Original article

Post-breakfast closed-loop glucose control is improved when accompanied with carbohydrate-matching bolus compared to weight-dependent bolus

A. Haidar a,*,g,1, D. Farid a,g,1, A. St-Yves a,1, V. Messier a, V. Chen b, D. Xing b, A.-S. Brazeau a, C. Duval a, B. Boulet c, L. Legault d, R. Rabasa-Lhoret a,e,f

a Institut de Recherches Cliniques de Montréal, Montreal, Canada
b Jaeb Center for Health Research, Tampa, FL, USA
c Centre for Intelligent Machines, McGill University, Montreal, Canada
d Montreal Children’s Hospital, McGill University Health Centre, Montreal, Canada
e Nutrition department, Faculty of medicine, Université de Montréal, Montreal, Canada
f Montreal diabetes research center, Montreal, Canada

Received 3 October 2013; received in revised form 11 December 2013; accepted 14 December 2013
Available online 19 March 2014

Abstract

Aim. – We compared post-breakfast closed-loop glucose control either matched with a carbohydrate-matching bolus or a weight-dependent bolus.

Methods. – Twelve adults with type 1 diabetes consumed a 75 g CHO breakfast on two occasions. In random order, the breakfast was accompanied by a full carbohydrate-matching insulin bolus (8.30 U [7.50 U–11.50 U]) or a partial weight-dependent insulin bolus (0.047 U/kg; 3.45 U [2.95 U–3.75 U]). Postprandial glucose was regulated by sensor-responsive insulin and glucagon delivery.

Results. – Glucose control after the weight-dependent bolus was safe and feasible (glucose values returned to pre-prandial levels after 5 h). However, 5-hr incremental area under the curve and percentage of time above 10 mmol/L, were lower after the full bolus compared to the partial bolus (IAUC, 2.1 [0.8–4.2] mmol/L/hr vs 8.3 [6.5–11.4] mmol/L/hr; time in hyperglycaemia, 24% [6%–29%] vs 50% [25%–63%]; P < 0.001).

Conclusions. – Post-breakfast closed-loop glucose control without carbohydrate counting, but based on weight-dependent bolus is feasible but a carbohydrate-matching bolus provides better glucose control.

Clinical trial registry. – NCT01519102
© 2014 Elsevier Masson SAS. All rights reserved.

Keywords: Type 1 diabetes; Closed-loop delivery; Postprandial control; Glucagon; Artificial pancreas

1. Introduction

Single-hormone and dual-hormone closed-loop systems are emerging technologies to treat type 1 diabetes (T1D) [1]. Recent randomized trials showed that closed-loop systems improve overnight glycaemic control compared to conventional pump therapy [2,3]. However, closed-loop control of postprandial glucose remains a major challenge despite various strategies adopted to address prandial boluses [3–6]. Some systems deliver full boluses based on pre-programmed insulin-to-carbohydrate (I:C) ratios but these strategies may lead to an increased risk of postprandial hypoglycaemia and do not reduce the burden and difficulties related to carbohydrate counting [4]. Other systems favour complete omission of prandial boluses and rely exclusively on sensor detection of glucose excursions [6]. These approaches benefit from reduced risk of hypoglycaemia while alleviating the need for carbohydrate counting. However, this approach may lead to prolonged hyperglycaemia [5] due to lag times in glucose sensing [1] and rapid-acting insulin absorption [7].

An intermediate approach that has the potential to alleviate the risk for both hyperglycaemia and hypoglycaemia would be a
partial prandial bolus. The prandial bolus can be based on body weight, total daily insulin, or I:C ratio. Weinzimer et al. [5] have shown that partial boluses achieved better postprandial control compared to complete omission of prandial boluses.

No study has compared partial boluses with the current practice of carbohydrate-matching full boluses. Although the partial bolus benefits from a reduced risk of hypoglycaemia and relief from the need for carbohydrate counting, these benefits should be obtained without significant degradation in glycaemic control. In this study, we compared a weight-dependent partial bolus with an optimized carbohydrate-matching full bolus after a large breakfast meal while on dual-hormone closed-loop system. We hypothesized that a partial bolus would result in comparable glucose excursions to an optimized full bolus.

2. Design and methods

2.1. Study design

We conducted a randomized crossover study (Clinical trial registry: NCT01519102) to compare two prandial bolus strategies while on closed-loop system after a morning meal in adults with T1D. The two visits were separated by 3–30 days.

2.2. Sample size calculations

Power calculations were made based on equivalence test to be able to detect differences in both directions. In an equivalence test using two one-sided t-tests on data from a crossover design, twelve subjects achieved 80% power at a 5% significance level when the standard deviation of the paired differences is 3.3 mmol/L/h and the equivalence limits are −3.0 and 3.0 mmol/L/h.

2.3. Participants

We studied twelve adults (age 37.5 ± 9.4 years, BMI 25.6 ± 3.5 kg/m², A1c 7.9 ± 1.2%, total daily dose 0.6 ± 0.2 U/kg/day; mean ± SD) at the Institut de Recherches Cliniques de Montréal, Montréal, Canada. Participants were on pump therapy for at least 3 months. Subjects with HbA1c above 12% were excluded. Other exclusion criteria were applied as detailed in the clinical trial registry. All participants provided informed consent. The study was approved by the IRCM ethics committee.

2.4. Study procedures

After overnight fasting, participants ingested a standardized breakfast around 08 h 00. The meal was composed of banana, crackers, cereals, milk and cheddar cheese. The nutritional value was: 75 g carbohydrate, 18.5 g protein, 17.7 g fat and 523 calories.

On the partial bolus visits, boluses were calculated based on body weight (0.047 U/kg). We chose this ratio as a compromise considering that it should be used for all sizes of meals as well as patients over a wide range of body weights. A higher partial bolus might lead to better results in this study but would increase the risk of hypoglycaemia when used with smaller meals (e.g. 30 g CHO). Even in the presence of glucagon, overdosing of insulin might lead to hypoglycaemia [8,9].

On the full bolus visits, boluses were calculated using individualized I:C ratios. The breakfast I:C ratios were optimized over 3–10 days prior to the intervention with the help of a nutritionist.

During both visits, glucose levels were regulated using dual-hormone (insulin and glucagon) closed-loop delivery [3]. Insulin Aspart (Novorapid®, Novo-Nordisk, Mississauga, Canada) and recombinant glucagon (Glucagen®, Novo-Nordisk, Canada) were delivered using two subcutaneous infusion pumps (MiniMed Paradigm Veo®, Medtronic, Northridge, USA) according to recommendations at 10-min intervals by a dosing algorithm [3]. Closed-loop delivery started at the time of the breakfast and lasted for 5 h. Algorithm recommendations were based on CGM readings (Soft-sensor®, Medtronic, Northridge, USA) calibrated using a glucometer and inserted one to three days before the test. On the full bolus visits, the carbohydrate content of the meal was entered into the algorithm reflecting that a carbohydrate counting was done.

The dosing algorithm was based on a fuzzy-supervised model predictive controller combined with Kalman filtering and a set of heuristic rules. It utilized a compartmental model that consists of submodels for insulin and glucagon absorption kinetics, insulin and glucagon action, meal absorption kinetics, plasma glucose kinetics and interstitial glucose kinetics. Two two-compartment models were used to describe meal absorption and insulin bolus dynamics, and their parameters were updated online using the Kalman filter. The supervisory layer recommended intermittent glucagon delivery (mini-boluses) based on the heuristic rules that employed estimates of plasma glucose levels and their trends as provided by the Kalman filter. The algorithm was initialized using body weight, total daily insulin, and basal insulin profile. The maximum allowable insulin infusion rate was set to seven times the average basal rate. This safety constrain was set to prevent overdosing in situations that might jeopardize patient’s safety (e.g. sensor malfunction).

On the partial bolus visits, the algorithm was informed about the meals but not the quantity of the carbohydrate. On the full bolus visits, the algorithm was informed about the meals and the quantity of the carbohydrate.

Venous blood samples were taken at −15, 0, 10, 20, 30, 40, 60, 80, 100, 120, 140, 160, 180, 210, 240, 270 and 300 min after meal ingestion for the determination of plasma glucose using YSI12300 STAT Plus Analyser (Yellow Springs, Ohio, USA). Participants were discharged after withdrawing the last sample.

2.5. Statistical analysis

The primary endpoint was the incremental area under the curve of postprandial glucose levels. We used mixed effect model controlling for starting glucose levels and period effect. Ranked normal transformation was used to correct non-normality. Data are presented as median [IQR].

© 2019 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 28/03/2019 Il est interdit et illégal de diffuser ce document.
3. Results

Fig. 1 shows the plasma glucose profiles, insulin delivery, and the histogram of glucagon delivery. The weight-dependent bolus was lower than the carbohydrate-matching bolus (3.45 U [2.95–3.75] vs 8.30 U [7.50–11.50]; P < 0.001). Glucose levels before the meal ingestion were 7.5 mmol/L [7.2–8.8] and 7.1 mmol/L [6.4–8.4] (P = 0.01) on the full bolus and the partial bolus visits, respectively, and increased by 3.15 mmol/L [1.59–6.12] and 7.11 mmol/L [5.09–8.23] at the peak (P = 0.006). Plasma glucose returned to baseline levels 2 h after the full bolus whereas it decreased slowly to the pre-prandial levels within 5 h after the partial bolus. Incremental area under the curve was lower after the full bolus compared to the partial bolus (IAUC; 2.1 mmol/L/h [0.8–4.2] vs 8.3 mmol/L/h [6.5–11.4]; P < 0.001). The percentage of time above 10 mmol/L was also lower after the full bolus compared to the partial bolus (24% [6%–29%] vs 50% [25%–63%]; P < 0.001).

Basal insulin delivery over 300 min was doubled on the partial bolus visits compared to the full bolus visits (8.05 U [6.74–8.98] vs 3.90 U [3.05–6.81]; P < 0.01) and the maximum allowable insulin infusion rate was often reached at the early postprandial period. Despite this difference, the total insulin delivery remained higher on the full bolus visits (14.16 U [11.06–7.03] vs 11.70 U [9.81–13.16]; full vs partial; P = 0.03). Two hypoglycaemia events (<3.0 mmol/L) were observed on the full bolus visits compared to none in the partial bolus visits.

On the full bolus visits, the average number of glucagon boluses was 2.5 boluses compared to 0.9 boluses on the partial bolus visits. However, the size of the glucagon boluses (19 µg [11–22] vs 21 µg [19–23]; full vs partial; P = 0.3) and the total glucagon delivery (33 µg [26–58] vs 0 µg [0–40]; P = 0.12) did not differ between the two visits. Most of the glucagon boluses (87%) were delivered in the late postprandial period between 3 to 5 h after from meal ingestion.

4. Discussions

We tested whether a simplified weight-dependent bolus strategy during closed-loop operation results in an acceptable postprandial control compared to optimized carbohydrate-matching full bolus. With the full bolus, glucose excursions were significantly better compared to the simplified partial bolus.

We tested a large breakfast meal as breakfast is typically the most difficult meal to control. Breakfast is associated with an increased resistance of hepatic glucose production compared to other meals [10,11] and there is also evidence that postprandial glucagon concentration is higher after breakfast compared to lunch and dinner [10]. Our results should not be extrapolated for lunch and dinner meals.

The difference in the glucose area under the curve between the two interventions (i.e. the treatment effect) did not correlate with the partial bolus, total daily dose, or the difference in basal delivery (P = NS). However, a strong negative correlation (r = −0.9) was found between the difference in the glucose area under the curve between the two interventions and the partial bolus divided by the I:C ratio (i.e., the hypothetical amount of carbohydrate that matches the given partial bolus calculated using the I:C ratio). This suggests that an alternative bolus strategy proportional to I:C ratios (not necessary matching) might achieve better control compared to weight-dependent bolus. A strategy based on I:C ratios would also allow for:

- the ability to have different partial boluses at different times of the day;
- granting the patients the freedom to tune the aggressiveness of these partial boluses.

These are of special importance given the diurnal patterns and inter-individual variability in postprandial insulin requirements [10]. This strategy warrants further investigation.

Current insulin therapy typically involves carbohydrate counting. Accuracy of counting might improve glycaemic control and lower HbA1c levels [12–14] but it is a challenging task for many patients with an average error of 20% [14]. Closed-loop systems combined with partial prandial boluses might alleviate the need for carbohydrate counting. Our study suggests that weight-dependent prandial bolus is safe and feasible but not as effective as full bolus. Optimal strategies for partial boluses with closed-loop systems remain to be established.

Disclosure of interest

Rémi Rabasa-Lhoret is a consultant for AstraZeneca, Boehringer, Eli Lilly, Merck, Novo-Nordisk, Sanofi-Aventis and Takeda; he has received grants from AstraZeneca, Eli Lilly, Merck, Novo-Nordisk and Sanofi-Aventis; he has received speaking fees from AstraZeneca, Eli Lilly, Medtronic, Merck, Novo-Nordisk and Sanofi-Aventis. All other authors declare no competing financial interests.
Acknowledgments

Cherylene Pinaroc and Maryse Dallaire provided nursing support. Sonia Fortin provided dietary support. Hortensia Mircescu helped with recruitment of participants. We thank study participants for their participation.

Author contributions: AH and RRL coordinated and supervised the study. AH, RRL, LL, and BB co-designed the study. DF, ASY, AH, CD, ASB, RRL, and LL conducted the study. AH designed the dosing algorithm. VM, DF, AH, DX, VC, and ASY carried out the data analysis including the statistical analyses. All authors contributed to the interpretation of the results and the writing and critical review of the manuscript. AH had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript.

Funding/support: This study was supported by the J.-A. De Sève Chair held by Rémi Rabasa-Lhoret. Medtronic supplied the pumps and sensors. Medtronic read the manuscript before submission. No sponsor had any role in the study design, data collection, data interpretation, or writing the report.

Appendix A. Supplementary data

Supplementary data (French abstract) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.12.001.

References