Prevention of Hypoglycemia With Predictive Low Glucose Insulin Suspension in Children With Type 1 Diabetes: A Randomized Controlled Trial

Tadej Battelino,[1,2] Revital Nimri,[3] Klemen Dovc,[1] Moshe Phillip,[3,4] and Natasa Bratina[1]

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OBJECTIVE

To investigate whether predictive low glucose management (PLGM) of the MiniMed 640G system significantly reduces the rate of hypoglycemia compared with the sensor-augmented insulin pump in children with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This randomized, two-arm, parallel, controlled, two-center open-label study included 100 children and adolescents with type 1 diabetes and glycated hemoglobin A_{1c} ≤10% (≤86 mmol/mol) and using continuous subcutaneous insulin infusion. Patients were randomly assigned to either an intervention group with PLGM features enabled (PLGM ON) or a control group (PLGM OFF), in a 1:1 ratio, all using the same type of sensor-augmented insulin pump. The primary end point was the number of hypoglycemic events below 65 mg/dL (3.6 mmol/L), based on sensor glucose readings, during a 14-day study treatment. The analysis was performed by intention to treat for all randomized patients.

RESULTS

The number of hypoglycemic events below 65 mg/dL (3.6 mmol/L) was significantly smaller in the PLGM ON compared with the PLGM OFF group (mean ± SD 4.4 ± 4.5 and 7.4 ± 6.3, respectively; $P = 0.008$). This was also true when calculated separately for night ($P = 0.025$) and day ($P = 0.022$). No severe hypoglycemic events occurred; however, there was a significant increase in time spent above 140 mg/dL (7.8 mmol/L) in the PLGM ON group ($P = 0.0165$).

CONCLUSIONS

The PLGM insulin suspension was associated with a significantly reduced number of hypoglycemic events. Although this was achieved at the expense of increased time in moderate hyperglycemia, there were no serious adverse effects in young patients with type 1 diabetes.

Continuous subcutaneous insulin infusion (CSII) combined with continuous glucose monitoring (CGM) is already a well-established therapeutic option for the management of type 1 diabetes in different patient populations. Alarms based on real-time sensor glucose (SG) values alert patients to hypoglycemia and hyperglycemia, allowing them to adjust the treatment, preferably after confirmation by self-monitoring of blood

[1]Department of Pediatric Endocrinology, Diabetes and Metabolism, University Medical Centre–University Children's Hospital, Ljubljana, Slovenia
[2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3]The Jesse Z and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center, Petah Tikva, Israel
[4]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Corresponding author: Tadej Battelino, tadej.battelino@mf.uni-lj.si.

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T.B. and R.N. contributed equally to the manuscript.

glucose (SMBG). Randomized controlled trials in different populations demonstrate that CGM is safe and effective: it helps to lower the mean glycated hemoglobin A_{1c} (HbA_{1c}) value without increasing hypoglycemia (1) and reduces hyperglycemic and hypoglycemic excursions in patients with type 1 diabetes (2–4).

Automated low glucose threshold insulin suspend (i.e., low glucose suspend [LGS]) was integrated to sensor-augmented pumps (SAPs), allowing suspension of basal insulin delivery in response to low SG levels. Randomized controlled trials demonstrate that the use of LGS reduces the area under the curve (AUC) in hypoglycemia, time spent in hypoglycemia (5,6), and frequency of moderate and severe hypoglycemia (7,8). In an attempt to even further reduce hypoglycemic excursions and possibly provide protection to the user, predictive low glucose management (PLGM) was introduced. Early in silico modeling demonstrates advantages of PLGM compared with standard LGS in further reduction of severity of hypoglycemia (9). Additionally, nocturnal PLGM use (10–14), as well as random 2-h nightly insulin suspension (15), significantly reduced overnight hypoglycemia without increased risk of morning ketosis.

The MiniMed 640G system (Medtronic, Northridge, CA) offers the SmartGuard technology with PLGM. The "suspend before low" feature of this technology stops insulin delivery when the SG value is predicted to reach or fall below a preset low glucose limit within 30 min and automatically resumes basal insulin delivery after recovery from hypoglycemia. A study with 40 participants with type 1 diabetes evaluated the ability of the MiniMed 640G system to prevent predicted hypoglycemia, and the results indicated a high rate of sensor-detected hypoglycemic events that were prevented (16).

The current study compared the incidence of hypoglycemia in a pediatric population with type 1 diabetes using the MiniMed 640G system with PLGM turned ON or PLGM turned OFF and therefore using the system as a regular SAP. We hypothesized that the PLGM ON group would show a reduced number of hypoglycemic excursions.

RESEARCH DESIGN AND METHODS

This randomized, two-arm, parallel, controlled, open-label study was conducted at two clinical sites, in Slovenia and Israel (Supplementary Table 1). Pediatric patients with type 1 diabetes treated with CSII were invited to participate. The protocol was designed by researchers and approved by the applicable medical ethics committee for each site. The study was conducted in line with Good Clinical Practice and the Declaration of Helsinki, with independent data and safety monitoring provided by a clinical research organization.

Patients between 8 and 18 years of age diagnosed with type 1 diabetes >12 months before the study and treated by CSII, with or without CGM, for at least 3 months before the inclusion were eligible for the study. Additionally, their screening HbA_{1c} level needed to be ≤10% (86 mmol/mol), and they were not allowed to use the LGS feature of the CGM during the last 2 weeks before inclusion.

After the informed consent procedure and inclusion, patients were trained in the use of the MiniMed 640G system that included a MiniMed 640G insulin pump, Enhanced Enlite sensor (Medtronic), Guardian 2 Link transmitter (Medtronic), and Bayer CONTOUR NEXT (or PLUS) LINK 2.4 blood glucose meter (Ascensia Diabetes Care, Parsippany, NJ) before entering a 3-day run-in period. All components and accessories of the system (infusion sets, sensors, insulin reservoirs, blood glucose meters, test strips, and transmitter) were provided by Medtronic and are listed in Supplementary Table 2.

The purpose of the run-in period was to help patients and their parents get familiar with the study device and protocol-mandated activities and thus improve their compliance during the treatment period. During the run-in period, the PLGM feature of the study device was turned off for all patients, and the data collected were not included in the final analysis.

Visit 1 was considered the start of a 2-week study treatment. If the patients met interim inclusion criteria (i.e., compliance with study requirements during the 3-day run-in period), they were randomly assigned to either the intervention (PLGM feature turned on) or the control (PLGM feature turned off) group. Randomization was performed in a 1:1 ratio at each site (25 patients/study group/site). Study staff set up the devices in line with the allocated study group (PLGM ON or PLGM OFF). The alert thresholds were set the same for both groups: alert on low at 65 mg/dL (3.6 mmol/L) and alert on high at maximum 250 mg/dL (13.9 mmol/L), with audible alarms turned off for all. All other insulin pump settings were set and adjusted individually as appropriate for each patient. Owing to the nature of the protocol, the blinding of the treatment was not applicable.

Patients used the MiniMed 640G system continuously for 2 weeks and were provided with a patient diary. They were required to record morning (0700 h) glucose value and at least seven additional SMBG values during the day, morning urine ketones, all food consumption with carbohydrate counts, duration of daily physical activity along with self-assessed intensity, and any adverse events (AEs) or device malfunctions.

Study visits were performed for both groups after each week of study treatment. At the site, the study staff uploaded the data from the pump using the CareLink Therapy Management Software (Medtronic) and reviewed the patient diary. The visit at the end of the second week was considered the final visit, and patients returned all devices to the site.

Safety Monitoring

The patients and parents were encouraged to report any AE or adverse device effect. For the purpose of this study, every hypoglycemic event was not reported as an AE. All values of SG falling under 70 mg/dL (3.9 mmol/L) were recorded by the study device and included in the statistical analysis. Hypoglycemia was regarded as an AE only if glucose fell below 50 mg/dL (2.8 mmol/L). Severe hypoglycemia was considered a serious AE (SAE); hypoglycemia was considered severe with glucose under 50 mg/dL (2.8 mmol/L), accompanied by a seizure or loss of consciousness, as per International Society for Pediatric and Adolescent Diabetes guidelines, or if intravenous glucose and/or intramuscular glucagon administration was required.

Hyperglycemia or diabetic ketoacidosis (DKA) was considered an SAE only if blood glucose rose above 250 mg/dL (13.9 mmol/L) and was associated with low serum bicarbonate (<15 mEq/L) or low pH (<7.3) and either ketonemia or ketonuria, requiring treatment within a health care facility. Per study protocol, other hyperglycemic events were not reported as AEs; however, they were

recorded by the study device and included in the final analysis.

The absolute relative difference and percentage of readings meeting the International Organization for Standardization criteria for the Enlite sensor were recently reported to be mean/median 12.38/11.95% and 76.9%, respectively (17).

End Points

The primary end point was the number of hypoglycemic events below 65 mg/dL (3.6 mmol/L), based on SG readings, with a minimum duration of 20 min and each separated by a minimum of 30 min. All hypoglycemic events were preferably confirmed by SMBG; however, only the values captured by CGM were included in the analysis.

The secondary end points were *1*) number of hypoglycemic events below 50 mg/dL (2.8 mmol/L), 60 mg/dL (3.3 mmol/L), and 70 mg/dL (3.9 mmol/L), also considered separately for night (2300–0700 h) and day (0701–2259 h); *2*) change in time and AUC in hypoglycemia (below 65, 60, and 50 mg/dL [3.6, 3.3, and 2.8 mmol/L]), hyperglycemia (above 140, 180, and 250 mg/dL [7.8, 10, and 13.9 mmol/L]), and within range 70–140 mg/dL (3.9–7.8 mmol/L) and 70–180 mg/dL (3.9–10 mmol/L); *3*) mean blood glucose, mean SG, and mean morning blood glucose (0700 h); *4*) change in glycemic variability expressed as mean amplitude of glycemic excursions (MAGE), 24-h SD of glucose values; and *5*) Kovatchew low index.

Statistical Analysis

Per study statistical analysis plan, the intention-to-treat cohort, which included all randomly assigned patients, but excluding subjects with $<$2 days of CGM data, was used for the data analysis.

The study examined the null hypothesis that there is no difference between the intervention (PLGM ON) and control (PLGM OFF) groups with respect to the primary end point. A sample size of 86 (43 per group) for the 1:1 randomization was calculated to have at least 80% power to detect a difference ($>$1.9 events per week, i.e., $>$40% reduction) in weekly number of hypoglycemic events between groups, assuming SDs of 3.77 (control) and 2.26 (treatment group) and a two-sided α level of 0.050. Fifty subjects per group accounted for a $\sim$15% dropout rate.

For analysis of the primary efficacy end point, a two-sample *t* test was used to compare the rate of hypoglycemic events (SG $\leq$65 mg/dL [3.6 mmol/L], expressed as events per week) in the randomized arms of the study, as is appropriate for a parallel design. As a sensitivity analysis, the Wilcoxon test was also performed. For the secondary end points, both two-sample *t* tests and Wilcoxon tests were performed. The hypoglycemic event rates of daytime (0701–2259 h) and nighttime (2300–0700) below 50, 60, 65, and 70 mg/dL (2.8, 3.3, 3.6, and 3.9 mmol/L) were expressed for each subject in terms of events per week. The time and AUC end points below 50, 60, and 65 mg/dL (2.8, 3.3, and 3.6 mmol/L), within ranges 70–140 mg/dL (3.9–7.8 mmol/L) and 70–180 mg/dL (3.9–10 mmol/L), and above 140, 180, and 250 mg/dL (7.8, 10, and 13.9 mmol/L) were expressed as daily averages. The AUC was calculated as a normalized AUC for each subject and was subsequently provided as summary statistics for all subjects. The mean blood glucose, mean SG, mean morning glucose, MAGE, daily SG SD, and Kovatchew low index were calculated as daily values for each subject and then averaged over all respective data. Incidence rate of severe hypoglycemic AEs was presented as a rate per 100 patient-years. Patient demographics and baseline characteristics were presented using summary statistics (mean, SD, median, minimum, maximum, Q1, Q3, and 95% confidence limit for continuous variables and frequency counts and percentages for categorical variables). All reported *P* values were two-sided; a *P* value of $<$0.05 was considered to indicate statistical significance for comparisons of the outcomes. SAS version 9.4 (SAS Institute, Cary, NC) was used to perform analyses.

RESULTS

Between November 2014 and February 2015, 100 patients between the ages of 8 and 18 years were enrolled in the study (50 per site). Two patients discontinued the study early (one before the randomization), and 98 completed the study per protocol (i.e., performed all study visits). Because the primary end point was based on CGM, two additional patients were later excluded from statistical analysis owing to lack of sensor data. In the end, the final analysis included 47 patients from PLGM ON and 49 from PLGM OFF group (*N* = 96). The study flow is presented in Supplementary Fig. 1. There were no significant differences in population baseline characteristics between the two groups, as shown in Table 1. All patients were of Caucasian ethnicity.

At least one hypoglycemic AE, i.e., SG below 50 mg/dL (2.8 mmol/L), was reported for 71 of 99 randomized patients. Twenty-eight patients were without CGM-recorded hypoglycemic AEs during the study treatment. There were no severe hypoglycemic events reported.

The primary end point results showed a significant difference between the two groups (PLGM ON vs. PLGM OFF) in number of hypoglycemic events below 65 mg/dL (3.6 mmol/L), based on SG readings with a minimum duration of 20 min, with each separated by a minimum of 30 min, during 2 weeks (*P* = 0.008). This difference was also significant when calculated separately for night (*P* = 0.025) and day (*P* = 0.022) (Fig. 1).

The number of hypoglycemic events below 70 mg/dL (3.9 mmol/L) and 60 mg/dL (3.3 mmol/L) was significantly smaller in the PLGM ON group (*P* = 0.001 and 0.013, respectively). This difference was also significant when calculated separately for day and night. The number of hypoglycemic events below 50 mg/dL (2.8 mmol/L) was not significantly different between the two groups (Fig. 2).

Time spent below 65 mg/dL (3.6 mmol/L), 60 mg/dL (3.3 mmol/L), and 50 mg/dL (2.8 mmol/L) was analyzed with the Wilcoxon test and was significantly shorter in the PLGM ON group (*P* = 0.0106, 0.089, and 0.0203, respectively) (Supplementary Table 3).

AUC of time spent below 65 mg/dL (3.6 mmol/L), 60 mg/dL (3.3 mmol/L), and 50 mg/dL (2.8 mmol/L) was also significantly smaller in the PLGM ON group when analyzed with the Wilcoxon test (*P* = 0.009, 0.011, and 0.037, respectively) (Supplementary Table 3).

As shown in Table 2, the time spent above 140 mg/dL (7.8 mmol/L) was significantly longer in the PLGM ON group (Wilcoxon test *P* = 0.0165), while time spent above 180 mg/dL (10 mmol/L) and 250 mg/dL (13.9 mmol/L) was not different between the two groups.

AUC of time spent above 140 mg/dL (7.8 mmol/L), 180 mg/dL (10 mmol/L), and 250 mg/dL (13.9 mmol/L) was not different between the groups.

Table 1—Baseline characteristics of study population included in the analysis

	Intervention group: PLGM ON	Control group: PLGM OFF
N	47	49
Age (years)		
Mean (SD)	12.8 (2.52)	13.1 (2.71)
Median	12.0	13.0
Min, max	8.0, 18.0	8.0, 18.0
Sex, number (%)		
Female	22 (46.8)	32 (65.3)
Male	25 (53.2)	17 (34.7)
Height (cm)		
Mean (SD)	156.8 (12.72)	157.7 (14.88)
Median	159.7	159.8
Min, max	126.9, 184.4	131.0, 190.0
Weight (kg)		
Mean (SD)	50.1 (13.98)	53.5 (16.43)
Median	50.1	51.5
Min, max	24.6, 77.5	26.0, 84.0
BMI (kg/m^2)		
Mean (SD)	20.0 (3.54)	21.0 (4.10)
Median	19.5	21.2
Min, max	14.4, 29.2	15.2, 32.7
Systolic blood pressure (mmHg)		
Mean (SD)	112.9 (12.85)	111.5 (12.15)
Median	114.0	112.0
Min, max	85.0, 142.0	82.0, 143.0
Diastolic blood pressure (mmHg)		
Mean (SD)	68.0 (11.43)	66.1 (9.90)
Median	69.0	67.0
Min, max	39.0, 88.0	47.0, 97.0
Heart rate (bpm)		
Mean (SD)	82.6 (13.03)	81.4 (13.66)
Median	81.0	80.0
Min, max	60.0, 120.0	60.0, 120.0
Temperature (°C)		
Mean (SD)	36.7 (0.24)	36.7 (0.27)
Median	36.7	36.7
Min, max	36.0, 37.3	36.2, 37.4
Screening HbA_{1c}		
Mean (SD) in % [mean in mmol/mol]	7.8 (0.92) [62]	7.5 (0.79) [58]
Median, % [mmol/mol]	7.7 [61]	7.5 [58]
Min, max, %	5.8, 9.8	6.1, 9.6
Total daily insulin dose/weight (units/kg)		
Mean (SD)	0.8 (0.26)	0.8 (0.19)
Median	0.8	0.8
Min, max	0.3, 1.7	0.5, 1.3
Basal-to-bolus ratio		
Mean (SD)	0.8 (0.33)	0.9 (0.55)
Median	0.8	0.7
Min, max	0.2, 1.5	0.4, 4.1

One hundred percent of included subjects were of Caucasian ethnicity. bpm, beats per minute; max, maximum; min, minimum.

Time spent within range 70–140 mg/dL (3.9–7.8 mmol/L) was significantly shorter in the PLGM ON group (Wilcoxon test $P = 0.0387$), while there was no significant difference in time spent within range 70–180 mg/dL (3.9–10 mmol/L).

Mean and median SG, SG at 0700 h, blood glucose, and blood glucose at 0700 h were not statistically different between the groups. Similarly, MAGE and daily SG SD were not statistically different between the groups (Supplementary Table 4). Kovatchew low index was significantly smaller in the PLGM ON group (Wilcoxon test $P = 0.0329$).

Morning ketones were measured with semiquantitative urine strips (Keto-Diastix, Bayer) with a 0–5 scale representing the severity of ketonuria. Of 1,419 available morning ketone values, 95.4% were reported as 0 (<5 mg/dL), i.e., negative. The average value was 0.10 with 0.52 SD, and there was no significant difference in values between the two study groups.

There were no other SAEs, episodes of DKA, or device-related serious adverse effects observed (all reported AEs that were not related to hypo- or hyperglycemia are listed in Supplementary Table 5).

Four device complaints were reported for the MiniMed 640G pump, but none of them was considered a major device malfunction that could jeopardize a patient's safety or study results. On three occasions, the device was replaced, and the patient continued with study treatment. One malfunction occurred during the run-in period and caused the parents to decide the child would not stay in the study. The problems with sensors were more abundant and mostly related to lost connectivity.

CONCLUSIONS

In the current study, the use of the PLGM feature was safe and associated with a significantly reduced number and duration of hypoglycemic events below 65 mg/dL (3.6 mmol/L). Although this was achieved at the expense of increased time spent in moderate hyperglycemia (above 140 mg/dL [7.8 mmol/L]), there was no change in mean blood glucose levels in young patients with type 1 diabetes. The two secondary end points of our study confirmed the primary end point, with significantly lower numbers of hypoglycemic events below 70 mg/dL (3.9 mmol/L) and 60 mg/dL (3.3 mmol/L), facilitating comparison with other studies consistently showing advantages of LGS and PLGM in the reduction of hypoglycemia (5–8,10,12,13,18), adding for the first time direct evidence for prevention of hypoglycemia.

Despite the increasing use of insulin pumps and CGM with demonstrated benefits (19,20), mostly positive user experience and effect on the overall quality of life (16,21), and comprehensive national strategies in treatment and education of patients (22), glycemic control for most patients is still suboptimal. Hypoglycemia continues to be a major barrier to better adherence to therapeutic decisions (2,5,7,10) and thus further reduction in HbA_{1c}. Our study demonstrated that PLGM might further improve metabolic

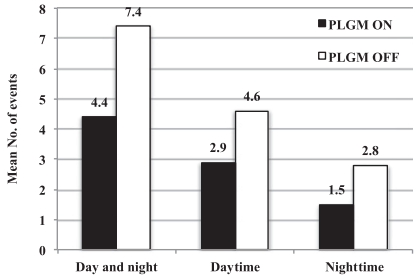

Figure 1—Primary end point. Mean number of hypoglycemic events per patient, i.e., SG below 65 mg/dL (3.6 mmol/L), each of minimum 20 min duration and separated by at least 30 min, as measured during the 14-day continuous SAP wear with PLGM either turned ON or OFF the whole time. Results demonstrate the significant reduction of events below 65 mg/dL (3.6 mmol/L) in the PLGM ON group ($P = 0.008$), also considered separately for daytime ($P = 0.022$) and nighttime ($P = 0.025$).

Table 2—Time spent in hyperglycemia, defined as above 140, 180, and 250 mg/dL (7.8, 10, and 13.9 mmol/L)

Time spent in hyperglycemia*	Intervention group: PLGM ON	Control group: PLGM OFF
N	47	49
Time spent above 140 mg/dL (7.8 mmol/L)		
Mean (SD)	936.3 (142.1)	860.7 (150.4)
Median	938.8	855.1
Q1, Q3	801.5, 1,023.1	765.0, 963.3
Wilcoxon test $P = 0.0165$		
Time spent above 180 mg/dL (10 mmol/L)		
Mean (SD)	597.5 (152.6)	534.0 (147.1)
Median	571.6	552.8
Q1, Q3	481.7, 711.3	425.9, 612.8
Wilcoxon test $P = 0.0606$		
Time spent above 250 mg/dL (13.9 mmol/L)		
Mean (SD)	189.3 (96.0)	163.6 (96.7)
Median	204.5	154.9
Q1, Q3	105.6, 230.3	96.7, 198.4
Wilcoxon test $P = 0.1311$		

*Time spent in hyperglycemia during 14-day study therapy, expressed as min/day.

control by reducing the hypoglycemia burden.

As per protocol, only CGM-recorded hypoglycemic events were included in the final analysis. Patients were encouraged to confirm the events with SMBG and to enter at least eight measurements per day, but other than morning (0700 h) measurement, there were no specific instructions regarding the time frame. We could not ascertain that in this study every hypoglycemic event was confirmed with SMBG.

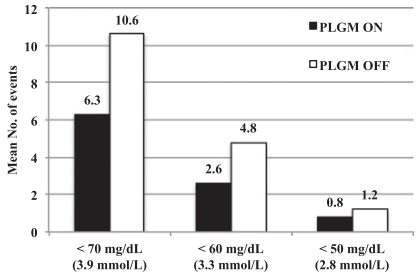

Figure 2—Secondary end points. Comparison of mean number of hypoglycemic events below 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L), and 50 mg/dL (2.8 mmol/L), each of minimum 20 min duration and separated by at least 30 min; SG measured during the 14-day continuous SAP wear with PLGM either turned ON or OFF the entire time. The results demonstrate the significant reduction in mean number of events below 70 mg/dL (3.9 mmol/L) and 60 mg/dL (3.3 mmol/L) in the PLGM ON group ($P = 0.001$ and 0.013, respectively). The number of hypoglycemic events below 50 mg/dL (2.8 mmol/L) was not significantly different between the two groups.

Our results indicate that the use of PLGM did not prevent hypoglycemia below 50 mg/dL (2.8 mmol/L). However, we cannot generalize this, since our population consisted of patients with relatively well-managed type 1 diabetes and the study was of short duration. The overall number of hypoglycemic events below 50 mg/dL (2.8 mmol/L) was too small to give statistically significant results, although there was a trend for a lower rate when PLGM was used.

There seems to be a possible correlation between the reduction of hypoglycemic events and increase in the mean blood glucose values when using PLGM. The shorter time spent within the range of 70–140 mg/dL (3.9–7.8 mmol/L) and longer average time above 140 mg/dL (7.8 mmol/L) in the group using PLGM may indicate this. The phenomenon of higher SG values has been reported previously in other studies, especially after the nighttime use of insulin suspension (5,8,12). However, the slightly increased SG values are not a relevant predictor of higher ketone presence (11), and the risk for severe rebound hyperglycemia after the PLGM is believed to be very low (7,8,12,14,15). This is also consistent with the results of the current study, with no severe hyperglycemic or DKA episodes reported and with no significant differences in morning ketones between the two groups. Additionally, the AUC in hyperglycemic ranges was not different between the groups.

A recent study by Scaramuzza et al. (23) reported that PLGM reduced the time spent above 160 mg/dL (8.9 mmol/L) with no differences in hypoglycemia below 70 mg/dL (3.9 mmol/L). In the current study, no obvious reasons for higher glucose concentrations in the PLGM ON group could be determined. Insulin usage (units/kg) was not significantly different between the groups. We cannot determine whether the increased SG values were directly linked to individual PLGM events, as we did not specifically follow the SG values in the hours immediately after the PLGM events. Because the study intervention was not blinded, it is possible that patients did not necessarily trust the new PLGM feature of the insulin pump and had exaggerated rescue carbohydrate intake during the study.

The PLGM was very efficient in reducing hypoglycemic excursions, and as long as a full closed-loop control to deliver insulin is not available, a certain increase in mean glucose level may be inevitable (12). However, although there were no severe hyperglycemic excursions reported, and the moderate increase in blood glucose without increased ketones is deemed acceptable, the average time spent above 140 mg/dL (7.8 mmol/L) in the PLGM ON group should not be neglected, especially in the pediatric population. Glycemic dysregulation was shown to cause widespread neuroanatomical differences in brain structures. Hyperglycemia in young children is associated with smaller gray matter volume, among other changes (24), and chronic hyperglycemia and glucose variability

are suspected to be detrimental to the white matter structures (25). Further studies and close observations are needed to determine the safety of long-term use of PLGM and possibly associated higher mean blood glucose levels.

This study had several limitations. The study population consisted mainly of patients with substantial experience with CSII and relatively well-managed type 1 diabetes (mean HbA_{1c} 7.6% [60 mmol/mol]), and this could have contributed to the small overall number of hypoglycemic events. Better HbA_{1c} values suggest a lower frequency of DKA (26) and thus a lower incidence of severe hyperglycemia despite higher mean glucose values. The duration of the trial was short, and efficacy of the PLGM on the rate of hypoglycemia should be studied over a longer period and possibly include the effect on HbA_{1c} levels over time. Future studies should aim to blind the therapy to exclude patient bias with regard to food consumption, exercise, and overall modified behavior as a reaction to the allocated therapy (14). Additionally, physical activity and food consumption in our study were self-reported by the patients or parents, and the data could not be considered solid enough for formal analysis. A controlled environment should be considered for future trials to study the direct effect of the exercise and food intake on PLGM performance. More specific instructions on the use of rescue carbohydrates with the PLGM alarms could help with this as well. Trials investigating age- and patient-specific requirements for successful use of PLGM systems provide important data (27) for improved use of this technology.

In conclusion, the use of PLGM was associated with a significantly reduced number of hypoglycemic events, without any SAEs in young patients with type 1 diabetes.

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Author Contributions. T.B. contributed to the study concept and design, collected data, supervised the study, participated in data analysis and interpretation, and drafted, reviewed, and edited the manuscript. R.N. contributed to the study concept and design, collected data, participated in data analysis and interpretation, and reviewed and edited the manuscript. K.D. collected data, participated in data analysis and interpretation, and reviewed the manuscript. M.P. contributed to the study concept and design, collected data, supervised the study, participated in data analysis and interpretation, and reviewed and edited the manuscript. N.B. collected data, participated in data analysis and interpretation, and reviewed and edited the manuscript. T.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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