Original Investigation

Effect of Sensor-Augmented Insulin Pump Therapy and Automated Insulin Suspension vs Standard Insulin Pump Therapy on Hypoglycemia in Patients With Type 1 Diabetes
A Randomized Clinical Trial

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IMPORTANCE Hypoglycemia is a critical obstacle to the care of patients with type 1 diabetes. Sensor-augmented insulin pump with automated low-glucose insulin suspension has the potential to reduce the incidence of major hypoglycemic events.

OBJECTIVE To determine the incidence of severe and moderate hypoglycemia with sensor-augmented pump with low-glucose suspension compared with standard insulin pump therapy.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 95 patients with type 1 diabetes, recruited from December 2009 to January 2012 in Australia.

INTERVENTIONS Patients were randomized to insulin pump only or automated insulin suspension for 6 months.

MAIN OUTCOMES AND MEASURES The primary outcome was the combined incidence of severe (hypoglycemic seizure or coma) and moderate hypoglycemia (an event requiring assistance for treatment). In a subgroup, counterregulatory hormone responses to hypoglycemia were assessed using the hypoglycemic clamp technique.

RESULTS Of the 95 patients randomized, 49 were assigned to the standard-pump (pump-only) therapy and 46 to the low-glucose suspension group. The mean (SD) age was 18.6 (11.8) years; duration of diabetes, 11.0 (8.9) years; and duration of pump therapy, 4.1 (3.4) years. The baseline rate of severe and moderate hypoglycemic events in the pump-only group was 20.7 vs 129.6 events per 100 patient months in the low-glucose suspension group. After 6 months of treatment, the event rates decreased from 28 to 16 in the pump-only group vs 175 to 35 in the low-glucose suspension group. The adjusted incidence rate per 100 patient-months was 34.2 (95% CI, 22.0-53.3) for the pump-only group vs 9.5 (95% CI, 5.2-17.4) for the low-glucose suspension group. The incidence rate ratio was 3.6 (95% CI, 1.7-7.5; P <.001). There was no change in glycated hemoglobin in either group: mean, 7.4 (95% CI, 7.2-7.6) to 7.4 (95% CI, 7.2-7.7) in the pump-only group vs mean, 7.6 (95%, CI, 7.4-7.9) to 7.5 (95% CI, 7.3-7.7) in the low-glucose suspension group. Counterregulatory hormone responses to hypoglycemia were not changed. There were no episodes of diabetic ketoacidosis or hyperglycemia with ketosis.

CONCLUSIONS AND RELEVANCE Sensor-augmented pump therapy with automated insulin suspension reduced the combined rate of severe and moderate hypoglycemia in patients with type 1 diabetes.

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Hypoglycemia is a critical obstacle to the care of patients with type 1 diabetes. Sensor-augmented pump therapy with an automated insulin suspension or low glucose suspension function allows insulin delivery to be ceased automatically for up to 2 hours when sensor glucose falls below a preset threshold. This technology has the potential to reduce the duration and frequency of significant hypoglycemia. Early reports suggest that automated insulin suspension is safe[1,2] and may reduce the time patients' glucose levels are in the hypoglycemic range.[1,3-6] It remains to be determined, however, whether the use of this approach in ambulatory patients is associated with a reduced incidence of significant hypoglycemic events.

The primary objective of this study was to determine the incidence of severe and moderate hypoglycemia with sensor-augmented pump therapy with a low-glucose suspension function compared with standard insulin pump therapy. The primary outcome was the incidence of severe and moderate hypoglycemia.

For the patient, a reduction in the risk of a major hypoglycemia event is the most relevant potential benefit of insulin suspension. However, such events are rarely the primary outcome of clinical trials involving patients with type 1 diabetes because such events are uncommon. To overcome this, we selected patients with impaired awareness of hypoglycemia because these individuals are at significantly higher risk of experiencing hypoglycemic events.[7] Approximately one-third of patients with type 1 diabetes have evidence of impaired hypoglycemia awareness.[8-10] Including patients in the trial with impaired hypoglycemia awareness also provided the opportunity to study whether the use of automated insulin suspension can improve counterregulatory hormone responses to hypoglycemia.

Methods

Patients

Eligible patients included those aged 4 to 50 years with type 1 diabetes receiving insulin pump therapy, having been diagnosed with diabetes for at least a year, being treated with an insulin pump for at least 6 months, having a glycated hemoglobin level of 8.5% or lower, and having impaired awareness of hypoglycemia. Hypoglycemia unawareness score (HUS) was determined with the modified Clarke questionnaire[11] with a minimum score of 4, suggestive of impaired hypoglycemia awareness. Exclusion criteria included use of sensor-augmented insulin pump therapy and pregnancy. The ethics committees of participating institutions approved the protocol, and participants gave written informed consent. Participants were recruited from tertiary adult and pediatric hospitals in Western Australia between December 2009 and January 2012.

Randomization was computer-generated and stratified by 5 age groups (4-7, 8-11, 12-17, 18-25, and 26-50 years) with random block size. Patients were randomized either to continue using the insulin pump or to use the sensor-augmented pump with low-glucose suspension activation. As with other studies using these technologies, it was not possible to blind the patients to the intervention.

Study Protocol

All patients attended a screening visit 3 months before and were randomized a week before their baseline visit. Patients then attended 2 more visits, 3 months and 6 months after the baseline visit. A retrospective continuous glucose-monitoring device (Medtronic iPro2, Medtronic Minimed) was inserted at baseline and at each visit during the intervention period to allow measurement of glucose values over 6 days to determine the amount of time they were in the hypoglycemic range.

Treatment

Patients in the low-glucose suspension group began using the sensor-augmented pump (Medtronic Paradigm Veo System, Medtronic Minimed) with automated insulin suspension when the sensor glucose reached a preset low-glucose threshold of 60 mg/dL (to convert glucose to mmol/L, multiply by 0.0555). As sensor glucose decreases to this level, the pump emits an alarm. If the patient does not respond to the alarm, insulin delivery is suspended for up to 2 hours, after which standard basal insulin delivery resumes. The patient may intervene at any stage throughout this 2-hour period to either continue suspension or resume insulin delivery.

Patients in the low-glucose suspension group received a standardized education session before commencing sensor-augmented pump therapy at the baseline visit. Patients were asked to contact the research team if they required technical assistance with the device during the 6-month study period. Patients uploaded their pumps to the Medtronic CareLink website weekly, allowing evaluation of patient use and patterns of insulin suspension. Those using the low-glucose suspension device were advised to use the system throughout the intervention.

Patients randomized to insulin pump only continued on their own pump for the 6-month study period. All patients were advised to continue under the management of their usual clinical team for regular clinical review. Patients in both groups were advised to continue on their usual fingerstick blood glucose-monitoring schedule. Clinical advice regarding diabetes management was not given by the research team. Patient questions were directed to the treating physician.

Outcome Measures

At the screening visit, patients were asked about severe and moderate hypoglycemic events in the previous 3 months. Patients were then asked to keep a diary for prospective documentation of the date, time, symptoms, blood glucose value, and treatment administered for each severe and moderate hypoglycemic event occurring from the screening visit through the final study visit. The primary outcome was the combined incidence of severe and moderate hypoglycemia. *Severe hypoglycemia* was defined as a hypoglycemic seizure or coma. *Moderate hypoglycemia* was defined as a hypoglycemic event requiring assistance from another person. Parents of patients 12 years or younger were asked about specific symptoms of neuroglycopenia such as impaired consciousness or confusion, re-

quiring assistance. Data were collected by a limited number of clinical staff (T.T.L. and J.A.N.).

Both groups had equal opportunity to detect hypoglycemic events since the events were identified in an identical manner and, where possible, confirmed by fingerstick glucose. All patients received instruction on how to record and respond to defined events. These data were reviewed and recorded at each subsequent study visit. Baseline hypoglycemia rates were obtained from data obtained in the 6 months prior to the baseline visit (at the screening and the baseline visits). End point hypoglycemia rates were obtained from data collected in the 6 months after the baseline visit. Potential adverse events were also recorded. Patients were instructed to test blood ketones if glucose values were greater than 270 mg/dL. In addition, episodes of diabetic ketoacidosis requiring hospitalization were documented.

The average percentage of time spent in the hypoglycemic range was obtained from 6-day retrospective continuous glucose monitoring obtained at each visit. The day period represents data from 06:00 to 22:00 hours and night period from 22:00 to 06:00 hours.

The modified Clarke questionnaire[11] for hypoglycemia unawareness was completed by patients who were 12 years or older. Parents of participants aged 4 to 18 years completed the parent version of HUS.

Hypoglycemic Clamp Studies

All recruited patients between 12 and 26 years were invited to participate in hypoglycemic clamp studies before and after the intervention period. The first 15 patients who agreed from each group were included. Clinical characteristics of this subgroup were similar to those of the overall group (mean [SD] age, 16.4 [3.2] years; diabetes duration, 9.5 [4.3] years; insulin dose, 0.81 [0.15] units/kg; and hypoglycemia unawareness score, 5.7 [1.2]). The hypoglycemic clamp technique has been previously described.[12] In summary, intravenous insulin is infused at 80 mU/m^2 per minute and 20% glucose is infused simultaneously to maintain blood glucose levels at 100 mg/dL for 60 minutes (euglycemia) before reducing over 30 minutes to 50 mg/dL for 40 minutes (hypoglycemia). Samples for epinephrine were taken every 10 to 30 minutes during the baseline euglycemia and hypoglycemia phases. Three samples were obtained in each phase. Epinephrine response was calculated as the mean difference in epinephrine concentration obtained during hypoglycemia compared with baseline euglycemia.

Laboratory Measurements

Glycated hemoglobin was assessed by an agglutination inhibition immunoassay (DCA Vantage, Siemens Medical). The interassay coefficient of variation was 2.8% and intraassay, 2.3%. Plasma epinephrine was measured by high-performance liquid chromatography (Ultimate 2000, Dionex). The interassay coefficient of variation at epinephrine concentrations of 83 pg/mL (to convert epinephrine from pg/mL to pmol/L, multiply by 5.459) was 9.9% and at 981.86 pg/mL, 10.9%.

Statistical Analysis

Sample size calculation was based on the combined incidence rate of moderate and severe hypoglycemic events from the type 1 diabetes clinic at Princess Margaret Hospital.[13] In a study examining the incidence of hypoglycemia in a population-based sample of children with type 1 diabetes, we found that children with impaired awareness of hypoglycemia had an incidence of severe hypoglycemia 5 to 6 times greater than patients reporting normal awareness.[7] The incidence rate for hypoglycemia has been between 1.4 to 4.0 episodes per 100 patient-months over the last 10 years.[13]

To observe a clinically significant reduction in the incidence of hypoglycemia events by 50%, a sample of 38 patients in each group followed up for 6 months was required. This assumed an α level of 5% and power of 80% and was calculated using person-year rate.[14] A sample size of 50 patients in each group allowed for withdrawals in each group of 24%.

All statistical analyses were performed using SAS for Windows, version 9.3 (SAS Institute Inc) and STATA version 11.2 (StataCorp). Unless otherwise specified, all data were analyzed using the intention-to-treat population, which was defined as all patients who were randomized and had at least 1 visit after baseline. *P* values <.05 were considered statistically significant; 2-sided *P* values are reported. Descriptive statistics were used to characterize patients at study entry.

To analyze the change in moderate and severe hypoglycemia from baseline to end point and to account for a large proportion of 0 events as well as baseline differences, a 0-inflated Poisson model[15] was implemented using PROC GENMOD.[16] The model adjusted for the treatment group and baseline hypoglycemia rate, and comparison of rates with their associated 95% confidence intervals are presented.

To analyze the effects of treatment over time, a likelihood-based, mixed-effects model repeated measures (MMRM) approach was used. Differences between study groups were examined using differences in mean changes in the outcome variables from baseline to end of treatment. The MMRM model included the fixed, categorical effects of treatment, age-group interaction, age-group × visit interaction, and treatment × visit interaction, as well as the continuous, fixed covariates of baseline score. The unstructured covariance matrix was fitted using Akaike information criterion. The MMRM includes all available data at each time point. Least square means and least square mean differences and their associated 95% confidence intervals are presented for each treatment group.

Rates of severe hypoglycemia were analyzed as unadjusted incidence rates based on the Poisson distribution. Incidence rates and incidence rate difference were presented with their associated 95% confidence intervals calculated as exact Poisson confidence limits.[17] The *P* value was calculated using the exact Poisson method in STATA.

Average percentage of time spent in the hypoglycemic range was examined using the Wilcoxon rank sum test to compare between groups. The sign test was used to compare within groups. The hypoglycemia unawareness score was compared

Figure. Study Enrollment and Randomization

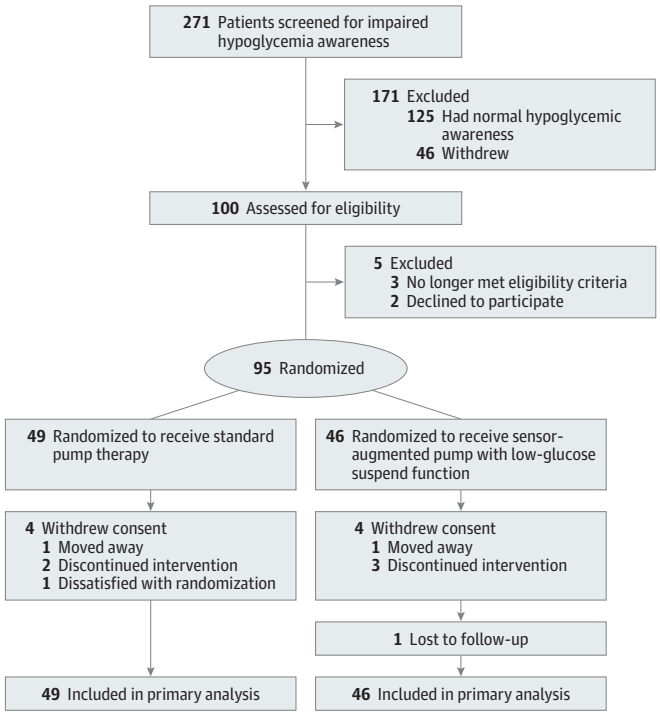

Table 1. Baseline Characteristics of Study Participants

	No. (%) of Participants	
	Insulin Pump (n = 49)	Sensor-Augmented Pump With Low-Glucose Suspension (n = 46)
Age, mean (SD) [range], y	19.7 (12.9) [5.4-48.6]	17.4 (10.6) [5.1-45.7]
Female	28 (57.1)	20 (43.5)
Age group, y		
4-<7	2 (4.1)	2 (4.3)
7-<12	14 (28.6)	13 (28.3)
12-<18	18 (36.7)	16 (34.8)
18-50	15 (30.6)	15 (32.6)
Duration of diabetes, mean (SD), y	12.1 (10.0)	9.8 (7.4)
Duration of pump therapy, mean (SD), y	4.4 (3.4)	3.8 (3.3)
Insulin/kg, mean (SD), U/kg	0.76 (0.23)	0.83 (0.17)
Hypoglycemia unawareness score, mean (SD)	6.4 (1.5)	5.9 (1.5)

across the 2 groups using analysis of covariance adjusting for baseline score and study group.

Results

Study Cohort

The study enrollment, randomization, and retention are shown in the **Figure**. Of the 100 patients who attended the screening visit, 95 were randomly assigned to each treatment group: 49 were assigned to pump-only therapy and 46 were assigned to sensor-augmented pump with low-glucose suspension function. Baseline clinical characteristics are shown in **Table 1**. The median sensor use over 6 months in the low-glucose suspension group was 68%, with the sensor use ranging from median of 71% for those younger 12 years, 54% for those 12 through 18 years old, and 81% for those older than 18 years.

Combined Severe and Moderate Hypoglycemia

The baseline rate of severe and moderate hypoglycemia was significantly higher for patients in the low-glucose suspension group with an incidence rate per 100 patient-months of 129.6 (95% CI, 111.1-150.3) compared with 20.7 (95% CI, 13.8-30) in the pump-only group. After 6 months of treatment and controlling for the baseline hypoglycemia rate, the number of severe and moderate hypoglycemia events in the low-

Table 2. Clinical Outcomes

	Insulin Pump (n = 49)	Sensor-Augmented Pump With Low-Glucose Suspension (n = 46)
Sum of Severe and Moderate Hypoglycemia		
Baseline		
Rate per 100 patient-months (95% CI)[a]	20.7 (13.8 to 30)	129.6 (111.1 to 150.3)
No. of events (total No. of patients)	28 (45)	175 (45)
End point		
6-Month rate per 100 patient-months (95% CI)[a]	11.9 (6.8 to 19.3)	28.4 (19.8 to 39.6)
No. of events (total No. of patients)	13 (45)	35 (41)
Incidence rate per 100 patient-months (95% CI)[b]	34.2 (22.0 to 53.3)	9.5 (5.2 to 17.4)
Patients modeled	45	41
Incidence rate ratio per 100 patient-months (95% CI)[b]		3.6 (1.7 to 7.5)
P value		<.001
Severe hypoglycemia[a]		
Baseline		
Rate per 100 patient-months (95% CI)	2.1 (0.8 to 4.6)	1.8 (0.6 to 4.3)
No. of events (total No. of patients)	6 (49)	5 (46)
End point		
6-Month rate per 100 patient-months (95% CI)	2.2 (0.5 to 6.5)	0 (0 to 2.4)
No. of events (total No. of patients)	6 (45)	0 (41)
Incidence rate difference from baseline to end point (95% CI)		1.5 (0.3 to 2.7)
P value		.02
Moderate hypoglycemia		
Baseline		
Rate per 100 patient-months (95% CI)	20 (13.2 to 29.1)	128.1 (109.8 to 148.7)
No. of events (total No. of patients)	27 (45)	173 (45)
End point		
6-Month rate per 100 patient-months (95% CI)	9.6 (5.1 to 16.5)	28.5 (19.8 to 39.6)
No. of events (total No. of patients)	13 (45)	35 (41)
Incidence rate per 100 patient-months (95% CI)[b]	26.3 (15.4 to 45.0)	9.6 (5.1 to 18.1)
Patients modeled	45	41
Incidence rate ratio per 100 patient-months (95% CI)[b]		2.7 (1.2 to 6.1)
P value		.01
Glycated hemoglobin, %		
Baseline, mean (95% CI)	7.4 (7.2 to 7.6)	7.6 (7.4 to 7.9)
End point, mean (95% CI)	7.4 (7.2 to 7.7)	7.5 (7.3 to 7.7)
Change, least square mean (95% CI)[c]	−0.06 (−0.2 to 0.09)	−0.1 (−0.3 to 0.03)
P value	.42	.11
Least square mean difference (95% CI)[c]		0.07 (−0.2 to 0.3)
P value		.55

[a] Incidence rates and incidence rate difference from Poisson distribution.

[b] Results from a 0-inflated Poisson model adjusted for study group and baseline rate.

[c] Results from mixed-effects model repeated measures adjusted for baseline score, visit, treatment, age × group, age × group × visit interaction, age-group × treatment, and treatment × visit interaction.

glucose suspension group decreased from 175 to 35, whereas the number of events decreased from 28 to 16 in the pump-only group. The adjusted incidence rate per 100 patient-months, fitted using the 0-inflated Poisson model, was 34.2 (95% CI, 22.0-53.3) for the pump-only group and 9.5 (95% CI, 5.2-17.4) for the low-glucose suspension group. The incidence rate ratio was 3.6 (95% CI, 1.7-7.5; $P < .001$) favoring the low-glucose suspension group (**Table 2**).

A sensitivity analysis was conducted for patients younger than 12 years. Although the sample size was small (15 in each group), there was a significant reduction in the number of severe and moderate hypoglycemia events for the those in the low-glucose suspension group (from 136 to 29) compared with the pump-only group (from 19 to 8). The baseline incidence rate per 100 patient-months observed was 42.2 (95% CI, 25.4-65.9) and the end point rate was 17.8 (95% CI, 7.7-35.0) for the pump-only group, whereas the baseline incidence rate per 100 patient-months in the low-glucose suspension group was 302.2 (95% CI, 253.6-357.5) and the end point rate was 64.4 (95% CI, 43.2-92.6). The adjusted incidence rate ratio, using the 0-inflated Poisson model, was 5.5 (95% CI, 2.0-15.7; $P < .001$) favoring the low-glucose suspension group.

Analysis of baseline moderate hypoglycemia event rates identified 2 outliers; these were younger children (aged 9 and

Table 3. Average Percentage of Hours Spent in Hypoglycemic Range

	Median (Interquartile Range)		
	Insulin Pump	Sensor-Augmented Pump With Low-Glucose Suspension	*P* Value[a]
Average time of glucose levels <70 mg/dL[b]			
Day			
Baseline	8.3 (2.8-13.0)	5.7 (2.8-8.2)	.15
End point	6.9 (3.9-10.6)	4.1 (2.6-7.6)	.02
Night			
Baseline	11.1 (3.1-21.3)	7.3 (2.4-16.4)	.20
End point	11.8 (6.4-16.2)	4.4 (2.1-8.8)	<.001
Average time of glucose levels <60 mg/dL[b]			
Day			
Baseline	3.2 (0.7-9.0)	2.4 (0.4-4.4)	.15
End point	3.3 (1.6-5.9)	1.5 (0.9-3.7)	.01
Night			
Baseline	4.8 (0-12.9)	2.3 (0-9.5)	.38
End point	6.2 (4.2-9.9)	2.4 (0.4-5.3)	<.001

SI conversion factor: to convert glucose from mg/dL to mmol/L, multiply by 0.0555.

[a] Wilcoxon rank sum test, pump only vs low-glucose suspension group.

[b] The day period is measured from 06:00 to 22:00 hours and night period from 22:00 to 06:00 hours.

10 years). Incidence rate ratios on sensitivity analysis excluding these participants were 2.2 (95% CI, 0.9-5.3; *P* = .08) for moderate and severe events; 1.7 (95% CI, 0.7, 4.3; *P* = .23) for moderate events; and 1.5 (95% CI, 0.2-2.7; *P* = .02) for severe events.

Secondary Outcomes

At baseline, the rate of severe hypoglycemia in the pump-only group was 2.1 events per 100 patient-months (95% CI; 0.8-4.6) compared with 1.8 events per 100 patient-months (95% CI, 0.6-4.3) in the low-glucose suspension group. The actual event rate for the 6 months preceding the baseline visit was 6 events in the pump-only group compared with 5 events in the low-glucose suspension group. After the study period, in the number of severe events for the low-glucose suspension group decreased to 0 events compared with 6 events in the pump-only group or a rate of 2.2 events per 100 patient-months (95% CI, 0.5-6.5). The incidence rate difference at 6 months was 1.5 (95% CI, 0.3-2.7; *P* = .02; Table 2).

Glycated hemoglobin concentrations were similar in both groups at baseline and did not change in either group after the intervention period: 7.4 (95% CI, 7.2-7.7) in the pump-only (*P* = .46) vs 7.5 (95% CI, 7.3-7.7) in the low-glucose suspension group (*P* = .10). None of the participants experienced diabetic ketoacidosis or hyperglycemia with ketosis during the intervention.

The average percentage of time spent in the hypoglycemic range during day and night is shown in **Table 3**. Compared with the pump-only group, the low-glucose suspension group spent less time with glucose levels lower than both 70 mg/dL and 60 mg/dL during the intervention period.

There was an improvement in the HUS score in both groups, from 6.4 (95% CI, 5.9-6.8) to 5.1 (95% CI, 4.5-5.6) in the pump-only group (*P* < .001) and from 5.9 (95% CI, 5.5-6.4) to 4.7 (95% CI, 4.0-5.1) in the low-glucose suspension group (*P* < .001). There were no between-group differences (least square mean difference low-glucose suspension pump only (95% CI, −0.2; −0.9 to 0.5; *P* = .58).

Device failure occurred on 2 occasions and was corrected with replacement of the sensor transmitter (Minilink).

Hypoglycemic Clamp Studies

Comparison of the epinephrine response to hypoglycemia, measured before and after the intervention, found no difference between groups. For the pump-only group, the epinephrine response to hypoglycemia was 113 pg/mL (95% CI, 101-124 pg/mL) before the intervention period vs 123 pg/mL (95% CI, 110-137 pg/mL) at the end of 6 months (*P* = .74). For the low-glucose suspension group, the epinephrine response was 220 pg/mL (95% CI, 192-248 pg/mL) before the intervention period vs 148 pg/mL (95% CI, 134-168) after the intervention (*P* = .26).

Discussion

In this trial, we found that the use of sensor-augmented pump therapy with low-glucose suspension reduced the rate of severe and moderate hypoglycemia in patients with type 1 diabetes and impaired hypoglycemia awareness over a 6-month period. In addition, glucose levels in the hypoglycemic range during the overnight period were lower in the low-glucose suspension group than in the pump-only group. There was no associated change in glycated hemoglobin. Although an exploratory end point, it is notable that there were no seizure or coma episodes in the intervention group despite these continuing at the same rate in the control group. These findings suggest that automated insulin suspension can reduce the incidence of hypoglycemic events in those most at risk, that is, those with impaired awareness of hypoglycemia.

A recent report also found reduced hypoglycemia using insulin pump interruption,[6] although the study was of shorter

duration and the primary outcomes were assessed using sensor values. In contrast to this report, patients were older and were not selected on the basis of impaired hypoglycemia awareness.

Although it may be argued that sensor-augmented pump treatment without the low-glucose suspension algorithm should be a comparator group, in this trial we compared low-glucose suspension pump therapy to pump-only therapy because the latter is the most commonly used treatment. Furthermore, real-time continuous glucose monitoring has not been demonstrated to be effective in reducing hypoglycemia and is indeed unlikely to reduce nocturnal events during sleep.[18,19]

Hypoglycemia events are an end point of major interest to clinicians. Surrogate end points, such as data from continuous glucose-monitoring devices, are often used to test therapies that may alter hypoglycemia event frequency because the low frequency of severe hypoglycemic events may preclude sufficient power. In this trial, we targeted patients with impaired hypoglycemic awareness to enrich the study pool for the primary outcome. Although not tested in this trial, it is also possible that the use of the automated insulin suspension reduces the rate of hypoglycemia events for patients with normal awareness.

The reduction in rates of moderate hypoglycemia in the control group may have been due to participants' altering their behavior and recall because they were aware that they were being observed. This study effect, well described for glycemic control outcomes, also may have contributed to the improvement in hypoglycemia awareness seen in our pump-only group. This highlights caution in interpretation of the effects of treatment on rates of hypoglycemia in observational studies.

We observed no improvement in counterregulatory hormone responses to hypoglycemia. This may not be surprising given that low-glucose suspension technology does not eliminate all hypoglycemia; rather, it reduces the magnitude and duration of hypoglycemia. Previous studies have shown that meticulous avoidance of hypoglycemia is required to correct hypoglycemia-induced counterregulatory defects.[12,20]

There are several limitations to this study. The patients were younger and had shorter duration of diabetes than the more typical patient with hypoglycemia unawareness, so the conclusions may not be transferable to those patients. An important consideration is that the primary outcome relies on patient and parent recall of episodes, and we had assumed this would be similar in both intervention and control groups. We have focused on hypoglycemia end points and assessed glycemic control with glycated hemoglobin measures and have not closely evaluated hyperglycemia and glucose variability, which may have been of interest. The loss of statistical significance for the primary outcome measure after the exclusion of 2 children with the highest baseline rates of moderate hypoglycemia raises the possibility that the results are due to a chance imbalance rather than represent a true finding. These 2 outliers were younger children, and variability in moderate hypoglycemia is especially prevalent in children.[21,22]

Conclusion

Sensor-augmented pump therapy with automated insulin suspension reduced the combined rate of severe and moderate hypoglycemia in patients with type 1 diabetes.

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Author Contributions: Dr Jones had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ly, Davis, Jones.
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Drafting of the manuscript: Ly, Lim.
Critical revision of the manuscript for important intellectual content: Ly, Nicholas, Retterath, Davis, Jones.
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