Faster Compared With Standard Insulin Aspart During Day-and-Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial

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OBJECTIVE

We evaluated the safety and efficacy of day-and-night fully closed-loop insulin therapy using faster (Faster-CL) compared with standard insulin aspart (Standard-CL) in young adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

In a double-blind, randomized, crossover trial, 20 participants with type 1 diabetes on insulin pump therapy (11 females, aged 21.3 ± 2.3 years, HbA_{1c} 7.5 ± 0.5% [58.5 ± 5.5 mmol/mol]) underwent two 27-h inpatient periods with unannounced afternoon moderate-vigorous exercise and unannounced/uncovered meals. We compared Faster-CL and Standard-CL in random order. During both interventions, the fuzzy-logic control algorithm DreaMed GlucoSitter was used. Glucose sensor data were analyzed by intention-to-treat principle with the difference (between Faster-CL and Standard-CL) in proportion of time in range 70–180 mg/dL (TIR) over 27 h as the primary end point.

RESULTS

The proportion of TIR was similar for both arms: 53.3% (83% overnight) in Faster-CL and 57.9% (88% overnight) in Standard-CL ($P = 0.170$). The proportion of time in hypoglycemia <70 mg/dL was 0.0% for both groups. Baseline-adjusted interstitial prandial glucose increments 1 h after meals were greater in Faster-CL compared with Standard-CL ($P = 0.017$). The gaps between measured plasma insulin and estimated insulin-on-board levels at the beginning, at the end, and 2 h after the exercise were smaller in the Standard-CL group ($P = 0.029$, $P = 0.003$, and $P = 0.004$, respectively). No severe adverse events occurred.

CONCLUSIONS

Fully closed-loop insulin delivery using either faster or standard insulin aspart was safe and efficient in achieving near-normal glucose concentrations outside postprandial periods. The closed-loop algorithm was better adjusted to the standard insulin aspart.

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Despite improvements in insulin therapy, only a minority of individuals with type 1 diabetes, especially among adolescents and young adults, meet recommended glycemic targets (1). In addition to this, attainment of optimal glucose control is complicated by the variability in insulin requirements from one day or night to another and might be difficult to overcome with conventional therapeutic tools (2).

Hybrid closed-loop insulin therapy, characterized by automated insulin delivery apart from prandial boluses, is becoming a part of unsupervised routine clinical care for people with type 1 diabetes (3–8). While improvements seen in glycemic control with these state-of-the-art devices are reassuring, users of these systems still experience the everyday burden of feed-forward actions, such as carbohydrate counting or exercise announcement, and still require premeal insulin bolusing to prevent postprandial glycemic excursion (9–12). To fully close the loop, these systems might benefit from faster insulin action and clearance rates, which have been recently reported with novel faster insulin analogs, such as faster insulin aspart (13–15). A recent large trial including 472 adults with type 1 diabetes on insulin pump therapy demonstrated noninferiority of faster compared with standard insulin aspart in terms of change from baseline in HbA_{1c} after 16 weeks, while it improved postprandial glycemic profiles (16); however, to date there are no data on faster insulin use with closed-loop devices.

In the present double-blind randomized crossover trial, we hypothesized that the insulin therapy with fully closed-loop using faster insulin aspart improves glycemic control without an increased risk of hypoglycemia compared with standard insulin aspart in young adults with type 1 diabetes. Fully closed-loop was applied over a 27-h period including 40 min of moderate-vigorous exercise and unannounced/uncovered meals. We anticipated that faster insulin action of faster insulin formulation after meals and also faster insulin clearance during exercise could provide important benefits in fully closed-loop insulin therapy.

RESEARCH DESIGN AND METHODS

Trial Design

This double-blind, two-period, crossover, randomized (1:1) controlled trial evaluated safety and efficacy of fully automated closed-loop insulin delivery using faster insulin aspart (Faster-CL) compared with standard insulin aspart (Standard-CL) at the clinical research facility. The study was performed in compliance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The Slovenian National Medical Ethics Committee and the national competent authority approved the protocol. The study is listed on ClinicalTrials.gov under registration number NCT03212950.

Study participants were identified from the Slovenian National Diabetes Registry (17) and invited to participate through outpatient clinic, National Diabetes Society webpage, and social media. Main inclusion criteria were aged 18–25 years (inclusive), clinical diagnosis of type 1 diabetes for at least 1 year, at least 3 months of current use of an insulin pump, HbA_{1c} <9.0% (75 mmol/mol), BMI within normal range for age and sex (±2 SD), and the absence of other medical conditions (apart from well-controlled hypothyroidism or celiac disease). Exclusion criteria included concomitant diseases that could influence metabolic control or compromise a participant's safety and history of one or more episodes of diabetic ketoacidosis requiring hospitalization within 1 month prior to the screening. All participants provided written informed consent before trial initiation.

Randomization and Masking

The order of the interventions was random according to a computer-generated allocation sequence with permuted blocks of four. The treatment allocation was blinded to both participants and investigators.

Procedures

This study adopted similar procedures as the previous study evaluating closed-loop glucose control during and after physical activity (18). The screening and the baseline visits included obtainment of informed consent, physical examination, confirmation of inclusion/exclusion criteria, a lung function test, resting electrocardiogram, and a cycle ergometer exercise test to determine VO_{2max} of study participants (Supplementary Data and Supplementary Fig. 1). Participants were trained in the use of the glucose sensor before entering a run-in period. We rescheduled the inpatient visit if a participant had a hypoglycemic event (blood glucose level <2.8 mmol/L) on the day before or on the day of intervention. Participants were instructed to insert the sensor on the day before their inpatient visit. Upon admission, the sensor/pump insertion set was checked, a backup sensor was inserted, and the insulin set was replaced when in doubt (Supplementary Data).

After screening/baseline visit and at least 1-week run-in period using standard insulin aspart with continuous glucose monitoring (CGM) use, during which the CGM data were derived for the initial personalized closed-loop system settings, participants attended the clinical research facility in pairs on two occasions for a 27-h assessment 1 week apart, with identical study protocol performed on both occasions: participants first underwent Faster-CL or Standard-CL.

The whole observational period was defined as the time between 1500 h on day 1 and 1800 h the next day, overnight period from 2300 h to 0700 h, and exercise period from the beginning of the exercise protocol to 2 h after the end of exercise. For inpatient visits, participants were admitted at ~1200 h. Before lunch at 1300 h (covered with a manual bolus), a masked insulin cartridge was inserted into a study pump. At 1500 h, fully automated closed-loop was initialized. During the hospitalization, all participants received standardized meals containing ~1 g of carbohydrate/kg of body mass for the main meals and about half of this amount for the snack and consumed identical meals during each admission. The meal contained ~50% carbohydrates, 20% proteins, and 30% fat (<10% saturated) (detailed meal contents are given in Supplementary Table 2). All of the meals during the observational period were uncovered and unannounced to the closed-loop control algorithm and were scheduled at ~1500 h (snack), 1 h after the end of exercise protocol between 1900 h and 2000 h (dinner), 0800 h (breakfast), and 1200 h on the following day (lunch).

Between 1630 and 1930 h of the first day, participants performed 40 min of moderate-vigorous exercise protocol on a cycle ergometer, a combination of moderate physical activity at 55% VO_{2max} with incorporated five 20-s high-intensity sprints at 80% VO_{2max}. The load on the cycle ergometer was adjusted in real time to maintain predetermined VO_{2max} values. Throughout the exercise, a continuous electrocardiogram was

recorded, and inhaled O_2 and exhaled CO_2 were measured.

Closed-Loop, Devices, and Assays

The closed-loop algorithm DreaMed GlucoSitter (DreaMed Diabetes, Petah Tikva, Israel) uses a modified vendor-supplied communication module application programming interface to retrieve glucose/insulin data from the MiniMed Paradigm Veo pump and set insulin treatment according to a fuzzy-logic–based algorithm (19). The software version 01.05.02 operated on a commercial laptop/tablet computer (ThinkPad T450s; Lenovo, Beijing, China), which had a physical connection to a communication dongle (provided by the manufacturer of the insulin pump). The closed-loop software was implemented using the MATLAB platform (MathWorks, Natick, MA). The exercise protocol was performed on a cycle ergometer (PowerCube LF8.5G with Schiller software; Ganshorn, Niederlauer, Germany). The closed-loop system requires an individual-specific log file for its operation. This log file includes the treatment settings for an individual that are downloaded based on run-in period data: an individual's sensitivity factor, carbohydrate factor, and basal insulin settings. Once this premade log file resides inside the closed-loop device (dedicated laptop in this case) for each individual, the physician can launch the application, check and approve the settings, and insert the pump serial number. From there, the system automatically connects to the pump and sensor and controls them. To reach the final dosing recommendation, the system takes into consideration the recommendation of the control-to-range module, the predefined glucose target level, insulin dosing regimen history, and safety constraints related to the insulin pharmacodynamics. Additionally, the system uses a detector in order to identify special glucose dynamics indicative of a sign of events that require special treatment, such as meals, and adjusts the dosing accordingly (Supplementary Data) (19).

All participants used an identical insulin pump (Paradigm Veo; Medtronic Diabetes, Northridge, CA) with low-glucose threshold suspend disabled, a subcutaneous glucose sensor (Enlite II sensor with MiniLink REAL-Time transmitter; Medtronic Diabetes), and a glucose meter (Contour Link meter; Ascensia Diabetes Care, Basel, Switzerland).

The HbA_{1c} level was determined locally by an immunochemical method using the Siemens DCA Vantage Analyzer (Siemens Healthcare, Erlangen, Germany). Venous blood samples were collected for the measurement of insulin concentrations at the beginning and end of exercise protocol and 2 h after it (i.e., 1 h after the dinner), anticipating that the controller will be decreasing insulin delivery from the beginning to the end of exercise protocol, while a significant increase will follow up to 2 h postexercise (i.e., 1 h after dinner). Capillary blood glucose was checked at every meal, at the beginning of each exercise session, every 15 min during the exercise, and every 30 min for 2 h after the exercise. Free (unbound) serum insulin concentration was assessed by polyethylene glycol precipitation using an insulin aspart-specific (both standard or faster) ELISA at a lower limit of quantification of 10 pmol/L (Novo Nordisk, Gentofte, Denmark) (20).

Study End Points

The primary end point was the between-group difference for time in range 70–180 mg/dL (TIR) during the 27-h study period. Secondary end points included mean sensor glucose concentrations; time spent at glucose levels $<$60 mg/dL, $<$70 mg/dL, and $>$250 mg/dL; postprandial glucose profiles; and the amount of insulin delivered (21–24). End points were calculated over the 27-h period and a subset of end points, to limit multiple comparisons, during the overnight (2300–0700 h) and exercise (beginning of the afternoon exercise to 2 h after the end of the 40-min exercise protocol) periods.

The safety analysis assessed the rate of severe hypoglycemia (defined as severe cognitive impairment requiring external assistance, as per International Society for Pediatric and Adolescent Diabetes guidelines) (25), diabetic ketoacidosis (glucose level $>$250 mg/dL and associated with low serum bicarbonate [$<$15 mmol/L] or low pH [$<$7.3] and either ketonemia [β-hydroxybutyrate level $>$3 mmol/L] or ketonuria requiring intravenous treatment), and other adverse or serious adverse events. All sensor glucose-detected hypoglycemic ($<$60 mg/dL) events were additionally confirmed with self-monitoring of blood glucose. As per standard in-hospital procedures, 16 g rescue carbohydrates (four glucose tablets) were administered at blood glucose value $<$60 mg/dL in participants experiencing symptoms of hypoglycemia and at $<$50 mg/dL in all participants regardless of symptoms.

Statistical Analysis

All prespecified analyses were carried out on an intention-to-treat basis. We analyzed end points from participants with at least 67% of sensor data in one study period similar to previously published studies (18,19,26,27). Safety analysis included data from all randomized participants. All end points were analyzed per arm, while for each end point, each participant provided just one value as an average of all study periods. Comparisons between Faster-CL and Standard-CL for glycemic measures and insulin concentrations were performed using a paired-sample *t* test with two-tailed distribution when the normality assumption holds according to Shapiro-Wilk test or using the paired nonparametric Wilcoxon signed-rank test. Two methods were used to evaluate the amount of insulin in units each participant had at the time of the beginning and the end of exercise and 2 h after it (Supplementary Data). First, the measured insulin concentration values were converted from picomoles per liter units to units of insulin in the participant's body or insulin-on-board (IOBc) based on insulin concentration and estimated total blood volume (28). Secondly, the estimated insulin-on-board amount (IOBe) was calculated from the insulin pump data based on basal and bolus insulin amounts delivered. For this prediction, a 3-h insulin activity model was used, as this was the preset in the insulin pump. Finally, we calculated the gap (IOBc − IOBe) between the measured and estimated IOB for each participant. Sensor-based prandial glucose (PG) levels at meal time and at 15-min intervals after meals were used. All meals' $\Delta PG_{0–1h}$ and $\Delta PG_{0–2h}$ were calculated using median PG level from breakfast, lunch, and dinner at each time point. $\Delta PG_{0–1h}$ was calculated as the area under the curve $(AUC)_{PG,\ 0–1h}/1\ h - PG_{meal}$, in which $AUC_{PG,\ 0–1h}$ was the area under the PG concentration-time profile between 0 and 1 h and PG_{meal} was the PG concentration at mealtime. For $\Delta PG_{0–2h}$, the PG concentration time profile between 0 and 2 h was used.

All AUC values were calculated using the trapezoidal technique. All ΔPG_{0-1h} values were evaluated with a linear mixed model, with treatment and time difference between meal and bolus as fixed factors and subject as a random effect. *P* values of the model were calculated using two-way ANOVA. We have further investigated the influence of time difference between meal and bolus on ΔPGs in each group separately with linear regression. A 5% significance level was used to declare statistical significance.

Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Between July and October 2017, 23 eligible young adults with type 1 diabetes volunteered to participate, and 20 (11 female) were randomized, completed the study, and provided data for the analysis (study flow diagram is presented in Supplementary Fig. 1).

The mean ± SD age was 21.3 ± 2.3 years, duration of diabetes 13.0 ± 4.2 years, duration of pump therapy 10.8 ± 3.6 years, and baseline HbA_{1c} was 7.5 ± 0.5% (58 ± 5.5 mmol/mol). Participants in this study were of average physical fitness: mean BMI was 22.0 ± 2.0 kg/m^2 and VO_{2max} 41.4 ± 9.7 mL kg^{-1} min^{-1} (36.0 ± 4.9 mL kg^{-1} min^{-1} for girls and 47.9 ± 10.4 mL kg^{-1} min^{-1} for boys (Supplementary Table 1).

Glucose Control and Insulin Therapy

Primary and secondary end points are summarized in Table 1. Sensor data were available for 96.0% in Faster-CL and 95.1% in Standard-CL. The median (interquartile range [IQR]) proportion of TIR for the 27-h observational period was 53.8% (50.3, 60.4) for the Faster-CL and 58.6% (51.9, 62.3) for the Standard-CL group ($P = 0.167$). There was no difference between the two groups in TIR for the overnight period (83.9% in Faster-CL compared with 88.0% in Standard-CL; $P = 0.227$) or for the exercise period (79.2% in Faster-CL compared with 83.3% in Standard-CL; $P = 0.227$). Time in hypoglycemia <60 mg/dL and <70 mg/dL was 0.00% for both groups for the whole observational period, for the overnight, and for the exercise period (Fig. 1). Across all study visits, participants received rescue carbohydrates on two occasions in the Standard-CL group and on one occasion in the Faster-CL group; all three events were during the exercise period. There was no difference between the two groups in mean glucose, SD of mean glucose, or time in hyperglycemia >250 mg/dL. Amount of insulin delivered was similar in both groups: 37.9 units/day in Faster-CL and 36.6 units/day in Standard-CL ($P = 0.204$).

Considering all three meals together, baseline-adjusted prandial interstitial glucose increments 1 h after the meal were greater in Faster-CL (30.9 mg/dL [25.8, 38.9]) compared with Standard-CL (21.7 mg/dL [7.3, 30.6]) ($P = 0.017$), while there was no difference between the two groups for each meal separately (Table 2 and Fig. 2).

The observed median time of delivered prandial bolus was 38.4 min (32.7, 55.8) after meals in the Faster-CL and 30.1 min (26.9, 54.6) in the Standard-CL arm ($P = 0.388$). Timing of the automated prandial bolus had a significant impact on the postprandial glycemic profiles 1 h after the meal only in the Faster-CL ($P = 0.011$) but not in the Standard-CL arm ($P = 0.496$) (Fig. 2). There was no difference in measured or estimated IOB between the two study arms at the beginning of exercise, at the end, and 2 h after the exercise protocol. However, there was a significant difference in IOBc − IOBe gap between the two study arms ($P = 0.029$ at the beginning of the exercise, $P = 0.003$ at the end of the exercise, and $P = 0.004$ 2 h after the exercise), with smaller differences for the Standard-CL group (Supplementary Table 3).

Adverse Events

No diabetic ketoacidosis, severe hypoglycemia, or other serious adverse events occurred during the study period. One participant in the Standard-CL group experienced ketonemia 1.1 mmol/L, which was associated with antecedent set occlusion and hyperglycemia that resolved within 2 h after the infusion set was changed. Data were included into the analysis.

CONCLUSIONS

To our knowledge, our trial is the first randomized controlled trial to investigate faster insulin delivery with day-and-night closed-loop insulin therapy. No benefits associated with the use of faster insulin formulation were observed.

The present clinical trial extends previous observations of improved glycemic control in children and adolescents with a similar study protocol using hybrid closed-loop insulin delivery with the same fuzzy-logic control algorithm (18). For people living with type 1 diabetes, everyday decision making, including meal carbohydrate content estimation, insulin dose calculation, exercise-related insulin adjustments, and also unpredictable glycemic responses to these events, represents an important burden. The majority of present artificial pancreas systems require manual insulin bolus for meals to deliver insulin in so-called hybrid closed-loop (4). Especially for those with suboptimal metabolic control due to frequent missed boluses (9), fully automated insulin delivery could provide a benefit.

In this study, fully automated insulin therapy effectively limited hypoglycemia. On only three occasions, participants required rescue carbohydrates (twice in the Standard-CL and once in the Faster-CL group) over 40 visits; all three occasions were during or directly after the afternoon exercise. Sensor glucose values were sustained close to normal range, especially during the night. The primary end point, superiority of faster compared with standard insulin aspart in TIR over the whole observation period, was not met. In contrast to overnight glucose control with TIR of 84% with Faster-CL and 88% with standard-CL, over the 27-h period TIR proportions were lower due to postprandial glycemic excursions (54% in the Faster-CL and 59% in the Standard-CL group), which poses an important limitation of fully closed-loop compared with hybrid closed-loop insulin therapy in achieving recommended TIR of 70% for the general population with type 1 diabetes (3,7,24). One possible explanation could be that due to relatively common sensor underreadings and lower sensor accuracy during the postprandial period, the system was not able to respond by delivering a sufficient amount of insulin in time to prevent postprandial hyperglycemia with either of the insulin formulations (29–32).

In the past few years, there have been few trials evaluating fully closed-loop

Table 1—Glycemic measures

	Faster-CL (N = 20)	Standard-CL (N = 20)	P value
Whole observational period (1500–1800 h on the following day)			
Time in target 70–180 mg/dL (%)	53.8 (50.3, 60.4)	58.6 (51.9, 62.3)	0.167
Time in hypoglycemia <60 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.779
Time in hypoglycemia <70 mg/dL (%)	0.0 (0.0, 1.0)	0.0 (0.0, 1.2)	0.721
Time in hyperglycemia >250 mg/dL (%)	6.8 (1.0, 13.8)	8.7 (2.4, 17.5)	0.948
Mean glucose (mg/dL)	172.9 (162.6, 190.0)	174.0 (161.4, 182.5)	0.218
SD of mean glucose (mg/dL)	50.2 (43.8, 56.9)	53.1 (44.9, 65.5)	0.179
TDD (units/day)	37.9 (31.9, 45.1)	36.6 (28.3, 44.3)	0.204
Sensor availability (%)	96.0 (93.9, 97.3)	95.1 (91.4, 96.5)	0.472
Overnight period (2300–0700 h)			
Time in target 70–180 mg/dL (%)	83.9 (74.0, 91.7)	88.0 (81.0, 100)	0.227
Time in hypoglycemia <60 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.674
Time in hypoglycemia <70 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.600
Time in hyperglycemia >250 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.465
Mean glucose (mg/dL)	137.9 (127.0, 155.7)	133.3 (124.0, 143.6)	0.117
SD of mean glucose (mg/dL)	30.1 (22.1, 35.5)	33.5 (24.8, 35.9)	0.737
TDD (units)	8.4 (7.2, 9.8)	7.8 (6.3, 9.0)	0.079
Exercise period (Start–2 h after exercise)			
Time in target 70–180 mg/dL (%)	79.2 (62.5, 100)	83.3 (52.1, 100)	0.485
Time in hypoglycemia <60 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.180
Time in hypoglycemia <70 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.273
Time in hyperglycemia >250 mg/dL (%)	0.0 (0.0, 0.0)	0.0 (0.0, 5.2)	0.012
Mean glucose (mg/dL)	137.7 (122.0, 163.6)	148.3 (129.0, 161.2)	0.167
SD of mean glucose (mg/dL)	27.9 (25.8, 34.9)	33.6 (18.3, 61.0)	0.179

Data are median (IQR). TDD, total daily dose.

insulin delivery (10–12,33–35). Forlenza et al. (10) recently reported results using multiple-model probabilistic predictive control fully closed-loop insulin delivery, challenged by unannounced meals and announced exercise in a supervised hotel setting. While TIR over 24 h in this less supervised environment was modestly better (63.6%), it was achieved with more time spent in hypoglycemia <70 mg/dL (3.0%) and lower TIR overnight (77.9%). Contrasting both dual-hormone (insulin and glucagon) to single-hormone (insulin only) hybrid closed-loop systems during and after physical activity, Castle et al. (36) demonstrated reduced risk of hypoglycemia <70 mg/dL (3.4% for the exercise period and 1.3% for the entire study in dual-hormone compared with 8.3% and 2.8% in single-hormone closed-loop); however, there was also a significant increase in time spent in hyperglycemia >250 mg/dL with the dual-hormone system (6.0% compared with 3.3% with the single-hormone). With a higher proportion of time in hypoglycemia, the dual-hormone system achieved similar TIR for the exercise period (84.3%) compared with our results (79.2% in Faster-CL and 83.3% in Standard-CL).

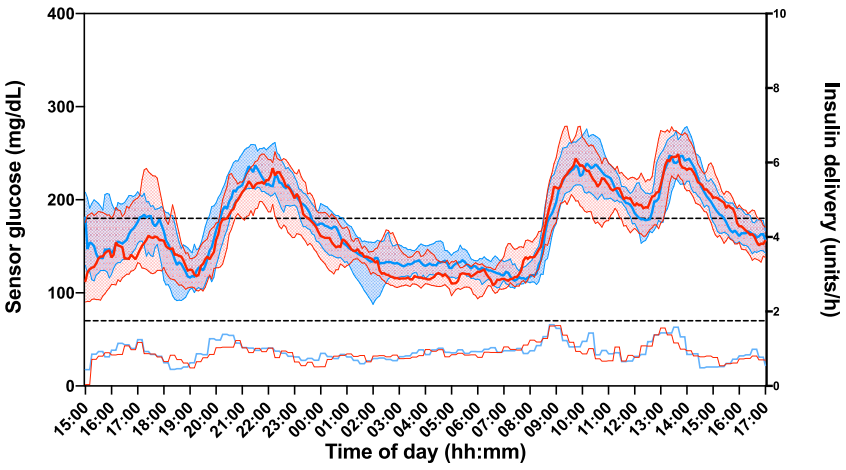

Figure 1—Sensor glucose and insulin delivery. Shown are the median (IQR) sensor glucose levels during the day-and-night Faster-CL (blue) and Standard-CL (red). Dashed horizontal lines indicate the target glucose range between 70 and 180 mg/dL.

Superiority of faster over standard insulin aspart in the postprandial glucose profiles was not confirmed, with a small but statistically significant difference in favor of standard insulin aspart for all three meals combined. Previous reports showed an improvement in postprandial glucose profiles of faster compared with standard insulin aspart (13,15,16). However, previous studies used optimized manual insulin bolus based on self-monitoring of blood glucose measurements before each meal, without dependency on CGM to detect postprandial glucose excursion. We observed a significant impact of delayed prandial bolus on postprandial glycemic control only in the Faster-CL arm: a higher postprandial peak and faster decline of glucose concentration after it. One possible explanation for this could be that the system was not optimized for the faster insulin action and for faster clearance in the Faster-CL treatment arm. The system settings were derived (and patient log

Table 2—Mean change in PG concentration and the estimated effect of time difference between meal and prandial bolus

	Mean change in interstitial glucose concentration (mg/dL), treatment arm			Estimate (95% CI) effect of time difference on mean change in interstitial glucose concentration (mg/dL × min)			
	Faster-CL	Standard-CL	*P* value	Faster-CL	*P* value	Standard-CL	*P* value
All meals $\Delta PG_{0–1h}$	30.9 (25.8, 38.9)	21.7 (7.3, 30.6)	0.017	−0.57 (−0.99, −0.15)	0.011	−0.14 (−0.56, 0.28)	0.496
All meals $\Delta PG_{0–2h}$	258.4 (240.6, 295.1)	234.8 (218.6, 296.1)	0.280	−1.17 (−2.3, 0.01)	0.052	0.17 (−0.94, 1.29)	0.746
Breakfast $\Delta PG_{0–1h}$	37.0 (17.4, 46.6)	22.7 (18.5, 36.0)	0.303	0.07 (−0.20, 0.35)	0.583	−0.01 (−0.42, 0.39)	0.944
Breakfast $\Delta PG_{0–2h}$	254.2 (222.6, 309.9)	237.7 (215.8, 275.0)	0.405	0.21 (−0.52, 0.95)	0.552	−0.28 (−1.68, 1.11)	0.670
Lunch $\Delta PG_{0–1h}$	−3.9 (−12.5, 7.9)	6.3 (−4.6, 21.1)	0.065	−0.16 (−0.51, 0.18)	0.325	−0.23 (−0.42, −0.04)	0.020
Lunch $\Delta PG_{0–2h}$	250.9 (194.1, 267.2)	264.2 (200.2, 280.3)	0.880	−0.55 (−1.43, 0.33)	0.209	−0.97 (−1.36, −0.57)	<0.001
Dinner $\Delta PG_{0–1h}$	33.1 (25.0, 42.4)	31.3 (17.5, 39.0)	0.382	−0.52 (−0.85, −0.18)	0.004	−0.15 (−0.58, 0.27)	0.445
Dinner $\Delta PG_{0–2h}$	250.5 (225.4, 291.9)	241.4 (217.1, 271.8)	0.603	−1.54 (−2.73, −0.36)	0.014	−0.22 (−1.22, 0.77)	0.639

The left side of the table shows the influence of treatment arm on a mean change in prandial interstitial glucose concentration. Data are median (IQR). The right side represents the univariate influence of 1 min of the time difference between meals and automated bolus on mean changes in prandial interstitial glucose concentration. Estimates (95% CI) and *P* values represented were derived from linear regression calculated for each group separately. For example, for the Faster-CL treatment arm in each additional minute between a meal and an automated bolus delivered, $\Delta PG_{0–1h}$ calculated for all meals together dropped 0.57 mg/dL. ΔPG, baseline-adjusted interstitial PG increment.

file created) from the run-in period based on standard insulin aspart only, and due to the double-blind design, the closed-loop system settings were not optimized for each insulin formulation separately. We observed a significant difference in the gap between the IOBc and IOBe between treatment arms, suggesting that different insulin pharmacokinetics of faster insulin aspart and insulin aspart should have been considered. We hypothesized that due to distinct pharmacokinetic and pharmacodynamic properties of the faster insulin aspart, the closed-loop algorithm should be tuned specifically for this faster insulin formulation in order to observe expected benefits; this, however, should be interpreted with caution and validated in a separate trial.

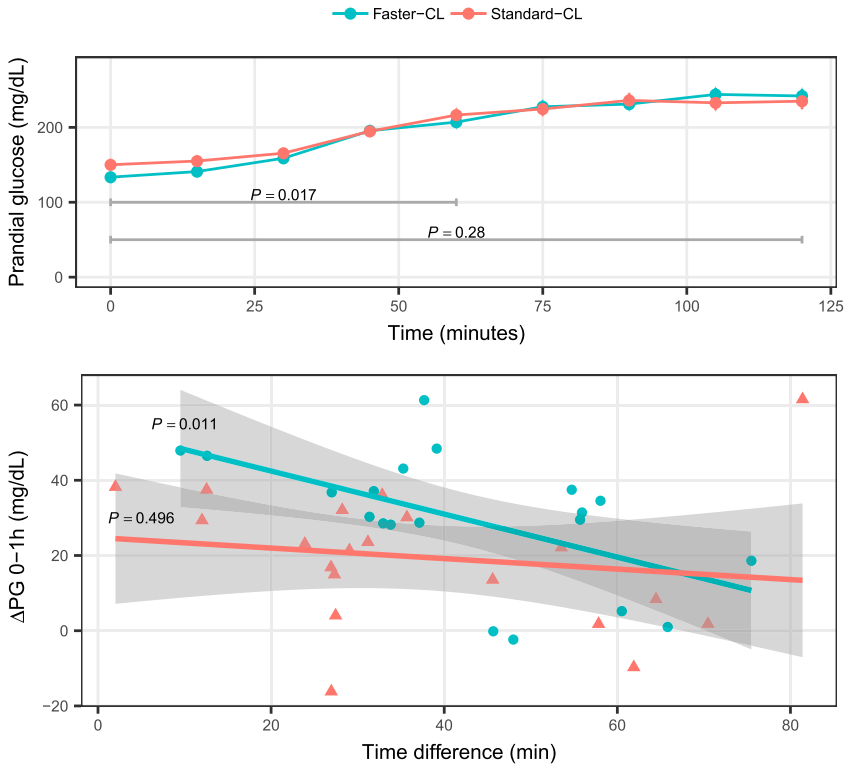

Figure 2—Shown are the median (IQR) sensor postprandial glucose levels (top) 1 and 2 h after meals during Faster-CL (blue) and Standard-CL (red). Bottom shows the effect of the gap between meals and automated prandial bolus on the baseline-adjusted interstitial PG increment after 1 h with a significant correlation between higher $\Delta PG_{0–1h}$ and the shorter time difference between meals and automated bolus only in the Faster-CL treatment arm (blue).

The strengths of our study include the double-blind crossover randomized design and the use of faster insulin over day-and-night fully closed-loop insulin therapy. One limitation of the present clinical trial was its short duration that did not allow the self-learning algorithm adjustments of the control parameters according to different insulin formulations' properties, and the system was not optimized for each insulin formulation through an insulin-specific run-in period because of the double-blind study design. The generalizability of our observations to the broader population of people with type 1 diabetes might be challenging due to possible selection bias, as study participants were experienced and highly motivated pump users within a tight age range, willing to complete the study protocol with intensive physical activity and frequent venous and capillary blood sampling. The clinical trial was not designed for calculating standard pharmacodynamic metrics, was conducted in a supervised setting, and was closely monitored 24 h/day, 7 days a week by research staff.

In conclusion, the current study demonstrated that fully closed-loop insulin delivery with faster insulin aspart was as safe and effective as, but not superior to, standard insulin aspart when using the same algorithm settings. Our observations indicate that the difference in insulin pharmacodynamics should be taken into account when optimizing insulin delivery settings in order to allow for

potential additional benefits from the faster insulin formulations. Larger and longer free-living studies using fully or hybrid closed-loop insulin therapy optimized for faster insulin analog formulations are necessary.

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Duality of Interest. N.B. received honoraria for participation on the speakers' bureau of Medtronic and Roche. N.B., R.N., O.K., T.D., M.P., and T.Ba. own DreaMed Diabetes stocks. R.N. received honoraria for participation in the speakers' bureau of Novo Nordisk, Pfizer, and Sanofi. E.A. and I.M. are employees of DreaMed Diabetes. O.K. received honoraria for being on the advisory board of Novo Nordisk as well as speaker honoraria from Eli Lilly and Company and Sanofi. T.Bi. received speaker honoraria from Medtronic, Ypsomed, Roche, Dexcom, and AstraZeneca. T.D. received speaker honoraria and research support from and has consulted for Abbott Laboratories, AstraZeneca, Bayer, Becton Dickinson, Boehringer Ingelheim, Dexcom, Eli Lilly and Company, Medtronic, Novo Nordisk, Roche, Sanofi, and Ypsomed. M.P. is a member of the advisory board of AstraZeneca, Sanofi, Medtronic, Eli Lilly and Company, Novo Nordisk, and Insulet Corporation and is a consultant to RSP Systems A/S and Qulab Inc.; his institute received research support from Medtronic, Novo Nordisk, Eli Lilly and Company, Dexcom, Sanofi, Insulet Corporation, OPKO Health, Inc., DreaMed Diabetes, Bristol-Myers Squibb, and Merck. M.P. has been paid honorarium from Pfizer, is a stock/shareholder of NG Solutions and Nutriteen Professionals, and reports two patent applications. T.Ba. served on the advisory boards of Novo Nordisk, Sanofi, Eli Lilly and Company, Boehringer Ingelheim, Medtronic, and Bayer HealthCare Pharmaceuticals, and his institution received research grant support, with receipt of travel and accommodation expenses in some cases, from Abbott Laboratories, Medtronic, Novo Nordisk, GluSense, Sanofi, Sandoz, and Diamyd Medical. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.D., C.P., G.Y.M., N.B., B.J.B., and I.M. collected data. K.D., N.B., D.L., R.N., E.A., I.M., O.K., T.Bi., T.D., M.P., and T.Ba. contributed to the study concept and design. The manuscript was drafted by K.D. and T.Ba., reviewed by K.D., C.P., G.Y.M., B.J.B., D.L., R.N., E.A., O.K., T.Bi, T.D., M.P., and T.Ba., and edited by K.D. and T.Ba. All authors participated in data analysis and interpretation and approved the final version of the manuscript. R.N., T.D., M.P., and T.Ba. supervised the study. T.Ba. 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 the data and the accuracy of the data analysis.

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