Home use of day-and-night hybrid closed-loop insulin delivery in suboptimally controlled adolescents with type 1 diabetes: a 3-week, free-living, randomized cross-over trial

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24/7 hybrid closed-loop in adolescents with T1D

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Abstract

Objective

To evaluate the feasibility, safety and efficacy of day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes under free-living conditions.

Research Design and Methods

In an open-label randomized crossover study,12 suboptimally controlled adolescents on insulin pump therapy (age 14.6±3.1years; HbA1c 69±8mmol/mol [8.5±0.7%]; duration of diabetes 7.8±3.5years; mean±SD) underwent two 21-day periods comparing hybrid closed-loop insulin delivery and sensor-augmented insulin pump therapy in random order. During closed-loop, a model predictive algorithm automatically directed insulin delivery between meals and overnight; prandial boluses were administered by participants using a bolus calculator.

Results

The proportion of time that sensor glucose was in the target range (3.9 to 10mmol/l; primary endpoint) was increased during closed-loop intervention compared to sensor-augmented insulin pump therapy by 18.8±9.8 percentage points (mean±SD; p<0.001), the mean sensor glucose level was reduced by 1.8±1.3 mmol/l (p=0.001), and the time spent above target was reduced by 19.3±11.3 percentage points (p<0.001). The time spent with sensor glucose levels below 3.9mmol/l was low and comparable between interventions [difference 0.4 (-2.2 to 1.3) percentage points; median (IQR), p=0.33). Improved glucose control during closed-loop was associated with increased variability of basal insulin delivery (p<0.001) and an increase in total

daily insulin dose [53.5 (39.5 to 72.1) vs. 51.5 (37.6 to 64.3)U/day; p=0.006). Participants expressed positive attitudes and experience with closed-loop.

Conclusions

Free-living home use of day-and-night closed-loop in suboptimally controlled adolescents with type 1 diabetes is safe, feasible and improves glucose control without increasing the risk of hypoglycemia. Larger and longer studies are warranted.

The majority of adolescents and young adults with type 1 diabetes are poorly controlled (1-3) accelerating the onset of early micro- and macrovascular complications (4; 5). Reduced therapy adherence linked to psychosocial and physiological changes in adolescence is contributory (6) as omissions of prandial insulin boluses are frequent (7), and acceptance of insulin pump therapy and continuous glucose monitoring systems is lower (8-10). Threshold-suspend and predictive low glucose management insulin pump therapy may alleviate the burden of hypoglycemia (11; 12) but do not address the issue of hyperglycemia, the major challenge of diabetes management in adolescence.

The artificial pancreas (closed-loop systems) modulates insulin delivery below and above pre-set insulin pump delivery in response to real-time sensor glucose levels and can potentially reduce both hypo- and hyperglycemia. Following evaluations in children and adolescents in laboratory settings (13-15) and diabetes camps (16-18), first at-home studies of up to three-month applications of overnight closed-loop have demonstrated improved glucose control and reduced the burden of hypoglycemia (19-21). However, randomized outpatient trials evaluating day-and-night closed-loop in adolescents are limited to a maximum of a one week follow up (16; 18; 22).

Here, we present results of a 21-day-long day-and-night closed-loop trial in young people aged 10 to 18 years with suboptimally controlled type 1 diabetes during free living settings. We hypothesized that prolonged use of a 24/7 hybrid single hormone closed-loop system without remote monitoring or close supervision would be feasible, safe and improve glycemic control compared to sensor-augmented insulin pump therapy.

Research Design and Methods

Study management and regulatory approvals

The study received approval from the local independent research ethics committee and the UK competent authority (Medicines & Health products Regulatory Agency). An independent Data Safety and Monitoring Board oversaw the study.

Participants

Study participants were identified from pediatric diabetes clinics at Addenbrooke's Hospital (Cambridge, United Kingdom) and University College London Hospital (London, United Kingdom). Key inclusion criteria were age 10-18 years, diagnosis of type 1 diabetes, treatment with insulin pump therapy for at least three months, willingness to perform at least four fingerstick glucose measurements per day, and HbA1c ≤11% (97mmol/mol). Exclusion criteria included established nephropathy, neuropathy, or proliferative retinopathy, total daily insulin dose ≥2.0 U/kg or <10 U/day, significant hypoglycaemia unawareness, more than one incident of severe hypoglycemia within 6 months prior to enrollment, more than one episode of diabetic ketoacidosis within 12 months prior to enrolment, pregnancy and breast-feeding. Participants aged ≥16 years and parents or guardians of participants aged <16 years signed informed consent; written assent was obtained from minors before study related activities.

Study design and procedures

The study adopted an open-label, randomized, two-period crossover design comparing automated closed-loop insulin delivery with sensor-augmented pump

therapy in free-living home settings (Supplemental Material Figure S1). Study intervention periods lasted three weeks each with a 1 to 4-week washout period.

At enrolment, blood samples were taken for analysis of HbA1c. Random C-peptide levels were measured with concomitant plasma glucose >4mmol/l. At the start of the run-in phase, participants received training regarding the use of the study pump (DANA Diabecare R; Sooil, Seoul, South Korea) and the study real-time continuous glucose monitoring system (FreeStyle Navigator II; Abbott Diabetes Care, Alameda, CA) which are off-the-shelf devices and do not offer low glucose suspend functionality. Rapid-acting insulin analog aspart (Novo Nordisk, Bagsvaerd, Denmark) or lispro (Eli Lilly, Indianapolis, US) was administered by the pump. Participants used a standard bolus calculator for all meals throughout the study.

At the end of the 1 to 2-week run-in period, compliance in the use of study pump and continuous glucose monitoring were assessed. Participants with at least 5 days' worth of continuous glucose monitoring data were randomly assigned to receive either 3 weeks of automated closed-loop insulin delivery followed by sensor-augmented pump therapy, or vice versa. Permuted block randomization was applied and assignment was unblinded.

The two intervention periods were separated by a 1 to 4-week washout period during which the participants could continue using the study insulin pump. Continuous glucose monitoring was discontinued during washout.

On the first day of the closed-loop period, participants attended the clinical research facility. This 2 to 3-hour visit included training on initiation and discontinuation of the closed-loop system, switching between closed-loop and usual pump therapy, meal bolus procedure, and the use of study devices during exercise.

Competency on the use of closed-loop system was assessed. Following discharge, participants continued the study intervention for the next 21 days under free-living settings in their home and school environment. The participants were free to consume meals of their choice and no restrictions were imposed on travelling. We encouraged participants to continue closed-loop use during exercise, and to announce physical activity to the algorithm. However, participants were advised to discontinue closed-loop and follow their usual insulin pump therapy for activities such as diving or contact sports. At the end of the closed-loop intervention, participants completed a feedback questionnaire to assess user-friendliness and satisfaction with study devices. Participants were not remotely monitored or supervised.

The number of planned contacts with the study team was identical during the two study periods. The study pump and the study real-time continuous glucose monitoring device were used during both study periods. Participants were advised to calibrate the continuous glucose monitoring device according to the manufacturer's instructions; they were free to decide on alarm settings for the continuous glucose monitoring device. All participants were provided with a 24-hour telephone helpline to contact the study team in the event of study-related issues. All helpline contacts resulting in an immediate action by research staff (i.e. device replacement, adverse event reporting) were documented.

Closed-loop system

The FlorenceD2A closed-loop system (University of Cambridge, Cambridge, UK)(23) comprised a model predictive control algorithm (version 0.3.41, University of Cambridge) residing on a smartphone (Galaxy S4, Samsung, South Korea), which communicated wirelessly with continuous glucose monitoring receiver through a

purpose made translator unit (Triteq, Hungerford, UK) (Supplemental Material Figure S2). Every 12 min, the control algorithm calculated an insulin infusion rate which was set on the study insulin pump. In this trial, a hybrid closed-loop approach was applied, in which participants were required to count carbohydrates and use a standard bolus calculator for premeal boluses as per usual practice. Bolus calculations as provided by the study pump's built-in bolus calculator took into account carbohydrate content of meals, insulin on board, and entered capillary blood glucose readings. The control algorithm was initialized using preprogrammed basal insulin delivery downloaded from the study pump. Additionally, information about participant's weight and total daily insulin dose were entered at setup. During closed-loop operation, the algorithm adapted itself to the particular participant. The apparent total daily dose was modified based on sensor glucose levels achieved during closed-loop on previous days. In the current version of the algorithm this learning capability was made more responsive and enhanced adaptability was further supported by adaptation to varied insulin needs during the daytime and overnight periods. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8mmol/l and 7.3mmol/l and adjusted the actual target glucose level depending on fasting versus postprandial status and the accuracy of model-based glucose predictions.

Safety precautions during closed-loop

Participants were trained to perform a calibration check before breakfast and evening meal. If the sensor glucose was above the fingerstick glucose by >3.0mmol/l, the continuous glucose monitoring device was recalibrated. These

instructions resulted from an in silico evaluation of hypoglycemia and hyperglycemia risk (24) using the validated Cambridge simulator (25).

If sensor glucose became unavailable or in case of other failures, pre-programmed insulin delivery automatically restarted within 30-60 min. This limited the risk of insulin under- and over delivery (36). Safety rules limited maximum insulin infusion and suspended insulin delivery if glucose was ≤4.3mmol/l or when sensor glucose was rapidly decreasing.

Assays

C-peptide measurements were performed using chemiluminescence immunoassay (IV2-004; Invitron, Monmouth, UK; inter-assay variation 7.8%, 4.3% and 6.7% at 268pmol/l, 990pmol/l and 1,862pmol/l, respectively). Analytical sensitivity for the C-peptide assay was 5pmol/l. HbA1c was measured centrally using ion exchange high performance liquid chromatography (G8 HPLC Analyzer, Tosoh Bioscience, CA, USA; interassay CVs 1.3% at 31.2mmol/mol, 0.8% at 80.5mmol/mol).

Questionnaire

The evaluation of participant-reported outcomes included a trial experience questionnaire completed by participants at the conclusion of the closed-loop phase. The questionnaire was composed of seven questions, four of which were closed questions. The three open questions requested comments and suggestions from participants regarding (1) what they liked about the closed-loop system, (2) what they did not like about the system, and (3) what additional features they would like to have in a closed-loop system.

Study outcomes

The primary efficacy outcome was the proportion of time when glucose was in the target range (3.9-10.0mmol/l) during the 21-day study periods as recorded by continuous glucose monitoring. Secondary outcomes included mean sensor glucose concentrations, glucose variability, time spent at glucose levels <3.9mmol/l (hypoglycemia) and >10.0mmol/l (hyperglycemia), and insulin delivery. Secondary outcomes were calculated over 24h, daytime and overnight periods; daytime was classified between 08:00 and midnight, and night-time between midnight and 08:00. Glucose variability was assessed by the standard deviation and the coefficient of variation of sensor glucose. Hypoglycemia burden was assessed by calculating the glucose sensor area under the curve less than 3.5mmol/l.

Statistical analysis

The statistical analysis plan was agreed upon by investigators in advance. All analyses were carried out on an intention-to-treat basis. Efficacy and safety data from all randomized participants were included in the analyses. The respective values obtained during the 21-day randomized interventions were compared using a least-square regression model. Sensor glucose and insulin outcomes were adjusted for period effect. Rank normal transformation analyses were used for highly skewed endpoints. Outcomes were presented as mean ± SD for normally distributed values or as median (interquartile range) for non-normally distributed values. Outcomes were calculated using GStat software (University of Cambridge, version 2.2). Analysis was done using SPSS (IBM Software, Hampshire, UK version 21). A 5% significance level was used to declare statistical significance. All p-values are two-sided.

Results

Participants

We approached 17 subjects, of whom 12 gave consent/assent and completed the study (7 males; age 14.6±3.1 years; diabetes duration 7.8±3.5 years; HbA1c 8.5±0.7% [69±8mmol/mol]; insulin pump therapy duration 5.5±2.6years; total daily insulin dose 0.82±0.18 U/kg/day], all C-peptide negative except for two participants with levels of 61 and 262 pmol/l) (Supplemental Material Table S1 and Figure S3).

Day-and-night glucose control and insulin delivery

Primary and secondary endpoints are summarized in Table 1. Twenty-four hour sensor glucose and insulin delivery profiles are shown in Figure 1. The proportion of time that sensor glucose was in the target glucose range 3.9 to 10.0mmol/l (primary endpoint), was increased during closed-loop compared to control period ($p<0.001$, Table 1). The mean glucose level was significantly lower with closed-loop use ($p=0.001$, Figure 2) as was the time spent above the target glucose range ($p<0.001$). The proportion of time spent with sensor readings in hypoglycemia (below 3.9mmol/l and 2.8mmol/l, Figure 2) and the area under the curve when sensor glucose was less than 3.5mmol/l were low and comparable during the study interventions.

Glucose variability, measured as the standard deviation and the coefficient of variation of sensor glucose level within 24 hours and between days, did not differ between study periods. Higher percentage of time when glucose was in target range and lower mean glucose levels were achieved by closed-loop through increased

variability of basal insulin delivery (p<0.001; Figure 1) and slightly higher total daily insulin dose (p=0.006). Basal insulin delivery during closed-loop was significantly higher than during control intervention (p=0.001). Overall bolus insulin requirements during closed-loop were significantly lower (p=0.009), as was the number of overall bolus administrations per day (p=0.015). Fewer correction boluses [0.2 (0.1 to 0.4) vs. 0.9 (0.1 to 1.4) per day, closed-loop vs. control, p=0.015] but not meal boluses [4.8 (4.6 to 6.1) vs. 5.8 (4.1 to 7.0), p=0.48) were observed during closed-loop.

Daytime and overnight glucose control and insulin delivery

Secondary outcomes calculated for daytime (08:00 to midnight) and overnight periods (midnight to 08:00) are shown in Table 2. The daytime (p=0.002) and overnight (p=0.002) mean glucose were significantly lower during closed-loop use (p=0.002). The proportion of time that the glucose level was within the wide target range (3.9 to 10.0mmol/l) and overnight target range (3.9 to 8.0mmol/l) were higher during closed-loop compared to control (p<0.001) without a difference in total daytime and overnight insulin amount. The percentage of time spent with sensor readings below target range did not differ between the two interventions during daytime and overnight.

Adverse events

No serious adverse events or severe hypoglycemic episodes were observed during either study period. Three adverse events were documented, none of which was related to study devices or study procedures. One participants during control intervention measured elevated urine ketone levels associated with hyperglycemia. This event was attributed to a viral infection and was self-managed. One participant

during closed-loop and another participant during control period required oral antibiotic treatment due to respiratory tract infections without metabolic deterioration.

Utility analysis

Availability of sensor glucose data was 95% (91% to 98%) during closed-loop and higher than 90% (73% to 96%) recorded during control period (p=0.036). Closed-loop was operational over 82% (76% to 88%) of time. Overall frequency of recorded helpline contacts (device replacement, adverse event reporting) was higher during closed-loop: The study pump had to be replaced on three occasions (once during run-in, and twice during control period), two translator modules were replaced during the closed-loop period, and the closed-loop system had to be reset by research staff on eight occasions.

Questionnaire

All 12 participants completed the questionnaire. Results of the four closed questions are shown in Figure S4 (Online Supplement); 100% (12/12) of the participants were confident with the closed-loop system regulating their blood glucose and insulin delivery. 83.3% (10/ 12) of subjects stated that using the closed-loop system, they spent less time to manage their diabetes, and two participants (16.7%) were unsure about this statement. The majority of participants (91.7% [11/12]) expressed fewer concerns about their glucose control while using closed-loop. Improved sleep was indicated by 75% (9/12) of participants, whereas 8.3% (1/12) slept worse, and 16.7% (2/12) were unsure about the impact of the closed-loop system on their sleep.

Key positive themes of the closed-loop system as described by participants in the free-text section of the questionnaire were improved glucose control, a relief of

diabetes management, and specific features of the closed-loop handset allowing remote meal bolusing and data review. Key negative themes were the number and size of devices, the necessity to carry around the equipment all the time, CGM and pump alarms, connectivity and CGM calibration issues. According to participants, future closed-loop systems should be smaller, ideally integrating all different devices into one single device. Sensor life should be longer, and additional features to facilitate carbohydrate estimation should be implemented.

Conclusions

To our knowledge, this is the longest randomized controlled trial investigating day-and-night application of closed-loop insulin delivery in adolescents with type 1 diabetes during free-living conditions. We demonstrate the feasibility and benefits of prolonged use of single hormone 24/7 closed-loop. It increased the time when glucose was in the target range by 19 percentage points whilst reducing mean glucose by 1.8mmol/l. Though more insulin was delivered during closed-loop in these suboptimally controlled adolescents, improvements were achieved without increasing the risk of hypoglycemia.

The present study extends findings from our previous home trials in children and adolescents (19; 21; 22), which were limited by either overnight application (19; 21) or a shorter intervention period (22). While benefits of closed-loop in these trials as well as in our previous adult trials (21; 26) tended to be greater overnight compared to daytime, results of the present study show consistent improvements in glucose levels overnight and during daytime. Possible explanations include closed-

loop mitigating against missed meal boluses in suboptimally controlled adolescents. Additionally, we applied control algorithm with enhanced adaptivity. Poorly controlled teenagers may be among those most benefiting from closed-loop systems.

Hypoglycemia rates were low, and there was no significant difference in the time spent in hypoglycemia between interventions in line with findings from our previously published 24/7 closed-loop home trial in adolescents (22). Significant reductions in hypoglycemia risk were observed in populations with greater rates of hypoglycemia or in more challenging environments such as diabetes camps during prolonged outpatient closed-loop studies in adults using single-hormone (21; 27) or dual hormone (glucagon co-administration) closed-loop approaches across different age groups (16-18).

Prolonged periods of sensor under-reading resulting in hypoglycemia over-reporting were identified in one participant during closed-loop intervention underscoring challenges associated with quantifying hypoglycemia using glucose sensor data. No similar findings were observed during control intervention. While results in Table 1 & 2 and in the results section are based on the original data, Figure 2 shows data excluding periods of sensor under-reading (see Figure S5 to S9, Supplemental Material, for details of excluded data).

Total daily insulin requirements during closed-loop were modestly higher than during control intervention, which was due to higher basal insulin delivery. Inherent to closed-loop systems, algorithm directed insulin delivery was more variable than basal insulin delivery during the control period. More pronounced increases in total insulin delivery during closed-loop intervention [24% (28) to 33% (16) of total daily insulin dose] were previously described in studies of dual hormone systems, where

potential insulin overdosing can be mitigated by co-administration of glucagon. Higher insulin requirements during closed-loop in the present study may reflect underinsulinisation in sub-optimally controlled adolescents. Of interest, we observed reduced bolus amounts and fewer boluses per day during closed-loop intervention. We attribute this finding to fewer correction doses, but the observation could also reflect reduced bolus adherence for meals and snacks during closed-loop. The unsupervised design of the study precludes reliable interpretation of the finding.

Closed-loop usage and sensor wear were high. The closed-loop technology was well perceived in line with previously published data (29). Though the number of devices and system alarms were reported to be drawbacks, participants expressed trust in the technology, and reduced burden of diabetes including a less time spent to manage diabetes and fewer worries about glycemic control. Further miniaturization and integration of devices, prolonged sensor life, and simplified meal management are preferable features of future closed-loop systems which may enhance usability. A fully closed-loop system without meal announcement would be particularly applicable in the adolescent population. However, the absorption rate of currently available rapid acting insulin analogues is not fast enough to effectively control postprandial glucose excursions without anticipatory insulin bolus. Our premise is that present closed-loop systems will benefit from meal announcement but have to be able to cope with missed meal boluses safely and efficaciously, should these occur.

The strengths of our study include randomized crossover design, the integration of closed-loop into normal life with participants performing their usual free-living activities while at home or at school, and during weekends and holidays. The study was performed without remote monitoring or close supervision to assess

real-world applicability of the technology. We did not restrict participants' dietary intake, physical activity or geographical movement. The comparator was state-of-the-art sensor-augmented insulin pump therapy. Weaknesses include a small sample size and the need to carry multiple devices during closed-loop intervention. The study duration was still relatively short.

In conclusion, we found that use of a day-and-night hybrid closed-loop system at home over a period of 21 days during free daily living without close supervision is feasible, safe and effective in suboptimally controlled adolescents with type 1 diabetes. Benefits include increased time when glucose is in the target range and reduced mean glucose. Larger and longer studies are warranted.

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Author contributions: RH had full access to all of the data in the studies and takes responsibility for the integrity of the data and the accuracy of the data analysis. RH coordinated the studies. RH, MT, MEW, DBD, CLA, and HT co-designed the studies. MT and JMA were responsible for screening and enrolment of participants, and arranged informed consent from the participants. MT, JMA, MEW, and HT provided patient care and/or took samples. MEW managed randomization. MT, MEW, and RH carried out or supported data analysis, including the statistical analyses. RH designed and implemented the glucose controller. RH, MT, and HT contributed to the interpretation of the results. All authors critically reviewed the report. MT and RH wrote the manuscript. No writing assistance was provided.

Conflict of interest disclosures: RH reports having received speaker honoraria from Eli Lilly and Novo Nordisk, serving on advisory panel for Eli Lilly and Novo Nordisk, receiving license fees from BBraun and Medtronic; and having served as a consultant to BBraun. MEW has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. RH and MEW report patents and patent applications. MT reports having received speaker honoraria from Novo Nordisk. JMA, HT, and CLA declare no competing financial interest exists.

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Abbott Diabetes Care read the manuscript before submission. No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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TABLES

Table 1. Comparison of glucose control and insulin delivery during closed-loop and control period over 21 days.

	Closed-loop (n=12)	*Control (n=12)*	*Paired difference**	*p*
Day-and-night glucose control				
Time spent at glucose level (%)				
3.9 to 10.0mmol/l†	66.6±7.9	47.7±14.4	18.8±9.8	<0.001
>10.0mmol/l	29.7±9.2	49.1±16.5	-19.3±11.3	<0.001
>16.7mmol/l	5.1 (0.8 to 5.6)	8.0 (1.9 to 17.4)	-3.6 (-11.9 to -0.65)	<0.001
<3.9mmol/l	4.3 (1.4 to 5.2)	2.4 (0.3 to 5.7)	0.4 (-2.2 to 1.3)	0.33
<2.8mmol/l	0.3 (0.0 to 0.5)	0.1 (0.0 to 0.7)	-0.1 (-0.4 to 0.2)	0.49
AUC_{day} <3.5mmol/l (mmol/l x min) ‡	11.1 (1.2 to 17.4)	2.7 (0.2 to 20.4)	0.0 (-10.5 to 6.8)	0.21
Mean glucose (mmol/l)	8.7±0.9	10.5±1.8	-1.8±1.3	0.001
Within day SD of glucose (mmol/l)	3.7±0.7	4.2±0.8	-0.5±0.7	0.013
CV of glucose within day (%)	40.5 (38.1 to 47.7)	38.3 (36.7 to 43.7)	1.2 (-2.6 to 6.7)	0.18
CV of glucose between days (%)	19.0 (13.8 to 23.7)	17.4 (14.9 to 24.0)	-0.5 (-3.9 to 6.0)	0.94
Day-and-night insulin delivery				
Total daily insulin (U/day)	53.5 (39.5 to 72.1)	51.5 (37.6 to 64.3)	4.5 (1.6 to 6.5)	0.006
Total bolus insulin (U/day)	28.3 (16.7 to 32.6)	29.4 (23.6 to 37.6)	-4.4 (-8.1 to -1.4)	0.009
Total basal insulin (U/day)	25.8 (23.0 to 41.2)	19.9 (14.8 to 26.3)	7.6 (3.8 to 14.4)	0.001
SD of basal insulin delivery (U/hour)	1.2 (1.0 to 1.9)	0.3 (0.1 to 0.3)	1.1 (0.8 to 1.6)	<0.001
CV of basal insulin delivery	106.7 (97.2 to 111.1)	23.9 (12.8 to 35.2)	79.2 (77.1 to 91.3)	<0.001
Bolus administrations (Number/day)	4.9 (4.8 to 6.3)	6.3 (5.1 to 7.6)	-1.1 (-1.5 to -0.2)	0.015

Data are presented as mean±SD or median (interquartile range). p-values adjusted for period effect.
*Closed-loop minus control. A positive value indicates the value was higher on the closed-loop compared with control
† Primary endpoint
‡AUC_{day}, Glucose area under curve below 3.5mmol/l per day

Table 2. Daytime and night-time glucose control and insulin delivery during closed-loop and control period.

	Closed-loop (n=12)	Control (n=12)	*Paired difference**	*p*
Daytime (from 08:01 to 23:59)				
Time spent at glucose level (%)				
3.9 to 10.0mmol/l	62.9±8.9	45.7±13.7	17.1±12.2	0.001
>10.0mmol/l	33.0±10.7	51.8±15.7	-18.7±13.7	0.001
<3.9mmol/l	4.2 (1.0 to 6.5)	1.2 (0.3 to 3.9)	0.3 (-0.8 to 4.1)	0.15
AUC_{day} <3.5mmol/l (mmol/l x min) †	11.2 (0.9 to 17.0)	2.0 (0.2 to 12.3)	-0.4 (-5.0 to 12.8)	0.26
Mean glucose (mmol/l)	9.0±1.0	10.8±1.9	-1.8±1.5	0.002
Within day SD of glucose (mmol/l)	3.9±0.8	4.3±0.9	-0.4±0.9	0.10
CV of glucose within day (%)	42.8 (37.9 to 49.8)	39.0 (36.0 to 42.6)	3.0 (-3.7 to 8.7)	0.20
CV of glucose between days (%)	19.2 (17.4 to 25.6)	21.6 (16.5 to 23.1)	-2.4 (-5.8 to 3.5)	0.86
Daytime insulin delivery (U)	42.7 (31.2 to 53.6)	42.8 (30.9 to 48.4)	3.5 (0.0 to 6.3)	0.24
Night-time (from midnight to 08:00)				
Time spent at glucose level (%)				
3.9 to 8.0mmol/l	54.4±13.8	33.4±16.3	20.9±12.7	<0.001
>8.0mmol/l	42.8±14.0	62.0±19.4	-19.3±14.5	0.001
<3.9mmol/l	2.5 (1.1 to 4.2)	3.9 (0.3 to 7.2)	-1.3 (-4.9 to 1.4)	0.70
AUC_{day} <3.5mmol/l (mmol/l x min)*	5.3 (1.6 to 19.7)	4.7 (0.0 to 21.8)	1.2 (-20.0 to 5.9)	0.56
Mean glucose (mmol/l)	8.2±1.1	9.8±2.0	-1.6±1.4	0.002
Within night SD of glucose (mmol/l)	3.1±0.9	3.8±0.7	-0.7±0.7	0.008
CV of glucose within night (%)	37.3±6.8	39.3±7.3	-2.0±9.9	0.53
CV of glucose between nights (%)	26.7±8.5	30.9±6.4	-4.2±10.1)	0.20
Overnight insulin delivery (U)	11.5 (9.5 to 17.3)	11.0 (8.5 to 15.0)	0.6 (-0.5 to 3.5)	0.18

Data are presented as mean±SD, median (interquartile range)

* Closed-loop minus control. A positive value indicates the value was higher on the closed-loop compared with control

† AUC_{day}, glucose area under curve below 3.5mmol/l per day

FIGURE LEGENDS

Figure 1. Median (interquartile range) of sensor glucose (top panel) and insulin delivery (bottom panel) during closed-loop (solid red line and red shaded area) and control period (dashed black line and gray shaded area) from midnight to midnight. The glucose range 3.9 to 10.0 mmol/l is denoted by horizontal dashed lines (top panel).

Figure 2. Individual values of mean sensor glucose during day-and-night closed-loop study. The size of bubble indicates the proportion of time spent with low glucose below 2.8mmol/l.