Letters

RESEARCH LETTER

Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes

Closed-loop artificial pancreas technology uses a control algorithm to automatically adjust insulin delivery based on subcutaneous sensor data to improve diabetes management. Currently available systems stop insulin in response to existing[1] or predicted[2] low sensor glucose values, whereas hybrid closed-loop systems combine user-delivered premeal boluses with automatic interprandial insulin delivery.[3] This study investigated the safety of a hybrid closed-loop system in patients with type 1 diabetes.

Methods | Patients aged 14 to 75 years with type 1 diabetes for at least 2 years, glycated hemoglobin (HbA_{1c}) less than 10%, and more than 6 months of insulin pump use were recruited from 10 centers (9 in the United States, 1 in Israel) between June 2, 2015, and November 11, 2015. This before and after study had a 2-week run-in period (baseline) for patients to learn the devices without the automated features followed by a 3-month study period with the initial 6 days used to collect insulin and sensor glucose data for the hybrid closed-loop algorithm. In the study period, there was a 6-day hotel stay during which 1 day was used for frequent sampling of venous blood glucose to verify the accuracy of the system. The last patient visit was March 7, 2016. Two central and 4 local institutional review boards approved the study. Written informed consent was obtained from adults and parents, and written assent from minors.

The system included investigational continuous glucose monitoring sensors with transmitters, insulin pumps displaying real-time glucose data, a proprietary algorithm, and blood glucose meters.[4] Patients were required to periodically calibrate sensors and enter carbohydrate estimates for meal boluses. Every midnight, multiple parameters were automatically adjusted by the algorithm.

Safety end points obtained during the run-in and study periods (including the hotel stay) were the incidence of severe hypoglycemia and diabetic ketoacidosis, serious adverse events, and device-related serious and unanticipated adverse events. Prespecified descriptive end points included time in open vs closed-loop systems; the percentage of sensor glucose values below, within, and above target range (71-180 mg/dL), including at night time; changes in HbA_{1c}, insulin requirements and body weight; and measures of glycemic variability. End points were collected during both periods and analyzed with SAS (SAS Institute), version 9.4.

Results | Of the 124 participants (mean age, 37.8 years [SD, 16.5]; men, 44.4%), mean diabetes duration was 21.7 years, mean total daily insulin dose was 47.5 U/d (SD, 22.7), and mean HbA_{1c} was 7.4% (SD, 0.9). Over 12 389 patient-days, no episodes of severe hypoglycemia or ketoacidosis were observed. There were 28 device-related adverse events (**Table 1**) that were resolved at home. There were 4 serious adverse events (appendicitis, bacterial arthritis, worsening rheumatoid arthritis, *Clostridium difficile* diarrhea) and 117 adverse events not related to the system, including 7 episodes of severe hyperglycemia due to intercurrent illness or other nonsystem causes.

Table 1. Device-Related Adverse Events Among Patients Using Hybrid Closed-Loop Insulin Systems[a]

Adverse Event	No. of Events	
	Run-in Period[b]	Study Period[b]
Total	8	20
Skin irritation	3	1
Hyperglycemia	0	6
Rash	0	1
Severe hyperglycemia[c]		
Due to infusion set	5	6
Due to software or hardware issues	0	5
Due to sensor issues	0	1

[a] A data and safety monitoring board was used to adjudicate all serious adverse events and severe hyperglycemia events. A serious adverse event was defined as an event leading to death or serious deterioration in health.

[b] Run-in period was 2 weeks and study period was 12 weeks.

[c] Glucose greater than 300 mg/dL (to convert glucose to mmol/L, multiply by 0.0555) and serum ketones greater than 0.6 mmol/L or symptoms of nausea, vomiting, or abdominal pain.

The system was in closed-loop mode for a median of 87.2% of the study period (interquartile range, 75.0%-91.7%). Glycated hemoglobin levels changed from 7.4% (SD, 0.9) at baseline to 6.9% (SD, 0.6) at study end (**Table 2**). From baseline to the end of the study, daily dose of insulin changed from 47.5 U/d to 50.9 U/d, and weight changed from 76.9 kg to 77.6 kg. The percentage of sensor glucose values within the target range changed from 66.7% at baseline to 72.2% at study end. The percentage of sensor glucose values below and above the target and glycemic variability are also shown in Table 2. Sensor and reference glucose values collected during the hotel stays were in good agreement, with an overall mean absolute relative difference of 10.3% (SD, 9.0).

Discussion | To our knowledge, this is the largest outpatient study to date[5,6] and it demonstrated that hybrid closed-loop automated insulin delivery was associated with few serious or device-related adverse events in patients with type 1 diabetes. Limitations include lack of a control group, restriction to relatively healthy and well-controlled patients, the relatively short duration, and an imbalance between the length of the study periods. Differences in HbA_{1c} levels may be attributable to participation in the study. A similar study in

Table 2. Glucose Control, Insulin Usage, and Weight Among Patients Using Hybrid Closed-Loop Systems

Parameter	Run-in Period	Study Period
Sensor glucose, mean (SD) [median], mg/dL	150.2 (22.7) [150.1]	150.8 (13.7) [149.9]
Percentage of time with glucose level in range, mean (SD); median (IQR)		
Sensor glucose values		
>300 mg/dL	2.3 (4.2); 1.3 (0.2-2.6)	1.7 (1.9); 0.9 (0.5-2.1)
>180 mg/dL	27.4 (13.7); 26.7 (16.0-37.2)	24.5 (9.2); 24.1 (17.3-29.8)
71-180 mg/dL	66.7 (12.2); 67.8 (59.0-75.1)	72.2 (8.8); 73.4 (67.7-78.4)
≤70 mg/dL	5.9 (4.1); 5.2 (3.0-7.6)	3.3 (2.0); 2.9 (1.7-4.3)
≤50 mg/dL	1.0 (1.1); 0.6 (0.2-1.3)	0.6 (0.6); 0.4 (0.2-0.8)
Sensor glucose values at night time only[a]		
>180 mg/dL	26.8 (15.2); 26.4 (15.3-35.8)	21.6 (9.9); 20.6 (13.6-28.5)
71-180 mg/dL	66.8 (14.0); 67.0 (57.6-75.2)	75.3 (9.8); 76.4 (69.0-83.1)
≤70 mg/dL	6.4 (5.3); 5.4 (2.3-8.5)	3.1 (2.2); 2.6 (1.7-4.2)
Within-day SD of glucose, mean (SD); median (IQR), mg/dL[b]	50.1 (9.9); 48.9 (43.7-56.2)	46.7 (7.3); 45.6 (41.7-50.4)
Within-day coefficient of variation of glucose, mean (SD); median (IQR), %[b]	33.5 (4.3); 33.1 (30.3-36.4)	30.8 (3.3); 30.7 (28.2-33.0)
Glycated hemoglobin, mean (SD) [median], %	7.4 (0.9) [7.3]	6.9 (0.6) [6.8]
Total daily dose of insulin, mean (SD) [median], U	47.5 (22.7) [43.9]	50.9 (26.7) [44.1]
Weight, mean (SD) [median], kg	76.9 (17.9) [73.5]	77.6 (16.1) [74.7]

Abbreviations: IQR, interquartile range.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

[a] Night time was defined as 10:00 PM to 7:00 AM.

[b] Measures of glycemic variability.

children (NCT02660827) is under way. Longer-term registry data and randomized studies are needed to further characterize the safety and efficacy of the hybrid closed-loop system.

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