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Effect of Sensor-Augmented Patch Pump with Predictive Low-Glucose Suspend Feature Compared to Multiple-Dose Insulin in Patients with Brittle Type 1 Diabetes

ABSTRACT

Objective: The conventional approach to brittle diabetes is the treatment of underlying causes and optimization with multiple-dose insulin injections. The goal of multiple-dose insulin therapy is to exactly mimic physiological insulin secretion; however, it often results in hypoglycemia. This study investigates the effectiveness of continuous subcutaneous insulin infusion therapy with a patch pump with the sensor augmented with predictive low-glucose suspend algorithm system in patients with uncontrolled type 1 diabetes who were treated with multiple-dose insulin and have high glycated hemoglobin values.

Methods: The data of patients whose glycemic control could not be achieved with multiple-dose insulin therapy and who were switched to sensor-augmented tubeless pump with predictive low-glucose suspend feature (Medtrum A7+ TouchCare patch pump and integrated A7+ continuous glucose monitoring system) were analyzed retrospectively.

Results: A total of 16 patients (male: 9; 56.3%) were included. After 3 months of the sensor-augmented pump with predictive low-glucose suspend treatment, patients' median (interquartile range) glycated hemoglobin level decreased to 7.55 (1.43) from 9.20 (3.55) ($P = .008$). Time below 56 mg/dL was 0.34%, time between 56 and 70 mg/dL was 1.01%, time between 70 and 180 mg/dL was 72.90%, time above 180 mg/dL was 25.67%, time between 70and 250 mg/dL was 95.98%, and time above 250 mg/dL was 2.76%.

Conclusions: A pump system with predictive low-glucose suspend feature improves glycemic targets in patients with brittle uncontrolled type 1 diabetes without the expense of hypoglycemia compared to multiple-dose insulin treatment.

Keywords: Predictive low-glucose suspend, multiple-dose insulin, brittle diabetes

Introduction

Brittle diabetes is one of the most difficult types of diabetes physicians have to treat. It presents with high glucose variability with frequent fluctuations in blood glucose and unpredictable attacks of severe hyperglycemia or hypoglycemia.[1] It can also present with recurrent diabetic ketoacidosis, wide glycemic excursions, serious hyperglycemia, or severe hypoglycemia.

The main causes of brittleness include depletion of endogen insulin reserve, insufficient or excessive activation of counter-insulin hormones, defects in the absorption of carbohydrates, and delayed gastric emptying. Also, malignancy/chemotherapy, systemic infections, steroid use, and so on cause the management of diabetes to be difficult.[2]

The conventional approach to brittle diabetes is the treatment of underlying causes and optimization with multiple-dose insulin (MDI) injections. Guidelines recommend the administration of multiple doses of intensive insulin to prevent hyperglycemic attacks. The goal of MDI therapy is to exactly mimic physiological insulin secretion. Although pancreatic pulsatile insulin secretion is limited to short intervals such as 8-10 minutes,[3,4] in exogenous MDI therapy, the injection intervals are 4-5 hours apart and accordingly the insulin doses are higher compared to the physiological release. This is an important cause of hypoglycemic attacks.

This condition is associated with excess carbohydrate consumption and the release of counter-regulatory hormones. These hypo–hyperglycemia periods result in high glycated

M Temel Yılmaz[1]
Özge Telci Çaklılı[2]
Hülya Hacişahinoğulları[2]
Ramazan Çakmak[3]
Elif Şahiner[4]
Ela Keskin[1]

[1]*Department of Endocrinology and Metabolism, Demiroğlu Bilim University, Istanbul, Turkey*
[2]*Department of Endocrinology and Metabolism, İstanbul University, Faculty of Medicine, İstanbul, Turkey*
[3]*Department of Endocrinology and Metabolism, Medical Park Hospital Gaziosmanpaşa, İstanbul, Turkey*
[4]*Department of Nutrition and Dietetics, Hacettepe University, Faculty of Medicine, Ankara, Turkey*

Corresponding author:
Ozge Telci Caklili
✉ wattersonx@gmail.com

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haemoglobin (HbA1c) levels and lack of stability. After this period with increased HbA1c, antihyperglycemic treatment-oriented insulin protocols aiming to reduce the high HbA1c in brittle diabetes force the physician/patient to increase the dose of insulin continuously, which deepens the main problem by increasing the number of hypoglycemic attacks and therefore triggering variability.

In this study, we sought an answer to the question of whether the primary goal of intensive insulin therapy is to control hyperglycemic attacks or to prevent hypoglycemic attacks to regulate glycemia and reduce HbA1c levels in difficult-to-control brittle type 1 diabetes. We investigated the effectiveness of continuous subcutaneous insulin infusion (CSII) therapy with a patch pump with the sensor augmented with predictive low-glucose suspend (PLGS) algorithm system in patients with uncontrolled type 1 diabetes with high HbA1c values who were treated with MDI.

Materials and Methods

Subjects

The data of patients whose glycemic control could not be achieved with MDI therapy and who were switched to sensor-augmented tubeless pump with PLGS feature (Medtrum A7+ TouchCare patch pump and integrated A7+ continuous glucose monitoring system) were analyzed retrospectively from database of Demiroğlu Bilim University Diabetes Clinic. Patients whose data were not available were excluded.

A total of 16 patients (male: 9; 56 %) were included. Demographic characteristics of patients are as follows: the mean age was 33.7 ± 7.8 years, the mean diabetes duration was 16 ± 4.9 years, and the body mass index was 25.4 ± 3.9 kg/m^2.

Glycated haemoglobin level, weight, total daily insulin requirement, C-peptide, creatinine, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and triglyceride levels with MDI treatment for at least 3 months and after treatment with sensor-augmented tubeless pump with PLGS feature for at least 3 months were obtained from records of patients.

Ethics

Ethics committee approval of the study was obtained from Ethics Committee of Demiroğlu Bilim University (rule number: 21.06.2022/2022-12-02). Written informed consent was obtained from all patients.

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences software version 16.0 (IBM Inc, Chicago, IL, USA) (histogram) and analytic methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) were used to determine whether they are normally distributed. An overall 5% type I error level was used to infer statistical significance. Wilcoxon signed-rank tests were used for before–after comparison.

Results

A total of 16 patients (male: 9; 56 %) were included (Table 1). Patients' basal median (interquartile range (IQR)) HbA1c was 9.20 (3.55) and C-peptide was 0.10 (0.75) ng/mL. Their median (IQR) total daily dose of insulin was 40.00 (15.00) units.

After 3 months of sensor-augmented pump (SAP) with PLGS treatment, patients' median (IQR) HbA1c level decreased to 7.55 (1.43), $P = .008$. The median (IQR) total insulin dose decreased from 40.00 (15.00) to 39.85 (15.46), $P = .363$. Patients' median (IQR) weight reduced from 64.15 (33.00) kg to 63.80 (32.90) kg; however, this decrease was not statistically significant ($P = .842$).

Patients with brittle type 1 diabetes had time below 56 mg/dL was 0.34%, time between 56 and 70 mg/dL was 1.01%, time between 70 and 180 mg/dL was 72.90%, time above 180 mg/dL was 25.67 %, time between 70 and 250 mg/dL was 95.98%, and time above 250 mg/dL was 2.76% (Table 2).

Discussion

The goal of diabetes treatment is to lower HbA1c and minimize glucose variability to reduce the risk of long-term complications, thereby improving quality of life.

Intensive insulin therapy is crucial to reduce the development of microvascular complications in patients with type 1 DM.[5] However, recent data from type 1 DM registries demonstrate that only a minority of adults and youth with type 1 DM meet American Diabetes Association targets for HbA1c.[6] One of the important barriers against achieving strict glycemic control is hypoglycemia attacks that develop during MDI therapy. Also, hypoglycemia is associated with increased morbidity.[7]

Hypoglycemic attacks cause rebound hyperglycemia and contribute to the increase of HbA1c values and glucose variability by stimulating the release of counter-regulatory hormones.

Studies have found a linear relationship between the frequency of hypoglycemia and the increase in HbA1c value.[8] It also reported that

Table 1. Demographic Characteristics of Patients' During Intensive Multiple-Dose Insulin Therapy Period and Changes in These Characteristics with 3 Months of Sensor-Augmented Pump with Predictive Low-Glucose Suspend Therapy

Parameters	Basal Median (IQR)	After the Pump Median (IQR)	*P*
HbA1c (%)	9.20 (3.55)	7.55 (1.43)	**.008**
C-Peptide (ng/mL)	0.10 (0.75)	0.10 (0.84)	.766
Creatinine (mg/dL)	0.81 (0.39)	0.89 (0.33)	.092
Triglyceride (mg/dL)	81.00 (224.00)	88.50 (216.00)	.344
Total cholesterol(mg/dL)	167.50 (60.00)	158.00 (54.00)	.345
HDL cholesterol(mg/dL)	56.00 (26.00)	52.00 (23.00)	.600
LDL cholesterol (mg/dL)	94.00 (82.00)	87.00 (43.00)	.499
Weight (kg)	64.15 (33.00)	63.80 (32.90)	.842
Total dose(units)	40.00 (15.00)	39.85 (15.46)	.363

HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

MAIN POINTS

- Patients with brittle diabetes can benefit from a pump system with predictive low glucose suspend feature.
- This study shows that patients with type 1 diabetes have better outcomes with a patch pump system that has predictive low-glucose suspend feature.
- Glycated haemoglobin improved with this system possibly due to more time spent in time in range and only 1.01% of the time spent in level 1 and 0.34% of time spent in level 2 hypoglycemia.

Table 2. Distribution of Time in Range Percent

	<56 mg/dL	56-70 mg/dL	70-180 mg/dL	>180 mg/dL	70-250 mg/dL	>250 mg/dL
Time in range percent (%)	0.34 ± 0.78	1.01 ± 1.39	72.90 ± 13.43	25.67 ± 14.36	95.98 ± 3.15	2.76 ± 2.96

in adult patients with type 1 diabetes, compared with HbA1c < 7%, HbA1c ≥ 9% was associated with 2-fold and 12-fold higher incidences of severe hypoglycemia and diabetic ketoacidosis, respectively.[9] In our study, although hypoglycemia frequency with MDI could not be evaluated, it is our opinion that it had a major contribution to initial high HbA1c values.

Another important issue in the treatment of diabetes mellitus is glucose variability. The term glucose variability describes oscillations in blood glucose throughout the day, including hypoglycemic periods and postprandial increases.[10] In vitro and in vivo studies demonstrated that glycemic variability is more deleterious than chronic hyperglycemia in determining endothelial damage.[11] It was emphasized that glycemic variability is associated with vascular complications in both type 1 and type 2 diabetes mellitus.[11]

Herewith prevention of hypoglycemia episodes and treatment of postprandial hyperglycemia are very important. Both case–control, non-randomized, and randomized controlled trials showed less glycemic variability among patients using CSII compared to MDI.[12-14]

A meta-analysis of 25 studies enrolling 543 children and 1456 adults with type 1 diabetes demonstrated a significant reduction in glycosylated hemoglobin in patients treated with classical CSII compared to multiple injections (mean difference 0.37).[15] In this meta-analysis, HbA1c reduction was 0.42% (95 % CI, 0.23-0.61; *P* = .001).

A meta-analysis of randomized controlled trials in type 1 diabetic patients comparing MDI and CSII indicated that the HbA1c difference between treatments was 0.5%.[16] In our study, with sensor augmented with predictive low-glucose management patch pump, HbA1c reduction was 1.68%. The reduction in HbA1c was higher than most of the results in the literature, especially in patients treated with classical CSII.

Apart from the low glucose prediction feature, the tubeless pump itself may have contributed to the major reduction of HbA1c. Hermanides et al[17] reported that in patients with type 1 diabetes after switching to tubeless pump therapy, a significant HbA1c reduction was obtained. In a retrospective study examining the data of 3657 patients (n = 3582 type 1, n = 25 type 2, n = 50 Latent Autoimmune Diabetes in Adults [LADA]) using tubeless pumps, it was reported that tubeless insulin pump therapy was associated with better glycemic control and a lower frequency of diabetic ketoacidosis and severe hypoglycemia in an age group prone to acute complications.[18] Our results have shown better control with a tubeless system.

Continuous subcutaneous insulin infusion is also associated with a lower incidence of nocturnal hypoglycemia. In the study by Bosi et al.[19] it was reported LGS feature of insulin pump use was associated with a significant reduction in the duration of nocturnal hypoglycemia (median 46.2 vs.1.8 min/day, LGS-OFF vs. LGS-ON). Benkhadra et al[15] also showed a reduction in nocturnal hypoglycemia in adult patients who used CSII compared to MDI.

In our study, the effects of a sensor-augmented tubeless pump with PLGS feature were tested on glycosylated hemoglobin and on time spent in hypoglycemia in patients with brittle type 1 DM whose glycemic control could not be achieved. Our findings indicate better glycemic control and possible lower hypoglycemic periods compared to MDI treatment.

The PILGRIM study demonstrated that the median duration of hypoglycemia with PLGS was significantly lesser than with LGS feature (58 minutes vs. 101 minutes, respectively).[20]

In another study, in patients with type 1 diabetes, it was shown that PLGS provided a 31% relative reduction in mean time <70 mg/dL compared to SAP therapy.[21] A real-world study of a PLGS system showed that PLGS provided a rapid and sustained reduction in hypoglycemia without a significant increase in mean blood glucose.[22]

Hypoglycemia rate was evaluated in 2 stages during the 3-month treatment period. The first stage was the rate of glucose below 56 mg/dL; the rate was 0.34%, and in the second stage, values between 56 mg/dL and 70 mg/dL were found to be 1.01%. These data demonstrate that the application of the predictive low glucose management patch pump system is successful in controlling hypoglycemia in brittle patients. Also, the 'time interval' target was 72.9%.

The total insulin dose of the patients was reduced by 10%. This finding shows that in patients with type 1 diabetes pump system distributes almost the same amount of insulin more physiologically mimicking a pancreas. In a meta-analysis, Jiao et al[23] have reported no difference in total insulin dose in type 1 diabetes patients with a closed-loop pump system compared to controls.

In conclusion, a pump system with a predictive LGS feature improves glycemic targets in patients with brittle uncontrolled type 1 diabetes without the expense of hypoglycemia compared to MDI treatment.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Demiroğlu Bilim University (Date June 21, 2022, Decision No: 2022-12-02).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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