Fully Closed Loop Glucose Control With a Bihormonal Artificial Pancreas in Adults With Type 1 Diabetes: An Outpatient, Randomized, Crossover Trial

Helga Blauw,[1,2] A. Joannet Onvlee,[2,3] Michel Klaassen,[2] Arianne C. van Bon,[3] and J. Hans DeVries[1]

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OBJECTIVE

To demonstrate the performance and safety of a bihormonal (insulin and glucagon) artificial pancreas (AP) in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

In this outpatient, randomized, crossover trial, 2-week fully closed loop glucose control (AP therapy) was compared with 2-week open loop control (patient's normal insulin pump therapy with a glucose sensor if they had one).

RESULTS

A total of 23 patients were included in the analysis. Time in range (70–180 mg/dL [3.9–10 mmol/L]) was significantly higher during closed loop (median 86.6% of time [interquartile range 84.9–88.5]) compared with open loop (53.9% [49.7–67.2]; $P < 0.0001$).

CONCLUSIONS

Compared with insulin pump therapy, the bihormonal AP provided superior glucose control, without meal or exercise announcements, and was safe in adults with type 1 diabetes.

Hybrid closed loop therapy has been demonstrated to improve glucose control compared with standard insulin therapies in type 1 diabetes (1–4). Bihormonal closed loop systems may further improve glucose control, as the addition of glucagon more closely mimics physiologic glucose control and enables tighter glucose control by adding a "brake" to the control system (5). In addition, bihormonal closed loop systems may relieve patients from carbohydrate counting (6,7).

After our previous study (7), the prototype of our bihormonal artificial pancreas (AP) was further developed into a product version intended to obtain CE (Conformité Européenne) marking. The aim of this trial was to demonstrate the performance and safety of this AP in patients with type 1 diabetes during a 2-week period.

RESEARCH DESIGN AND METHODS

This study was a single-center, randomized, unblinded, crossover trial (clinical trial reg. no. NCT03858062, ClinicalTrials.gov) to compare home treatment with the AP (closed loop period) with the patients' normal insulin pump therapy (open loop period).

[1]Department of Internal Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
[2]Inreda Diabetic, Goor, the Netherlands
[3]Department of Internal Medicine, Rijnstate Hospital, Arnhem, the Netherlands

Corresponding author: Helga Blauw, h.blauw@amsterdamumc.nl

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During open loop, patients used their continuous glucose monitor (CGM) or flash glucose monitor (FGM) if they had one.

Adults between 18 and 75 years of age with type 1 diabetes who used an insulin pump for at least 6 months could be included. Main exclusion criteria were impaired awareness of hypoglycemia (according to the Clarke et al. [8] and/or Gold et al. [9] questionnaire), BMI >35 kg/m^2, and glycated hemoglobin (HbA_{1c}) >11% (97 mmol/mol).

Patients were randomized to start with either closed loop or open loop, and there was a washout period of at least 2 weeks between the two study periods. Both study periods consisted of 2 weeks, and the closed loop period was preceded by a 4-day training period. At the start of the training, as well as at the start and end of the two study periods, patients visited the clinical research center. Furthermore, there was one scheduled phone contact on day 4–6 of both study periods to discuss the progress.

The AP (Inreda Diabetic, Goor, the Netherlands) consists of two wireless transmitters for obtaining the glucose measurements and a wearable device, which integrates the CGM, accelerometer, control algorithm, insulin pump, and glucagon pump (Supplementary Fig. 1). The control algorithm included self-learning properties to adjust to the individual's insulin sensitivity. No manual input such as meal or exercise announcements was possible.

During open loop, patients continued their usual care. In addition, they received a masked CGM (G6; Dexcom, San Diego, CA) for data collection. At baseline and at the end of both study periods, patients completed multiple questionnaires (Supplementary Material).

Main study end point was the percentage of time in range (70–180 mg/dL [3.9–10 mmol/L]). According to the protocol, the closed loop training period was excluded from the analysis and patients who completed at least 1 week of both the closed loop and open loop period were included in the analysis. End points were calculated per patient and summarized as median (interquartile range [IQR]). The two treatments were compared with use of the Wilcoxon signed rank test for paired data, with significance at $P \leq 0.05$. MATLAB (version R2019a; MathWorks, Natick, MA) was used to calculate the end points, and statistical analysis was performed with R (version 3.5.3).

RESULTS

Twenty-three patients were included in the analysis (Supplementary Fig. 2): 15 male, median age 43.0 years (IQR 26.5–51.0), BMI 24.9 kg/m^2 (23.2–26.6), diabetes duration 23.0 years (14.0–34.5), HbA_{1c} 7.3% (7.1–8.1) (56 mmol/mol [54–65]), and insulin pump use 11.0 years (9.0–13.5). Twelve patients used FGM, and five patients used CGM.

The time in range was significantly higher during closed loop (median 86.6% of time [IQR 84.9–88.5]) compared with open loop (53.9% [49.7–67.2]; $P < 0.0001$) (Fig. 1*A*). The main safety end points, time in hypoglycemia (<70 mg/dL [<3.9 mmol/L]) and time in hyperglycemia (>180 mg/dL [>10 mmol/L]), were significantly improved during closed loop compared with open loop: 0.4% (0.1–0.8) vs. 2.0% (0.7–3.6) ($P < 0.0001$) and 12.8% (11.1–14.4) vs. 38.8% (30.5–48.9) ($P < 0.0001$), respectively (Fig. 1*B*). The glucose profile over 24 h is shown in Fig. 1*C* and *D*.

Median glucose was 129 mg/dL (IQR 126–132) (7.2 mmol/L [7.0–7.4]) during closed loop and 167 mg/dL (149–178) (9.3 mmol/L [8.3–9.9]) during open loop ($P < 0.0001$). Improved glucose control during closed loop was also found for the other glucose end points calculated for the full study or day and night period separately (Supplementary Tables 1 and 2). Postprandial median glucose was lower after lunch during closed loop compared with open loop, while there was no significant difference for breakfast and dinner (Supplementary Table 3).

Insulin use was slightly higher during closed loop (median 41.4 units/day [IQR 33.0–53.0]) compared with open loop (40.1 units/day [31.4–46.5]; $P = 0.0017$). During closed loop, glucagon use was

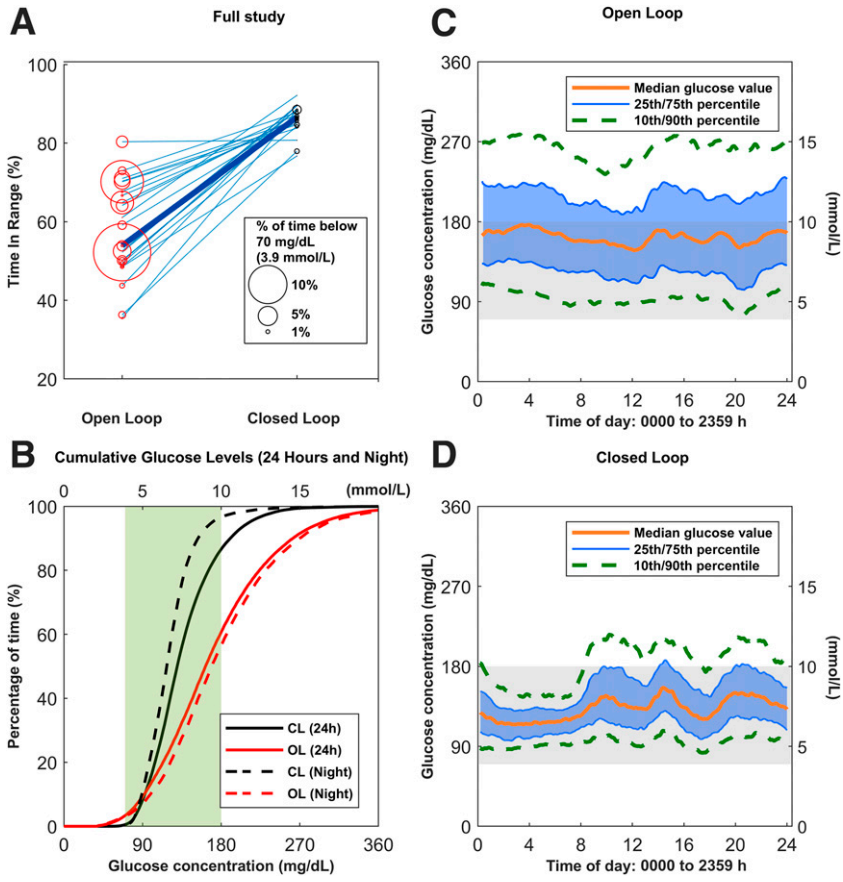

Figure 1—Glucose control during open loop and closed loop. *A*: Time in range from open loop (left) to closed loop (right). The thin lines represent the individual patients, and the bold line represents the median. The size of each circle is proportional to the time spent in a state of hypoglycemia. *B*: Cumulative glucose levels for the full study and night separately. Demonstrates the improved time spent in the different glycemic ranges for the closed loop. Glucose profile over 24 h for the open loop (C) and for the closed loop (*D*). CL, closed loop; OL, open loop.

0.66 mg/day (0.55–0.85) and the control algorithm was active for 97.2% (96.4–97.6) of the time.

The (change in) perceived frequencies of hyperglycemia and hypoglycemia (Diabetes Treatment Satisfaction Questionnaire [DTSQ]) were significantly different between closed loop and open loop, with lower perceived frequencies during closed loop. Other questionnaire scores were not significantly different between the two treatments (Supplementary Tables 4–6 [AP usability questionnaire results]). No severe hypoglycemia, ketoacidosis, or other serious adverse events occurred during the study. Adverse events, including nausea, and technical issues are listed in Supplementary Tables 7 and 8.

CONCLUSIONS

Our bihormonal AP increased time in range and reduced time in hypoglycemia and time in hyperglycemia compared with standard insulin pump therapy. Importantly, the AP enabled each individual patient to reach the international consensus treatment goals, being time in range >70%, time in hypoglycemia <4%, and time in hyperglycemia <25% (10). The Inreda Diabetic AP received CE marking on 24 February 2020.

In contrast to other (hybrid) closed loop systems, this bihormonal AP is a fully closed loop system and relieves patients from making treatment decisions, carbohydrate counting, and adapting their behavior to achieve good glycemic control. However, we found no differences in quality of life, psychological adaptation, and treatment satisfaction. The number of patients and study duration may have been insufficient to demonstrate any differences in these questionnaire scores. In addition, being a fully closed loop and bihormonal system adds to the complexity of the device, which may pose a burden on patients and (partly) counteract positive effects on patient-reported outcomes.

Although the use of glucagon is indispensable for this AP to achieve tight glucose control, it currently has several drawbacks. The glucagon had to be replaced every day, and multiple tube occlusions and other issues (such as formation of a lump or pain) occurred. These drawbacks may be solved by the use of a stable glucagon analog, currently under development (5). A causal relation of adverse events with glucagon administration was difficult to determine or exclude because these symptoms could also be related to (patients not being used to) low glucose levels.

A limitation of this trial was that treatment with the AP was compared with insulin pump therapy with either CGM or FGM if the patients had one, and we acknowledge that the open loop period did not include the most advanced glucose monitoring tools in all patients; however, it was reflective of commonly used diabetes therapy. Also, glucose outcomes were derived from different glucose monitoring devices for the two study periods.

In conclusion, this trial demonstrates that the Inreda Diabetic AP provides superior glucose control compared with insulin pump therapy and is safe in adults with type 1 diabetes. The available clinical evidence resulted in the first CE-marked bihormonal AP. Before widespread use in clinical practice becomes possible, the long-term effectiveness and safety should be investigated in a multicenter setting, with sufficient attention for patient-reported outcomes.

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Duality of Interest. Inreda Diabetic funded the glucose sensors and glucagon and was involved in study design and data analysis. Dexcom read the manuscript before submission. H.B., A.J.O., and M.K. are employees of Inreda Diabetic. J.H.D.V. is also employed by Profil Institute for Metabolic Research; is a consultant for Novo Nordisk, Roche, and Zealand Pharma; and received speaker honoraria from Novo Nordisk and Senseonics. No other potential conflicts of interest relevant to this article were reported.

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