Cardioinfantil and its research committee for their support in reviewing and evaluating the protocol and ethical aspects of the study.
References:


