Randomized Summer Camp Crossover Trial in 5- to 9-Year-Old Children: Outpatient Wearable Artificial Pancreas Is Feasible and Safe

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OBJECTIVE

The Pediatric Artificial Pancreas (PedArPan) project tested a children-specific version of the modular model predictive control (MMPC) algorithm in 5- to 9-year-old children during a camp.

RESEARCH DESIGN AND METHODS

A total of 30 children, 5- to 9-years old, with type 1 diabetes completed an outpatient, open-label, randomized, crossover trial. Three days with an artificial pancreas (AP) were compared with three days of parent-managed sensor-augmented pump (SAP).

RESULTS

Overnight time-in-hypoglycemia was reduced with the AP versus SAP, median (25^{th}–75^{th} percentiles): 0.0% (0.0–2.2) vs. 2.2% (0.0–12.3) ($P = 0.002$), without a significant change of time-in-target, mean: 56.0% (SD 22.5) vs. 59.7% (21.2) ($P = 0.430$), but with increased mean glucose 173 mg/dL (36) vs. 150 mg/dL (39) ($P = 0.002$). Overall, the AP granted a threefold reduction of time-in-hypoglycemia ($P < 0.001$) at the cost of decreased time-in-target, 56.8% (13.5) vs. 63.1% (11.0) ($P = 0.022$) and increased mean glucose 169 mg/dL (23) vs. 147 mg/dL (23) ($P < 0.001$).

CONCLUSIONS

This trial, the first outpatient single-hormone AP trial in a population of this age, shows feasibility and safety of MMPC in young children. Algorithm retuning will be performed to improve efficacy.

Only three artificial pancreas (AP) trials have focused on the prepubertal population so far: two single-hormone AP studies, performed inpatient for less than 1 day (1,2) and a recent dual-hormone AP study, performed in a camp for 5 days (3). Here we report the first outpatient single-hormone AP trial focusing on 5- to 9-year-old children.

Data were collected in the Pediatric Artificial Pancreas (PedArPan) camp, where sensor-augmented pump (SAP) therapy was compared with the modular model predictive control algorithm (MMPC) (4,5), running on the wearable platform Diabetes Assistant (DiAs) (6).

RESEARCH DESIGN AND METHODS

Study Oversight

This was an open-label, randomized, crossover trial dealing with prepubertal children with type 1 diabetes performed in a supervised outpatient setting at a summer camp where patients were accompanied by parents or caretakers. The aim was to compare glucose control achieved under an AP system (intervention arm), based on a children-specific version of the MMPC algorithm and running on DiAs versus the SAP managed by parent/caretakers (control arm). Both interventions lasted 72 h and were separated by a 24 h washout.

The study was done in accordance with the Declaration of Helsinki and approved by the local Research Ethics Committee. Informed consent was signed by parent/caretaker before enrollment.

Population

The study recruited 33 patients in 5 Italian pediatric centers (Verona, Milan, Turin, Naples, and Rome). Inclusion criteria were age 5–9 years, a diagnosis of type 1 diabetes of at least 12 months, use of insulin pump and sensor for $\geq$3 months, HbA_{1c} $<$10%, and attendance by at least one relative/caretaker. Exclusion criteria were diabetic ketoacidosis or severe hypoglycemia within the last month, concomitant disease, and any medication or conditions that could influence metabolic control, compromise safety, or prevent study completion.

Technology

Patients from both study arms wore the Dexcom G4 Platinum Share continuous glucose monitoring (CGM) system (Dexcom, Inc., San Diego, CA) and the Accu-Chek Spirit Combo insulin pump (Roche Diabetes Care AG, Burgdorf, Switzerland). Capillary blood glucose concentration was measured using the Accu-Chek Aviva Combo blood glucose meter. Patients in both study arms used rapid-acting insulin analog aspart (Novo Nordisk, Bagsvaerd, Denmark), diluted 1:4 (25 IU/mL) with diluting medium received from Novo Nordisk. Dilution allows a more precise insulin delivery, with minimum increments of 0.025 units instead of 0.1 units. Moreover, the diluted analog has been shown to have the same pharmacokinetics of nondiluted insulin and smaller absorption variability among the patients (2,7). During the AP arm, the patients used also the DiAs system (6).

Study Procedures

After enrollment, participants and parents underwent a 2-week run-in period at home, during which they were trained in the use of the study pump and CGM. Children and parents/caretakers met the study team at the camp location, Bardonecchia (Italy; elevation, 1,312 m) the day before the trial start (day 0) and were randomized. The first study period started at 0730 of day 1 and lasted 72 h. After a 24-h washout, the second period started at 0730 on study day 5.

During the 3 days of each study period, breakfast was served at 0800–0830, lunch at 1200–1300, and dinner at 1900–2000. A snack was served at 1030 and before physical activity, at 1530–1600. The amount of carbohydrates (CHO) ingested at the meals/snacks was known.

In the morning, patients were engaged in static activities (e.g., art laboratories), mimicking activities on school days. In the afternoon, they were involved in 90–120 min of structured moderate to high intensity physical activities. Diet and physical activities were kept as constant as possible during the two study periods.

Given the large fluctuations of insulin needs in young patients during a camp, patients' data were reviewed by the medical team at the end of the first day of each study period, and therapy adjustments were made and used without further corrections for the remaining 2 days.

Calibrations were performed according to the manufacturer's instructions. If sensor readings differed significantly from meter-measured glucose ($>$30% over 100 mg/dL or $>$30 mg/dL below 100 mg/dL) and no calibration had been done in the previous 6 h, the CGM was recalibrated. In the AP arm, if recalibration was not possible, closed-loop was suspended until calibration was possible.

Study Outcomes

The two primary outcomes were *1*) the percentage of time spent below 70 mg/dL (time-in-hypoglycemia [time-in-hypo]), assessing safety, and *2*) the percentage of time spent in the target range 70–180 mg/dL (time-in-target), assessing efficacy. Secondary outcomes included low blood glucose index (LBGI) (8) and percentage of time below 50 mg/dL for safety; mean glucose and percentage of time spent in the range 80–140 mg/dL (time-in-tight-target) for efficacy; amount of CHO administered and number of hypotreatments. Outcomes were based on CGM and evaluated day and night (0000–2400), during the nighttime (0000–0730) only, and at wake-up (0630–0730).

Statistical Methods

Analyses were on an intention-to-treat basis, including all of the data from the participants who completed the study. A least-square regression model was fit to the data, including patient, treatment, and period as explanatory factors. When a period effect was found ($P <$ 0.05), treatment effect was evaluated on the basis of the *P* value of the regression model. If no period effect was found, normally distributed data were compared with a paired *t* test and nonnormally distributed data with the Wilcoxon signed rank test. Normally distributed data are reported as mean (SD) and nonnormally distributed as median (25th–75th percentile). A post hoc analysis investigating the existence of carryover was performed as previously published (9). If a carryover was found ($P < 0.05$), data of the second period were discarded (9). Unless otherwise stated, no carryover or period effect was found. Analyses were performed with Matlab R2012a software using the Statistics 8.0 toolbox. All *P* values are two tailed.

RESULTS

Participants

Of 33 enrolled patients, 1 discontinued because of a febrile illness, 1 because of illness of the parent attending the camp, and 1 because of poor acceptance of camp lifestyle. Thus, 30 patients (19 boys and 11 girls) completed the study: age, 7.6 years (SD 1.2); body weight, 26.0 kg (6.1); height, 123 cm (8); BMI, 16.9 kg/m^2 (2.1), BMI z-score, $-$0.09 (0.91); HbA_{1c}, 7.3% (0.9) (57 mmol/mol [10]); duration of diabetes, 4.7 years (1.6); pump users for 3.3 years (1.9), and total daily insulin, 20.3 units (6.2) (0.78 units/kg per day [0.16]).

Glucose and Insulin Delivery

Nighttime

From 0000 to 0730 the time-in-hypo decreased from 2.2% (0.0–12.3) with SAP to 0.0% (0.0–2.2) with the AP ($P = 0.002$) (Table 1 and Fig. 1). Similarly, the AP

Table 1—Results

Metric name	Open loop	Closed loop	*P* value
Overall (0000–2400)			
Time-in-hypo (%)	6.7 (2.3–11.5)	2.0 (1.2–4.5)	<0.001
Number of SMBG <70 mg/dL	3.5 (2.0–6.0)	1.5 (0.0–4.0)	<0.001
LBGI (–)	1.7 (0.7–2.6)	0.5 (0.3–1.2)	<0.001
Time <50 mg/dL (%)	0.9 (0.0–2.2)	0.1 (0.0–0.4)	<0.001
Time-in-target (%)	63.1 (11.0)	56.8 (13.5)	0.022
Mean glucose (mg/dL)	147 (23)	169 (23)	<0.001
SD glucose (mg/dL)	58 (10)	61 (11)	0.173
Number of hypotreatments	5 (4–8)	3.5 (1–7)	0.018
Total amount of CHO			
Hypotreatments (g/kg per day)	0.61 (0.36–0.96)	0.33 (0.17–0.87)	0.005
Meal (g/kg per day)	7.74 (1.67)	8.03 (1.56)	0.053
Mean basal insulin (units/h)‡	0.35 (0.12)	0.26 (0.09)	<0.001
SD basal insulin (units/h)	0.16 (0.06)	0.24 (0.05)	<0.001
Total basal insulin (units/kg per day)‡	0.32 (0.10)	0.24 (0.08)	<0.001
Total amount of insulin			
Boluses (units/kg per day)‡	0.46 (0.14)	0.48 (0.12)	0.269
Basal and boluses (units/kg per day)‡	0.78 (0.15)	0.72 (0.14)	0.001
Night (0000–0730)			
Time-in-hypo (%)	2.2 (0.0–12.3)	0.0 (0.0–2.2)	0.002
Number of SMBG <70 mg/dL	0.0 (0.0–2.0)	0.0 (0.0–0.0)	0.005
LBGI (–)	0.8 (0.1–3.0)	0.1 (0.0–0.6)	<0.001
Time <50 mg/dL (%)	0.0 (0.0–2.7)	0.0 (0.0–0.0)	0.008
Time-in-target (%)	59.7 (21.2)	56.0 (22.5)	0.430
Time-in-tight-target (%)	33.0 (19.8)	31.3 (20.2)	0.694
Mean glucose (mg/dL)	150 (39)	173 (36)	0.002
SD glucose (mg/dL)‡	44 (14)	47 (14)	0.244
Number of hypotreatments	0 (0–2)	0 (0–0)	0.005
Total amount of CHO for hypotreatment (g/kg per day)	0.00 (0.00–0.20)	0.00 (0.00–0.00)	0.011
Mean basal insulin (units/h)	0.35 (0.12)	0.37 (0.12)	0.085
SD basal insulin (units/h)	0.10 (0.05–0.13)	0.20 (0.17–0.25)	<0.001
Total basal insulin (units/kg per day)	0.10 (0.03)	0.11 (0.03)	0.120
Total amount of insulin			
Boluses (units/kg per day)	0.00 (0.00–0.01)	0.00 (0.00–0.00)	0.123
Basal and boluses (units/kg per day)	0.11 (0.03)	0.11 (0.03)	0.601
Wake-up (0630–0730)			
Time-in-hypo (%)†	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.604
LBGI (–)†	0.0 (0.0–0.3)	0.0 (0.0–0.1)	1.000
Time <50 mg/dL (%)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.063
Time-in-target (%)	66.7 (42.6–77.8)	80.0 (66.7–100.0)	0.096
Time-in-tight-target (%)	31.3 (27.0)	47.7 (33.1)	0.024
Mean glucose (mg/dL)‡	149 (46)	152 (37)	0.590
SD glucose (mg/dL)	34 (19)	27 (15)	0.122
System functioning			
Time in closed loop (%)	—	96.8 (93.5–98.4)	—
DiAs-pump successful communications (%)	—	99.2 (99.0–99.2)	—
CGM-DiAs successful communications (%)	—	98.3 (96.3–99.2)	—
CGM MAD (mg/dL)	17.9 (3.7)	19.0 (6.0)	0.369
CGM MARD (%)	14.5 (4.7)	13.4 (4.0)	0.309

Normally distributed data are reported as mean (SD), nonnormally distributed as median (25th–75th) percentile. Time-in-hypo indicates the percentage of time with CGM <70 mg/dL; time-in-target indicates the percentage of time with CGM in the range 70–180 mg/dL; time-in-tight-target is the percentage of time with CGM in the range 80–140 mg/dL. CGM MAD, mean absolute deviation of CGM reading from self-monitored blood glucose; CGM MARD, mean absolute relative deviation; SMBG, self-monitored blood glucose. †Highlights outcome metrics affected by carryover. ‡Highlights outcome metrics affected by significant period effect.

reduced other safety metrics, such as time below 50 mg/dL, LBGI, and number and entity of hypotreatments: 43% of the children treated with SAP required at least one hypotreatment in three study nights and 25% of the children required two or more hypotreatments (0.2 g/kg or more of rescue CHOs eaten per night). On the other hand, only 16% of the children required a hypotreatment during the three study nights with the AP.

Time-in-target and time-in-tight-target did not differ significantly between the two arms: time-in-target was 59.7% (21.2) with SAP vs. 56.0% (22.5) with the AP ($P = 0.430$); time-in-tight-target (80–140 mg/dL) was 33.0% (19.8) with SAP vs. 31.3% (20.2) with the AP ($P = 0.694$). Mean glucose was increased from 150 mg/dL (39) with SAP to 173 mg/dL (36) with the AP ($P = 0.002$). Glucose SD was not affected by the treatment ($P = 0.244$), but was by the period: a reduction of

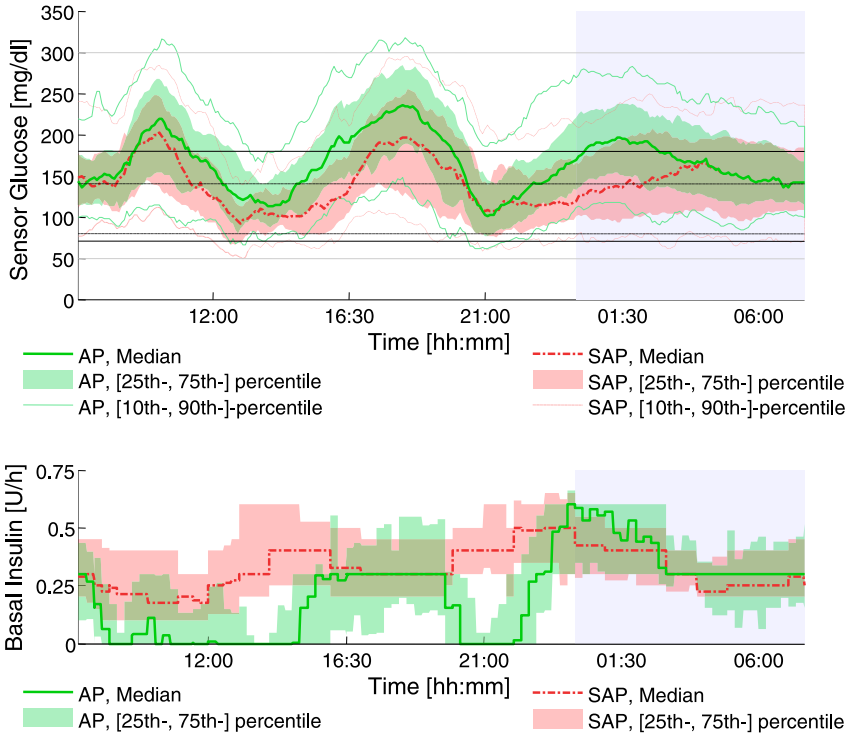

Figure 1—Sensor glucose (upper panel) and insulin dosing (lower panel) during the AP arm and the SAP arm. The tick lines denote median profiles and the colored envelope indicates the 25th and 75th percentile limits. In the upper panel, the dashed line depicts the 10th and 90th glucose percentiles.

−9.3 mg/dL (CI [−15.5, −3.1]; P = 0.016) with respect to period 1 was recorded in period 2.

Wake-up

At wake-up (0630–0730), the AP induced a significant increase of time-in-tight-target (31.3% [27.0] with SAP vs. 47.7% [33.1] with the AP, P = 0.024) and a trend toward improved time-in-target (66.7% [42.6–77.8] with SAP vs. 80.0% [66.7–100.0] with the AP, P = 0.096). Mean glucose was not affected by the treatment (P = 0.590) but was by the period (decrease of −18 mg/dL; CI [–34, −1]; P = 0.0416 in the period 2). Time-in-hypo was affected by carry-over effect (P = 0.008); therefore, data of the study period 2 were discarded. No difference between the treatments was found in study period 1 (0.0% [0.0–0.0] with SAP vs. 0.0% [0.0–0.0] with the AP, P = 0.600).

Day and Night

Overall (0000–2400), the AP reduced more than three times the time-in-hypo: 6.7% (2.3–11.5) with SAP vs. 2.0% (1.2–4.5), with the AP (P < 0.001). Similarly, the AP reduced the time below 50 mg/dL, LBGI, and the number and entity of hypotreatments (Table 1 and Fig. 1). However, safety improvement with the AP had a cost: it was achieved at the expense of a 10% decrease of time-in-target (63.1% [11.0] with SAP vs. 56.8% [13.5] with the AP, P = 0.022) and 15% increase of mean glucose, 147 mg/dL (23) with SAP to 169 mg/dL (23) with AP (P < 0.001).

Safety improvement was likely generated by a reduction of basal insulin administration and by better basal insulin timing with the AP. In fact, total and mean basal insulin were both 25% lower during AP (P < 0.001 for both changes).

Mean basal insulin infusion rate and daily dose were affected by the period, decreasing by −0.03 units/h (CI [–0.04, −0.01]; P = 0.016) and 0.02 units/kg per day (CI [–0.03, −0.01]; P = 0.003) in period 2 with respect to period 1. Total insulin injected as a bolus also decreased during period 2: −0.02 units/kg per day (CI [−0.03, −0.01]; P = 0.003) with no difference between the two treatments (P = 0.269). Therapy adjustments were performed 18 times during SAP and 18 times during the AP; 21 during period 1, and 15 during period 2.

Adverse Events

No serious adverse event occurred.

Technology

Closed-loop remained fully operational for 97.0% (93.5–98.4) of the time. DiAs-pump and CGM-DiAs were successful 99.2% (99.0–99.2) and 98.3% (96.3–99.2) of the time, respectively. Sensor accuracy was similar in the two arms (Table 1).

CONCLUSIONS

This study shows that outpatient closed-loop glucose control using the DiAs wearable platform is feasible in young children, complementing the evidence collected in adults (10) and adolescents (11). Furthermore, this study reinforces the evidence of diluted-insulin usability in AP, as previously reported (2).

The AP system improved safety compared with SAP, greatly decreasing the incidence of hypoglycemia, a fact of special relevance in this age population which is characterized by a higher frequency of hypoglycemic episodes (12), blunted sympathoadrenal response to falling blood glucose, and reduced warning symptoms and sluggish arousal from sleep (13). This beneficial effect was likely achieved by reducing the administration of basal insulin (25% less than during SAP). Interestingly, nocturnal hypoglycemia was reduced without changing the amount of basal insulin administered. Of note, a reduction of insulin needs throughout the camp was recorded, as often happens in children and adolescents at camps.

Hypoglycemia prevention with the AP came at a cost. Overall mean glucose increased by 15% and time-in-target went up by 10%, whereas the mean glucose increase during the night was significant, but the comparison of time-in-target and time-in-tight-target was not conclusive.

The deterioration of blood glucose levels during the AP could be related to the good metabolic control at study entry. Indeed, mean HbA_{1c} at the start was 7.3% (56 mmol/mol), corresponding roughly to a mean glucose of 162 mg/dL. During the SAP arm, mean glucose was further reduced to 147 mg/dL, corresponding to an HbA_{1c} of 6.7% (50.2 mmol/mol), but with a large incidence of hypoglycemia. The AP largely reduced hypoglycemia but only at the expenses of an increased mean glucose, brought to

169 mg/dL, corresponding to HbA_{1c} of 7.5% (58.7 mmol/mol).

Another reason for worse mean glucose and time-in-target during the AP is the prudent-by-design tuning of the algorithm, because this trial was the first with the children-specific version of our MMPC algorithm, previously tested only in adults (10,14,15).The data collected in this camp trial will allow a more effective tuning of the algorithm, thus likely improving its efficacy.

Three previous AP studies focused on prepubertal children. The first two were done inpatient for 14 h (1) and 16 h (2). Recently, a dual-hormone AP system, injecting both insulin and glucagon, was tested on 19 preadolescents, 6–11 years old, in a summer camp (3), in which 5 days of AP use were compared with 5 days of SAP. The dual-hormone AP managed to simultaneously reduce hypoglycemia from 2.8 to 1.2% ($P < 0.001$) and to reduce mean glucose from 167 mg/dL with SAP to 137 mg/dL with AP. Furthermore, Thabit et al. (16), reported a long outpatient unsupervised use of AP in children aged 12.0 years (SD 3.4) and adolescents, but no specific subanalysis focusing on prepuberal age was done.

MMPC algorithm retuning and further investigation is needed to determine whether the simultaneous reduction of time-in-hypo and of mean glucose, achieved by the dual-hormone AP, can be achieved also by our single-hormone system.

Other limitations of the current study are the short duration of the interventions, the short duration of the washout period, and supervised conduct of the experiment, which will be relaxed in the future with longer, unsupervised trials at home.

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Duality of Interest. F.B. has received personal fees from Roche Diagnostics outside the submitted work. I.R. has received fees for consulting from Roche Diagnostics, Eli Lilly, Sanofi, and Menarini. R.B. has received fees for consulting and advisory board from Roche Diagnostics, Sanofi, Eli Lilly, Medtronic, LifeScan, and Theras Diabetes Care. R.S. received fees for consulting from Abbott and Eli Lilly. A.G. reports research support from Dexcom, Inc., USA, outside the submitted work. A.R. received speaker honoraria from Eli Lilly, Roche, and Sanofi. L.M. holds patent applications related to the study control algorithms. C.C. holds patent applications related to the study control algorithms, received research support from Sanofi and Adocia, and nonfinancial research support from Dexcom, Inc. and Roche Diagnostics. D.B. reports nonfinancial research support from Roche Diagnostics, Abbott Diabetes Care, and Novo Nordisk during this study; has received lecture fees from Eli Lilly, LifeScan, Roche Diagnostics, and Sanofi; and has provided advisory services to Abbott. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors reviewed and provided edits and comments on manuscript drafts. In addition, authors had the following responsibilities: S.D.F. was the senior camp engineer, designed the protocol, collected data, analyzed the data, and drafted the manuscript; F.B. was a camp physician, designed the protocol, and analyzed data; M.Me. developed the algorithm; I.R. was the chief pediatrician of the Turin site, a camp physician, and designed the protocol; R.B. was the chief pediatrician of the Milan site, a camp physician, and designed the protocol; A.S. was the chief pediatrician of the Verona site, a camp physician, and designed the protocol; D.I. was the chief pediatrician of the Naples site, a camp physician, and designed the protocol; R.S. was the chief pediatrician of the Rome site, a camp physician, and designed the protocol; R.V. was in charge of the controller in silico testing, camp engineer, designed the protocol, and collected data; R.C. and Y.L.M. were camp engineers and collected data; S.G. and D.C. were camp physicians and designed the protocol; A.G., V.V., D.T., A.R., M.Ma., A.Z., and N.R. were camp physicians; F.D.P. implemented the control algorithm on the DiAs; E.L. was the camp engineer and designed and implemented the remote monitoring system; G.L. was the chief responsible for the design and implementation of the remote monitoring system used during the trial; A.A. was the chief of the Padua unit; L.M. was the principal investigator of the Pavia unit, developed the algorithm, analyzed data, and drafted the manuscript; C.C. was the principal investigator of the Padua unit, the camp engineer, designed the protocol, collected data, and drafted the manuscript; and D.B. was the study coordinator, the camp chief physician, designed the protocol, analyzed data, and drafted the manuscript. S.D.F., C.C., and D.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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