Predictive Low-Glucose Insulin Suspension Reduces Duration of Nocturnal Hypoglycemia in Children Without Increasing Ketosis

Bruce A. Buckingham,[1] Dan Raghinaru,[2] Fraser Cameron,[3] B. Wayne Bequette,[3] H. Peter Chase,[4] David M. Maahs,[4] Robert Slover,[4] R. Paul Wadwa,[4] Darrell M. Wilson,[1] Trang Ly,[1] Tandy Aye,[1] Irene Hramiak,[5] Cheril Clarson,[6] Robert Stein,[6] Patricia H. Gallego,[6] John Lum,[2] Judy Sibayan,[2] Craig Kollman,[2] and Roy W. Beck,[2] for the In Home Closed Loop Study Group*

OBJECTIVE

Nocturnal hypoglycemia can cause seizures and is a major impediment to tight glycemic control, especially in young children with type 1 diabetes. We conducted an in-home randomized trial to assess the efficacy and safety of a continuous glucose monitor–based overnight predictive low-glucose suspend (PLGS) system.

RESEARCH DESIGN AND METHODS

In two age-groups of children with type 1 diabetes (11–14 and 4–10 years of age), a 42-night trial for each child was conducted wherein each night was assigned randomly to either having the PLGS system active (intervention night) or inactive (control night). The primary outcome was percent time <70 mg/dL overnight.

RESULTS

Median time at <70 mg/dL was reduced by 54% from 10.1% on control nights to 4.6% on intervention nights (*P* < 0.001) in 11–14-year-olds (*n* = 45) and by 50% from 6.2% to 3.1% (*P* < 0.001) in 4–10-year-olds (*n* = 36). Mean overnight glucose was lower on control versus intervention nights in both age-groups (144 ± 18 vs. 152 ± 19 mg/dL [*P* < 0.001] and 153 ± 14 vs. 160 ± 16 mg/dL [*P* = 0.004], respectively). Mean morning blood glucose was 159 ± 29 vs. 176 ± 28 mg/dL (*P* < 0.001) in the 11–14-year-olds and 154 ± 25 vs. 158 ± 22 mg/dL (*P* = 0.11) in the 4–10-year-olds, respectively. No differences were found between intervention and control in either age-group in morning blood ketosis.

CONCLUSIONS

In 4–14-year-olds, use of a nocturnal PLGS system can substantially reduce overnight hypoglycemia without an increase in morning ketosis, although overnight mean glucose is slightly higher.

In individuals with type 1 diabetes, hypoglycemia frequently occurs overnight and can result in a severe hypoglycemic event. In a randomized trial in children and adults (1) with 36,467 nights of continuous glucose monitor (CGM) data, the glucose level was ≤60 mg/dL (3.3 mmol/L) for at least 10 consecutive min on 8.5% of nights, and on 23% of those nights, the duration was >2 h. Several studies have reported a greater relative frequency of severe hypoglycemia during sleeping than during waking hours (2–4).

[1]Stanford University, Stanford, CA
[2]Jaeb Center for Health Research, Tampa, FL
[3]Rensselaer Polytechnic Institute, Troy, NY
[4]Barbara Davis Center for Childhood Diabetes, Aurora, CO
[5]St. Joseph's Health Care, London, ON, Canada
[6]Children's Hospital, London Health Sciences Centre, London, ON, Canada

Corresponding author: Roy W. Beck, rbeck@jaeb.org.

One of the benefits of real-time CGM is the ability of these devices to alarm for hypoglycemia; however, patients often do not awaken to these alarms (5). In a review of patients who had a nocturnal seizure while wearing a CGM device (6), the minimum duration of hypoglycemia before the seizure was >2 h, and often, there were 3–4 h of hypoglycemia before the seizure, allowing an opportunity for a system to suspend insulin delivery to prevent a seizure from occurring. A system is currently available that will suspend insulin delivery for up to 2 h or until the patient responds to the hypoglycemic alarm when a low-glucose threshold is reached (MiniMed 530G pump in the U.S., MiniMed Paradigm REAL-Time Veo pump in other countries; Medtronic MiniMed, Inc., Northridge, CA) (7,8). With this system the patient may already be hypoglycemic before insulin is suspended, and with currently available insulins, there is an ~60-min delay before the effective insulin action has been attenuated sufficiently so that glucose increases above the hypoglycemic threshold (9,10). A more sophisticated and potentially more effective approach is to suspend insulin delivery earlier on the basis of a prediction algorithm (11–14). We recently tested such a system in 15–45-year-old participants and found an 81% reduction in the median hypoglycemia area under the curve and a 74% reduction in hypoglycemia lasting >2 h (15).

In younger children, the prevention of nocturnal hypoglycemia may be particularly important because children may have a higher susceptibility to long-term neurologic damage due to repeated episodes of severe hypoglycemia (16,17). Recent studies using magnetic resonance imaging have shown changes in the gray matter of children with a history of hypoglycemia (18,19). In addition, fear of hypoglycemia, particularly overnight, has a major adverse impact on the quality of life of children with type 1 diabetes and their families (20,21). Because nocturnal hypoglycemia is a major concern in younger children, the goal of this study was to extend our previous studies of an overnight predictive low-glucose suspend (PLGS) system to young children in their home environment.

RESEARCH DESIGN AND METHODS

The study was conducted at three clinical centers. The protocol was approved by each institutional review board, and written informed consent was obtained from each participant or parent, with assent obtained as required. An independent data and safety monitoring board provided oversight. The protocol is available at http://jdrfconsortium.jaeb.org/Studies.aspx?RecID=228. Key aspects of the study protocol are described herein.

Study participants were enrolled in two age-cohorts: 11–14 and 3–10 years of age. In addition to age, major eligibility criteria were type 1 diabetes with use of daily insulin therapy for ≥1 year and an insulin infusion pump for ≥6 months and a glycated hemoglobin (HbA_{1c}) level measured with a point-of-care device ≤8.5% (69 mmol/mol). Additional criteria are listed in Supplementary Table 1.

The pump suspension system comprised a MiniMed Paradigm REAL-Time Veo System with Enlite glucose sensor (Medtronic Diabetes), in which the CGM and pump communicated with a bedside laptop computer running the hypoglycemia prediction algorithm (referred to as "the system"). The system used a Kalman filter to estimate the glucose level and rate of change and suspended basal insulin delivery if the current sensor glucose was <230 mg/dL and predicted to fall to <80 mg/dL in the next 30 min. Insulin was automatically suspended for sensor glucose values ≤70 mg/dL. Basal insulin was restored on the first CGM rise during insulin suspension. An algorithm to detect pressure-induced sensor attenuations also was incorporated into the pump suspension algorithm (22). For safety reasons, pump suspension could not exceed 120 min in a 150-min window or a cumulative total of 180 min per night. Audible alarms were set at 60 mg/dL on both intervention and control nights. For a system or sensor failure, there were no additional alarms, and the participant continued to receive his or her usual basal rate. This was designed with the goal of minimizing the number of alarms that would disrupt a participant's sleep. Additional details about the system have been published (13,15,23). There was no real-time remote monitoring; however, each morning, data from the previous night were reviewed by the coordinating center, and research staff were notified of severe events that required contacting the family (overnight sensor glucose readings <50 mg/dL [2.8 mmol/L] or >300 mg/dL [16.7 mmol/L] for >30 min).

Initially, only participants 11–14 years of age were enrolled until 200 nights in the randomized trial were completed and the data reviewed by the data and safety monitoring board. Enrollment was then opened to participants 7–10 years of age, and similarly, after data from 200 randomized nights were reviewed in this age-group, enrollment was opened to 3–6-year-olds. Training on the use of the Medtronic pump-CGM system and a run-in phase preceded the randomized trial. During the initial part of the run-in phase, the CGM was used for 10–15 days to verify that the participant could successfully use the CGM device and to document a minimum amount of nocturnal hypoglycemia, defined as at least 1 night with a sensor glucose value ≤60 mg/dL or at least 3 different nights with a sensor glucose value ≤70 mg/dL. Participants who met these criteria then used the complete system at home for 5 nights to verify successful system use. Eight participants in the 11–14-year age-group and seven in the 4–10-year age-group did not successfully complete the run-in phase.

During the randomized trial, the system was used until 42 nights with at least 4 h of sensor glucose data per night were completed. Clinic visits occurred after 21 days and after completion of 42 successful nights. Treatment adjustments were permitted during the course of the study for diabetes management purposes. The laptop contained a randomization schedule, to which the participant was blinded, that indicated whether the hypoglycemia prediction algorithm would be in operation that night (intervention night) or would not be activated (control night), with one-half being the intervention nights and one-half being the control nights. A bedtime meter blood glucose level between 90 and 270 mg/dL was required to initialize the system each night. Participants were instructed to use the system on consecutive nights if possible but to avoid system use during periods of illness. The maximum number of days to complete the 42 nights of the study was 90. When the system was stopped in the morning, measurements of blood glucose (with CONTOUR NEXT LINK meter and CONTOUR NEXT USB; Bayer HealthCare, Whippany, NJ), blood ketone (with Precision Xtra meter; Abbott Diabetes Care, Alameda, CA), and urine ketone (with Ketostix

Reagent Strips for Urinalysis; Bayer, Pittsburgh, PA) levels were performed, and overnight carbohydrate intake was recorded. During the day, the participants used the CGM device and pump as they would for usual diabetes management (without the algorithm being active). The threshold-based low-glucose suspend feature of the Veo pump was disabled during the study.

HbA_{1c} was measured using a point-of-care device (Siemens DCA Vantage analyzer). Adverse event reporting included severe hypoglycemia, diabetic ketoacidosis, and any study- or device-related event.

Statistical Methods

The primary outcome was percent time <70 mg/dL pooled across nights. However, sample size was calculated to have at least 80% statistical power with a type I error rate of 5% for a secondary outcome comparison of the frequency of intervention versus control nights with at least one CGM glucose value <60 mg/dL. For this outcome in each of the two age-cohorts, sample size was calculated to be 45 participants using the system for 42 nights (21 nights with the system active and 21 control nights), assuming true population outcome rates of 25% of control nights and 15% of intervention nights after adjusting for the correlation from repeated nights and misclassification due to sensor inaccuracy. With this sample size, the statistical power in each age-group was 90% for a 40% relative reduction in the primary outcome of percent time <70 mg/dL. Enrollment was discontinued before the recruitment goal was achieved in the 3–10-year-old cohort, with the youngest enrolled child being 4.5 years of age.

Analyses were conducted separately for the two age-cohorts as if they were separate trials. The analysis followed a modified intention-to-treat principle with prespecified data exclusion described next, with each night analyzed by the randomly assigned treatment arm. The time period for outcome assessment each night was from the participant's activation of the system at bedtime until deactivation the following morning. All randomized nights were included in safety analyses; however, based on an a priori rule, the efficacy analysis included only randomized nights with ≥4 h of CGM glucose data and only participants with ≥80 h of CGM glucose data in each treatment

arm (71 intervention nights and 105 control nights were excluded for <4 h of CGM data, and one participant with 5 intervention nights and 5 control nights was excluded for <80 h of CGM glucose data). A sensitivity analysis including all nights produced similar results (data not shown).

The primary outcome measure of percent time <70 mg/dL and other continuous measures were calculated by pooling CGM data across nights by treatment arm for each participant. Safety outcomes were morning blood glucose and ketone levels. For pooled outcomes, continuous repeated-measures regression models with an unstructured covariance structure were used to test the differences between the two treatment arms while adjusting for the averaged bedtime blood glucose value across nights. Logarithmic or square root transformations were used for outcome variables with a skewed distribution. For night-level secondary outcomes (e.g., proportion of nights with at least one CGM glucose concentration <60 mg/dL), generalized linear mixed models with a logistic link function for the binary outcomes were used to test the differences between the two treatment arms using random participant effects and a within-participant autocorrelation structure to account for multiple nights from the same participant while adjusting for bedtime blood glucose level. HbA_{1c} values before and after the study were compared using the signed rank test.

For sensor accuracy analysis, glucose measurements from the home blood glucose meter during system use were paired to the closest CGM measurement within ±5 min. The relative absolute difference (RAD) was calculated for each pair.

No adjustment was made for multiple comparisons. The percent time <70 mg/dL was the primary outcome, and the other efficacy metrics were considered secondary exploratory analyses. All P values are two-tailed, and analyses were performed using SAS 9.4 software.

RESULTS

Participants 11–14 Years of Age

The trial included 45 children 11–14 years of age (median age 13 years, 56% male, 96% Caucasian, median type 1 diabetes duration 6 years, median HbA_{1c} 7.7% [61 mmol/mol]) (Supplementary Table 2). All 45 completed the trial (Supplementary

Fig. 3A), with 44 (98%) completing the protocol-specified 42 nights of the study and 1 completing 31 nights. The median number of nights to complete the study was 59 (Supplementary Table 4). Overall, 1,896 valid nights were included in the analyses, with 955 being intervention nights (8,673 h of CGM data) and 941 being control nights (8,565 h of CGM data).

One or more pump suspensions occurred on 671 of the 955 intervention nights (70%) with a median total duration of pump suspension of 60 min (interquartile range [IQR] 24, 115; mean ± SD glucose at first pump shutoff 108 ± 31 mg/dL). On 81 (12%) nights, there was a pump suspension lasting 120 min within a 150-min window, and on 14 (2%) nights, cumulative suspension time was the maximum 3 h.

Median percent time <70 mg/dL was reduced by 54% from 10.1% (IQR 5.9, 13.8) during control nights to 4.6% (IQR 2.9, 7.3) during intervention nights (P < 0.001) (Table 1). Results were consistent for other outcomes (Table 1). At least one CGM glucose reading <60 mg/dL occurred on 29% of control nights vs. 21% of intervention nights (P < 0.001). At least one hypoglycemic event with CGM glucose <60 mg/dL continuously for >120 min occurred on 8% of control nights vs. 3% of intervention nights (P < 0.001), with similarly significant reductions for events lasting at least 10, 25, and 60 min. There also were significant reductions in percentage of intervention nights compared with control nights in which CGM glucose concentrations were <60 mg/dL for at least 30, 60, 120, and 180 min cumulatively over the entire night (Fig. 1A and Supplementary Table 5). As shown in Fig. 2A, the treatment arm difference in occurrence of overnight CGM values <70 mg/dL was most prominent after the first 3 h. Supplementary Fig. 6A and B show the glucose values before and after the occurrence of events <70 mg/dL.

Overnight mean glucose was higher on intervention nights than on control nights (mean 152 vs. 144 mg/dL, P < 0.001). Mean time in the target range of 70–180 mg/dL was 66% vs. 64% (P = 0.10), median time >180 mg/dL was 30% vs. 25% (P = 0.04), and median time >250 mg/dL was 6% vs. 4% (P = 0.18) on intervention versus control nights, respectively (Table 1).

Mean ± SD morning blood glucose was 176 ± 28 mg/dL following

Table 1—Efficacy and safety outcomes*

	Participants 11–14 years of age (n = 45)			Participants 4–10 years of age (n = 36†)		
	Control nights (n = 941)	Intervention nights (n = 955)	P value	Control nights (n = 755)	Intervention nights (n = 769)	P value
Bedtime glucose, baseline						
Blood glucose (mg/dL)	168 ± 20	166 ± 18	—	162 ±18	165 ± 15	—
Primary analysis						
Time spent <70 mg/dL (%)	10.1 (5.9, 13.8)	4.6 (2.9, 7.3)	<0.001	6.2 (3.0, 7.6)	3.1 (1.6, 5.0)	<0.001
Secondary analysis						
Hypoglycemia outcomes						
Time spent <60 mg/dL (%)	5.8 (2.9, 8.1)	1.9 (1.4, 3.9)	<0.001	2.3 (1.1, 4.6)	1.2 (0.5, 2.8)	<0.001
Time spent <50 mg/dL (%)	2.8 (0.9, 3.9)	0.8 (0.2, 1.9)	<0.001	0.5 (0.1, 2.5)	0.6 (<0.1, 1.2)	0.03
Low blood glucose index	2.33 (1.62, 3.03)	1.08 (0.80, 1.84)	<0.001	1.45 (0.74, 2.00)	0.76 (0.47, 1.31)	<0.001
Percent of nights with ≥1 value						
<70 mg/dL	39	34	0.01	33	28	0.04
<60 mg/dL	29	21	<0.001	24	19	0.01
<50 mg/dL	17	12	<0.001	14	10	0.005
Percent of nights with events of glucose <60 mg/dL continuously§ for						
>10 min	27	19	<0.001	22	15	<0.001
>25 min	21	14	<0.001	17	10	<0.001
>60 min	13	7	<0.001	7	5	0.03
>120 min	8	3	<0.001	5	1	<0.001
Overall outcomes						
Overnight mean glucose (mg/dL)	144 ± 18	152 ± 19	<0.001	153 ± 14	160 ± 16	0.004
Time in range 70–180 mg/dL (%)	64 ± 10	66 ± 10	0.10	63 ± 10	63 ± 11	0.50
Hyperglycemia outcomes						
Time spent >180 mg/dL (%)	25 (18, 32)	30 (23, 33)	0.04	31 (23, 37)	32 (24, 43)	0.23
Time spent >250 mg/dL (%)	4 (3, 8)	6 (4, 9)	0.18	7 (4, 10)	6 (5, 12)	0.77
Morning glucose outcomes						
Blood glucose (mg/dL)	159 ± 29	176 ± 28	<0.001	154 ± 25	158 ± 22	0.11
Percent of mornings with blood glucose						
<50 mg/dL	<1	0	NA‡	<1	<1	NA‡
<60 mg/dL	1	1	0.01	1	1	0.15
<70 mg/dL	4	1	<0.001	5	1	<0.001
70–180 mg/dL	64	57	<0.001	66	70	0.11
>180 mg/dL	32	42	<0.001	29	29	0.97
>250 mg/dL	10	11	0.57	9	7	0.18
With blood ketones ≥1.0 mmol/L	0.4	1.0	0.16	2.9	2.3	0.39
With blood ketones ≥0.6 mmol/L	1.7	2.2	0.39	8.0	9.9	0.10
With urine ketones ≥ "small"	1.4	1.7	0.53	2.6	3.5	0.28

Data are mean ± SD, median (IQR), or %. NA, not applicable. *Glucose results from CGM unless specified as blood glucose. †One participant with 5 intervention nights and 5 control nights was excluded for <80 h of CGM glucose data. §Hypoglycemia event assessment based on CGM values below threshold was added to statistical analysis plan post hoc. ‡Too few events for formal statistical comparison.

intervention nights vs. 159 ± 29 mg/dL following control nights ($P < 0.001$) (Table 1), with increased sensor glucose levels persisting for several hours after system deactivation (Fig. 3A). As seen in Table 1, the frequency of elevated morning urine or blood ketones was low and similar in the two treatment arms. Median change in HbA_{1c} level from baseline to the end of the trial was −0.2% (IQR −0.6%, 0.2%; $P = 0.06$).

Participants 4–10 Years of Age

The trial included 37 children 4–10 years of age (median age 8 years, 46% male; 95% Caucasian, median type 1 diabetes duration 3 years, median HbA_{1c} level 7.8% [62 mmol/mol]) (Supplementary Table 2). Thirty-six completed the trial (Supplementary Fig. 3B), with 34 (92%) completing the protocol-specified 42 nights of the study and the other 3 completing 10, 39, and 40 nights. The median number of nights to complete the study was 63 (Supplementary Table 4). Overall, 1,524 valid nights were included in the analyses, with 769 being intervention nights (7,230 h of CGM data) and 755 being control nights (7,143 h of CGM data).

One or more pump suspensions occurred on 503 of the 769 intervention nights (65%), with a median total duration of pump suspension of 53 min (IQR 24, 101; mean ± SD glucose at pump shut off 106 ± 27 mg/dL). On 37 (7%) nights, there was a pump suspension lasting 120 min within a 150-min window and on 9 (2%) nights; cumulative suspension time was the maximum 3 h.

Median percent time <70 mg/dL was reduced by 50% from 6.2% (IQR 3.0, 7.6) during control nights to 3.1% (IQR 1.6, 5.0) during intervention nights ($P < 0.001$) (Table 1). Results were consistent for other outcomes (Table 1). At least one CGM glucose reading
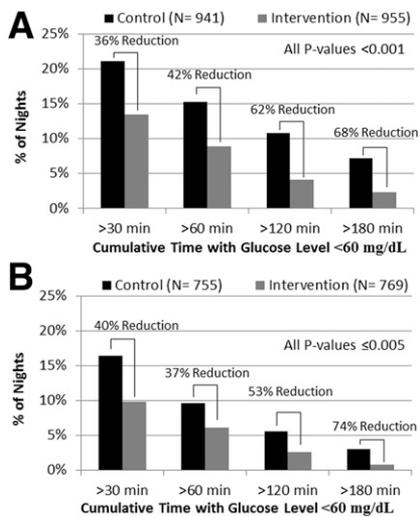
Figure 1—Percentage of nights with various durations of glucose levels <60 mg/dL for the two treatments groups. A: Among participants 11–14 years of age, the percentages of nights when total cumulative time with sensor glucose <60 mg/dL was >30, 60, 120, and 180 min are shown for the intervention and control arms along with the relative percent reduction. B: The same data as A for participants 4–10 years of age.

Figure 2—Median glucose and percent time when glucose was <70 mg/dL from system activation for the two treatment groups. A: Among participants 11–14 years of age, median sensor glucose (mg/dL) and percent time <70 mg/dL every 10 min by minutes from system activation are shown for the intervention and control arms. B: The same data as A for participants 4–10 years of age.

<60 mg/dL occurred on 24% of control nights vs. 19% of intervention nights (*P* = 0.01). At least one hypoglycemic event with CGM glucose <60 mg/dL continuously for >120 min occurred on 5% of control nights vs. 1% of intervention nights (*P* < 0.001), with similarly significant reductions for events lasting at least 10 and 25 min. There also were significant reductions in percentage of intervention nights compared with control nights in which CGM glucose concentrations were <60 mg/dL for at least 30, 60, 120, and 180 min cumulatively over the entire night (Fig. 1*B* and Supplementary Table 5). As shown in Fig. 2*B*, the treatment arm difference in occurrence of overnight CGM values <70 mg/dL was most prominent after the first 3 h. Supplementary Fig. 6*C* and *D* show the glucose values before and after the occurrence of events <70 mg/dL.

Overnight mean glucose was higher on intervention than on control nights (mean 160 mg/dL vs. 153 mg/dL, *P* = 0.004). Mean time in the target range of 70–180 mg/dL was 63% in both arms (*P* = 0.50), median time >180 mg/dL was 32% vs. 31% (*P* = 0.23), and median time >250 mg/dL was 6% vs. 7% (*P* = 0.77) on intervention versus control nights, respectively (Table 1).

Mean ± SD morning blood glucose was 158 ± 22 mg/dL following intervention

nights vs. 154 ± 25 mg/dL following control nights (*P* = 0.11) (Table 1). Following system discontinuation in the morning, sensor glucose values appeared similar after either intervention or control nights (Fig. 3*B*). As seen in Table 1, the frequencies of elevated morning urine or blood ketones were higher than those in the 11–14-year-old group but similar in the two treatment arms. Median change in HbA$_{1c}$ level from baseline to end of the trial was −0.2% (IQR −0.4%, 0.2%; *P* = 0.23).

Additional Analyses in Both Age-Groups
CGM data were available for an average across participants of 98% of the time the

system was active on nights included in the efficacy analysis. An analysis applying the algorithm to the data collected on control nights predicted a glucose level <80 mg/dL on 1,148 of 1,696 nights (68%). The sensor glucose level actually dropped to <80 mg/dL within 2 h on 600 (52%) nights (Supplementary Table 7). On intervention nights, there was no significant difference in the frequency of hypoglycemic events when comparing nights where the system was active the previous night versus nights where the system was not active the prior night (data not shown).

After adjusting for the reported negative bias of the Enlite sensor from a prior
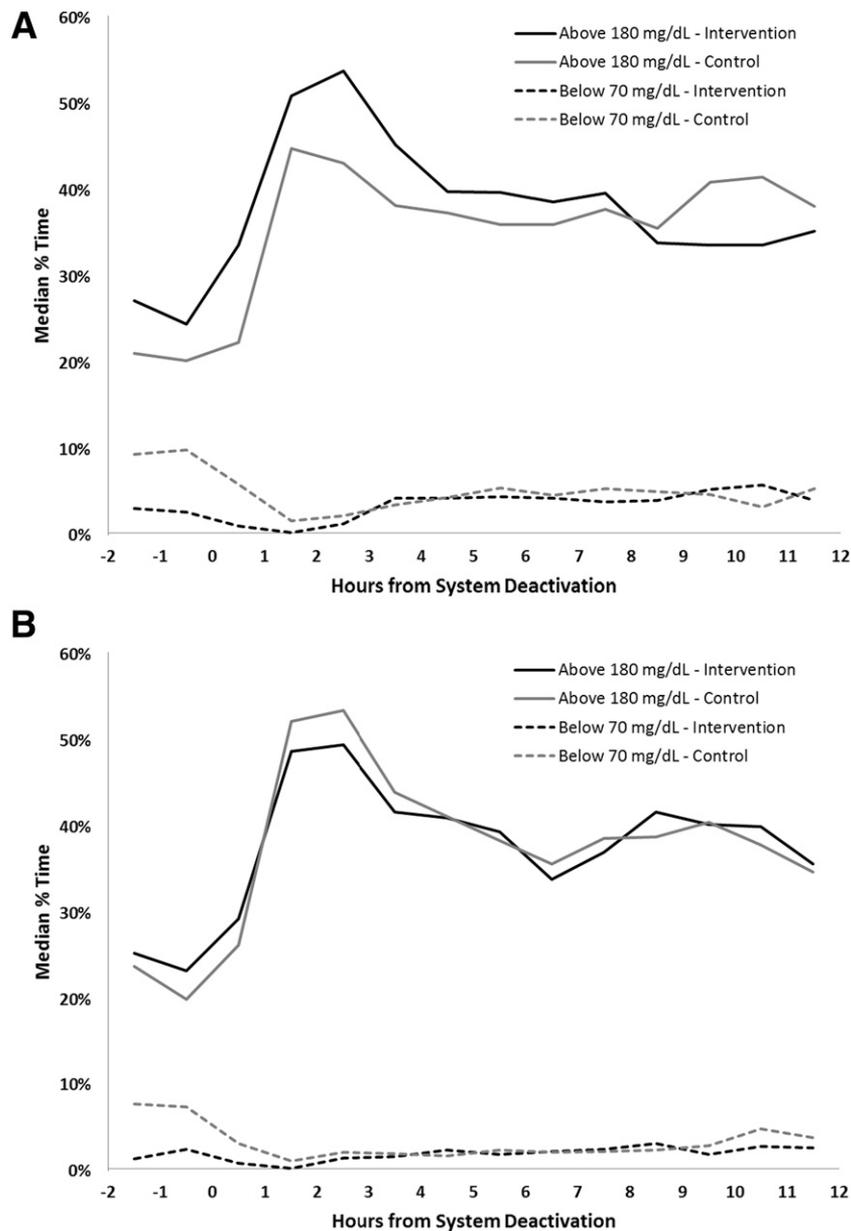
Figure 3—Median percent time when glucose was <70 mg/dL and >180 mg/dL after system deactivation for the two treatment groups. *A*: Among participants 11–14 years of age, hourly median percentage of time sensor glucose was <70 mg/dL and >180 mg/dL, starting 2 h before and ending 12 h after system deactivation, are shown for the intervention and control arms. *B*: The same data as *A* for participants 4–10 years of age.

accuracy study (24), the percent reduction in median time <70 mg/dL remained similar (data not shown). Sensor accuracy results were similar on control and intervention nights (mean RAD 18% vs. 19%, respectively, in 11–14-year-olds and 18% vs. 18%, respectively, in 4–10-year-olds). Additional data on sensor accuracy are provided in Supplementary Tables 8 and 9. Supplementary Table 10 shows the distribution of pump suspensions and their duration by time of night.

Adverse Events
There were no cases of severe hypoglycemia, diabetic ketoacidosis, or other serious adverse events during the trial. One reportable adverse event (a methicillin-resistant *Staphylococcus aureus* infection at a pump infusion set site) was related to use of a study device.

CONCLUSIONS
In this study in a home setting, an overnight PLGS system substantially reduced nocturnal hypoglycemia in children 4–14

years of age. Mean overnight glucose concentrations were slightly increased on intervention nights, but there was no increase in morning ketones. These effects of the system are similar to what was observed in our previously published study in adolescents and adults (15). In the current study, the percentage of nights with a pump suspension decreased with the age of the participants (70% and 65% for 11–14- and 4–10-year-olds, respectively), which coincided with an increase in mean sensor glucose values overnight (144 and 153 mg/dL on control nights, respectively). The median duration of pump suspensions also decreased from 60 min in 11–14-year-olds to 53 min in 4–10-year-olds, whereas the mean glucose at first suspension did not differ (108 and 106 mg/dL, respectively).

There have been concerns that a system that suspends insulin delivery overnight will increase nocturnal and fasting glucose levels and morning ketones or even result in ketoacidosis. In this study, pump suspensions were frequent partly as a result of the hypoglycemia-prone study population but often brief because of the algorithm design. In both age-groups, there was no increase in morning ketones following intervention nights compared with control nights. Fasting meter glucose levels were increased by 17 mg/dL after intervention compared with control nights in the 11–14-year-olds, similar to the 15 mg/dL increase we previously observed in 15–45-year-olds on intervention nights; however, an insignificant increase of 4 mg/dL was seen in the 4–10-year-olds. The increased fasting glucose levels in the 11–14-year-olds resulted in a slight increase in glucose levels, which persisted until lunchtime (Fig. 3*A*), an effect that was not seen in the 4–10-year-olds (Fig. 3*B*). Because randomization was nightly, HbA$_{1c}$ levels between intervention and control cannot be compared; however, we can extrapolate the potential effect of increasing glucose levels on HbA$_{1c}$ levels. If we assume the PLGS raised mean glucose levels by 8 mg/dL for 12 h, this would extrapolate to an increase in HbA$_{1c}$ of ~0.16% (25,26). This small increase in HbA$_{1c}$ levels would have a minimal impact on long-term complications, whereas the risk for prolonged nocturnal hypoglycemia was significantly decreased by the PLGS system.

There are some limitations to this study. To better judge the efficacy of

the system, we selected participants likely to experience nocturnal hypoglycemia by including only those who had an HbA_{1c} level ≤8.5% (69 mmol/mol) and at least a minimum amount of nocturnal hypoglycemia during a run-in phase. We only tested one continuous glucose sensor, the Enlite by Medtronic. Although sensor accuracy was less than optimal for a PLGS system (median RAD 14%), because accuracy was similar on intervention and control nights, sensor inaccuracy should not have affected the comparative outcome metrics. However, absolute numbers of hypoglycemic events may have been different using a sensor with greater accuracy. Participants did not know whether the system was active before they went to bed, which was a valuable aspect of the study design for minimizing bias, but it precluded the ability to observe what would happen if the participants knew the system was active each night. There is a possibility that such knowledge might result in more aggressive insulin bolusing at bedtime and overnight basal rates. As with many of the other nocturnal closed-loop studies (15,27–30), the system was only able to mitigate hypoglycemic events about 3 h after the system was activated, probably because of the inability of pump suspension to compensate for insulin on board from previous insulin boluses given before the system was activated (dinner and bedtime insulin boluses).

Fear of nocturnal hypoglycemia causes many parents of younger children with type 1 diabetes to perform overnight blood glucose tests, which can adversely affect patient quality of life and that of their families (20,21). In addition, because of this fear for many of these young children, high overnight glycemic targets are set, resulting in substantial periods of hyperglycemia. A system such as the one proposed that reduces the incidence of nocturnal hypoglycemia may have a substantial beneficial effect on patient and parent quality of life.

Implementation of full, closed-loop control overnight would achieve a reduction in both nocturnal hypoglycemia and nocturnal hyperglycemia. In the diabetes setting, closed-loop studies have significantly decreased the rate of nocturnal hypoglycemia without increasing mean glucose levels (29,30). Recently, several overnight closed-loop control studies have been done in the home setting with or without remote monitoring

(27,28), demonstrating significant improvement in glycemic variability and time in range; however, a significant improvement in the percent time <70 mg/dL was only seen in one (28). When a bihormonal system is used with the addition of a second glucagon pump, a significant decrease in nocturnal hypoglycemia was seen in adults (31). Compared with studies with insulin pump suspension, implementing full closed-loop control at night has the added risk of delivering insulin based on sensor glucose measurements, although with improving glucose sensor accuracy and reliability, full nocturnal closed-loop control becomes increasingly practical. However, for those unwilling to risk overdelivery of insulin due to sensor error, a PLGS system remains attractive for decreasing the risk of nocturnal hypoglycemia while causing only a minimal increase in glucose levels.

Appendix

In Home Closed Loop Study Group

Clinical Centers. Listed with clinical center name, city, and state. Personnel are listed as (PI) for Principal Investigator, (I) for co-Investigator, (C) for Coordinators, and (O) for Other Personnel. *Division of Pediatric Endocrinology and Diabetes, Stanford University, Stanford, CA:* Bruce A. Buckingham (PI); Darrell M. Wilson (I); Trang Ly (I); Tandy Aye (I); Paula Clinton (C); Kimberly Caswell (C); Jennifer Block (C); Breanne P. Harris (O). *Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver, CO*: H. Peter Chase (PI); David M. Maahs (I); Robert Slover (I); R. Paul Wadwa (I); Dena Gottesman (C); Laurel Messer (C); Emily Westfall (O); Hannah Goettle (C). *St. Joseph's Health Care, London, ON:* Irene Hramiak (PI); Marsha Driscoll (C); Sue Tereschyn (O). *Children's Hospital, London Health Sciences Centre, London, ON:* Cheril Clarson (PI); Robert Stein (I); Patricia H. Gallego (I); Margaret Watson (C); Keira Evans (O). *Rensselaer Polytechnic Institute, Troy, NY:* B. Wayne Bequette (PI); Fraser Cameron (I). *JDRF Canadian Clinical Trial Network:* Olivia Lou (O).

Coordinating Center. Jaeb Center for Health Research, Tampa, FL: Roy W. Beck (PI); John Lum (O); Craig Kollman; Dan Raghinaru; Judy Sibayan (O); Nelly M. Njeru (O); Denny Figuerres (O); Carlos Murphy (O).

Data and Safety Monitoring Board. John C. Pickup (chair); Irl Hirsch; Howard Wolpert.

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