Day and Night Closed-Loop Control Using the Integrated Medtronic Hybrid Closed-Loop System in Type 1 Diabetes at Diabetes Camp

OBJECTIVE
To evaluate the feasibility and efficacy of a fully integrated hybrid closed-loop (HCL) system (Medtronic MiniMed Inc., Northridge, CA), in day and night closed-loop control in subjects with type 1 diabetes, both in an inpatient setting and during 6 days at diabetes camp.

RESEARCH DESIGN AND METHODS
The Medtronic MiniMed HCL system consists of a fourth generation (4S) glucose sensor, a sensor transmitter, and an insulin pump using a modified proportional-integral-derivative (PID) insulin feedback algorithm with safety constraints. Eight subjects were studied over 48 h in an inpatient setting. This was followed by a study of 21 subjects for 6 days at diabetes camp, randomized to either the closed-loop control group using the HCL system or to the group using the Medtronic MiniMed 530G with threshold suspend (control group).

RESULTS
The overall mean sensor glucose percent time in range 70–180 mg/dL was similar between the groups (73.1% vs. 69.9%, control vs. HCL, respectively) \( (P = 0.580) \). Meter glucose values between 70 and 180 mg/dL were also similar between the groups (73.6% vs. 63.2%, control vs. HCL, respectively) \( (P = 0.086) \). The mean absolute relative difference of the 4S sensor was 10.8 \pm 10.2\%, when compared with plasma glucose values in the inpatient setting, and 12.6 \pm 11.0\% compared with capillary Bayer CONTOUR NEXT LINK glucose meter values during 6 days at camp.

CONCLUSIONS
In the first clinical study of this fully integrated system using an investigational PID algorithm, the system did not demonstrate improved glucose control compared with sensor-augmented pump therapy alone. The system demonstrated good connectivity and improved sensor performance.

There have been a number of advances in developing automated insulin delivery systems for optimizing glucose control in patients with type 1 diabetes with the ultimate aim of reducing the burden of care for this condition (1–7). Early studies (8–10) demonstrated the feasibility of automated insulin modulation using...
subcutaneous insulin pumps and subcutaneous continuous glucose sensors with the main focus being algorithm development. Further advances in both sensor performance and algorithms incrementally demonstrated improved protection against hypoglycemia, reduced variability, and decreased mean glucose levels in controlled inpatient settings (11–13) as well as in outpatient studies (2,4,6). The strategies for different control algorithms are well described in several recent reviews (14,15).

The hybrid closed-loop (HCL) system of Medtronic MiniMed Inc. (Northridge, CA) is the first fully integrated system designed for continuous day and night HCL control with the algorithm incorporated within the insulin pump. The HCL system requires meal announcement with an estimate of carbohydrate intake and a premeal insulin bolus to optimize postprandial glucose excursions (9).

The system consists of a Medtronic fourth generation sensor (4S) and uses a proportional-integral-derivative with insulin feedback (PID-IFB) algorithm with safety constraints to continuously modulate basal insulin delivery based on sensor glucose values. The system configuration places the closed-loop controller on the pump and removes the need for an intermediary device that contains the algorithm, such as a phone or portable computer. This reduces the need for connectivity between a controller and the insulin pump as well as between the controller and sensor, two points of potential interrupted communication in a multi-device system (3–5).

This report describes the clinical experience with using this HCL system in a supervised environment over multiple days for both day and night closed-loop control. The objective of this study was to test the feasibility and efficacy of a preliminary algorithm in adolescents and adults with type 1 diabetes over 48 h in a research center followed by a 6-day period at a diabetes camp.

**RESEARCH DESIGN AND METHODS**

**Medtronic HCL System**

The Medtronic HCL system is a fully integrated continuous glucose sensor and insulin delivery system designed for continuous closed-loop control. The system consists of a 4S glucose sensor, a sensor transmitter, and an insulin pump, as shown in Fig. 1. A PID-IFB algorithm with safety constraints is incorporated in the pump, allowing for continuous closed-loop control of basal insulin delivery. The system also uses a next-generation Bayer CONTOUR NEXT LINK glucose meter, which allows the patient to automatically send meter glucose values to the pump via radio-frequency connection.

Specifics of the control algorithm have been previously described (16–18). Insulin delivery was modeled on the multiphasic insulin response of the β-cell and consisted of three principal components: proportional, integral, and derivative, with a modification to include feedback of a model-predicted insulin profile (17,19).

The system operates in two modes: manual and closed loop. In the manual mode, the system uses patient-specific settings, including basal rates, carbohydrate/insulin ratio, insulin sensitivity factor, and glucose targets. The pump may function as a stand-alone insulin pump. When used in conjunction with the continuous glucose sensor, there are also features such as automatic insulin suspension or predictive low glucose insulin suspension; however, these functions were not activated during this study.

With continuous glucose sensor input, closed loop may also be activated. The system uses the PID-IFB algorithm to continuously modulate basal insulin delivery. Instead of a preset basal rate, the algorithm determines insulin delivery as sensor glucose inputs arrive and delivers insulin as a small bolus or “microbolus.” The system was set to a target glucose of 120 mg/dL. Users may also inform the system of exercise, during which the target is increased to 160 mg/dL.

The maximum insulin limit constrains the maximum insulin delivered at any time by the algorithm. This value is specific to each patient and is calculated from fasting glucose values and total daily dose of insulin (TDD). The maximum insulin limit adapts over time and, for example, will increase in response to elevated fasting glucose values. At the initialization of closed-loop control, the TDD for each day of the preceding week was manually entered into the system.

A fixed carbohydrate/insulin ratio based upon the TDD rule of 500/TDD, was used for premeal boluses. Correction doses were initiated with meter glucose values >200 mg/dL, with a target glucose of 180 mg/dL. The insulin sensitivity factor was algorithm derived and also based upon the TDD.
Study Design
Participants were eligible to participate if they were between 14 and 40 years of age, had a diagnosis of type 1 diabetes for at least 1 year, and had been using an insulin pump for at least 3 months. Exclusion criteria included diabetes ketoacidosis in the preceding 30 days, hypoglycemic seizure or loss of consciousness in the preceding 3 months, and pregnancy or a medical condition considered to interfere with the completion of the protocol. There was no A1C exclusion criterion. The protocol was approved by Stanford University Institutional Review Board.

Inpatient Phase
An initial inpatient study was conducted to evaluate the feasibility of system use in eight subjects, primarily between 14 and 18 years of age, with type 1 diabetes. The HCL system was evaluated for 48 h for each participant. A description of the inpatient procedures is included in the Supplementary Data.

Camp Phase
For the main camp sessions, 21 subjects were recruited. Randomization occurred after the enrollment visit and was stratified by A1C. Subjects were randomized to use either a sensor-augmented pump with insulin suspension using the commercially available Medtronic MiniMed 530G (Medtronic MiniMed, Inc.) (control group) or closed-loop control with the HCL system.

For the control group, an Enlite sensor was inserted and linked to the 530G pump. The 4S sensor was not compatible with the 530G pump. The suspend threshold was set to 60 mg/dL. In addition, a low alert was set at 70 mg/dL, and a high alert was set at 250 mg/dL. Meter glucose testing was conducted using a Bayer CONTOUR NEXT LINK glucose meter.

For the HCL group, a 4S glucose sensor was inserted. The HCL pump was programmed with the subject’s current pump settings and placed in manual mode. All calibrations were performed using a capillary meter glucose value measured by a Bayer glucose meter. The first calibration was entered between 30 min and 2 h after sensor insertion. Sensors were calibrated at least every 12 h. A low alert was also set at 70 mg/dL, and a high alert at 250 mg/dL. After 5 h of manual operation, closed loop was started.

Both groups used premeal boluses and were advised to enter the carbohydrate amount into the bolus calculator. Research staff did not provide input for carbohydrate counting. Subjects continued in their group for the duration of the 6 days and 6 nights of diabetes camp. All subjects were instructed either to wash their hands with soap or use alcohol to clean fingers, discard the first drop of blood, and use the second drop of blood for meter glucose testing. Capillary glucose testing was supervised in the HCL group. There were no restrictions for subjects in either group, and all subjects participated in the camp program.

Glucose Monitoring and Management in the HCL Group
Meter glucose testing was routinely performed every 3–4 h, including before meals, before exercise, and before bed. Overnight, subjects were tested at 0000, 0300, and 0700 h. The HCL system does not have the capability for remote monitoring. Given that this was the first clinical experience with the system, a member of the research team accompanied each subject to ensure that all system use was supervised and that alarms were appropriately managed. During the day, research staff was present in close proximity to the subject. During the overnight period, subjects slept in their cabin with fellow campers without research staff present; however, in addition to the glucose testing at 0000 and 0300 h, the system was visually checked at 0100 and 0500 h.

Subjects were advised to obtain a meter glucose value if the sensor glucose was <70 mg/dL and to treat with 15 g of fast-acting carbohydrates. A repeat meter glucose was obtained after 15 min to ensure that glucose values were >70 mg/dL. If the sensor glucose was >250 mg/dL, subjects were advised to check for meter glucose and ketones and advise the camp medical staff prior to giving insulin.

Sample Size
The inpatient study was designed to assess the feasibility of system use and was not powered for significance. A cohort of eight subjects was recruited to generate 384 h of 4S sensor use and closed-loop control.

The sample size estimate for the camp study was based upon data from our previous camp studies (5). Power analysis was performed for a repeated-measures ANOVA. The variance-covariance structure was assumed to follow a compound symmetry with a variance of 27 mg/dL and covariance of 14 mg/dL. The mean percent time in range from 70 to 180 mg/dL for the control group was estimated to be 62%, and the mean percent time in range for the treatment group was estimated to be 75%. A sample of 10 patients in each group, for a total of 20 patients, would provide at least 80% power to observe a difference between 62% and 75% in a two-sided test with an α level of 0.05. We aimed to recruit 20 participants to account for subject withdrawal.
Statistics
For the primary outcome of percent time in range, sensor glucose values were compared between the groups using a two-way repeated-measures ANOVA, and results are shown as the least squares mean ± SE. Given the marked difference in sensor performance between the Enlite and 4S, only sensors with a daily median absolute relative difference (ARD) of <15% were used in both groups for analyses of glucose outcomes.

Depending on distribution, other data are expressed as mean ± SD or as median (interquartile range [IQR]). Comparisons for meter glucose levels were made using a Mann-Whitney U test for non-parametric data and a Student t test for data conforming to a normal distribution. Analyses were performed using SigmaStat version 11.0. The sample size calculation was performed in Stata version 13.1.

RESULTS
Inpatient Studies
Data for the inpatient studies are included in the Supplementary Data.

Camp Session
During the camp session, 21 subjects were enrolled and studied for a total of 120 person-days. One subject from the HCL group had to leave camp after 24 h and was replaced. The mean ± SD age was 18.6 ± 3.7 years (range 15.3–31.4), duration of diabetes was 9.1 ± 4.7 years, A1C was 8.6 ± 1.5% (range 5.9–11.6) (70 ± 16 mmol/mol, range 41–103), and insulin dose was 0.8 ± 0.2 units/kg/day. Subjects in the HCL group remained in closed loop for 93 ± 3% of the scheduled time. There was continuous sensor glucose data available for 98.9% of the time. Time off closed loop was attributed to sensor change or temporarily suspending HCL after infusion set failure.

There were no instances of diabetic ketoacidosis or severe hypoglycemia resulting in seizure or coma that resulted in stopping closed loop for subjects in the HCL group. There was an episode of a hypoglycemic generalized tonic-clonic seizure in a control participant, which occurred after a dinner bolus of 8.3 units was delivered with delayed food consumption. The meter glucose obtained at the time of the seizure was 46 mg/dL. The subject made a full recovery with the administration of intramuscular glucagon.

Sensor Performance
The overall mean ARD for the 4S sensor compared with meter glucose values was 12.6 ± 11.0%. The median ARD was 9.7% (IQR 4.7, 17.6) (n = 742). A Bland-Altman plot of 4S sensor glucose compared with meter glucose is shown in Supplementary Fig. 1A. The mean ARD values for the 4S sensor from day 1 through day 6 were 15.9 ± 12.4%, 11.3 ± 8.6%, 11.6 ± 12.1%, 13.3 ± 10.3%, 13.1 ± 11.9%, and 11.3 ± 9.9%, respectively.

The overall mean ARD value for the Enlite sensor, compared with meter glucose values, was 21.7 ± 23.4%. The median ARD was 15.9% (IQR 7.5, 28.2) (n = 383). A Bland-Altman plot for Enlite sensor compared with meter glucose is shown in Supplementary Fig. 1B.

To assess the efficacy of the system, only sensor data with a daily median ARD of <15% were included in the analysis for both the control and HCL groups. This left 32 person-days for the control group and 51 person-days for the HCL group from a total possible of 60 in each group.

Glucose Control
Glucose control, from sensor glucose values, for both groups using days with a daily median ARD of <15% is shown in Table 1. In terms of the primary outcome, the mean percent time in range 70–180 mg/dL during the day and night was similar between the groups (73.1% vs. 69.9%, control vs. HCL, respectively) (P = 0.580). The effect changed over time (days of wear) (P = 0.009), with the HCL group tending to improve from 64.8% on day 1 to 77.7% on day 6, compared with the control group, which deteriorated from 90.3% on day 1 to 56.2% on day 6. Data for median percent time in range 70–180 mg/dL per day are shown in Fig. 2A. Mean glucose values exhibited a similar pattern, with mean glucose improving from 154 mg/dL on day 1 to 147 mg/dL on day 6 for the HCL group, whereas the mean glucose in the control group increased from 130 mg/dL on day 1 to 173 mg/dL on day 6.

During the overnight period, the overall percent time in range 70–180 mg/dL was 68.2% for the control group versus 79.9% for the HCL group (P = 0.111). The HCL group performed more favorably over the course of the study and by day 6 had achieved 80.6% in range compared with 42.8% in the control group. Data for median percent time in range per night (70–180 mg/dL) are shown in Fig. 2B. There was also a trend toward less hypoglycemia as well as a trend for less hyperglycemia, which again were more prominent by day 6.

Overall, the mean ± SD percent time in range 70–180 mg/dL was 70.6 ± 9.8% for the HCL group compared with 70.3 ± 14.9% for the control group. The median (IQR) for the same range was 70.0% (68.3, 74.9) for the HCL group compared with 74.4% (58.5, 82.0) for the control group.

Meter glucose values were also compared, and these data are shown in Table 1. There were more than double the number of meter glucose values obtained in the HCL group (n = 782) compared with the control group (n = 383). This occurred mainly due to the testing procedures in the HCL group, with meter glucose values obtained for all sensor glucose values outside of the 70–250 mg/dL range as well as during the overnight period. For all meter glucose values >250 mg/dL, a repeat test was performed after 1 h in the HCL group. There was an average of 0.4 events/person/day with meter glucose >250 mg/dL in the control group versus 0.7 events/person/day in the HCL group (P = 0.055). There were double the number of tests performed 4 h after a meter glucose level of >250 mg/dL with a median of 4 tests (IQR 3, 4) for the HCL group compared with 2 tests (IQR 1, 3) for the control group (P < 0.001), in part because of the less aggressive correction boluses given in the HCL group compared with the control group.

There was only one meter glucose value <50 mg/dL in the HCL group compared with four values in the control group over the week (P = 0.278). There were two meter glucose values >400 mg/dL in the HCL group, compared with one in the control group.

The median sensor glucose values over the course of 24 h for the control group versus the HCL group are shown in Fig. 3.

Total Daily Insulin
The average daily insulin dose tended to decrease during the week of camp for both the control and the intervention groups. In the control group, the average...
TDD was 63 ± 17 units/day at baseline compared with 57 ± 23 units/day during camp (P = 0.078). In the HCL group, the average TDD was 58 ± 17 units/day at baseline versus 49 ± 17 units/day during camp (P = 0.001).

**Carbohydrate Consumption**

The average daily amount of carbohydrates consumed in the HCL group was 179 ± 27 g for females (n = 5, mean weight 73 kg) and 259 ± 23 g for male subjects (n = 5, mean weight 77 kg). This was similar to the amount of carbohydrates consumed in the control group (158 ± 56 g for females [n = 6, mean weight 63 kg] and 222 ± 99 g for males [n = 4, mean weight 82 kg]).

**CONCLUSIONS**

Closed-loop control using a fully integrated sensor, algorithm, and pump system is an exciting innovation in this rapidly advancing field, and this report describes the first clinical experience using the Medtronic HCL system with the 4S sensor and an investigational algorithm. In a supervised camp setting, glucose control was comparable to that achieved with automated insulin suspension alone.

Over multiple days, however, there was improved performance of the system, achieving between 70% and 77% time in range. The results are promising for the potential impact of reducing the burden of care of type 1 diabetes.

The overall glycemic control was favorable compared with other hybrid, single-hormone systems, such as presented by the AP@home Consortium, where Leelarathna et al. (2) achieved a median of 75% of time between 70 and 180 mg/dL in an at-home, outpatient study over 7 days, compared with a median of 70% for our cohort. Our results are also similar to those of Kovatchev et al. (6), who reported a mean of 66% of time between 70 and 180 mg/dL in a 40-h outpatient study of adults, compared with our mean of 70.6% for the same range. For a dual hormone system using both insulin and glucagon, Russell et al. (4) achieved an impressive 76–80% of time in a similar range over 5 days for both adults and adolescents, in a supervised study with remote monitoring. The systems described, however, are not fully integrated.

The HCL system was simple to navigate and use. Once the pump was operational in manual mode with sensor glucose data available, only the addition of TDD data was required to start closed loop. In future versions, the system would be used in manual mode for 3–5 days, and no data would be required to be entered prior to initializing closed loop.

During closed-loop operation in this study, both the carbohydrate/insulin ratio as well as the insulin sensitivity factor were algorithm derived. There was no ability to dictate predetermined carbohydrate/insulin ratios for specific times of the day. This did not reflect individualized patient-derived settings, which may include, for example, more aggressive carbohydrate/insulin ratios for breakfast. This contributed to the postprandial hyperglycemia seen in the HCL group. In future versions, there will be the option of entering patientspecific carbohydrate/insulin ratios in specific time blocks. With the limitations of current insulin pharmacokinetics, optimizing premeal boluses remains the challenge in an insulin-only delivery system.

Although the system was safe, in that there was not a greater incidence of
hypoglycemia, the automatic corrections did not correct glucose values into target as rapidly as patients expected with their own standard therapy. This was particularly problematic for subjects who were accustomed to actively correcting their glucose values to achieve optimal time in range. This certainly contributed to the higher mean glucose values as well as the more prolonged postprandial hyperglycemia seen in the HCL group. Future versions of the algorithm may have a lower threshold to initiate a correction dose as well as a lower correction dose target to allow for increased insulin dosing. In this investigational algorithm, correction boluses were given automatically, and subjects were not able to see the amount to accept, reject, or adjust the bolus. Subjects were only able to see the amount delivered after it was given. Although this involved fewer buttons to push for the subject, many patients complained that they did not feel comfortable not knowing how much insulin was given. These are important user interface considerations for future closed-loop development. The degree of automation will affect patient behaviors and the acceptability of the devices. Automated insulin delivery systems represent a shift in the current concepts of basal/bolus insulin delivery, and it is clear that patients will want some degree of control of insulin delivery as preliminary versions of these devices become commercially available.

As system use extends, there needs to be flexibility and adaptability to individuals with variable insulin sensitivities that may change with exercise, stress, illness, and hormone levels. Although there was a component of adaptability with the maximum insulin limit, this needs to be further investigated with studies testing system use over a longer time period. A system that is able to quickly adapt, such as in the bihormonal approach used by Russell et al. (4), will undoubtedly be important for optimizing individual control.

The Medtronic 4S sensor demonstrated vast improved accuracy over the current commercially available Enlite sensor, with a mean ARD of 12.5%. Sensor accuracy is one of the critical determinants of a successful algorithm and affects how aggressively the algorithm can be set in achieving glucose targets as well as in affecting patient satisfaction and the potential uptake of the technology. The 4S sensor was well accepted by all our participants, among both naive and experienced sensor users.

We have consistently observed a decrease in sensor accuracy when we move from inpatient to outpatient studies. In a recent study (5), the Dexcom G4P sensor error increased from a mean ARD of 10.4% during inpatient studies to 17.5% in the camp setting. In both the inpatient and outpatient settings, sensors were calibrated against meter glucose values. In the inpatient setting, the reference glucose was measured by YSI, and in the camp setting the reference was a meter glucose. The decreased accuracy of sensor glucose values may be attributed to the technique in obtaining the capillary sample. In the current study, subjects were asked to wash their hands or use an alcohol swab, and to discard the first drop of blood and use the second drop for testing. This resulted in only a minimal decrease in 4S performance when moving from the inpatient to the camp setting. When glucose sensors are being used to deliver insulin in a closed-loop
between the two groups. We did not use, which created a discrepancy in care proximity for the supervision of system. The system did not have remote monitoring available pump. This investigational HCL received at camp using a commercially available pump.

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References


| Figure 3—Glucose control over 24 h. Results are reported as median (IQR).