

Study design

Additional exclusion criteria were: use of heparin, coumarin derivatives or oral corticosteroids; limited ability to see, hear or feel alarm signals; or pregnancy or breastfeeding. During the closed loop period, patients were not allowed to live alone or to use acetaminophen (because of interference with sensor glucose measurements).

Patients were randomized to start with either the closed loop or the open loop period using variable block randomization with an equal allocation ratio, with block sizes of 2, 4 or 6 patients. Randomization was performed using the web-based randomization tool of Castor EDC (Amsterdam, the Netherlands).

The study was preceded by a feasibility phase which entailed the training and closed loop procedures. Nine patients participated in this feasibility phase. As predefined, no glucose data analysis was performed, but the user manual of the artificial pancreas and the study procedures were evaluated and optimized.

The study protocol was approved by the ethics committee of the Academic Medical Centre at the University of Amsterdam (Amsterdam, the Netherlands), the local review board of Rijnstate Hospital (Arnhem, the Netherlands) and the Dutch national competent authority (Health and Youth Care Inspectorate, Utrecht, the Netherlands). The study was performed in concordance with the Declaration of Helsinki. The patients were recruited from the outpatient clinic of Rijnstate Hospital. All patients provided written informed consent.

Procedures

The closed loop training period consisted of one day instructions and practicing with the artificial pancreas, after which the treatment was started. The glucose sensors were placed two days before the start of the training. On the second day, the investigators visited the patients at home and on day three and four there was a scheduled phone contact to discuss progress and patients' questions.

The transmitters of the artificial pancreas were connected to two subcutaneous glucose sensors (Enlite 2, Medtronic, Northridge, CA, USA). After a warm-up period of 24 hours, sensors were calibrated using two self-monitored blood glucose (SMBG) measurements taken at least seven minutes apart. One sensor was used as the primary sensor and the other as back-up and control. The artificial pancreas requested at least one control SMBG per day and more in case of a deviation between the sensor and SMBG or between the two sensors. In case only one calibrated sensor was available, an SMBG was requested twice per day.

The control algorithm determined when the pumps should deliver insulin (Humalog, Eli Lilly, Indianapolis, IN, USA) or glucagon (GlucaGen, Novo Nordisk, Bagsvaerd, Denmark), based on the difference between the current and target blood glucose levels, and the rate of change of blood glucose. The initial setting of the insulin sensitivity was calculated with the daily insulin dose of the patient. During the four-day training period, the insulin setting was evaluated daily and when necessary manually adjusted to accelerate the fine-tuning by the self-learning algorithm. The patients were instructed to replace the glucagon infusion set and cartridge with freshly reconstituted glucagon every day.

Patients were alarmed by an auditory alarm in case of hypoglycemia below 3.5 mmol/L or hyperglycemia above 15 mmol/L. Patients were instructed to conduct an SMBG in case of a

hypoglycemia alarm. If the SMBG confirmed hypoglycemia, patients were advised to take oral carbohydrates.

Every ten minutes, logged data was sent by the artificial pancreas to a database via a dedicated mobile Wi-Fi access point. During the four-day training period, the patients were monitored 24 hours per day using an online technical remote monitoring portal. Subsequently, during the two week closed loop period, only alarm-based monitoring took place.

During both study periods, patients were asked to complete a diary regarding carbohydrate intake, physical activity and (for open loop) insulin use. At the start of the study and at the end of the closed loop and open loop periods, patients completed several questionnaires regarding: health-related quality of life (EuroQol 5D [EQ5D]) (1); psychological adaptations to diabetes (Problem Areas in Diabetes [PAID]) (2), and treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire-status [DTSQ-s]) (3). Additionally, at the end of the closed and open loop period patients completed a questionnaire regarding the change in treatment satisfaction (DTSQ-change [DTSQ-c]) (4) and an adapted version of the Mobile Phone Usability Questionnaire (MPUQ) to assess user experiences regarding the artificial pancreas (only after the closed loop period) (5-7).

Statistical analysis

We hypothesized that the artificial pancreas provides better glucose control than standard patient-managed insulin therapy and is at least as safe.

Sample size calculation was based on the results of our previous report (8). In order to detect a 10% difference in time in range with a power of 80% and a 0.05 two-sided significance level, nine patients per treatment arm were required. To account for possible drop-out of patients, we aimed to include twelve patients per treatment arm, thus 24 patients in total.

The main study endpoint was the percentage of time in range (70-180 mg/dL [3.9-10 mmol/L]). The main safety endpoints were the percentage of time in hypoglycemia (<70 mg/dL [<3.9 mmol/L]) and hyperglycemia (>180 mg/dL [>10 mmol/L]). Secondary safety endpoints were the percentage of time in hypoglycemia (<60 mg/dL [<3.3 mmol/L]) and hyperglycemia (>250 mg/dL [>13.9 mmol/L]), and the total number of carbohydrate-treated hypoglycemic events (as noted in the patient diary). Secondary performance parameters were median sensor glucose concentration; glycemic variability, expressed as inter quartile range (IQR), coefficient of variation (CV), low blood glucose index (LBGI), high blood glucose index (HBGI), and blood glucose risk index (BGRI, being LBGI + HBGI) (9); day, night and postprandial median sensor glucose concentration; and day and night time in range, time in hypoglycemia (<70 mg/dL [<3.9 mmol/L]), and time in hyperglycemia (>180 mg/dL [>10 mmol/L]). The postprandial period was defined as three hours from the start time of a meal, the day period as the time between 07:00 and 24:00 hours, and the night period as the time between 24:00 and 07:00 hours.

Other study endpoints included daily insulin and glucagon use, daily carbohydrate intake, number of exercise moments, and percentage of time the control algorithm was active. Questionnaire results were difference in number of patients experiencing problems per EQ5D dimension from baseline, difference in EQ5D-visual analogue scale (VAS) score from baseline, and EQ5D change in health state from baseline (10); difference in PAID score from baseline; difference in DTSQ-s score and perceived frequency of hyperglycemia and hypoglycemia from baseline; DTSQ-c score and change in perceived frequency of

hyperglycemia and hypoglycemia; and MPUQ score. Furthermore, adverse events and technical issues were recorded.

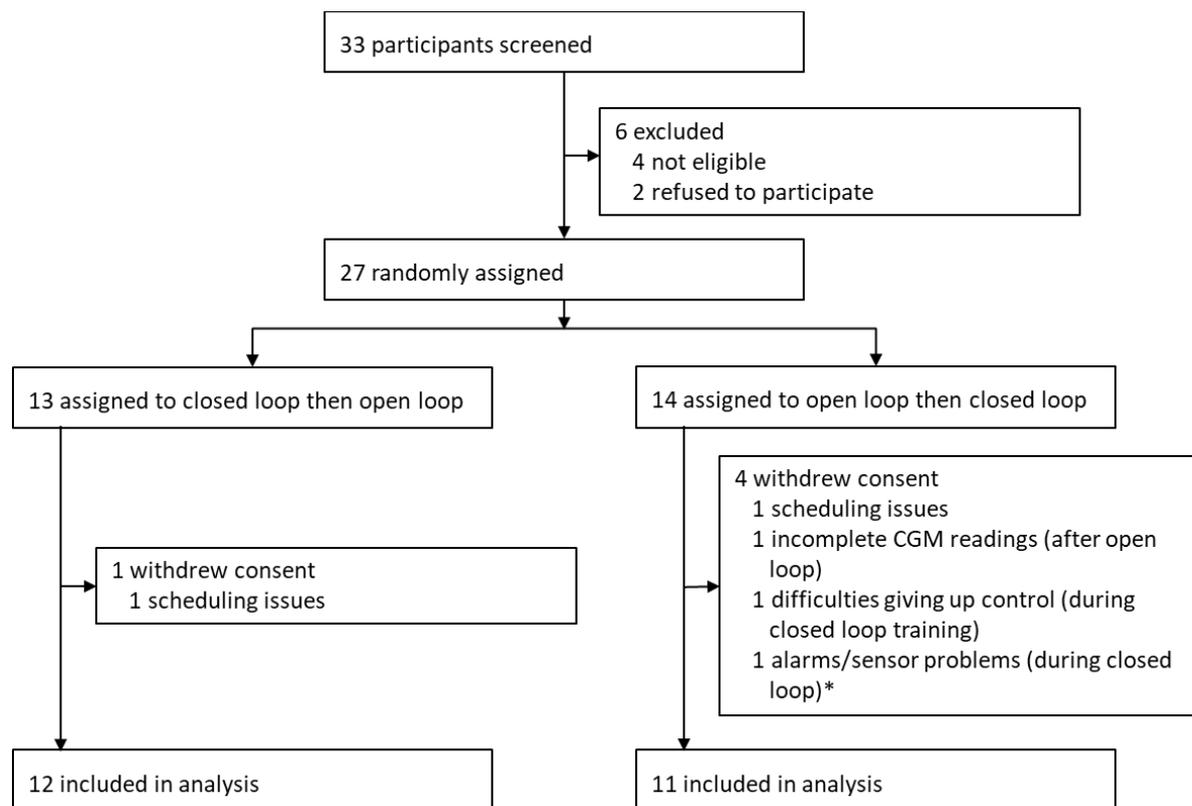
Glucose endpoints were calculated from the artificial pancreas' primary sensor for the closed loop period and from the masked CGM for open loop. Because of the cross-over design, we assessed potential carry over and period effects by comparing the sum and difference of the treatments between the two randomization groups using Mann-Whitney *U*-tests. No carry over and period effects were found.

Supplemental Figures and Tables

Supplementary Figure 1. Picture of the Inreda Artificial Pancreas. Improvements with respect to the previous prototype included the addition of self-learning properties to the control algorithm to cope with day-to-day variations in insulin sensitivity; the user-interface and alarm system were changed to enable patients to operate the system independently; and the continuous glucose monitoring software and transmitter were adapted to make the glucose measurements more reliable.



Supplementary Figure 2. Trial Profile.



*Almost eleven days of data available for the closed loop period, therefore included in analysis

Additional explanation: In total, 27 participants were randomized between April 19 and July 22, 2019. Two patients withdrew before starting with their first study period because of scheduling issues. For one patient it turned out after the open loop period that the data collection with the masked CGM had failed, after which the patient decided to withdraw. One patient had difficulties giving up control over the normal diabetes treatment and stopped within 19 hours after start of the artificial pancreas treatment. One patient ended the closed loop period prematurely, due to the large number of alarms and improper functioning of the transmitters and glucose sensors. However, the collected data of this patient was sufficient to be included in the analysis (open loop fully completed and almost eleven days for the closed loop). The remaining 22 patients completed the study.

Supplementary Table 1. Primary and secondary endpoints (full study: day and night together).

	Closed Loop	Open Loop	Difference (95% CI)*	p value
Time spent at glucose levels (%)				
Euglycemia	86.6 (84.9 – 88.5)	53.9 (49.7 – 67.2)	28.4 (23.4 – 34.8)	<.0001
Hypoglycemia <70 mg/dL (<3.9 mmol/L)	0.4 (0.1 – 0.8)	2.0 (0.7 – 3.6)	-1.7 (-2.9 – -0.8)	<.0001
Hyperglycemia >180 mg/dL (>10 mmol/L)	12.8 (11.1 – 14.4)	38.8 (30.5 – 48.9)	-26.2 (-32.6 – -19.6)	<.0001
Hypoglycemia <60 mg/dL (<3.3 mmol/L)	0.0 (0.0 – 0.03)	0.5 (0.1 – 1.8)	-1.1 (-2.0 – -0.5)	0.00018
Hyperglycemia >250 mg/dL (>13.9 mmol/L)	0.8 (0.4 – 1.8)	13.8 (4.1 – 19.3)	-11.1 (-15.6 – -7.4)	<.0001
Carbohydrate-treated hypoglycemic events (no.)	1 (0 – 4.5)	6 (3.5 - 9.5)	-5 (-6.5 – -2.5)	0.0039
Median glucose (mg/dL) (mmol/L)	129 (126-132) (7.2 [7.0 – 7.4])	167 (149-178) (9.3 [8.3 – 9.9])	-36 (-46 – -26) (-2.0 [-2.6 – -1.4])	<.0001
Glycemic variability				
IQR (mg/dL) (mmol/L)	47 (45 – 51) (2.6 [2.5 – 2.8])	86 (66 – 102) (4.8 [3.7 – 5.7])	-37 (-49 – -28) (-2.1 [-2.7 – -1.6])	<.0001
CV (%)	28.6 (27.1 – 30.7)	35.8 (32.1 – 39.7)	-7.3 (-9.8 – -4.8)	<.0001
LBGI (score)	0.43 (0.25 – 0.52)	0.55 (0.33 – 0.91)	-0.2 (-0.5 – -0.0)	0.042
HBGI (score)	2.8 (2.6 – 3.3)	9.5 (6.4 – 11.9)	-6.0 (-7.8 – -4.4)	<.0001
BGRI (score)	3.3 (3.1 – 3.8)	10.3 (6.9 – 12.7)	-6.4 (-8.2 – -4.9)	<.0001

Data are median (IQR). IQR, interquartile range; CV, coefficient of variation; LBGI, low blood glucose index; HBGI, high blood glucose index; BGRI, blood glucose risk index. *Difference is closed loop minus open loop.

Supplementary Table 2. Glucose control for day period and night period.

	Closed Loop	Open Loop	Difference (95% CI)*	p value
Day period				
Time spent at glucose levels (%)				
Euglycemia	81.8 (80.3 – 85.1)	58.6 (52.1 – 67.6)	22.9 (16.8 – 28.9)	<.0001
Hypoglycemia <70 mg/dL (<3.9 mmol/L)	0.1 (0.0 – 1.0)	2.3 (0.7 – 3.2)	-1.7 (-3.3 – -0.9)	<.0001
Hyperglycemia >180 mg/dL (>10 mmol/L)	17.5 (14.3 – 18.6)	41.1 (27.3 – 45.8)	-20.3 (-26.9 – -13.8)	<.0001
Median glucose (mg/dL) (mmol/L)	137 (133 – 140) (7.6 [7.4 – 7.8])	162 (147 – 173) (9.0 [8.2 – 9.6])	-25 (-34 – -15) (-1.4 [-1.9 – -0.8])	0.00019
Night period				
Time spent at glucose levels (%)				
Euglycemia	97.1 (95.1 – 98.4)	48.1 (39.3 – 68.1)	42.9 (35.0 – 50.1)	<.0001
Hypoglycemia <70 mg/dL (<3.9 mmol/L)	0.1 (0.0 – 0.3)	0.7 (0.0 – 2.8)	NA	0.0046
Hyperglycemia >180 mg/dL (>10 mmol/L)	2.1 (1.2 – 4.4)	49.4 (29.0 – 58.1)	-40.2 (-49.3 – -32.0)	<.0001
Median glucose (mg/dL) (mmol/L)	117 (113 – 122) (6.5 [6.3 – 6.8])	180 (158 – 205) (10.0 [8.8 – 11.4])	-60 (-75 – -46) (-3.4 [-4.2 – -2.6])	<.0001

Data are median (IQR). NA, not applicable. *Difference is closed loop minus open loop.

Supplementary Table 3. Postprandial glucose control and other endpoints.

	Closed Loop	Open Loop	Difference (95% CI)*	p value
Postprandial glucose control (mg/dL) (mmol/L)				
Breakfast	157 (149 – 170) (8.7 [8.3 – 9.5])	162 (139 – 179) (9.0 [7.7 – 10.0])	-7 (-22 – 9) (-0.4 [-1.2 – 0.5])	0.39
Lunch	148 (143 – 156) (8.2 [7.9 – 8.7])	173 (151 – 187) (9.6 [8.4 – 10.4])	-23 (-34 – -9) (-1.3 [-1.9 – -0.5])	0.0015
Dinner	147 (139 – 159) (8.2 [7.7 – 8.8])	158 (130 – 176) (8.8 [7.2 – 9.8])	-10 (-23 – 5) (-0.5 [-1.3 – 0.3])	0.18
Diary reported endpoints				
Daily carbohydrate intake (g)	163 (133 – 173)	172 (133 – 195)	-6.3 (-16.7 – 3.5)	0.16
Exercise moments (no.)	11 (6 – 20)	13 (7.5 – 22)	-1.0 (-5.0 – 2.5)	0.57

Data are median (IQR). *Difference is closed loop minus open loop.

Supplementary Table 4. PAID and DTSQ results.

Endpoint	Baseline	Closed Loop	Open Loop	p value
PAID score	18 (10.25–26.75)	14 (8.25–20.75)	15 (10.25–21)	0.61*
DTSQ-s				
Total score	27 (26–32.5)	30 (24.5–31)	26 (24–29.75)	0.55*
Perceived hyperglycemia	4 (3–5)	1 (1–3)	4 (2–4)	0.012*
Perceived hypoglycemia	2 (2–3)	1 (1–2)	3 (2–4.75)	0.00086*
DTSQ-c				
Total score	NA	7 (2.5–11.5)	0 (-0.5–2)	0.15
Perceived hyperglycemia	NA	-2 (-3–0.5)	0 (-1–0.5)	0.0050
Perceived hypoglycemia	NA	-2 (-3–1.5)	0 (0–1)	0.00014

Data are median (IQR). NA, not applicable. *Closed loop minus baseline vs. open loop minus baseline.

Supplementary Table 5. EQ5D results.

Endpoint	Baseline	Closed Loop	Open Loop	p value*
Experienced problems per dimension, no. (%) of patients				
Mobility	2 (8.7)	2 (8.7)	4 (17.4)	NA
Self-care	0 (0.0)	0 (0.0)	1 (4.3)	NA
Usual activities	9 (39.1)	6 (26.1)	7 (30.4)	NA
Pain/discomfort	8 (34.8)	8 (34.8)	9 (39.1)	NA
Anxiety/depression	6 (26.1)	4 (17.4)	9 (39.1)	NA
VAS score, median (IQR)	72 (67.5–80)	75 (70–85)	75 (68.5–80)	0.40
Change in health state, no. (%) of patients				
Improved	NA	7 (30.4)	4 (17.4)	NA
Worsened	NA	5 (21.7)	7 (30.4)	NA
No change	NA	8 (34.8)	9 (39.1)	NA
Mixed change	NA	3 (13.0)	3 (13.0)	NA

NA, not applicable. * Closed loop minus baseline vs. open loop minus baseline.

Supplementary Table 6. MPUQ results.

MPUQ dimension (score)	Perfect score	Closed Loop
Total score	310	250 (232–264)
Ease of learning and use	90	76 (69.5–79.5)
Helpfulness and problem solving capabilities	45	39 (35–41.5)
Affective aspect and multimedia properties	60	41 (37.5–43)
Commands and minimal memory load	20	18 (16–20)
Control and efficiency	35	27 (26–30)
Typical tasks for artificial pancreas	60	49 (44.5–51)

Data are median (IQR).

Supplementary Table 7. Adverse events.

Adverse events (no. of patients)	Closed Loop	Open Loop
Nausea*	13 (8**)	1
Headache*	3 (2**)	4
Restlessness*	2 (2**)	-
Skin reaction tape infusion sets or glucose sensors	14	1
Other issues (e.g. lump formation or pain), related to		
Glucagon infusion set	12	NA
Insulin infusion set	3	1
Glucose sensors	2	1

*For closed loop possibly related to glucagon administration or having lower glucose levels than used to.

**Number of total that occurred during the four-day closed loop training period.

Supplementary Table 8. Technical issues of the artificial pancreas.

Description issue	Action taken
The physical connection between the sensor and transmitter contacts was unstable on some occurrences, which resulted in temporarily lost contact with the sensor.	This hardware issue was solved by redesign of the sensor contact blocks. The improved transmitters became available during the conduct of the study: in four patients one transmitter and in three patients both transmitters were replaced during the second closed loop week, and the last five patients received the new transmitters from the start of the closed loop training.
Unrelated to the transmitters, the glucose sensors itself malfunctioned five times, with sensor current values being zero or close to zero.	These sensors were replaced by the patients.
Sensor deterioration with unexpected low sensor current values resulted in a faulty sensor calibration in one patient, which caused a symptomatic hypoglycaemic event after insulin dosing. At the time of this event, no back-up sensor was available because the second sensor was in its warm-up period.	The patient took oral carbohydrates and turned off the control algorithm for two hours until the second sensor was calibrated. The transmitter and sensor were replaced.
The battery lid of two transmitters did not close properly, due to a production error. These transmitters stopped functioning due to water damage.	The transmitters were replaced by the research team.
In two cases for the insulin pump of the artificial pancreas system and two cases for the glucagon pump the plunger rod did not retract at the first attempt.	The patients re-entered the specific procedure of the artificial pancreas.
Insulin leakage was reported eleven times and glucagon leakage once, these leakages occurred either at the cannula or at the connector of the infusion set.	All leakages were solved by the patients by replacing the infusion set (and insulin cartridge in some cases).
A pre-known software bug occurred four times: the self-learning algorithm reached incorrect boundaries.	The insulin setting was manually set by the research team.
A pre-known software bug occurred two times: a false safety alarm.	The artificial pancreas was reset by the research team.
For one artificial pancreas the batteries could not be placed due to the battery contacts being bent, caused by improper use or wearing of the material.	The artificial pancreas was replaced by the research team at the start of the training.

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