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Bihormonal Artificial Pancreas With Closed-Loop Glucose Control vs Current Diabetes Care After Total Pancreatectomy
A Randomized Clinical Trial

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IMPORTANCE Glucose control in patients after total pancreatectomy is problematic because of the complete absence of α- and β-cells, leading to impaired quality of life. A novel, bihormonal artificial pancreas (BIHAP), using both insulin and glucagon, may improve glucose control, but studies in this setting are lacking.

OBJECTIVE To assess the efficacy and safety of the BIHAP in patients after total pancreatectomy.

DESIGN, SETTING, AND PARTICIPANTS This randomized crossover clinical trial compared the fully closed-loop BIHAP with current diabetes care (ie, insulin pump or pen therapy) in 12 adult outpatients after total pancreatectomy. Patients were recruited between August 21 and November 16, 2020. This first-in-patient study began with a feasibility phase in 2 patients. Subsequently, 12 patients were randomly assigned to 7-day treatment with the BIHAP (preceded by a 5-day training period) followed by 7-day treatment with current diabetes care, or the same treatments in reverse order. Statistical analysis was by Wilcoxon signed rank and Mann-Whitney *U* tests, with significance set at a 2-sided $P < .05$.

MAIN OUTCOMES AND MEASURES The primary outcome was the percentage of time spent in euglycemia (70-180 mg/dL [3.9-10 mmol/L]) as assessed by continuous glucose monitoring.

RESULTS In total, 12 patients (7 men and 3 women; median [IQR] age, 62.5 [43.1-74.0] years) were randomly assigned, of whom 3 did not complete the BIHAP phase and 1 was replaced. The time spent in euglycemia was significantly higher during treatment with the BIHAP (median, 78.30%; IQR, 71.05%-82.61%) than current diabetes care (median, 57.38%; IQR, 52.38%-81.35%; $P = .03$). In addition, the time spent in hypoglycemia (<70 mg/dL [3.9 mmol/L]) was lower with the BIHAP (median, 0.00% [IQR, 0.00%-0.07%] vs 1.61% [IQR, 0.80%-3.81%]; $P = .004$). No serious adverse events occurred.

CONCLUSIONS AND RELEVANCE Patients using the BIHAP after total pancreatectomy experienced an increased percentage of time in euglycemia and a reduced percentage of time in hypoglycemia compared with current diabetes care, without apparent safety risks. Larger randomized trials, including longer periods of treatment and an assessment of quality of life, should confirm these findings.

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Visual Abstract

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Supplemental content

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Group Information: The members of the Dutch Pancreatic Cancer Group appear in Supplement 3.

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Total pancreatectomy is increasingly performed in highly selected patients with main duct intraductal papillary mucinous neoplasm, pancreatic cancer, or therapy-refractory painful chronic pancreatitis.[1,2] All these patients develop diabetes and require life-long intensive insulin replacement therapy because of the complete loss of the endogenous production of both insulin and glucagon, the latter presenting a substantial risk for severe hypoglycemia. These sequelae, inherent to the procedure, represent one of the main reasons for the strong reluctance toward total pancreatectomy among patients, gastroenterologists, and surgeons.[3]

The treatment of diabetes after total pancreatectomy is similar to the treatment of type 1 diabetes, including replacement therapy with insulin (ie, insulin pens and pumps) and delivery of glucagon in cases of severe periods of hypoglycemia.[4] Adequate glucose control in these patients remains challenging, and this so-called brittle diabetes often results in significant morbidity and mortality in the long term.[5-7] Patients' lifestyles are adapted to the need for actively measuring and regulating glucose levels, which is accompanied by fear of hypoglycemia and, thus, impaired quality of life.[3,8,9]

Recently, the first bihormonal artificial pancreas (BIHAP) was assessed in patients with type 1 diabetes in the Algorithm to Control Postprandial, Post Exercise and Night Glucose Excursions in a Portable Closed Loop Format (APPEL5) study.[10] This portable device contains both insulin and glucagon and has a reactive glucose control algorithm that is self-learning to cope with day-to-day variations in insulin sensitivity.[11]

The fully automated BIHAP may improve glucose control in patients after total pancreatectomy. If so, this could potentially decrease the current strong reluctance toward total pancreatectomy when indicated. The aim of this pilot study was to investigate the efficacy and safety of the BIHAP in patients after total pancreatectomy.

Key Points

Question What is the efficacy and safety of the novel bihormonal artificial pancreas (BIHAP) in patients after total pancreatectomy?

Findings This randomized crossover clinical trial compared treatment with a portable, fully automated, European Commission–marked BIHAP with current diabetes care in 12 outpatients after total pancreatectomy. BIHAP was found to increase time in euglycemia (78.30% vs 57.38%) and reduce time in hypoglycemia.

Meaning In this study, bihormonal artificial pancreas treatment improved glucose regulation in patients with insulin dependent diabetes after total pancreatectomy; future, large, pragmatic randomized trials should assess the long-term effectiveness and safety of the BIHAP, including the effect on patient quality of life.

Methods

Study Design

The APPEL5+ was a randomized crossover trial comparing the BIHAP to current diabetes care (ie, insulin pump or pen therapy) in outpatients with diabetes after total pancreatectomy. Recruitment was performed between August 21 and November 16, 2020. This trial was conducted in accordance with the Good Clinical Practice guidelines, principles of the Declaration of Helsinki, and Consolidated Standards of Reporting Trials (CONSORT) guidelines.[12,13] The study protocol is available in Supplement 1.

Study Participants

Patients were referred by surgeons from hospitals participating in the Dutch Pancreatic Cancer Group and screened for eligibility during a visit at the Amsterdam UMC by the study coordinator (C.L.v.V.) while supervised by an endocrinologist. Patients after total pancreatectomy aged 18 years or older and receiving treatment for diabetes (ie, insulin pen or pump) were eligible for inclusion. Main exclusion criteria were recent total pancreatectomy (within 3 months) and impaired patient awareness of hypoglycemia (score ≥4) according to the Gold or Clarke questionnaire.[14,15] The study was approved by the medical ethics committee of the Amsterdam UMC. All patients provided written informed consent before randomization.

Randomization

For safety reasons, because this was a first-in-patient study, the main study was preceded by a 5-day feasibility phase with the BIHAP in 2 patients. After successful completion of the feasibility phase, subsequent patients were randomly assigned in a 1:1 ratio to start with either the BIHAP treatment (preceded by a 5-day training phase) or current diabetes care, using the Castor Electronic Data Capture randomization module. Subsequently, patients crossed over to the other treatment (**Figure 1**).

Procedures

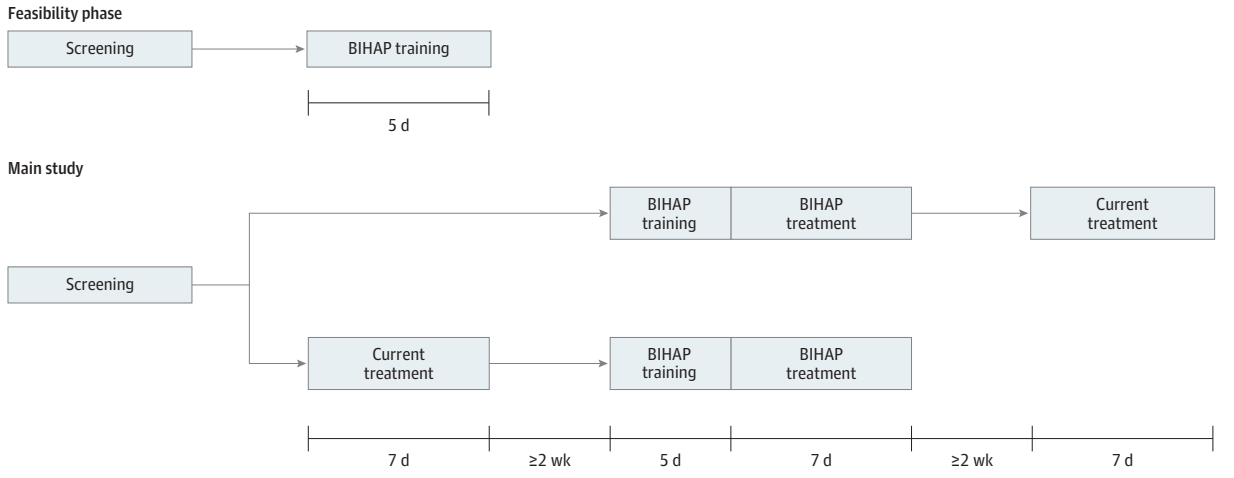
Feasibility Phase

Before the start of the feasibility phase, patients attended a 1-day instruction at our center on using the BIHAP. In addition to the device's self-learning algorithm, insulin settings were evaluated daily and changed manually if necessary. Continuous (24 hours for 7 days a week) telemonitoring was provided by our technical and medical team. The feasibility phase was performed at patients' homes and considered successfully completed if none of the following occurred: severe hypoglycemia (hospital admission or unconsciousness related to hypoglycemia), hospital admission due to high-glucose levels, any error that had consequences for the safety of the patient, and failure of the algorithm resulting in an incorrect amount of insulin or glucagon administered.

Main Study

After successful completion of the feasibility phase, new patients were randomly assigned into the main study. Patients started with either a 7-day treatment with the BIHAP or a 7-day treatment using their current diabetes care (Figure 1). Both treatment phases were performed at home. To provide sufficient time for development and adjustment of the self-learning algorithm to the patient's specific insulin needs, the BIHAP phase was preceded by a 5-day training period, similar

Figure 1. Study Design



BIHAP indicates bihormonal artificial pancreas.

to that of the feasibility phase. During the BIHAP phase, alarm-based monitoring was provided. Additional home visits were scheduled when indicated. During the current diabetes care phase, standard of care for diabetes was continued. For registration of the glucose concentrations, the patients received an additional masked continuous glucose monitoring system (Dexcom G6).

Bihormonal Artificial Pancreas

In this study, the Inreda Diabetic BIHAP was used as previously described in detail (eFigure 1 in Supplement 2). The BIHAP is a 119 × 77 × 37-mm device, which, including medication (ie, insulin and glucagon) and batteries, weighs 345 g.[10] In short, the portable BIHAP is European Commission–marked and automatically maintains blood glucose levels within target limits (between 70 and 180 mg/dL) through a continuously closed-loop system. No manual input, such as meals or exercise, was required.

Outcomes

The primary outcome was the median percentage of time spent in euglycemia, defined as blood glucose levels between 70 and 180 mg/dL (3.9-10.0 mmol/L) during a 7-day treatment with the BIHAP in patients after a total pancreatectomy compared with current diabetes care.[16,17]

Secondary outcomes included safety and efficacy of the BIHAP. Details on secondary study parameters, adverse events reporting, and data collection are provided in the eMethods in Supplement 2. Other secondary end points were time that the algorithm of the BIHAP was active and glucose measurement performance. To compare the glucose sensors during the BIHAP phase, the precision absolute relative difference (PARD) was calculated. It was hypothesized that the mean absolute relative difference (MARD) and PARD were lower than 15%, indicating that the data were reliable.[18] The MARD was calculated for each methods patient over 7 measurements, and the PARD was calculated between the 2 sensors and divided by the mean of the 2 sensor values.

Statistical Analysis

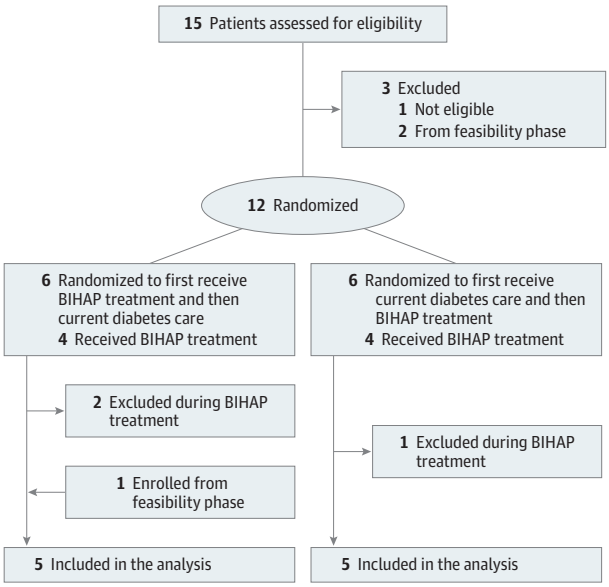
The sample size calculation was based on the results of the previous APPEL5 study,[10] wherein mean time spent in euglycemia was 57.5% (SD, 11.9%) for patients with current diabetes care vs 86.1% (SD, 3.6%) during the BIHAP phase. The mean time spent in euglycemia in the BIHAP phase of the current study was expected to be approximately 85%, comparable with APPEL5, with an SD of 11%. For a power of 80% (1 – β) and 2-sided α of .05, 10 patients were required. To account for dropout, the total sample size was 12 patients. Herein, the crossover study design was actually not taken into account, as we were unsure whether a period and/or carryover effect would occur, which would have necessitated analysis as a parallel trial using the data before crossover only.

The training period was excluded from the analysis. A per-protocol analysis was performed that included only patients who completed both study phases (ie, BIHAP and current diabetes care). End points were calculated per patient. The efficacy of the BIHAP was compared with current diabetes care using the Wilcoxon signed rank test for paired data. Results are presented as counts and medians and IQRs. Period and carryover effects were assessed for the primary outcome of the study by examining the effect of the period on the outcome per group using a Mann-Whitney *U* test. Significance was based on a 2-sided test, with $P < .05$ considered significant. Data were analyzed using SPSS Statistics for Windows, version 26.0 (IBM Corporation).

Results

Between August 21 and November 16, 2020, 15 patients were screened for eligibility, of whom 14 patients were randomly

Figure 2. Flow Diagram of Patient Inclusion in the Study and Analysis



BIHAP indicates bihormonal artificial pancreas.

Table 1. Baseline Characteristics of Participants

Characteristic	Value
No. of patients	10
Sex, No. (%)	
Female	3 (30)
Male	7 (70)
Age, median (IQR), y	62.5 (43.1-74.0)
Body mass index, median (IQR)[a]	22.63 (17.42-23.53)
Diabetes duration, median (IQR), y	4.5 (0.8-21.0)
Current diabetes care	
Insulin therapy, No. (%)	
Pen	8 (80)
Pump	2 (20)
Self-monitoring of blood glucose	0
FreeStyle Libre (Abbott)	10 (100)
Hemoglobin A_{1c}, median (IQR), mmol/L	58.50 (40.00-65.00)
Indication for total pancreatectomy	
IPMN	1 (10)
Benign[b]	3 (30)
Malignant[c]	6 (60)

Abbreviation: IPMN, intraductal papillary mucinous neoplasm.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Benign included pseudocysts (n = 2) and chronic pancreatitis (n = 1).

[c] Malignant included pancreatic tumors (n = 4), metastatic pancreatic tumor (n = 1), and duodenal carcinoma (n = 1).

assigned to the BIHAP or current diabetes care phase. One patient was excluded from the study because of impaired awareness of hypoglycemia. Of the remaining 14 patients, 2 participated in and completed the feasibility phase without dropout. Overall, 10 patients completed both phases of the main study. Three patients were withdrawn during the BIHAP phase for various reasons (1 had psychological difficulties with giving up control over diabetes treatment; 1 had medical issues unrelated to the BIHAP; and 1 had problems with the glucose sensors, preventing proper performance of the BIHAP system). Two patients were withdrawn during the training phase, and 1 was withdrawn during the main study. According to the study protocol, these patients were not included in our analyses, and 1 of these patients was replaced by a patient who also participated in the feasibility phase to acquire sufficient statistical power (**Figure 2**). Of the 10 patients included in the analyses, 7 (70%) were men and 3 (30%) were women. Median age was 62.5 years (IQR, 43.1-74.0 years), median body mass index (calculated as weight in kilograms divided by height in meters squared) was 22.63 (IQR, 17.42-23.53), and median diabetes duration was 4.5 years (IQR, 0.8-21.0 years) with a median hemoglobin A_{1c} of 58.50 mmol/L (IQR, 40.00-65.00 mmol/L) (**Table 1**). As current diabetes care, 8 patients (80%) were treated by insulin pen therapy, and 2 (20%) received insulin pump therapy.

Feasibility Phase

No adverse events or serious adverse events occurred, and the algorithm functioned properly. Therefore, this phase was successfully completed, and no adjustments were made to the algorithm. For the 2 patients in the 5-day feasibility phase, the median percentage of time spent in euglycemia was 70.38% (IQR, 69.26%-71.49%), without any time spent in hypoglycemia (median, 0.00%; IQR, 0.00%-0.00%). Median time spent in hyperglycemia was 29.64% (IQR, 28.52%-30.75%), with a median glucose level of 143.3 mg/dL (IQR, 141.1-145.4 mg/dL).

Main Study

The percentage of time spent in euglycemia during the 7-day treatment was significantly higher with the BIHAP than with current diabetes care (median, 78.30% [IQR, 71.05%-82.61%] vs 57.38% [IQR, 52.38%-81.35%]; $P = .03$) (**Table 2**). Time spent in level 1 hypoglycemia was lower with the BIHAP treatment vs current diabetes care (median, 0.00% [IQR, 0.00%-0.07%] vs 1.61% [IQR, 0.08%-3.81%]; $P = .004$), and time spent in level 2 hypoglycemia was lower in the BIHAP vs current diabetes care treatment (median, 0.00% [IQR, 0.00%-0.00%] vs 0.62% [IQR, 0.00%-1.66%]; $P = .02$). Patients spent less time in level 2 hyperglycemia during the BIHAP treatment vs current diabetes care (median, 1.17% [IQR, 0.60%-3.41%] vs 8.41% [IQR, 0.83%-18.30%]; $P = .049$), whereas time in level 1 hyperglycemia did not differ between the 2 treatments (median, 21.70% [IQR, 17.36%-28.95%] vs 38.92% [IQR, 15.85%-45.16%]; $P = .19$). In addition, the majority of patients (8 [80%]) showed individual improved glucose control (time in range) during the BIHAP phase (eFigure 2 in Supplement 2).

Glucose level was comparable between both phases (median, 7.95 [IQR, 7.71-8.11] vs 8.55 [IQR, 7.78-9.73] mmol/L; $P = .43$) (eFigure 3 in Supplement 2). Glycemic variability was significantly lower during the BIHAP phase vs current diabetes care at all end points, with the exception of the high blood glucose index (Table 2).

Table 2. Primary and Secondary Outcomes

Outcome	Median (IQR)		P value
	BIHAP	Current diabetes care	
Primary			
Time spent in euglycemia, %[a]	78.30 (71.05-82.61)	57.38 (52.38-81.35)	.03
Secondary			
Time spent at glucose levels, %			
Hypoglycemia			
<70 mg/dL (3.9 mmol/L)	0.00 (0.00-0.07)	1.61 (0.80-3.81)	.004
<54 mg/dL (3.0 mmol/L)	0.00 (0.00-0.00)	0.62 (0.00-1.66)	.02
Hyperglycemia			
>180 mg/dL (10.0 mmol/L)	21.70 (17.36-28.95)	38.92 (15.85-45.16)	.19
>250 mg/dL (13.9 mmol/L)	1.17 (0.60-3.41)	8.41 (0.83-18.30)	.049
Median glucose, mmol/L	7.95 (7.71-8.11)	8.55 (7.78-9.73)	.43
Glycemic variability			
IQR, mmol/L	3.05 (2.76-3.67)	4.05 (3.15-5.93)	.03
CV, %	26.03 (24.21-30.63)	32.50 (26.43-41.50)	.049
LBGI score	0.14 (0.07-0.20)	0.47 (0.33-0.97)	.03
HBGI score	4.34 (3.72-5.84)	8.17 (3.77-11.17)	.06
BGRI score	4.44 (3.86-6.03)	9.02 (4.60-11.69)	.01
Insulin/glucagon			
Insulin, U	45.18 (34.28-55.71)	43.08 (27.02-54.28)	.004
Glucagon, mg	0.30 (0.24-0.39)	NA	NA
Time algorithm active, %	97.91 (97.06-98.19)	NA	NA

Abbreviations: BGRI, blood glucose risk index; BIHAP, bihormonal artificial pancreas; CV, coefficient of variation; HBGI, high-blood glucose index; LBGI, low-blood glucose index; NA, not applicable.

[a] Euglycemia, 70-180 mg/dL (3.9-10.0 mmol/L).

Table 3. Secondary Outcomes

	Median (IQR)		P value
	BIHAP	Current diabetes care	
Daytime[a]			
Time spent at glucose levels, %			
Euglycemia, 70-180 mg/dL (3.9-10.0 mmol/L)	72.84 (62.06-77.89)	68.02 (56.97-80.22)	.49
Hypoglycemia			
<70 mg/dL (3.9 mmol/L)	0.00 (0.00-0.20)	1.37 (0.46-3.96)	.004
<54 mg/dL (3.0 mmol/L)	0.00 (0.00-0.00)	0.48 (0.00-1.53)	.04
Hyperglycemia			
>180 mg/dL (10.0 mmol/L)	27.16 (22.11-37.94)	28.09 (15.98-42.73)	.92
>250 mg/dL(13.9 mmol/L)	1.53 (0.80-4.07)	4.33 (1.11-13.52)	.08
Glucose, mmol/L	8.51 (8.04-9.31)	8.35 (7.30-9.53)	.43
Nighttime[b]			
Time spent at glucose levels, %			
Euglycemia, 70-180 mg/dL (3.9-10.0 mmol/L)	94.84 (90.98-99.76)	47.82 (24.18-83.13)	.002
Hypoglycemia			
<70 mg/dL (3.9 mmol/L)	0.00 (0.00-0.00)	0.00 (0.00-6.90)	.25
<54 mg/dL (3.0 mmol/L)	0.00 (0.00-0.00)	0.00 (0.00-3.62)	.25
Hyperglycemia			
>180 mg/dL (10.0 mmol/L)	5.16 (0.24-9.02)	47.12 (14.58-75.82)	.004
>250 mg/dL (13.9 mmol/L)	0.00 (0.00-0.05)	6.75 (0.00-31.07)	.06
Glucose, mmol/L	6.84 (6.49-7.68)	9.80 (7.15-12.75)	.01

Abbreviation: BIHAP, bihormonal artificial pancreas.

[a] 6:00 AM to 12:00 PM.

[b] 12:00 PM to 6:00 AM.

During the daytime, patients spent significantly less time in level 1 hypoglycemia during the BIHAP phase vs current diabetes care (median, 0.00% [IQR, 0.00%-0.20%] vs 1.37% [IQR, 0.46%-3.96%]; $P = .004$), as well as less time in level 2 hypoglycemia (median, 0.00% [IQR, 0.00%-0.00%] vs 0.48% [IQR, 0.00%-1.53%]; $P = .04$). Time spent in hyperglycemia levels 1 and 2 did not differ between the 2 treatments (**Table 3**).

During the nighttime, patients spent significantly more time in euglycemia during the BIHAP phase vs current diabetes care (median, 94.84% [IQR, 90.98%-99.76%] vs 47.82%

[IQR, 24.18%-83.13%]; $P = .002$). Moreover, the glucose levels during the nighttime were significantly lower during the BIHAP phase (median, 6.84 [IQR, 6.49-7.68] vs 9.80 [IQR, 7.15-12.75] mmol/L; $P = .01$) (Table 3 and eResults in the Supplement).

The control algorithm was active for a median of 97.91 (IQR, 97.06%-98.19%) of the time. Nine patients performed a 7-point glucose measurement during both the BIHAP and current diabetes care phases, and both phases showed a MARD value lower than the cutoff of 15% (median, 14.51% [IQR, 11.95%-17.01%] and 8.67% [IQR, 5.46%-10.21%], respectively). Based on the glucose-level data from the time that the 2 sensors were both active, the PARD value was calculated during the BIHAP phase. The PARD value was significantly lower than the cutoff of 15% (median, 6.83% [IQR, 6.18%-8.31%]).

During both main study phases, no severe hypoglycemia, ketoacidosis, or other serious adverse events were detected. All adverse events occurred during the BIHAP treatment. One patient (10%) had nausea, 2 (20%) experienced headache, and 4 (40%) experienced skin irritation due to the subcutaneous infusion set or sensor (eTable 1 in Supplement 2). In total, 30 device deficiencies were reported by our medical staff (eTable 2 in Supplement 2). During both the feasibility phase and main study, 2 additional home visits each were required to address a Wi-Fi and a sensor connection issue, totaling 4 home visits. All adverse events and technical issues are listed in eTable 3 and eTable 4 in Supplement 2; none of the device deficiencies led to a relevant risk for the patients. No carryover and period effects were identified.

We asked the patients whether they would recommend this treatment to others or would continue the BIHAP treatment if possible. The majority (7 [70%]) wished to continue the BIHAP treatment on the condition that the number of alarms given by the BIHAP and the size of the device would be reduced. Moreover, patients reported feeling that they had their life and freedom back and were supported in their treatment by the BIHAP, and were pleased by the improved glucose outcome.

Discussion

The findings from this first randomized crossover clinical trial in patients after total pancreatectomy show that the BIHAP resulted in increased time spent in euglycemia and reduced time in hypoglycemia compared with current diabetes care. Moreover, the BIHAP appeared to be safe in this patient group, as no adverse events were detected.

Adequate management of diabetes after total pancreatectomy remains highly challenging.[19] A prospective multicenter study reported that glycemic control is insufficient in these patients treated by conventional means, as reflected by frequent hypoglycemia events.[20] With all alternative systems of insulin treatment, manually entering the carbohydrate content of each meal is still required. Treatment with the BIHAP alleviates these disease-related burdens and restrictions and provides improved daytime and nighttime glucose control. The BIHAP appears to be a promising treatment strategy for patients with diabetes after total pancreatectomy.[10,11]

A randomized clinical trial from Japan is the only previously performed study on closed-loop glucose control after pancreatic resection.[21] The artificial pancreas used in that inpatient study of 30 patients included insulin but not glucagon, and only 2 of the patients had a total pancreatectomy. Hybrid closed-loop systems, which require manual meal input, have been investigated in the outpatient setting in patients with type 1 diabetes and are increasingly becoming available in clinical practice.[20,22-24] In contrast to these systems, the BIHAP, as used in the current study, contains both insulin and glucagon and is a fully closed-loop system with no need to input meals or activity-related events.[10,11] Because both insulin and glucagon are completely absent after total pancreatectomy, the BIHAP appears to be a suitable treatment for minimizing the burden of diabetes management after total pancreas resection.

Besides artificial pancreas devices, auto islet transplant has shown promising results on glucose regulation after total pancreatectomy.[25] Nevertheless, a substantial number of patients who underwent auto islet transplant still depend on insulin therapy. In addition, 2 main indications for total pancreatectomy, pancreatic cancer and neoplastic pancreatic cysts (ie, intraductal papillary mucinous neoplasms), are absolute or relative contraindications for auto islet transplant because of the small risk of transplanting malignant cells to the liver.[26]

Other than skin irritation, headache was the most common adverse event during treatment with the BIHAP. In theory, this adverse event could be (partly) due to pseudohypoglycemia, ie, symptoms patients experience as they first reach lower, normal blood glucose levels than they were used to during current diabetes care. The BIHAP does not require meal and physical activity restrictions. The majority of included patients reported feeling released from limitations after years of abstinence of specific high-carbohydrate meals or intensive activities that would result in fluctuations in glucose levels. These improvements in patient-reported outcomes deserve more attention and quantification in future studies.

Three of the 12 patients recruited needed to be withdrawn from the study because of difficulties giving up control over diabetes treatment (n = 1), worsening of a preexisting medical issue (diarrhea; n = 1), and procedures related to the BIHAP and its alarms, especially during the training phase while constant telemonitoring was provided (n = 1). Adequate psychological guidance and a longer period of BIHAP therapy to adapt to the new treatment could perhaps reduce discontinuation of and improve coping with the BIHAP. In addition, during the training period, continuous telemonitoring, including multiple alarms, is provided, which may be seen as a limitation of the device. With regard to implementation in daily use, continuous telemonitoring and the accompanying alarms will be minimized with optimization of the device. We also expect that in the future, patients will be able to start using the BIHAP sooner after total pancreatectomy, for instance, once they have shown proficiency in diabetes self-care if needed as a fallback in case of device failure.

Limitations

This study has some limitations. First, the 7-day BIHAP treatment period is relatively short. To establish feasibility and the true merits of the BIHAP for patients after total pancreatectomy, a larger number of patients in longer-term prospective and randomized studies (eg, assessment of hemoglobin A_{1c} levels and number of events related to hypoglycemia) is required. Based on previous studies, prolonged use of the BIHAP will likely result in even more improved glucose control over time because of optimization of the self-learning algorithm.[11]

Second, we did not evaluate quality of life, although this is an important outcome measure, especially in this group of patients. The majority were pleased with the improved glucose control with the BIHAP and wished to continue using the device. Assessment of quality of life should be included in future studies.

Third, no formal cost-effectiveness analysis was performed but will be included in a future, larger study. Direct treatment costs of the BIHAP treatment are expected to be higher compared with usual care because more disposables are required. However, costs related to treatment of complications and societal costs are expected to be lower because patients will experience less hypo- and hyperglycemia, resulting in fewer hospital visits and improved work capacity. For this reason, in the Netherlands, the BIHAP is expected to meet the bar for reimbursement in the near future.

Fourth, according to the study protocol, 3 patients discontinued the study, of whom 1 could be replaced. Thus, a per-protocol analysis rather than an intention-to-treat analysis was performed.

Fifth, glucose outcomes were derived from different glucose monitoring devices (ie, Dexcom G6 during the BIHAP phase vs Enlite [Medtronic] during the current diabetes care phase). In addition, we acknowledge that the currently used BIHAP device has its drawbacks. Daily replacement of glucagon is required to avoid occlusion of the infusion tube, which was time consuming for the patients. A stable glucagon, currently under development, is required to minimize the number of procedures for BIHAP users.[27] In addition, the size of the device (119 × 77 × 37 mm) remains an issue, but a smaller system will become available soon that will be more convenient and user friendly. Another disadvantage of the current device is that 2 glucose sensors are required for reliable continuous glucose monitoring because of warm-up time and occasional unreliability of the sensors.[18] Once more accurate sensors become available, this aspect may be improved.

Conclusions

This randomized crossover clinical trial demonstrated that the BIHAP has the ability to provide superior outcomes in terms of glucose control compared with current diabetes care (ie, insulin pump and pen therapy) in patients after total pancreatectomy. Moreover, the BIHAP appears to be safe, as no serious adverse events were observed. Larger randomized studies with a longer treatment period are necessary to justify the use and feasibility of BIHAP for the treatment of diabetes in patients after total pancreatectomy, with sufficient attention for patient-reported outcomes, such as quality of life.

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Invited Commentary

Artificial Pancreas and Expanding the Use of Total Pancreatectomy

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Historically nearly abandoned due to significant morbidity, total pancreatectomy (TP) has experienced reincarnation amid developments in the care for pancreatic endocrine and exocrine insufficiency, and also due to expansion of indications.[1] In cases with intraductal papillary mucinous neoplasm (IPMN) and multifocal pancreatic neoplasms, the surgeons need to make the difficult decision of performing TP. The use of TP remains limited, at least partially based on the difficulties in controlling glucose levels in the absence of glucagon-producing α-cells.

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In this issue of *JAMA Surgery*, van Veldhuisen et al[2] report a randomized clinical trial (RCT) comparing bihormonal artificial pancreas (BIHAP) (automatically administrating both insulin and glucagon) with standard diabetes care (manually administered insulin) in patients who had undergone TP for various reasons, such as IPMN, chronic pancreatitis, or cancer. Patients used BIHAP for 7 days and then received standard diabetes care for another 7 days, or the other way around depending on the randomization. Time at euglycemia (78% vs 57%) was increased, and time in either hypoglycemia or hyperglycemia was reduced while using BIHAP, indicating improved glucose level control.

While encouraging, the results are somewhat preliminary in their clinical applicability. Only 10 patients were included for a 2-week period. The study focused on safety and