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Hybrid closed-loop with faster insulin aspart compared with standard insulin aspart in very young children with type 1 diabetes: A double-blind, multicenter, randomized, crossover study

Running title: Closed-loop using Fiasp in very young children

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ABSTRACT

We evaluated the use of hybrid closed-loop (HCL) insulin delivery with faster insulin aspart (Fiasp) in very young children with type 1 diabetes (T1D). In a double-blind, multicenter, randomized, crossover study, children aged 2-6 years with T1D underwent two 8-week periods of HCL using CamAPS FX with Fiasp and standard insulin aspart (IAsp), in random order. Primary endpoint was between-treatment difference in time in target range 3.9-10.0mmol/L. We randomized 25 participants: mean(±SD) age 5.1±1.3 years, baseline HbA1c 55±9mmol/mol. Time in range was not significantly different between interventions (64±9% vs 65±9% for HCL with Fiasp vs IAsp; mean difference -0.33% [95% CI -2.13, 1.47; p=0.71]). There was no significant difference in time with glucose <3.9mmol/L. No post-randomization severe hypoglycemia or DKA events occurred. Use of Fiasp with CamAPS FX hybrid closed-loop demonstrated no significant difference in glycemic outcomes compared with IAsp in very young children with T1D. Clinical trials registration: NCT04759144.

Introduction

Hybrid closed-loop therapy has been shown to improve glycemic control and quality of life in very young children with type 1 diabetes compared to standard therapies, [1-3] but some challenges remain due to the high glycemic variability caused by variable insulin needs and unpredictable eating and activity patterns in this age-group. [4,5] Ultra-rapid acting insulin 'Fiasp' has faster onset and offset than currently used rapid-acting insulins, and has been shown to improve HbA1c compared to mealtime insulin aspart given by injection, [6] but performance of ultra-rapid insulins with hybrid closed-loop therapy has not been assessed in very young children. The adaptive CamAPS FX hybrid closed-loop algorithm automatically and continuously modifies active insulin time, enabling it to accommodate a variety of insulin action profiles. We aimed to evaluate whether using Fiasp with the CamAPS FX hybrid closed-loop system could improve glucose control compared to CamAPS FX HCL system with standard rapid-acting insulin in this vulnerable and challenging population.

Research Design and Methods

Study Participants

Key inclusion criteria were age 2-6 years, type 1 diabetes for ≥6 months, insulin pump therapy for ≥3 months, and screening HbA1c ≤11% (97mmol/mol). Key exclusion criteria included use of diluted insulin, and concomitant disease affecting metabolic control (Table S1, Supplementary Appendix).

Eligible children were recruited from diabetes clinics at Addenbrooke's Hospital (Cambridge, UK) including three local Patient Identification Centers, and Alder Hey Children's Hospital (Liverpool, UK).

Study Oversight

Prior to study commencement, approval was received from an independent research ethics committee in the UK. All parents/guardians gave written informed consent. Safety aspects were overseen by an independent data safety monitoring board. Trial registration NCT04759144.

Study Design and Procedures

The study adopted a double-blind, multicenter, randomized, crossover design comparing 8-week use of hybrid closed-loop insulin delivery using faster insulin aspart (Fiasp; Novo Nordisk, Bagsvaerd, Denmark) followed by 8-week use of hybrid closed-loop using standard insulin aspart (Novo Nordisk), in random order. A 2-4 week run-in period preceded randomization, during which participants used the study hybrid closed-loop system with their pre-study insulin.

At enrolment, blood samples were taken for local analysis of glycated hemoglobin, using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)-aligned method and following NGSP standards. At the start of run-in, participants received training on the study insulin pump, glucose sensor, and hybrid closed-loop system.

Participants were randomly assigned to receive either 8 weeks of hybrid closed-loop with standard insulin aspart followed by hybrid closed-loop with Fiasp or vice versa. Permuted block randomization was applied. Assignment was blinded to study participants and study personnel.

Participants continued the allocated intervention without remote monitoring by study personnel. Participants were advised to bolus 15 minutes prior to eating throughout the study as per standard clinical practice, but were free to adjust this as required. A 24h telephone helpline to contact the local study team was provided.

Closed-Loop System

The hybrid closed-loop system comprised an unlocked smartphone (Galaxy S8, Samsung, South Korea) hosting the CamAPS FX app (CamDiab, Cambridge, UK) running the Cambridge model predictive control algorithm (version 0.3.71), which communicated wirelessly with both the Dana Diabecare RS or Dana i insulin pump (Sooil, Seoul, South Korea), and Dexcom G6 transmitter (Dexcom, San Diego, CA, USA) (further details in Figure S1, Supplementary Appendix).

Study End Points

The primary endpoint was the between-treatment difference in time in target glucose range 3.9 to 10.0mmol/L during the study periods. Secondary endpoints included mean sensor glucose; standard deviation and coefficient of variation of glucose; time in hypo- and hyperglycemia; and insulin metrics. All glycemic endpoints were based on sensor glucose data. Secondary endpoints were calculated over the whole 8-week study periods, fortnightly and during daytime and night-time periods.

Three validated questionnaires were administered at baseline and at the end of each study period to evaluate hypoglycemia fear[7], diabetes distress[8] and closed-loop treatment satisfaction.[9]

Safety evaluation comprised the frequency of severe hypoglycemia and diabetic ketoacidosis events and other adverse events.

Statistical Analysis

This was an exploratory analysis aiming for 24 completed participants. All analyses were carried out on an intention-to-treat basis. We analyzed endpoints from participants with a minimum of 48h of sensor data in at least one study period. The treatment interventions were compared using a repeated measures linear mixed model adjusting for period as a fixed effect and site as a random effect and accounting for the baseline value as a separate period. A 95% confidence interval was reported for the difference between interventions and p values <0.05 were considered significant. Non-normally distributed data were winsorized. Missing data were not imputed for the primary analysis. Outcomes were calculated using GStat software, version 2.3 (University of Cambridge, Cambridge, UK), and statistical analyses carried out using SPSS Statistics software, version 28 (IBM Software, Hampshire, UK).

Results

Between March 2021 and March 2022, 27 participants were enrolled. During run-in, one participant chose to withdraw. Another participant was withdrawn on safety grounds. Twenty-five participants were randomized and all completed the trial. Study flow chart

and Consort flow diagram are shown in Figures S2 and S3, Supplementary Appendix. Participants had a mean age of 5.1±1.3 years (range 2.1 to 6.8 years), 68% (n=17) were male and the majority were of white ethnicity (n=20, 80%) (Table S2, Supplementary Appendix). Baseline HbA1c was 7.2±0.8% (55.5±8.6mmol/mol) with time in target range 3.9-10.0mmol/L of 63.9 ± 8.5%, total daily insulin requirements of 0.74 ± 0.14 units/kg/day and a mean duration of diabetes of 2.4±1.2 years. Nineteen participants (76%) were using hybrid closed-loop therapy at enrolment.

Primary and secondary endpoints for all randomized participants are shown in Table 1. Time in target range 3.9 to 10.0mmol/L was not significantly different between interventions (mean±SD 64.2±8.8% vs. 64.6±8.8% for hybrid closed-loop with Fiasp vs. hybrid closed-loop with standard insulin aspart, respectively), with mean adjusted difference of -0.33 percentage points (95% CI -2.13, 1.47; p=0.71). Figure 1 shows 24h sensor glucose profiles.

There was no significant difference in time spent in hypoglycemia <3.9mmol/L (median [IQR] 3.5% [2.6, 6.3] Fiasp vs 3.7% [2.6, 6.2] aspart) or time spent in significant hyperglycemia >16.7mmol/L between interventions (median [IQR] 4.5% [2.2, 6.6] Fiasp vs 4.1 [1.7, 7.7] aspart). Measures of glucose variability were not significantly different between interventions.

Total daily insulin delivery was slightly higher in the Fiasp period (mean±SD 0.74±0.12 vs 0.72±0.12 units/kg/day with aspart; p=0.04). The higher total daily insulin delivery in the Fiasp period was due to higher basal (i.e. automated) insulin delivery. Total daily bolus insulin was not significantly different between interventions (Table 2).

Closed-loop usage was high with median of 96.4% (IQR 91.7, 97.9) of the time with Fiasp and 96.7% (95.0, 98.0) with standard insulin aspart.

Sensor glucose metrics were similar during day and night-time periods using Fiasp compared to standard insulin aspart (Table S2, Supplementary Appendix). Time in range at fortnightly intervals over the 8-week periods remained stable (Figure S4, Supplementary Appendix).

Levels of diabetes distress and hypoglycemia fear were not significantly different between interventions, although there was a trend towards less hypoglycemia worry in the Fiasp period (Table S4, Supplementary Appendix). Treatment satisfaction as measured by INSPIRE was similar between interventions.

Adverse Events

One severe hypoglycemia event occurred in the run-in period. No severe hypoglycemia or DKA events occurred after randomization, one non-intervention related serious adverse event (hospital admission for gastroenteritis) occurred in the insulin aspart period. Thirty other adverse events were reported (17 Fiasp period, 8 aspart period, 5 run-in). Of these, 14 were hyperglycemia with ketosis (ketones≥0.6mmol/L) events, 9 in Fiasp period, 2 in aspart period, and 3 in run-in. The 9 hyperglycaemia with ketosis events in the Fiasp period occurred in 8 participants, and the 2 events in the aspart period occurred in 2 participants. Four (all Fiasp period) were associated with intercurrent illness, the others were most likely secondary to cannula failure or occlusion. All events resolved at home with pump cannula change and/or pen corrections. Safety-related events are summarized in Table S5, Supplementary Appendix.

Discussion

In the present study we demonstrated that using Fiasp with the CamAPS FX hybrid closed-loop system over 8-weeks did not lead to any significant difference in glycemic control compared with using standard insulin aspart in very young children with type 1 diabetes. In this age-group, closed-loop algorithms improve glycemic control primarily by reducing time in hyperglycemia, and are able to achieve this improvement with standard insulin aspart when compared to sensor-augmented pump therapy. [1,2] Fiasp is only marginally faster-acting in children, [10] and this difference may not be sufficient to provide additional benefit over and above the inherent benefit of closed-loop glucose control itself, but may still confer benefit in those on standard therapies. [6]

This is further reflected in our questionnaire outcomes, which were similar between interventions, and showed no significant change in diabetes distress or hypoglycemia fear with use of Fiasp. Treatment satisfaction was high at 86 (out of 100) at baseline and

remained consistently high during both study periods, suggesting that Fiasp does not appear to offer additional clinical benefit over and above the benefit of hybrid closed-loop therapy as a whole in this age-group.

Our efficacy outcomes are consistent with observations in several adult studies comparing hybrid closed-loop therapy using Fiasp to standard rapid-acting insulin, [11-14] where measures of glycemic control were either clinically similar with both insulins or improvements were statistically significant, but clinically modest. [14] Two adult studies demonstrated a reduction in hypoglycemia, [11,14] an effect not observed in the present study. This may be due to a higher proportion of bolus insulin delivery (57% compared to 47% in adults) in the day-time in our cohort, limiting the closed-loop algorithm's ability to mitigate hypoglycemia during this time. Additionally, inherent differences in eating behavior and insulin variability in very young children may be contributing to the observed differences in time in hypoglycemia.

We observed a higher rate of hyperglycemia with ketosis events (ketones≥0.6mmol/L) during treatment with Fiasp. An adult study investigating the safety of Fiasp in insulin pumps reported a higher number of unplanned infusion set changes in the Fiasp group, although unexplained hyperglycemia events were similar to standard insulin aspart. [15] Younger children produce ketones more readily whenfasting due to inherent physiological mechanisms where there is decreased availability of gluconeogenic substrates and precursors in this age-group, compared with older children and adults. [16,17] In a study comparing the effect of overnight suspension of insulin delivery using predictive low glucose suspend in young children (4-9 years) and older children (10-14 years), young children had ketones ≥0.6mmol/L on 23% of mornings compared with 2% in older children following pump suspensions of >120 minutes. [18] A similar picture would also be expected to occur in other clinical scenarios such as insulin infusion set failure or intercurrent illness. Thus, any factor increasing the likelihood of infusion set failures may increase the risk of hyperglycemia with ketosis events in very young children.

Strengths of our study include the multicenter, double-blind, crossover design with each participant being their own control. There was 100% retention of randomized participants,

suggesting high acceptability of closed-loop in this age-group. Limitations include a relatively small sample size, and a study population with good glycemic control at baseline. All participants used closed-loop therapy during the baseline period, however it has already been shown that closed-loop therapy improves glycemic control compared to sensor-augmented pump therapy in this age-group. [1]

Conclusion

The use of Fiasp with the CamAPS FX HCL system demonstrated no significant difference and clinically similar outcomes in glycemic control compared to standard insulin aspart in very young children with type 1 diabetes, suggesting that use of Fiasp with closed-loop therapy does not offer any additional clinical benefit over using standard insulin aspart. In contrast to adult studies, we observed a higher rate of hyperglycemia with ketosis events in the Fiasp period. Future research should aim to trial newer ultra-rapid insulins with faster onset and offset than Fiasp, as improved preparations in conjunction with hybrid closed-loop therapy may well be able to confer additional clinical benefit and address some of the remaining treatment challenges in this vulnerable age-group.

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Author Contributions and Guarantor Statement:

RH, JW, JMA, CKB, MEW and AT co-designed the study. JW, JMA, SH, MD, HL, KP and KT were responsible for screening and enrolment of participants, arranged informed consent, and provided patient care. AC supported study set up, coordination and randomization. JW and RH wrote the report. JW, MEW, and RH carried out or supported data analysis, including the statistical analyses. RH designed and implemented the glucose controller. RH,

JW, JMA, CKB, SH, MEW, and AT contributed to the interpretation of the results. All authors critically reviewed the report. JW, MEW and RH are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest:

RH reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving license fees from BBraun; patents related to closed-loop, and being director at CamDiab. JW reports receiving speaker honoraria from Ypsomed. JMA reports training fees from CamDiab. CKB reports receiving consultancy fees from CamDiab and speaker honoraria from Ypsomed. AC reports receiving consultancy fees from CamDiab. SH reports speaker & advisory board fees from Dexcom, Medtronic, Sanofi & Ypsomed; being director at ASK Diabetes Ltd and receiving consulting / training fees from CamDiab. MEW is a consultant at CamDiab and reports patents related to closed-loop. AT, MD, HL, KP and KT have no disclosures.

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Table 1. Glucose control and insulin delivery over 8 weeks of closed-loop with faster-acting insulin (Fiasp) and closed-loop with standard insulin aspart.

	Fiasp (n=25)	**Standard insulin aspart (n=25)**	**Mean adjusted difference (95% CI)****	**P value†**
Percent of time with sensor glucose level				
3.9 to 10.0 mmol/L*	64.2 ± 8.8	64.6 ± 8.8	-0.33 (-2.13, 1.47)	0.71
<3.9 mmol/L	3.5 (2.6, 6.3)	3.7 (2.6, 6.2)	-0.05 (-0.43, 0.34)	0.81
<3.5 mmol/L	2.0 (1.3, 4.2)	2.0 (1.4, 4.0)	-0.06 (-0.34, 0.22)	0.68
<3.0 mmol/L	0.8 (0.5, 1.8)	0.8 (0.4, 1.9)	0.01 (-0.14, 0.16)	0.92
>10.0 mmol/L	31.3 ± 9.0	31.0 ± 8.9	0.26 (-1.60, 2.11)	0.78
>16.7 mmol/L	4.5 (2.2, 6.6)	4.1 (1.7, 7.7)	-0.16 (-0.78, 0.46)	0.60
Mean glucose (mmol/L)	8.9 ± 0.9	8.9 ± 0.8	0.03 (-0.16, 0.21)	0.78
Glucose SD (mmol/L)	3.7 ± 0.6	3.7 ± 0.6	0.02 (-0.12, 0.16)	0.76
Glucose CV (%)	42.0 ± 4.6	41.9 ± 4.7	0.12 (-1.09, 1.32)	0.85

Total daily insulin (units/kg/day)	0.74 ± 0.12	0.72 ± 0.12	0.03 (0.00, 0.07)	0.04
Total daily basal Insulin (units/kg/day)	0.38 ± 0.10	0.35 ± 0.10	0.03 (0.00, 0.06)	0.04
Total daily bolus Insulin (units/kg/day)	0.37 ± 0.09	0.37 ± 0.10	0.00 (-0.01, 0.02)	0.71
% time using closed-loop	96.4 (91.7, 97.9)	96.7 (95.0, 98.0)	-	-
% time using CGM	97.8 (96.2, 98.3)	97.9 (96.0, 98.6)	-	-

Data presented are mean±SD or median (Q1, Q3) throughout the 8-week study periods.

Glucose data are based on sensor glucose measurements.

CV, coefficient of variation; SD, standard deviation.

*Primary end point.

**Treatment difference is calculated as Fiasp minus standard insulin aspart.

[†]Based on linear mixed model adjusting for period as a fixed effect and site as a random effect and accounting for the baseline value as a separate period.

Figure legends

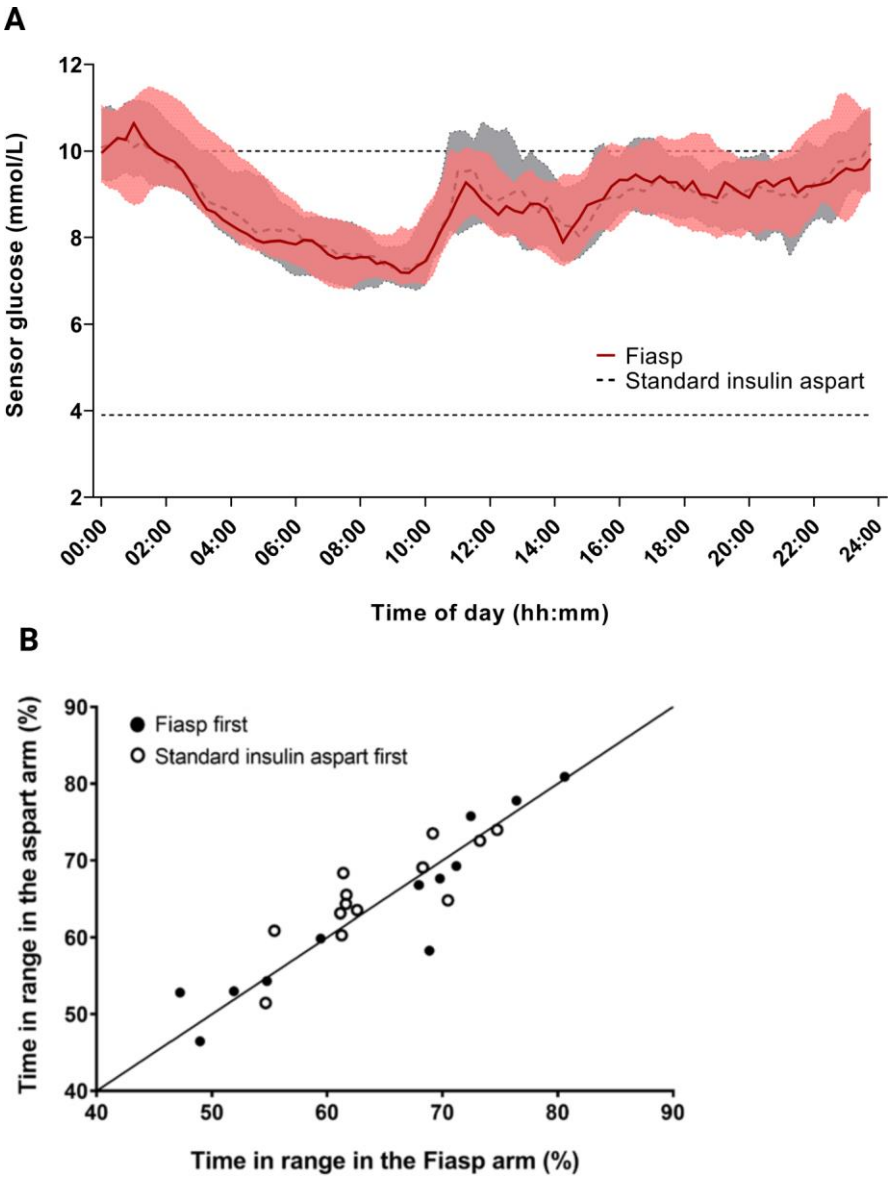

Figure 1. Panel A Sensor glucose levels (median, IQRs) during closed-loop with Fiasp (n = 25; solid red line and red shaded area) and during closed-loop with standard insulin aspart (n = 25; dashed black line and grey shaded area). Dashed horizontal lines indicate the target glucose range between 3.9 and 10 mmol/L. **Panel B** Percentage of time spent in the target glucose range using Fiasp compared with standard insulin aspart (n=25).