Original Article

Predictors of Hypoglycemia in the ASPIRE In-Home Study and Effects of Automatic Suspension of Insulin Delivery

Journal of Diabetes Science and Technology
2015, Vol. 9(5) 1016–1020

DOI: 10.1177/1932296815586014
dst.sagepub.com
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Abstract

Background: Hypoglycemia varies between patients with type 1 diabetes and is the main obstacle to therapy intensification. We investigated known and potential risk factors for hypoglycemia in subjects with type 1 diabetes.

Method: In the ASPIRE In-Home study (NCT01497938), a randomized trial of the threshold suspend (TS) feature of sensor-augmented insulin pump (SAP) therapy, subjects' propensity to nocturnal hypoglycemia (NH) was established in a 2-week run-in phase and assessed in a 3-month study phase via continuous glucose monitoring. Categorical variables were tested for association with NH rates in both phases.

Results: Elevated rates of NH were significantly associated with baseline A1C ≤7%, with bolus insulin deliveries unassisted by the bolus estimation calculator, and with assignment to the control group during the study phase.

Conclusions: Routine use of the TS feature and the bolus estimation calculator are strategies that may reduce the risk of NH.

Keywords

ASPIRE In-Home, hypoglycemia, low glucose suspend, prediction, sensor-augmented pump therapy, threshold suspend

Threshold suspend (TS) is an automated feature of sensor-augmented pump (SAP) therapy that aims to mitigate hypoglycemia by stopping insulin delivery for up to 2 hours when the sensor glucose (SG) value reaches or falls below a predetermined threshold value. In response to a threshold SG value and in the absence of patient intervention, it causes the pump to display an informative message, sound a continuous alarm, and initiate a 6-hour cycle that includes a 2-hour interval of no insulin delivery and a 4-hour interval of basal delivery.

The ASPIRE In-Home study (NCT01497938) was a randomized controlled trial of 247 patients with type 1 diabetes in which 121 were allocated to the TS group and 126 to the control group; the former group realized significant reductions in nocturnal hypoglycemia.[1] The strategy has also been evaluated in retrospective analyses of data from routine users of the Veo system in Europe[2] and of the 530G system in the United States (both Medtronic, Inc., Northridge, CA),[3] as well as 2 nonrandomized clinical studies,[4,5] 1 study of

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Table 1. Categorical Variables as Predictors of Nocturnal Hypoglycemia.

	Run-in phase				Study phase				
Variable	Subjects (n)	Events/week	*P*	*P* (adjusted)	Subjects (n)	Events/week	*P* (univariate)	*P* (model 1)	*P* (model 2)
Baseline A1C									
≤7%	92	2.53 ± 1.69	<.001	<.001	108	2.31 ± 1.30	<.001	<.001	<.001
>7%	222	1.90 ± 1.33			138	1.48 ± 0.96			
Basal/bolus ratio									
≤1	168	2.02 ± 1.47	.4	.5	137	1.81 ± 1.23	.8	.4	.4
>1	146	2.16 ± 1.47			110	1.89 ± 1.15			
Age (years)									
≤50	207	2.21 ± 1.47	.03	.4	165	1.86 ± 1.19	.6	.9	.5
>50	107	1.84 ± 1.44			82	1.82 ± 1.20			
Diabetes duration (years)									
≤15	69	2.49 ± 1.70	.02	.002	43	2.03 ± 1.45	.2	.1	.3
>15	245	1.97 ± 1.38			178	1.77 ± 1.14			
Food boluses/day									
≤3	118	2.17 ± 1.50	.4	.7	96	1.90 ± 1.27	.6	.6	.5
>3	196	2.03 ± 1.45			151	1.81 ± 1.14			
Correction boluses/day									
≤1	72	2.31 ± 1.77	.1	.09	55	1.72 ± 1.06	.7	.3	.2
>1	242	2.02 ± 1.37			192	1.88 ± 1.23			
Manual boluses/day									
≤1	213	2.05 ± 1.47	.5	.6	168	1.77 ± 1.13	.04	.02	.02
>1	101	2.16 ± 1.48			79	2.02 ± 1.30			
Treatment group									
Threshold suspend					121	1.5 ± 1.0			<.001
Control					126	2.2 ± 1.3			

intentionally induced hypoglycemia,[6,7] and a randomized clinical study focused on the rate of severe and moderate hypoglycemia and counterregulatory hormone responses to hypoglycemia.[8]

Many risk factors for nocturnal hypoglycemia (NH) in type 1 diabetes have been established; these include younger age, lower A1C values, medium- or high-intensity prior-day exercise, and prior-day hypoglycemia.[9] We assessed several demographic and behavioral variables measured during the run-in and randomized phases of the ASPIRE In-Home study and of the use of the TS feature with respect to the risk of NH.

Methods

The ASPIRE In-Home study included a 2-week run-in phase in which patients' baseline risk of NH was determined. Patients were not blinded to their CGM data during the run-in phase. A hypoglycemic event was defined as a single continuous interval lasting >20 minutes with all sensor glucose (SG) values ≤65 mg/dL and no evidence of user-pump interaction; NH events were those starting between 10:00 PM and 8:00 AM. To become eligible for the 3-month randomized study phase, at least 2 episodes of NH had to have been recorded during the run-in phase.[10]

We analyzed baseline patient characteristics and insulin delivery patterns (including use of the TS feature) during the study to determine associations with hypoglycemic events. For analysis of insulin delivery patterns, the basal/bolus ratio was the ratio of the daily total of programmed basal delivery divided by the daily amount of insulin delivered as a bolus. Food boluses were defined as those delivered using the bolus calculator in which a carbohydrate value of at least 1 gram was entered. Correction boluses were those delivered using the bolus calculator in which the carbohydrate value was 0 or not entered at all. Manual boluses were those delivered without using the bolus calculator. Bolus data were collected and are presented separately for the run-in and study phases. Baseline A1C values for the run-in phase were collected at the screening visit and baseline A1C values for the study phase were collected at the randomization visit.

Adjusted *P* values were adjusted for all other predictors. Poisson regression was used to study the association between hypoglycemia event rates and predictors of hypoglycemia. The first *P*-value column provided in Table 1 (for both run-in and study phases) was based on univariate analysis where only 1 predictor entered the model. The *P*-value (adjusted) columns were based on multivariate analyses where model 1 included all predictors except for treatment group assignment and model 2 included all predictors.

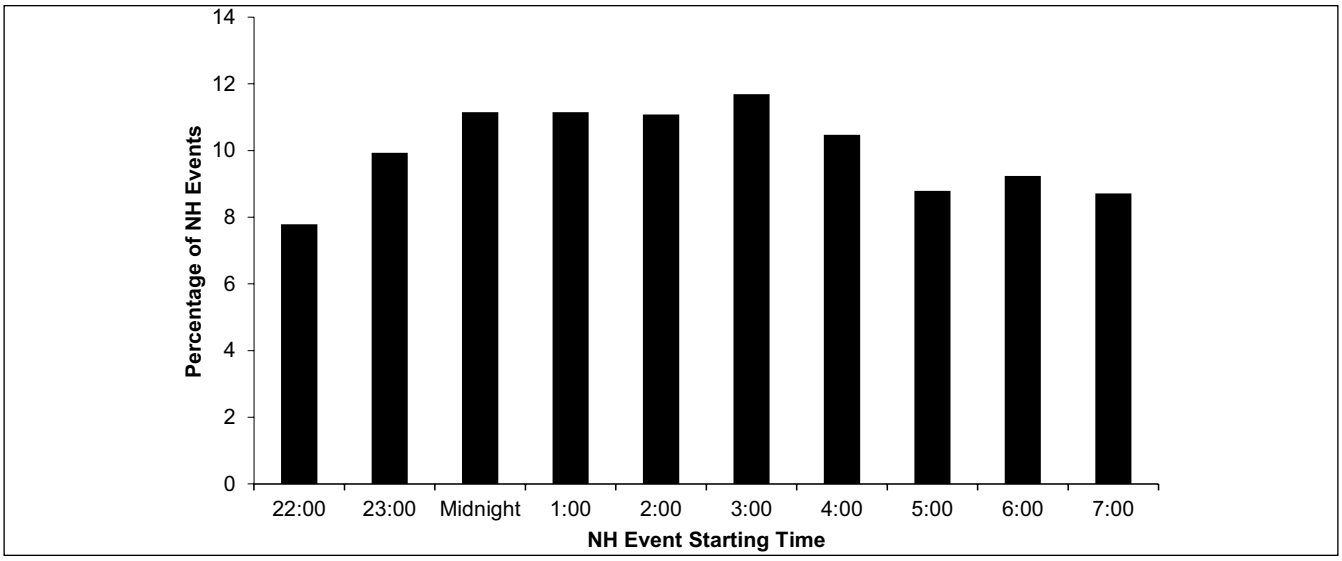

Figure 1. Distribution of the starting times of 1309 nocturnal hypoglycemia events.

Results

During the run-in phase, 2779 hypoglycemic events were observed, 1309 of which were nocturnal. The mean (± SD) duration of NH events was 116 ± 110 minutes (median, 75 minutes), and the mean nadir SG value was 48 ± 9.2 mg/dL. Of NH events, 67% lasted for <2 hours and 13% lasted >4 hours. Slightly over half (51%) of the NH events started between 10:00 PM and 3:00 AM; the remaining 49% started between 3:00 AM and 8:00 AM. Figure 1 shows the hour-by-hour distribution of the starting times of the NH events.

Table 1 shows that in univariate analyses, lower baseline A1C (≤7%, $P < .001$), younger age (≤50 years, $P = .03$), and shorter diabetes duration (≤15 years, $P = .02$) were associated with greater NH event rates. Age and diabetes duration were highly correlated with one another. Upon adjustment for the other predictors in a multivariate analysis, A1C ≤7% and shorter diabetes duration remained significant predictors of NH. Table 1 also shows that use of the bolus calculator was frequent, with most subjects using if for carbohydrate intake >3 times per day and to correct for hyperglycemia >1 time per day. Most gave themselves 1 or fewer manual boluses (ie, unassisted by the bolus calculator) per day.

During the 3-month study phase, 10 984 hypoglycemic events were observed, 5027 of which were nocturnal, and predictors of overall and NH were examined. The overall rate of NH events was significantly lower in the TS group than in the control group (3.3 ± 2.0 vs 4.7 ± 2.7 per week, respectively, $P < .001$). In univariate analysis, baseline A1C ≤7% ($P < .001$) and >1 manual bolus administration per day ($P = .04$) were associated with a greater NH event rate. Upon adjustment for all the other predictors, except the treatment group (model 1), baseline A1C ≤7% ($P < .001$) and delivering >1 manual bolus per day ($P = .02$) remained significant predictors of NH event rate per week, while shorter diabetes duration (≤15 years) and patient age were no longer significant predictors of NH. Upon adding the treatment group (TS or control) to the regression (model 2), assignment to the TS group was associated with a significantly reduced risk of NH ($P < .001$) yet baseline A1C ≤7% ($P < .001$) and delivering boluses manually ($P = .002$) were still significant predictors of NH. The adjusted relative NH event rate in the TS versus the control group was 0.70, indicating a 30% reduction in this model. Similarly, there was a 60% relative reduction in NH events lasting >2 hours in the TS versus control group.

Analysis using the total number of hypoglycemic events per week as the dependent variable in model 2 (instead of the nocturnal event rate) did not substantially alter the results: assignment to the control group, baseline A1C ≤7%, and delivery of >1 manual bolus per day remained significant predictors of the overall hypoglycemia event rate.

When the analysis was restricted to the 1973 NH events lasting >2 hours, the associations with assignment to the control group and with baseline A1C ≤7% remained significant. Subjects in the TS group experienced 60% fewer long-duration NH events than those in the control group.

Discussion

Intensive diabetes management has been shown to result in improved metabolic control at the cost of an increased risk of hypoglycemia. In this analysis, the run-in phase was designed to identify patients with a high risk of NH events to evaluate the efficacy of the TS feature. Subjects with relatively low A1C concentrations were at increased risk for NH, as were those with shorter disease duration. During the longer study phase, lower baseline A1C remained a significant predictor of NH, as did increased delivery of boluses without using the bolus calculator. Use of the TS feature significantly reduced

NH. In the adjusted model, while baseline A1C was still a predictor of NH rate, use of TS reduced the NH rate by 30% and NH >2 hours duration by 60%. A similar protective effect was observed for all hypoglycemic events throughout the day.

The association between shorter diabetes duration and greater risk of NH was seen only during the run-in phase of the study and contrasts with observations of increased hypoglycemic risk with longer diabetes duration made in larger population-based studies.[11-13] The discrepancy may be due to selection bias in the current study; subjects' behavior in the 2-week run-in phase may have been atypical and geared toward establishing eligibility for the study phase. The effect of diabetes duration on NH risk was not seen in the study phase in the model accounting for treatment group assignment.

The bolus calculator of the insulin pump incorporates input from the patient regarding expected carbohydrate intake, the fingerstick glucose level, and the amount of insulin still active from a previous correction bolus.[14] These are used to calculate a recommended insulin dose that can still be changed by the user if desired. The compliance rate of using the bolus calculator in this study was high, thus its efficacy in preventing hypoglycemia could be evaluated. In the 3-month study phase, delivery of >1 manual bolus per day was associated with a greater NH rate in all models tested. In the STAR 3 study that compared SAP therapy to multiple daily injection therapy,[15] the 244 patients randomized to SAP therapy were encouraged to use the bolus estimation calculator; analysis of A1C levels and bolus calculator use revealed that subjects in the low-A1C cohorts of both pediatric and adult age groups used the calculator more frequently than subjects in age-matched high-A1C cohorts.[16] An increased number of boluses delivered is a risk factor for hypoglycemia,[17] and our data suggest that this increased risk is attributable to boluses given without the aid of the calculator.

Conclusions

Optimal glucose control remains significantly associated with increased risk of hypoglycemia, yet use of the TS feature as part of SAP therapy reduces the risk of NH substantially, in a manner independent of additional risk factors. Avoidance of manual bolus behavior—that is, dosing without the use of the bolus estimation calculator—may also help to the risk of NH.

Abbreviations

A1C, hemoglobin A1C; ASPIRE, automation to simulate pancreatic insulin response; LGS, low glucose suspend; NH, nocturnal hypoglycemia; SAP, sensor-augmented pump; SD, standard deviation; SG, sensor glucose; TS, threshold suspend.

Acknowledgments

In addition to the authors, the following individuals are members of the ASPIRE In-Home Study Group: R. Brazg (Rainier Clinical Research Center, Renton, WA); L. Casaubon (Texas Diabetes and Endocrinology, Austin, TX); B. Horowitz (Palm Beach Diabetes and Endocrine Specialists, West Palm Beach, FL); D. Liljenquist (Rocky Mountain Diabetes and Osteoporosis Center, Idaho Falls, ID); O. Odugbesan (Physicians Research Associates, LLC, Lawrenceville, GA); A. Bhargava (Iowa Diabetes and Endocrinology Center, Des Moines, IA); R. Goland (Naomi Berrie Diabetes Center, Columbia University, New York, NY); R. Weinstock (Joslin Diabetes Center at SUNY Upstate Medical University, Syracuse, NY). The research was presented in part in poster form at the American Diabetes Association meeting, San Francisco, CA, June 13-17, 2014.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RW serves as a consultant to Medtronic, Inc. SKG, RMB, DCK, BWB, TSB, JT, and FS received research support from Medtronic, Inc. JBW and FRK are employees of Medtronic, Inc.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by Medtronic, Inc.

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