ORIGINAL ARTICLE

Retrospective Analysis of the Real-World Use of the Threshold Suspend Feature of Sensor-Augmented Insulin Pumps

Pratik Agrawal, MS, Alex Zhong, MS, John B. Welsh, MD, PhD,
Rajiv Shah, MS, and Francine R. Kaufman, MD

Abstract

Background: The automatic Threshold Suspend (TS) feature of the MiniMed 530G system (Medtronic MiniMed, Inc., Northridge, CA), when enabled, suspends insulin delivery for up to 2 h when the sensor glucose (SG) value reaches a preset threshold.

Materials and Methods: SG data from 20,973 patients who enabled the TS feature at their discretion and uploaded pump and sensor data to CareLink[®] (Medtronic MiniMed, Inc.) from October 15, 2013 to July 21, 2014 were analyzed. Comparisons between 758,382 patient-days wherein the TS feature was enabled at any time and 166,791 patient-days in which it was not enabled were made. Further comparisons were made between data collected during daytime (8:00 a.m. to 10:00 p.m.) and nighttime (10:00 p.m. to 8:00 a.m.) hours. Data from subsets of patients who enabled the TS feature all of the time ($n = 14,673$) versus those who never enabled the TS feature ($n = 2,249$) were also compared. Recovery from hypoglycemia during and after 2-h pump suspension events was also assessed.

Results: The TS feature was enabled on 82% of patient-days. Patient-days in which the TS feature was enabled, compared with patient-days in which it was not, had 69% fewer SG values ≤ 50 mg/dL (0.64% vs. 2.09%, respectively; $P < 0.001$). The reduction in hypoglycemia seen on TS-enabled days was more pronounced during nighttime than during daytime hours. SG data from full-time users of the TS feature reflected a 62% reduction in values ≤ 50 mg/dL and a 5.6% reduction in values ≥ 300 mg/dL compared with data from nonusers ($P < 0.001$ for each). The median SG value at the start of 2-h suspensions was 60 (interquartile range [IQR], 57–66) mg/dL, immediately after was 87 (IQR, 63–123) mg/dL, and 4 h later was 164 (IQR, 117–220) mg/dL.

Conclusions: The TS feature, when enabled consistently, reduced hypoglycemic exposure, and for those who had it enabled 100% of the time, hyperglycemia was also reduced.

Introduction

INSULIN PUMPS THAT AUTOMATICALLY suspend insulin delivery when a preset sensor glucose (SG) threshold is reached were designed to mitigate hypoglycemia, particularly prolonged nocturnal hypoglycemia that could lead to a severe hypoglycemic event. The Medtronic Paradigm[®] Veo[™] system (Medtronic MiniMed, Inc., Northridge, CA), which includes the Low Glucose Suspend (LGS) feature that can be programmed to suspend insulin delivery at SG values between 40 and 110 mg/dL, has been commercially available outside the United States since 2010. This system is identical to the MiniMed 530G system (Medtronic MiniMed, Inc.),

which includes the Threshold Suspend (TS) feature that can be programmed to suspend insulin delivery at SG values between 60 and 90 mg/dL and has been available in the United States since 2013. In response to a threshold value, both the LGS and TS features cause the pump to display an informative message, sound a continuous alarm, and initiate a 6-h cycle consisting of 2 h of no insulin delivery and 4 h of insulin delivery at the previously programmed basal rate. The automated suspension feature of the Veo and the 530G systems is intended to suspend insulin delivery when users are unable to avert or treat hypoglycemia themselves.

Automatic insulin pump suspension has been evaluated in a retrospective analysis,¹ two nonrandomized clinical studies,^{2,3}

one study of intentionally induced hypoglycemia,⁴ a randomized clinical study focused on the rate of severe and moderate hypoglycemia and counterregulatory hormone responses to hypoglycemia,⁵ and a randomized clinical study focused on the severity and duration of nocturnal hypoglycemia.⁶

The MiniMed 530G system is typically used with CareLink[®] (Medtronic MiniMed, Inc.) personal therapy management software for diabetes, which provides remote storage and analysis capabilities for data from the pump and continuous glucose monitoring subsystems. CareLink data from individual users can be reviewed in collaboration with healthcare providers to guide therapy adjustments, or they can be aggregated and analyzed to detect large-scale patterns and outcomes in an anonymized fashion. The effectiveness of the TS feature in the real-world setting was analyzed by studying CareLink data from anonymized users of the 530G system in the United States.

Materials and Methods

SG data from 20,973 patients who enabled the TS feature at their discretion and uploaded pump and sensor data to CareLink in the 40 weeks from October 15, 2013 to July 21, 2014 were analyzed. Comparisons between 758,382 patient-days wherein the TS feature was enabled at any time and 166,791 patient-days in which it was not enabled were made. Further comparisons were made between data collected during daytime (8:00 a.m. to 10:00 p.m.) and nighttime (10:00 p.m. to 8:00 a.m.) hours. Data were also stratified according to whether patients had the TS feature enabled either 100% of the time or 0% of the time. In total, 14,673 (70%) patients had the TS feature enabled for 100% of the time, and 2,249 (11%) patients had the feature enabled for 0% of the time; the remaining 4,051 (19%) patients used it intermittently. The percentages of SG values indicative of

various degrees of hypoglycemia and hyperglycemia were calculated.

TS events were defined as continuous glucose monitor-triggered pump stoppages. Recovery from hypoglycemia during and after 2-h TS events was also assessed. To study the effect of carbohydrate intake on recovery from hypoglycemia, SG trajectories surrounding TS events were categorized according to whether or not a bolus insulin dose corresponding to carbohydrate intake was recorded 2 h or less after the resumption of basal insulin delivery.

For recovery during and after 2-h pump suspension events, data were normalized such that 0 h represented the start of the pump suspension and insulin delivery resumed at 2 h. Median and interquartile range (IQR) of SG values before, during, and after 2-h pump suspension events were calculated.

Hypoglycemic events were defined as consecutive SG readings ≤ 65 mg/dL for >20 min; nocturnal hypoglycemic events were those starting between 10:00 p.m. and 8:00 a.m. The area under the curve (AUC) for hypoglycemic events was calculated as the absolute mean difference between each hypoglycemic SG value (in mg/dL) and 65 mg/dL, multiplied by the number of minutes spent in hypoglycemia.

Results

The mean TS setting used by subjects to trigger the TS feature was 62.8 ± 5.8 mg/dL. On TS-enabled days, 620,165 TS events were recorded, a rate of 0.82 per patient-day. Of the TS events, 56.4% lasted for 0–5 min, and 9.6% lasted for the maximum-allowed 2 h. Figure 1 shows the performance of the TS feature in all users by comparing patient-days when the TS feature was enabled for at least some of the time (TS ON) versus days when it was not enabled at all (TS OFF) in terms of the percentage of SG values in different ranges. SG values from TS ON days were ≤ 50 mg/dL only 0.64% of the

FIG. 1. Sensor glucose distributions in the hypoglycemic range for Threshold Suspend (TS) on versus TS off days: sensor glucose ≤ 50 mg/dL (black), >50 –60 mg/dL (gray), and >60 –70 mg/dL (white). Percentages are shown for sensor glucose values in various ranges from days when the TS feature was enabled for at least some of the time (TS ON) or not enabled at any time (TS OFF). Daytime was defined as the interval from 8:00 a.m. to 10:00 p.m. All pairwise comparisons between TS ON and TS OFF days at all sensor glucose intervals and time intervals showed statistically significant reductions on TS ON days ($P < 0.001$).

time (equivalent to 9 min/day; $P < 0.001$), compared with TS OFF days, when 2.1% of SG values were ≤ 50 mg/dL (equivalent to 30 min/day), a 69% reduction. SG values ≤ 70 mg/dL were present 4.1% of the time during TS ON days (equivalent to 59 min) compared with 8.1% of the time during TS OFF days (equivalent to 1 h 57 min; $P < 0.001$), a 49% reduction. A 73% reduction in hypoglycemia associated with TS ON days was seen in the percentages of SG values ≤ 50 mg/dL occurring at night (SG percentages equivalent to 17 min/night for TS OFF vs. 5 min/night for TS ON; $P < 0.001$). In contrast, TS ON days had slightly more SG values reflecting hyperglycemia than did TS OFF days, with 15% more values in the ≥ 180 mg/dL and ≥ 240 mg/dL ranges and 10% more in the ≥ 300 mg/dL range ($P < 0.001$ for each). Time spent in the 80–150 mg/dL target range was 42% for TS ON days and 43% for TS OFF days.

Data were also stratified according to whether patients had the TS feature enabled either 100% of the time or 0% of the time. Table 1 compares the percentage of SG values representing various levels of hypo- and hyperglycemia from these patients. Full-time users of the TS feature had 61.7% fewer SG values representing hypoglycemia ≤ 50 mg/dL ($P < 0.001$) compared with those who did not use TS. Full-time TS users had modest reductions in the percentage of SG values in the 50–60 and 60–70 mg/dL ranges ($P < 0.001$ for each), as well as 5.6% fewer SG values representing hyperglycemia ≥ 300 mg/dL ($P < 0.001$). Full-time TS users had higher percentages of SG values in the ≥ 180 and ≥ 240 mg/dL range than did nonusers.

Thirty-four percent of 2-h TS events (20,464 of 59,424) were followed within 2 h by a bolus insulin dose corresponding to carbohydrate intake. Compared with 2-h TS events with no such insulin bolus doses, SG values from events with carbohydrate intake boluses returned to the normal range more quickly and remained significantly higher at 0, 2, and 4 h after basal insulin delivery was resumed ($P < 0.001$ for each).

To assess the risk of hyperglycemia following long-duration pump suspension events, we identified 59,424 2-h pump suspensions in the database. Of these, most (40,832, 69%) occurred during the 10-h “nighttime” period; the per-hour rate was 3.1-fold higher than during the 14-h “daytime” interval. At the beginning of 2-h pump suspensions, the median SG

value was 60 (IQR, 57–66) mg/dL. Within 30 min of pump suspension, SG values began to increase, and by the time that basal insulin delivery was resumed at 2 h, the median SG value was significantly higher at 87 (IQR, 63–123) mg/dL. Six hours after the start of 2-h pump suspensions (4 h after resumption of basal insulin delivery), the median SG value was 164 (IQR, 117–220) mg/dL. By comparison, the median SG value for the entire dataset was 150 (IQR, 112–199) mg/dL.

Additional analysis was conducted of the AUC of hypoglycemic events. The mean AUC of events occurring on TS ON days (TS feature on for any portion of the day), compared with events occurring on TS OFF days, was 37% lower (716 vs. 1,132 mg/dL $\times$ min, respectively; $P < 0.001$). Hypoglycemic events lasting > 20 min with SG values ≤ 65 mg/dL occurred 43% less frequently on TS ON days than on TS OFF days (0.36 vs. 0.64 events per day, respectively; $P < 0.001$) and were 23% shorter in duration (1.39 vs. 1.8 h, respectively; $P < 0.001$). The difference between TS ON and TS OFF days was most pronounced at night, when the AUC of hypoglycemic events was 45% lower in the former group (838 vs. 1,520 mg/dL $\times$ min; $P < 0.001$).

Discussion

This report supports and extends previous observations of the use of the LGS feature,^{1–3} which differs only slightly from the TS feature with respect to the allowable range of SG values that can trigger a pump suspension event (40–110 vs. 60–90 mg/dL, respectively) and the required sensor calibration interval. The earlier Veo studies used data from the Sof-sensor[®] and Enlite[®] sensors (Medtronic), whereas the 530G system is only indicated for use with the Enlite sensor, which is smaller and more durable.^{6,7}

Two previous studies of the use of the TS feature have concluded that although there was a reduction in hypoglycemia, there was no negative impact on hemoglobin A1C levels.^{5,6} The present study showed little overall change in hyperglycemia ≥ 300 mg/dL, with patients who used the TS feature all of the time having 5.6% fewer readings in this range compared with nonusers. Data from days when the TS feature was on at least part of the time had 10% more readings in this range compared with days when TS was off. This suggests that to maximally benefit from the TS feature in reducing hypoglycemia without causing any increase in hyperglycemia, it should be enabled all of the time. A recent prospective observational study of 37 adolescent users of the Paradigm Veo system who wished to fast during Ramadan⁸ observed lower rates of hypoglycemia (blood glucose level < 70 mg/dL; $P = 0.001$) and hyperglycemia (blood glucose level > 250 mg/dL; $P = 0.03$) among the 21 who used the LGS feature than among the 16 who did not.

In this study, 56% of TS events lasted for 0–5 min. By comparison, 38% of LGS events lasted for < 5 min in a more recent observational study,⁸ and the median duration of nocturnal TS events was 11.9 min in an earlier randomized controlled trial.⁶ Scenarios in which the TS alarm prompts carbohydrate intake and is then dismissed (with restarting of basal insulin delivery) may represent some or most of these short-duration events. Nondelivery of basal insulin for 5 min or less is unlikely to result in hyperglycemia. However, scenarios in which the TS alarm prompts carbohydrate

TABLE 1. PERCENTAGES OF SENSOR GLUCOSE VALUES IN VARIOUS RANGES FROM PATIENTS WHO WERE FULL-TIME USERS VERSUS NONUSERS OF THE THRESHOLD SUSPEND FEATURE AND BETWEEN-GROUP DIFFERENCES

Sensor glucose value range (mg/dL)	Full-time users	Nonusers	Change
≤ 50	0.44	1.14	–61.7%
> 50 to 60	0.89	1.59	–44.3%
> 60 to 70	1.90	2.70	–30.0%
≥ 180	35.09	32.42	8.22%
≥ 240	13.31	12.39	7.37%
≥ 300	3.95	4.18	–5.6%

Full-time users were patients who used the Threshold Suspend (TS) feature 100% of the time; nonusers were patients who never used (0%) the TS feature. All between-group comparisons were statistically significant ($P < 0.001$).

intake and users choose to keep basal insulin delivery suspended may account for slightly higher percentages of SG readings in the ≥ 180 and ≥ 240 mg/dL ranges among TS users. As expected as the result of carbohydrate intake, there was a more rapid recovery and generally higher SG values for TS events in which bolus insulin corresponding to carbohydrate intake was recorded. The safety of 2-h pump suspension events was supported by the median SG value 4 h after the end of such events (164 mg/dL) versus that of the entire dataset (150 mg/dL).

The current study benefits from the large number of patients and patient-days available for analysis, and the real-world setting suggests that these results can be extrapolated to other 530G users. However, use of CareLink at home may have created a selection bias, and the study's conclusions may not be generalizable to patients who did not use CareLink. Data regarding motivations underlying individual patients' use of CareLink or of the TS feature, or the extent to which nonusers manually suspend their pumps to manage existing or predicted hypoglycemia, were unavailable, as was information on patients' demographic, anthropometric, and biochemical parameters. The amount and timing of carbohydrate intake are additional uncontrolled factors because carbohydrate estimates were not consistently recorded. Finally, sensor accuracy was not assessed.

The current results are similar in some respects to outcomes observed in the ASPIRE In-Home study in which subjects were randomly assigned to either standard sensor-augmented pump therapy (the control group) or to sensor-augmented pump therapy with required use of the TS feature (the TS group).⁶ SG trajectories representing recovery from hypoglycemia during and after 2-h pump suspension events were similar in the ASPIRE In-Home and real-world datasets, and in both datasets, there were significantly fewer SG values in the hypoglycemic range in subjects using the TS feature than in those in the control group using sensor-augmented pump therapy.⁹ The current results also confirm and extend results from the ASPIRE In-Home study with respect to reduction in the mean AUC of nocturnal hypoglycemic events. The ASPIRE In-Home study noted a 38% reduction (from 1,568 to 980 mg/dL $\times$ min in the control and TS groups, respectively), whereas in the current study, a 45% reduction was observed.

These real-life data support the use of the TS feature as a means to reduce hypoglycemia, particularly at night, without risking significant increases in hyperglycemia. Additional studies to characterize patterns of adoption of the TS feature and results of its sustained use are warranted.

Author Disclosure Statement

All authors are employees of Medtronic, Inc.

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Address correspondence to:
Pratik Agrawal, MS
Medtronic, Inc.
18000 Devonshire Street
Northridge, CA 91325

E-mail: pratik.j.agrawal@medtronic.com