The Bihormonal Bionic Pancreas Improves Glycemic Control in Individuals With Hyperinsulinism and Postpancreatectomy Diabetes: A Pilot Study

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OBJECTIVE

To determine whether the bihormonal bionic pancreas (BHBP) improves glycemic control and reduces hypoglycemia in individuals with congenital hyperinsulinism (HI) and postpancreatectomy diabetes (PPD) compared with usual care (UC).

RESEARCH DESIGN AND METHODS

Ten subjects with HI and PPD completed this open-label, crossover pilot study. Coprimary outcomes were mean glucose concentration and time with continuous glucose monitoring (CGM) glucose concentration <3.3 mmol/L.

RESULTS

Mean (SD) CGM glucose concentration was 8.3 (0.7) mmol/L in the BHBP period versus 9 (1.8) mmol/L in the UC period ($P = 0.13$). Mean (SD) time with CGM glucose concentration <3.3 mmol/L was 0% (0.002) in the BHBP period vs. 1.3% (0.018) in the UC period ($P = 0.11$).

CONCLUSIONS

Relative to UC, the BHBP resulted in comparable glycemic control in our population.

Diffuse congenital hyperinsulinism often requires palliative near-total pancreatectomy (1), which results in postpancreatectomy diabetes (PPD), glucagon deficiency, and pancreatic insufficiency; specifically, the clinical evolution of PPD is gradual and characterized by marked fluctuations between clinically significant hypo- and hyperglycemia due to dysregulation of residual endogenous insulin and glucagon secretion (2–4). The bihormonal bionic pancreas (BHBP) has been shown to improve glycemic control and to reduce the frequency of hypoglycemia in individuals with type 1 diabetes (5–8) by autonomously administering insulin and glucagon based on plasma glucose (PG) levels detected via continuous glucose monitoring (CGM) system. Given that individuals with HI and PPD have both insulin and glucagon deficiency, we hypothesize that, when compared with current standard diabetes care,

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the BHBP would reduce the mean glucose concentration and the fraction of time with glucose concentrations <3.3 mmol/L.

RESEARCH DESIGN AND METHODS

This random-order, crossover pilot study included 10 participants with HI and PPD. Participants completed two, unblinded, 3-night inpatient admissions in random order during which they used the BHBP ("BHPB period") or their own insulin pump ("UC period").

Procedures

The BHBP prototype used in this study consisted of an iPhone 6S running a mathematical dosing algorithm in the Beta Bionics mobile application, a Dexcom G5 CGM system, and two Tandem t:slim infusion pumps. The Beta Bionics app received CGM glucose values and communicated via Bluetooth with two t:slim pumps, one filled with insulin and the other with glucagon. The algorithm calculated doses of insulin or glucagon every 5 min based on CGM readings and then communicated with the pump to administer the dose. The BHBP was initialized using only the participant's body weight.

Fingersticks (reported by the glucose meter as plasma glucose [PG]) were done twice daily to calibrate the CGM, before meals, at bedtime, at 0300 h, and as-needed for reported symptoms of hypoglycemia or if the CGM glucose was <2.8 mmol/L. Participants completed a visual analog scale (VAS) every day to measure nausea.

Outcomes

Coprimary efficacy outcomes were mean CGM glucose concentration and the mean proportion of time that the CGM glucose concentration was <3.3 mmol/L during days 2 and 3 in each period (days 2 and 3 are expected to be more representative of long-term system performance) (5,6,8).

Secondary efficacy outcomes included the proportion of time that CGM glucose concentrations were in clinically relevant ranges (<2.8 mmol/L, <3.3 mmol/L, <3.9 mmol/L, 3.9–6.7 mmol/L, 3.9–10 mmol/L, >10 mmol/L, or >13.9 mmol/L), the percentage of subjects with mean CGM glucose concentration <8.6 mmol/L (estimated average glucose corresponding to a HbA_{1c} of 7% [53 mmol/mol]), and percentage of fingerstick PG values <3.9 mmol/L, <3.3 mmol/L, and <2.8 mmol/L.

Safety outcomes were number of symptomatic hypoglycemia episodes, number of carbohydrates interventions, insulin total daily dose (TDD), glucagon TDD during the

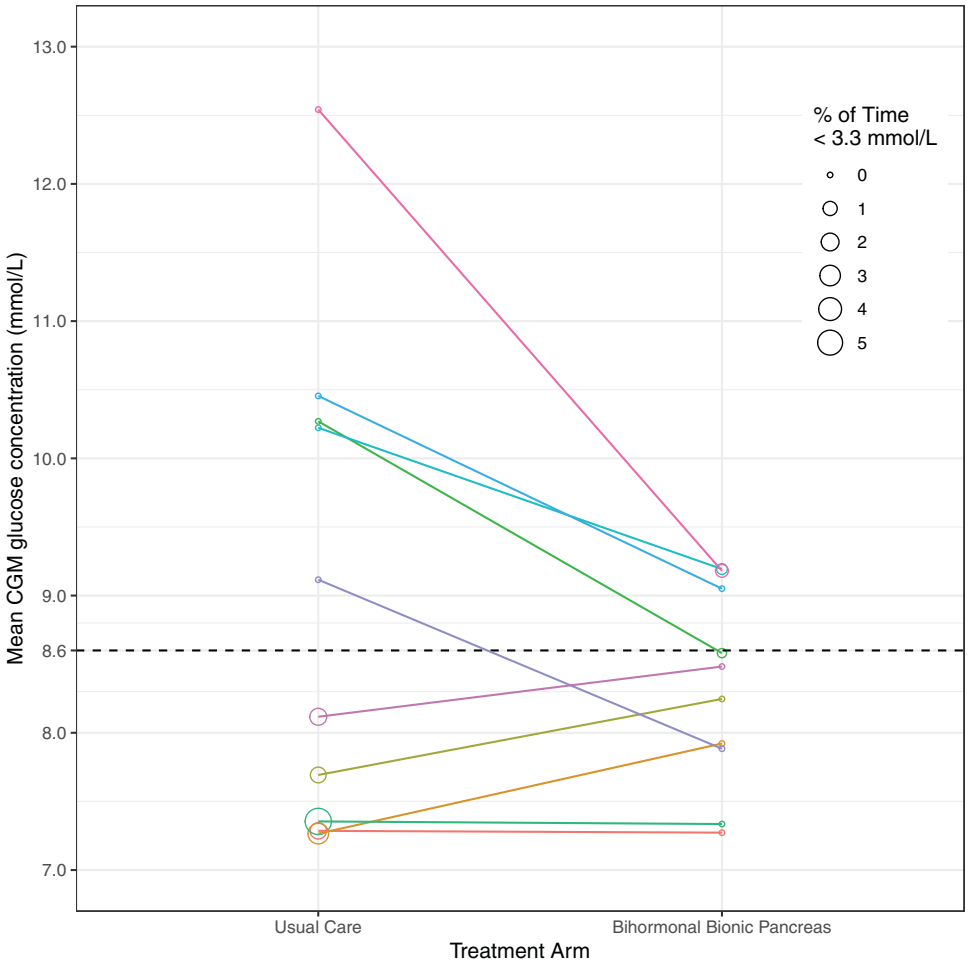

Figure 1—Comparison of mean CGM glucose concentration and frequency of hypoglycemia (<3.3 mmol/L) between UC and BHBP periods. Mean CGM glucose concentration in each participant on day 2 and 3 of the UC period is connected by a line to the corresponding mean CGM glucose concentration during the BHBP period. The diameter of each circle is proportional to the percentage of time that the subject spent with a CGM glucose concentration <3.3 mmol/L.

BHBP period, fraction of time BHBP was not functioning properly, and the mean daily VAS nausea score.

Statistical Analyses

This was a pilot study to assess the feasibility of using the BHBP to manage glycemia in individuals with HI and PPD and, as such, was underpowered to detect differences between periods for many outcome measures.

Data were primarily analyzed by first being aggregated to summary measures for each period and tested using the Wilcoxon paired signed rank test. Nonmissing time points were aggregated to proportions and means for binary and continuous variables, respectively.

For modeling, generalized estimating equations were used with compound symmetry assumed between records for the same patient. CGM values were analyzed using Gaussian distributed to estimate mean difference. The ranges of CGM were analyzed using a binomial distribution with log link to estimate relative risks. Modeling was done on the individual time points to avoid bias of aggregation and was adjusted for HbA_{1c}, age at enrollment, and sex. Analyses were generated using SAS 9.4 software.

RESULTS

Ten participants with HI (ages 7–26 years; 50% female) and on insulin pump therapy for management of their PPD completed this study. Participants were heterogeneous with respect to age, BMI, insulin requirements, and diabetes control. Participants' insulin requirements at home ranged from 0.23 to 1.26 units/kg/day.

The mean CGM glucose concentration was not significantly different between the BHBP and UC periods (8.3 mmol/L [SD 0.71] vs. 9 mmol/L [SD 1.79]; $P = 0.13$) nor was the mean percentage of time with CGM glucose concentration <3.3 mmol/L (0% [SD 0.23] vs. 1.3% [SD 1.9]; $P = 0.11$). The mean percentage of time with CGM glucose <3.9 mmol/L was 0.53% (SD 0.65) during the BHBP and 3.0% (SD 3.24) during the UC period ($P = 0.0547$).

The percentage of subjects that had a mean CGM glucose concentration <8.6 mmol/L during the BHBP and UC periods was not statistically different ($P = 0.16$) (Fig. 1). Compared with the UC period, subjects spent significantly more time with CGM glucose in range 3.9–10 mmol/L (78.0% [SD 10.5] vs. 59.8% [SD 17.3]; $P = 0.002$) and less time with CGM glucose concentration ≥ 10 mmol/L while on the BHBP (21.3% [SD 10.2] vs. 37.1% [SD 19.3]; $P = 0.004$) (Supplementary Fig. 1). When adjusted for HbA_{1c}, age at enrollment, and sex using the generalized estimating equation, the risk of spending a time point with CGM <3.3 mmol/L or <3.9 mmol/L or ≥ 10 mmol/L was significantly lower in the BHBP period than in the UC period. Mean PG concentration from fingerstick measurements (8.8 mmol/L [SD 1.32] vs. 9 mmol/L [SD 2.37], $P = 0.62$) and the number of fingerstick hypoglycemia episodes were not significantly different between the BHBP and UC periods.

The total number of interventions required for symptomatic hypoglycemia was higher in the UC period than in the BHBP period (5 vs. 0). The TDD of insulin was not different between BHBP and UC periods (0.649 vs. 0.767 units/kg/day; $P = 0.3$). Mean TDD of glucagon administered by the BHBP was 3.52 μg/kg/day (SD 1.44). During the BHBP analysis period, subjects were administered an average of 36.4 (median, 36.5; range, 23–50) doses of glucagon total.

The median nausea scores were not significantly different between the two periods ($P = 0.0625$). The only other adverse events reported were headaches.

CONCLUSIONS

While not all of our outcomes showed significant differences due to small sample size, they demonstrated a trend toward an overall improvement of mean glucose and frequency of hypoglycemia in the BHBP period relative to the UC period, consistent with previous studies in individuals with type 1 diabetes (6–8).

As seen in Fig. 1, during UC, subjects with lower mean glucose tended to have a higher frequency of hypoglycemia than those with higher mean glucose. Remarkably, despite subject heterogeneity, time spent in range (3.9–10 mmol/L) was significantly higher among participants during the BHBP period. Additionally, no severe hypoglycemia (<2.8 mmol/L) was detected by CGM for any subject in the BHBP period. This is important, because fear of hypoglycemia strongly influences when insulin therapy is initiated and how strict glycemic control parameters are enforced by parents/patients and physicians.

Limitations of this study include the small sample size, which may have limited our ability to demonstrate statistically significant differences in the two coprimary outcomes, and the use of a prototype version of the BHBP that relied on Bluetooth connectivity to the two pumps.

In conclusion, the use of the BHBP may be better suited for PPD in individuals with HI than current conventional insulin pump therapy. Given the promising results of this pilot study, larger and longer studies using the newer BHBP device will be pursued in this population to establish the long-term benefit and risks of the BHBP.

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Author Contributions. A.R. enrolled, admitted, and managed the subjects with the help of L.M.M. and D.D.D.L., and wrote the first draft of the manuscript. L.M.M. was the clinical research coordinator who helped with enrolling subjects, managing admissions, collecting data, and editing the manuscript. C.A.B. and S.J.R. contributed to study design, trained A.R., L.M.M., and D.D.D.L. on the use of the BHBP, and edited the manuscript. F.H.E.-K. and E.R.D. contributed to study design and edited the manuscript. K.L.L. and C.P.H. oversaw the study when D.D.D.L. was not available and edited the manuscript. L.S.B. analyzed the data and edited the manuscript. D.D.D.L. was responsible for the overall design and conduct of the study and edited the manuscript. D.D.D.L. 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 data and the accuracy of data analysis.

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