Home Use of Day-and-Night Hybrid Closed-Loop Insulin Delivery in Very Young Children: A Multicenter, 3-Week, Randomized Trial

Diabetes Care 2019;42:594–600 | https://doi.org/10.2337/dc18-1881

Martin Tauschmann,[1,2,3] Janet M. Allen,[1,2] Katrin Nagl,[3] Maria Fritsch,[3] James Yong,[4] Emily Metcalfe,[4] Dominique Schaeffer,[5] Muriel Fichelle,[5] Ulrike Schierloh,[5] Alena G. Thiele,[6] Daniela Abt,[7] Harald Kojzar,[8] Julia K. Mader,[8] Sonja Slegtenhorst,[9] Nicole Barber,[1] Malgorzata E. Wilinska,[1,2] Charlotte Boughton,[1] Gianluca Musolino,[1] Judy Sibayan,[10] Nathan Cohen,[10] Craig Kollman,[10] Sabine E. Hofer,[7] Elke Fröhlich-Reiterer,[11] Thomas M. Kapellen,[6] Carlo L. Acerini,[2] Carine de Beaufort,[5] Fiona Campbell,[4] Birgit Rami-Merhar,[3] and Roman Hovorka,[1,2] on behalf of KidsAP Consortium

OBJECTIVE

We aimed to assess the feasibility and safety of hybrid closed-loop insulin delivery in children with type 1 diabetes aged 1–7 years as well as evaluate the role of diluted insulin on glucose control.

RESEARCH DESIGN AND METHODS

In an open-label, multicenter, multinational, randomized crossover study, 24 children with type 1 diabetes on insulin pump therapy (median age 5 years [interquartile range 3–6] and mean ± SD HbA_{1c} 7.4 ± 0.7% [57 ± 8 mmol/mol] and total insulin 13.2 ± 4.8 units/day) underwent two 21-day periods of unrestricted living and we compared hybrid closed-loop with diluted insulin (U20) and hybrid closed-loop with standard strength insulin (U100) in random order. During both interventions, the Cambridge model predictive control algorithm was used.

RESULTS

The proportion of time that sensor glucose was in the target range between 3.9 and 10 mmol/L (primary end point) was not different between interventions (mean ± SD 72 ± 8% vs. 70 ± 7% for closed-loop with diluted insulin vs. closed-loop with standard insulin, respectively; *P* = 0.16). There was no difference in mean glucose levels (8.0 ± 0.8 vs. 8.2 ± 0.6 mmol/L; *P* = 0.14), glucose variability (SD of sensor glucose 3.1 ± 0.5 vs. 3.2 ± 0.4 mmol/L; *P* = 0.16), or the proportion of time spent with sensor glucose <3.9 mmol/L (4.5 ± 1.7% vs. 4.7 ± 1.4%; *P* = 0.47) or <2.8 mmol/L (0.6 ± 0.5% vs. 0.6 ± 0.4%; *P* > 0.99). Total daily insulin delivery did not differ (17.3 ± 5.6 vs. 18.9 ± 6.9 units/day; *P* = 0.07). No closed-loop–related severe hypoglycemia or ketoacidosis occurred.

CONCLUSIONS

Unrestricted home use of day-and-night closed-loop in very young children with type 1 diabetes is feasible and safe. The use of diluted insulin during closed-loop does not provide additional benefits compared with standard strength insulin.

Despite advances in the management of type 1 diabetes and supporting technologies, the majority of children with type 1 diabetes are unable to achieve recommended treatment targets (1,2). Closed-loop systems (3) delivering insulin in glucose-responsive fashion may provide benefits compared with existing treatment modalities including

[1]*Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, U.K.*
[2]*Department of Paediatrics, University of Cambridge, Cambridge, U.K.*
[3]*Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria*
[4]*Department of Paediatric Diabetes, Leeds Children's Hospital, Leeds, U.K.*
[5]*Department of Pediatric Diabetes and Endocrinology, Clinique Pédiatrique, Centre Hospitalier de Luxembourg, Luxembourg City, Luxembourg*
[6]*Division for Paediatric Diabetology, University of Leipzig, Leipzig, Germany*
[7]*Department of Pediatrics, Medical University of Innsbruck, Innsbruck, Austria*
[8]*Department of Internal Medicine, Medical University of Graz, Graz, Austria*
[9]*Department of Nutrition and Dietetics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, U.K.*
[10]*Jaeb Center for Health Research, Tampa, FL*
[11]*Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria*

Corresponding author: Roman Hovorka, rh347@cam.ac.uk

Received 6 September 2018 and accepted 18 December 2018

Clinical trial reg. no. NCT03101865, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1881/-/DC1.

improved glycemic control and reduced burden of hypoglycemia (4,5). Hybrid closed-loop systems are characterized by automated insulin delivery apart from when user manages insulin boluses at mealtime.

Rapid progress has been made in testing closed-loop delivery systems during unrestricted living in randomized clinical trials across a broad range of people with type 1 diabetes (6–10). However, investigations in preschool children have been confined to short study durations, round-the-clock supervision, and inpatient or diabetes camp settings (11–13). Performance of closed-loop systems in young children, including preschool children, in unsupervised home settings is unknown.

In preschool children, insulin infusion rates <0.1 units/h may be required compared with higher rates of 1.0 units/h and above in adolescents and young adults. Modern insulin pumps allow adjustments of basal rates but are limited by minimum increments of 0.01–0.05 units/h (14), inherent inaccuracies at low infusion rates (15), and temporal silent occlusions (16). Diluting insulin is applied in pediatric diabetes centers to mitigate against these factors, but compelling evidence to support the use of diluted insulin is missing. Anecdotal reports suggest that the use of diluted insulin in young children may be beneficial to decrease glycemic variability, reduce occurrence of unexplained hyperglycemia, and reduce infusion set failures (17). Diluting insulin as a strategy for delivering low basal infusion rates is in line with the latest clinical practice consensus guidelines provided by the International Society of Pediatric and Adolescent Diabetes in 2018 (18). Results from an overnight research facility closed-loop study suggested that the use of diluted insulin in very young children may lead to reduced hypoglycemia and reduced glucose variability as well as less variable insulin absorption (11,19).

The objective of the present multicenter randomized trial was to assess the feasibility and safety of closed-loop insulin delivery in home settings in children with type 1 diabetes aged 1–7 years. We hypothesized that the use of diluted insulin in a population with low insulin requirements will improve glucose control and reduce the risk of hypoglycemia. In a crossover randomized study design, closed-loop was applied over two 21-day periods comparing hybrid closed-loop with diluted insulin (U20) and hybrid closed-loop with standard strength insulin (U100).

RESEARCH DESIGN AND METHODS

Study Participants

Inclusion criteria included type 1 diabetes as defined by the World Health Organization for at least 6 months, age between 1 and 7 years (inclusive), insulin pump therapy for at least 3 months, and glycated hemoglobin $\leq$11% ($\leq$97 mmol/mol). Key exclusion criteria included total daily insulin dose $\geq$2.0 units/kg/day and more than two incidents of severe hypoglycemia within 6 months prior to enrollment.

We identified eligible children from pediatric diabetes clinics at Addenbrooke's Hospital (Cambridge, U.K.), Medical University of Vienna, Leeds Children's Hospital, Centre Hospitalier de Luxembourg, University of Leipzig, Medical University of Innsbruck, and Medical University of Graz.

Study Design and Procedures

The study adopted an open-label, multicenter, multinational, randomized, two-period crossover design contrasting hybrid closed-loop glucose control using diluted insulin (U20) and hybrid closed-loop using standard insulin strength (U100) during unrestricted living. Two intervention periods lasted 3 weeks, with each separated by 1–4 weeks of washout. The order of the two interventions was random. Training on study insulin pump and continuous glucose monitoring took place over a 2- to 4-week run-in period.

At enrollment, capillary blood samples were taken for analysis of glycated hemoglobin. At the start of the run-in phase, participants and their parents/guardians received training regarding the use of the study pump (a modified 640G insulin pump, for investigational use only; Medtronic, Northridge, CA) and the study real-time continuous glucose monitoring (Enlite 3 Glucose Sensor; Medtronic). Participants and their parents/guardians used the study pump's standard bolus calculator for all meals throughout the study.

At the end of the run-in period, compliance in the use of study pump and continuous glucose monitoring was assessed. Participants with at least 8 days' worth of continuous glucose monitoring data during the last 14 days of the run-in period were randomly assigned to receive either 3 weeks of hybrid closed-loop insulin delivery with standard insulin aspart (U100; Novo Nordisk, Bagsvaerd, Denmark) followed by hybrid closed-loop insulin delivery with diluted insulin aspart (U20; Novo Nordisk) or vice versa. Permuted block randomization was applied, and assignment was unblinded owing to the nature of the design. During the washout period, participants could continue using the study insulin pump and real-time continuous glucose monitoring system.

On the 1st day of the first closed-loop period, participants and their parents/guardians attended the clinical research facility. This 1- to 2-h visit included training on initiation and discontinuation of the closed-loop system, switching between closed-loop and usual pump therapy, the meal bolus procedure, and the use of study devices during periods of increased physical activity. Competency in using the closed-loop system by the parents/guardians was assessed. Following discharge, participants continued the study intervention for the next 21 days in free-living settings in their home and nursery/kindergarten or school environment. Participants were not remotely monitored or supervised. The participants were free to consume meals of their choice, and no restrictions were imposed on traveling or physical activity. We encouraged parents/guardians to continue closed-loop use during periods of increased physical activity and organized sports and to announce these periods to the algorithm.

At the start of the closed-loop period with use of diluted insulin, closed-loop training covered the use of diluted insulin. Prior to start of closed-loop with diluted insulin, pump settings were adapted accordingly and reviewed by two members of the research team. Carers at nursery/kindergarten or school also receive closed-loop training by the study team as required.

Parents/guardians 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 parents/guardians were provided with a 24-h telephone helpline to contact the

local study team in the event of study-related issues.

Insulin Dilution

Dilution of insulin aspart to U20 (20 units/mL) was performed by qualified members of study teams using Insulin Diluting Medium for NovoRapid (insulin aspart) and Levemir (insulin detemir) (Novo Nordisk). A 1:5 dilution ratio was used across all study participants.

Closed-Loop System

The FlorenceM closed-loop system (Supplementary Fig. 1) used a model predictive control algorithm (version 0.3.46; University of Cambridge, Cambridge, U.K.) residing on a smartphone (Galaxy S4; Samsung, Seoul, South Korea). Every 10 min, the control algorithm calculated an insulin infusion rate that was set on the study pump. The control algorithm was initialized using preprogrammed basal insulin delivery downloaded from the study pump. Information about participant's weight and total daily insulin dose was entered at setup. The treat-to-target control algorithm aimed to achieve glucose levels between 5.8 and 7.3 mmol/L depending on the accuracy of model-based glucose predictions.

The threshold suspend feature on the modified 640G pump was turned on during closed-loop operation and allowed insulin delivery to be suspended when the smartphone was not in range or not operational. Further safety mitigations during closed-loop can be found in Supplementary Data.

Study Oversight

Prior to study initialization, approval was received from independent research ethics committees in the U.K., Luxembourg, Germany, and Austria and regulatory authorities in the U.K. (Medicines and Healthcare Products Regulatory Agency), Luxembourg (Ministry of Health), Germany (Federal Institute for Drugs and Medical Devices), and Austria (Austrian Agency for Health and Food Safety).

Parents/guardians of participants signed informed consent before study-related activities were initiated. Whenever possible and in line with recommendations by local ethics committees, assent of study participants was obtained in addition to the consent of the parents/guardians or legal representatives.

Assays

Glycated hemoglobin at recruitment for characterization of the study population was measured locally using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)-aligned method and following NGSP standards.

Study End Points

The primary end point was the proportion of time when glucose was in the target range between 3.9 and 10.0 mmol/L during the 21-day study periods as recorded by continuous glucose monitoring. Secondary end points included mean sensor glucose concentrations; glucose variability measured by the SD and the coefficient of variation; time spent at glucose levels $<$3.9, $<$3.5, $<$2.8, $>$10.0, and $>$16.7 mmol/L; and insulin delivery (total, basal, and bolus amounts). Hypoglycemia burden was additionally assessed by calculating the glucose sensor area under the curve $<$3.5 mmol/L. Secondary end points were calculated over the whole study periods, and a subset of secondary end points (time in the target range, time $<$3.5 mmol/L, mean glucose, SD of glucose, and total insulin amount), to limit the number of comparisons, during daytime and nighttime periods; daytime was classified as between 6:00 A.M. and 9:59 P.M. and nighttime between 10:00 P.M. and 5:59 A.M.

Sample Size

Based on our overnight closed-loop study in young children (11) and an estimate of an 10-percentage-point improvement in time in target with diluted insulin using an SD of 13 percentage points for the paired difference between study periods, 20 subjects were required to achieve the desired 90% power and an α-level of 0.05 (two-tailed *t* test); 24 participants were planned to be randomized to allow for dropouts.

Statistical Analysis

The statistical analysis plan was agreed upon by investigators in advance. All analyses were carried out on an intention-

Table 1—Characteristics of the study participants at screening

	Overall	Diluted first	Standard strength first
n	24	12	12
Age (years)			
Median (IQR)	5 (3–6)	5 (3–6)	5 (3–6)
Range	1–7	1–7	2–7
Male sex, *n* (%)	15 (63)	6 (50)	9 (75)
Race/ethnicity, *n* (%)			
White	21 (88)	11 (92)	10 (83)
Asian	1 (4)	1 (8)	0 (0)
Mixed	2 (8)	0 (0)	2 (17)
Diabetes duration (years)			
Mean ± SD	3.1 ± 1.7	3.0 ± 1.6	3.3 ± 1.9
Range	0.5–6.4	0.5–5.5	0.5–6.4
Total daily insulin, mean ± SD			
Units/day	13.2 ± 4.8	13.2 ± 4.6	13.2 ± 5.2
Units/kg/day	0.65 ± 0.14	0.67 ± 0.15	0.62 ± 0.14
Total basal insulin, mean ± SD			
Units/day	4.9 ± 2.3	4.7 ± 2.2	5.1 ± 2.5
Units/kg/day	0.24 ± 0.08	0.24 ± 0.07	0.25 ± 0.09
Total bolus insulin, mean ± SD			
Units/day	8.2 ± 3.4	8.4 ± 3.4	8.1 ± 3.5
Units/kg/day	0.41 ± 0.13	0.43 ± 0.15	0.38 ± 0.11
Basal-to-bolus ratio, mean ± SD	0.66 ± 0.28	0.62 ± 0.24	0.70 ± 0.32
BMI* percentile, median (IQR)†	73 (4–91)	61 (49–75)	83 (31–91)
HbA_{1c}, mean ± SD			
%	7.4 ± 0.7	7.7 ± 0.7	7.1 ± 0.6
Millimoles per mole of nonglycated hemoglobin	57 ± 8	61 ± 8	54 ± 6

*BMI calculated as the weight in kilograms divided by the square of height in meters. †BMI *z* score adjusted for age and sex based on 2000 Centers for Disease Control and Prevention growth charts; excludes one subject $<$2 years of age who received diluted insulin first. For this subject, BMI percentile could not be calculated.

to-treat basis. We analyzed end points from participants with at least 24 h of sensor glucose data in one study period. Analysis of those with at least 24 h of glucose sensor data in both study periods was also carried out (prespecified analysis plan). The respective values obtained during the 21-day randomized interventions were compared using a linear mixed model adjusting for period as a fixed effect and site as a random effect. Rank normal transformation analyses were used for highly skewed end points. End points were presented as mean ± SD for normally distributed values or as median (interquartile range [IQR]) for nonnormally distributed values. Outcomes were calculated using gstat software, version 2.2.4 (University of Cambridge), and statistical analyses carried out using SAS software, version 9.4 (SAS Institute). A 5% significance level was used to declare statistical significance. All *P* values are two sided.

RESULTS

From August 2017 to February 2018, 24 subjects were enrolled and randomized (15 males of median age 5 years [IQR 3–6] and mean ± SD diabetes duration 3.1 ± 1.7 years, glycated hemoglobin 7.4 ± 0.7% [57 ± 8 mmol/mol], and total daily insulin 13.2 ± 4.8 units/day) (Table 1). The flow of participants through the trial is shown in Supplementary Fig. 2. Of 24 randomized participants, 23 completed the trial. One participant withdrew from the study during washout as a result of recurrent technical issues with the closed-loop system (i.e., sensor calibration and device communication issues).

Primary and secondary end points calculated using data from all randomized subjects are presented in Table 2. The primary end point, the proportion of time sensor glucose was in the target glucose range between 3.9 and 10.0 mmol/L, was not different between interventions (72 ± 8% vs. 70 ± 7% for closed-loop with diluted insulin vs. closed-loop with standard insulin, respectively; *P* = 0.16), with a mean adjusted difference of 2 percentage points in favor of diluted insulin (95% CI −1 to 4). Fig. 1 shows 24-h sensor glucose profiles. End points calculated using data from randomized subjects with a minimum of 24 h of sensor data in both treatment periods (*n* = 23 for both periods) were similar (Supplementary Table 1).

There was no difference in mean glucose levels (8.0 ± 0.8 vs. 8.2 ± 0.6 mmol/L for closed-loop with diluted insulin vs. closed-loop with standard insulin, respectively; *P* = 0.14) or glucose variability (Table 2) between study interventions. The proportion of time when sensor glucose was <3.9 mmol/L did not differ (4.5 ± 1.7% vs. 4.7 ± 1.4%; *P* = 0.47). The percentages of time spent with sensor readings <3.5 mmol/L and <2.8 mmol/L were low and not different between interventions (Table 2). The relative burden of hypoglycemia as measured by the area under the curve when sensor glucose was <3.5 mmol/L was not different (*P* = 0.71).

Total daily insulin delivery did not differ between interventions (17.3 ± 5.6 vs. 18.9 ± 6.9 units/day for closed-loop with diluted insulin vs. closed-loop with standard insulin; *P* = 0.07). There was no difference in basal insulin delivery (*P* = 0.76). However, a modest but statistically significant reduction of bolus insulin delivery during closed-loop with diluted insulin was observed (10.4 ± 3.5 vs. 11.8 ± 4.2 units/day; *P* = 0.006), presumably due to slightly lower glucose levels during closed-loop with diluted insulin resulting in a reduced amount of insulin delivered as correction boluses. Basal–to–bolus insulin ratios were not different between interventions (*P* = 0.10).

Glucose sensor use and closed-loop application were high. During closed-loop with diluted insulin, closed-loop was used for a median of 86% (IQR 84–91) of the time, and participants wore glucose sensor for 94% (91–95) of the time. During closed-loop with standard strength insulin, these values were 88% (82–91) and 95% (92–97), respectively.

Secondary end points calculated for daytime and nighttime are shown in Table 3. Tight glucose control was particularly prominent during the nighttime (Fig. 1 and Table 3). There was no evidence that the effect of treatment depended on time of day (Table 3).

Table 2—Comparison of glucose control and insulin delivery over 21 days during closed-loop with diluted insulin (U20) and closed-loop with standard strength insulin (U100)

	Diluted (*n* = 23)	Standard strength (*n* = 24)	*P*
Percent of time with sensor glucose level in range			
3.9–10.0 mmol/L*	72 ± 8	70 ± 7	0.16
<3.9 mmol/L	4.5 ± 1.7	4.7 ± 1.4	0.47
<3.5 mmol/L	2.4 ± 1.2	2.5 ± 1.0	0.32
<2.8 mmol/L	0.6 ± 0.5	0.6 ± 0.4	>0.99
>10.0 mmol/L	23 ± 9	25 ± 7	0.23
>16.7 mmol/L	1.2 (0.6–3.2)	1.5 (0.8–3.1)	0.28
Glucose AUC <3.5 mmol/L†	2.9 ± 1.9	3.0 ± 1.6	0.71
Glucose (mmol/L)	8.0 ± 0.8	8.2 ± 0.6	0.14
Glucose SD (mmol/L)	3.1 ± 0.5	3.2 ± 0.4	0.16
Glucose CV (%)	40 (39–41)	39 (38–42)	0.91
Total daily insulin (units/day)	17.3 ± 5.6	18.9 ± 6.9	0.07
Total daily basal insulin (units/day)	6.8 ± 2.5	7.2 ± 3.2	0.76
Total daily bolus insulin (units/day)	10.4 ± 3.5	11.8 ± 4.2	0.006
Basal-to-bolus ratio	0.67 ± 0.19	0.63 ± 0.20	0.10

Data are mean ± SD or median (IQR) unless otherwise indicated. CV, coefficient of variation. *Primary end point. †The area under the curve (AUC) is for a glucose level <3.5 mmol/L/24-h period.

Adverse Events

No severe hypoglycemia or diabetic ketoacidosis events were reported during the entire study. One participant was hospitalized during washout owing to a lower respiratory tract infection. Six other adverse events were reported, of which three occurred during run-in, one during washout, and two during closed-loop with standard strength insulin (Supplementary Table 1). None of the events were deemed related to study devices or study procedures. All participants recovered fully without clinical sequelae.

CONCLUSIONS

To our knowledge, this is the first and longest randomized controlled trial

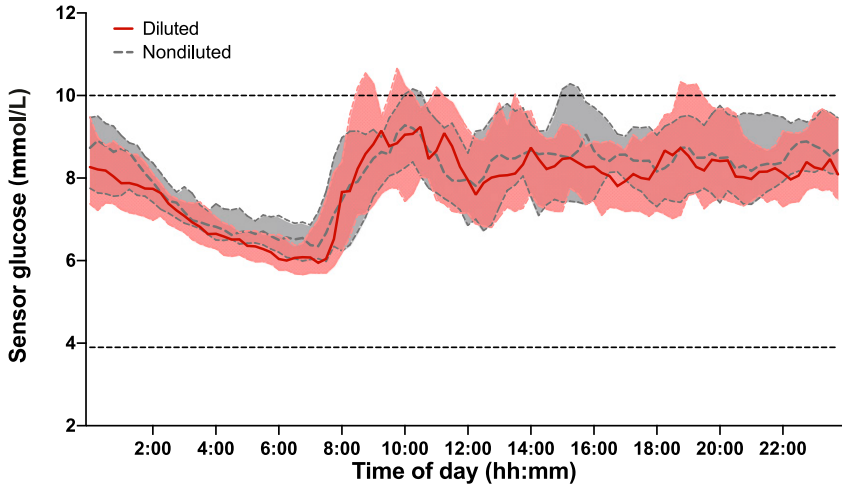

Figure 1—Sensor glucose levels. Shown are the median sensor glucose levels and IQRs during closed-loop with diluted insulin (n = 23 [solid red line and red shaded area]) and closed-loop with standard strength insulin (n = 24 [dashed black line and gray shaded area]). Dashed horizontal lines indicate the target glucose range between 3.9 and 10 mmol/L. m, minute.

investigating day-and-night application of closed-loop insulin delivery in very young children with type 1 diabetes during unrestricted living. Our findings document that hybrid closed-loop insulin delivery in a relatively well-controlled population is feasible and safe in managing glucose control. No benefits associated with the use of diluted insulin were observed.

Results of the current study are consistent with observations in older children (6), adolescents (6,7), adults (6,9), and pregnant women (20) about safety and efficacy of closed-loop therapy using Cambridge model predictive control. This confirms the robustness of our model predictive algorithm and supports the application of our closed-loop systems across a broad range of people with type 1 diabetes including preschool children.

Studies of outpatient closed-loop use in toddlers and preschoolers with type 1 diabetes are sparse. Hybrid insulin delivery using a modular model predictive control approach in children aged 5–9 years was investigated in diabetes camp settings under close supervision documenting reduced nocturnal hypoglycemia compared with sensor-augmented insulin pump therapy (12). This was offset by increased mean glucose levels during closed-loop use. DeBoer et al. (13) evaluated 68-h use of a hybrid closed-loop system in 12 children aged 5–8 years followed as an outpatient admission compared with home care. Closed-loop resulted in increased time with glucose levels in the target range and lower mean glucose levels without increasing the risk of hypoglycemia. These two trials were short, participants were supervised, and toddlers and preschoolers were excluded.

The rationale for the use of diluted insulin in the current study was to enhance accuracy of insulin delivery. Our assumption was that these benefits may manifest markedly in those with lower total daily dose, but we observed no relationship between the total daily insulin amount and the difference in time when glucose was in the target range when we compared diluted insulin with standard strength insulin closed-loop use (Supplementary Fig. 3). We enrolled participants with total daily insulin dose ranging from 4.3 to 26.6 units, but only two participants had a total insulin dose <10.0 units/day during closed-loop interventions (Supplementary Fig. 3).

Overnight glucose control is a major concern for parents and caregivers of young children with type 1 diabetes. More than 50% of severe hypoglycemic episodes occur during sleep in children and adolescents (21). Fear of hypoglycemia is a major cause of stress and anxiety for families and caregivers (22) and is also a major barrier to therapy intensification (21) and optimal glucose control (23). With >80% of time with sensor readings in the target range overnight, mean overnight glucose levels close to 7.0 mmol/L, and very low rates of hypoglycemia, our closed-loop system performed particularly well overnight (Fig. 1 and Table 3). A trend similar to that in the current study was observed in our previous trials in older populations (6,9,24). Because of this favorable nocturnal performance, hybrid closed-loop systems may be particularly appealing to families and caregivers of young children with type 1 diabetes.

We used a prototype modular closed-loop system with the size of devices as well as connectivity issues potentially limiting its utility. Nevertheless, sensor glucose wear was high, at a median 94–95% of the time, and, similarly, closed-

Table 3—Daytime and nighttime glucose control and insulin delivery during closed-loop with diluted insulin (U20) and closed-loop with standard strength insulin (U100)

	Daytime: 6:00 A.M. to 9:59 P.M.		Nighttime: 10:00 P.M. to 5:59 A.M.		
	Diluted (n = 23)	Standard strength (n = 24)	Diluted (n = 23)	Standard strength (n = 24)	P*
Percent of time with sensor glucose level in range					
3.9–10.0 mmol/L	68 ± 10	67 ± 8	80 ± 10	77 ± 9	0.41
<3.5 mmol/L	2.9 ± 1.7	3.0 ± 1.3	1.3 ± 1.2	1.7 ± 1.1	0.66
Glucose (mmol/L)	8.2 ± 0.9	8.3 ± 0.8	7.6 ± 0.8	7.9 ± 0.6	0.09
Glucose SD (mmol/L)	3.3 ± 0.5	3.4 ± 0.5	2.6 ± 0.6	2.8 ± 0.5	0.17
Total insulin (units/day)	14.8 ± 4.9	16.2 ± 5.7	2.3 ± 0.9	2.4 ± 1.1	0.06

Data are mean ± SD. *P value for treatment–by–time of day interaction.

loop use was high, at a median 86–88% of the time, demonstrating high compliance and potential interest among parents/guardians of young children and feasibility of closed-loop use in nurseries, kindergartens, and playgroups.

The strengths of our study include the multicenter, multinational, crossover, randomized design that had the benefit of each participant acting as his/her own control. The study was performed without remote monitoring or close supervision, thereby assessing real-world use and supporting generalizability of study findings. We did not restrict participants' dietary intake, physical activity, or geographical movements. Limitations include a relatively short duration of follow-up; a relatively small number of participants, particularly participants with total daily dose <10 units/day; nonstandardized sensor alarm settings; and a lack of a control group to assess efficacy compared with standard clinical practice. We aim to address some of these issues in a follow-up study.

In conclusion, hybrid closed-loop insulin delivery using the model predictive control approach is feasible and safe in young children with type 1 diabetes during unrestricted living. Insulin dilution does not appear to be of additional benefit with use of hybrid closed-loop insulin delivery.

Acknowledgments. Medtronic supplied discounted continuous glucose monitoring devices and sensors and provided details of communication protocol to facilitate real-time connectivity. The authors thank study volunteers for their participation and acknowledge support by the staff at the Addenbrooke's Wellcome Trust Clinical Research Facility. Jasdip Mangat (National Health Service Trust, University Hospitals of Leicester, Leicester, U.K.) supported development and validation of the closed-loop system. Josephine Hayes (University of Cambridge) provided administrative support.

Funding. This project has received funding from the European Union's Horizon 2020 Framework Programme for Research and Innovation under grant agreement no. 731560. Additional support for the artificial pancreas work was from National Institute for Health Research Cambridge Biomedical Research Centre and a Wellcome Trust Strategic Award (100574/Z/12/Z). The Jaeb Center for Health Research is funded by JDRF under grant 3-SRA-2016-297-M-N.

This material reflects only the authors' views, and the European Commission is not liable for any use that may be made of the information contained therein.

Duality of Interest. M.T. reports having received speaker honoraria from MiniMed Medtronic and Novo Nordisk. M.Fr. has received speaker honoraria from MiniMed Medtronic and has served on advisory boards for Eli Lilly. J.K.M. is a member of the advisory board of Becton Dickinson, Boehringer Ingelheim, Eli Lilly, Medtronic, and Sanofi and has received speaker honoraria from Abbott Diabetes Care, AstraZeneca, Eli Lilly, Nintamed, Novo Nordisk, Roche Diabetes Care, Sanofi, Servier, and Takeda. M.E.W. has received license fees from Becton Dickinson and has served as a consultant to Becton Dickinson. S.E.H. declares speaker honoraria from Eli Lilly and Sanofi. E.F.-R. reports having received speaker honoraria from MiniMed Medtronic and Eli Lilly and serving on advisory boards for Eli Lilly. T.M.K. has received speaker honoraria from MiniMed Medtronic, Roche, and Eli Lilly and is a member of an advisory board for Abbott Diabetes Care. C.d.B. has received speaker honoraria from MiniMed Medtronic and is a member of its European Psychology Advisory Board. B.R.-M. reports having received speaker honoraria from MiniMed Medtronic, Eli Lilly, Roche, Menarini, and Novo Nordisk and serving on advisory boards for Eli Lilly. R.H. reports having received speaker honoraria from MiniMed Medtronic, Eli Lilly, B. Braun, and Novo Nordisk; serving on an advisory panel for Eli Lilly; receiving license fees from B. Braun and Medtronic; and having served as a consultant to B. Braun, Sanofi, and Profil. M.E.W. and R.H. report patents and patent applications. Medtronic read the manuscript before submission. No other potential conflicts of interest relevant to this article were reported.

No sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Author Contributions. M.T., J.M.A., K.N., M.Fr., J.Y., E.M., D.S., M.Fi., U.S., A.G.T., D.A., S.S., S.E.H., E.F.-R., T.M.K., C.L.A., C.d.B., F.C., and B.R.-M. screened and enrolled participants and arranged informed consent from the participants. M.T., J.M.A., K.N., M.Fr., J.Y., E.M., D.S., M.Fi., U.S., A.G.T., D.A., H.K., J.K.M., S.S., S.E.H., E.F.-R., T.M.K., C.L.A., C.d.B., F.C., and B.R.-M. provided patient care and took samples. J.S. managed randomization. M.T., J.K.M., M.E.W., S.E.H., E.F.-R., T.M.K., C.L.A., C.d.B., F.C., B.R.-M., and R.H. designed the study. M.T., N.C., C.K., M.E.W., C.B., G.M., and R.H. performed or supported data analyses, including the statistical analyses. R.H. designed and implemented the glucose controller. M.T., J.K.M., M.E.W., S.E.H., E.F.-R., T.M.K., C.L.A., C.d.B., F.C., B.R.-M., and R.H. interpreted the results. M.T. and R.H. wrote the manuscript. N.B. and R.H. coordinated the study. M.T., J.M.A., K.N., M.Fr., J.Y., E.M., D.S., M.Fi., U.S., A.G.T., D.A., H.K., J.K.M., S.S., N.B., M.E.W., C.B., G.M., J.S., N.C., C.K., S.E.H., E.F.-R., T.M.K., C.L.A., C.d.B., F.C., B.R.-M., and R.H. critically reviewed the manuscript. No writing assistance was provided. R.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the International Society of Pediatric and Adolescent Diabetes 44th Annual Conference, 11–14 October 2018, Hyderabad, India.

References

1. McKnight JA, Wild SH, Lamb MJ, et al. Glycaemic control of type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet Med 2015;32:1036–1050

2. Sherr JL, Hermann JM, Campbell F, et al.; T1D Exchange Clinic Network, the DPV Initiative, and the National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health Registries. Use of insulin pump therapy in children and adolescents with type 1 diabetes and its impact on metabolic control: comparison of results from three large, transatlantic paediatric registries. Diabetologia 2016;59:87–91

3. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia 2016;59:1795–1805

4. Bekiari E, Kitsios K, Thabit H, et al. Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ 2018;361:k1310

5. Weisman A, Bai JW, Cardinez M, Kramer CK, Perkins BA. Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:501–512

6. Thabit H, Tauschmann M, Allen JM, et al. Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 2015;373:2129–2140

7. Tauschmann M, Allen JM, Wilinska ME, et al. 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 crossover trial. Diabetes Care 2016;39:2019–2025

8. Stewart ZA, Wilinska ME, Hartnell S, et al. Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. N Engl J Med 2016;375:644–654

9. Bally L, Thabit H, Kojzar H, et al. Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 2017;5:261–270

10. Kropff J, Del Favero S, Place J, et al.; AP@home consortium. 2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial. Lancet Diabetes Endocrinol 2015;3:939–947

11. Elleri D, Allen JM, Tauschmann M, et al. Feasibility of overnight closed-loop therapy in young children with type 1 diabetes aged 3-6 years: comparison between diluted and standard insulin strength. BMJ Open Diabetes Res Care 2014;2:e000040

12. Del Favero S, Boscari F, Messori M, et al. Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe. Diabetes Care 2016;39:1180–1185

13. DeBoer MD, Breton MD, Wakeman C, et al. Performance of an artificial pancreas system for

young children with type 1 diabetes. Diabetes Technol Ther 2017;19:293–298
14. Adolfsson P, Ziegler R, Hanas R. Continuous subcutaneous insulin infusion: special needs for children. Pediatr Diabetes 2017; 18:255–261
15. Borot S, Franc S, Cristante J, et al.; Diabeloop Study Group. Accuracy of a new patch pump based on a microelectromechanical system (MEMS) compared to other commercially available insulin pumps: results of the first in vitro and in vivo studies. J Diabetes Sci Technol 2014;8: 1133–1141
16. McVey E, Keith S, Herr JK, Sutter D, Pettis RJ. Evaluation of intradermal and subcutaneous infusion set performance under 24-hour basal and bolus conditions. J Diabetes Sci Technol 2015;9: 1282–1291
17. Mianowska B, Fendler W, Tomasik B, Młynarski W, Szadkowska A. Effect of insulin dilution on lowering glycemic variability in pump-treated young children with inadequately controlled type 1 diabetes. Diabetes Technol Ther 2015;17:605–610
18. Sundberg F, Barnard K, Cato A, et al. ISPAD Guidelines. Managing diabetes in preschool children. Pediatr Diabetes 2017;18: 499–517
19. Ruan Y, Elleri D, Allen JM, et al. Pharmacokinetics of diluted (U20) insulin aspart compared with standard (U100) in children aged 3-6 years with type 1 diabetes during closed-loop insulin delivery: a randomised clinical trial. Diabetologia 2015;58:687–690
20. Stewart ZA, Wilinska ME, Hartnell S, et al. Day-and-night closed-loop insulin delivery in a broad population of pregnant women with type 1 diabetes: a randomized controlled crossover trial. Diabetes Care 2018;41:1391–1399
21. Davis EA, Keating B, Byrne GC, Russell M, Jones TW. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997;20:22–25
22. Monaghan MC, Hilliard ME, Cogen FR, Streisand R. Nighttime caregiving behaviors among parents of young children with type 1 diabetes: associations with illness characteristics and parent functioning. Fam Syst Health 2009;27:28–38
23. Johnson SR, Cooper MN, Davis EA, Jones TW. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with type 1 diabetes and their parents. Diabet Med 2013;30:1126–1131
24. Tauschmann M, Allen JM, Wilinska ME, et al. Day-and-night hybrid closed-loop insulin delivery in adolescents with type 1 diabetes: a free-living, randomized clinical trial. Diabetes Care 2016;39: 1168–1174