Cambridge Hybrid Closed-Loop System in Very Young Children With Type 1 Diabetes Reduces Caregivers' Fear of Hypoglycemia and Improves Their Well-being

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OBJECTIVE

To evaluate the impact of CamAPS FX hybrid closed-loop (HCL) automated insulin delivery in very young children with type 1 diabetes (T1D) on caregivers' well-being, fear of hypoglycemia, and sleepiness.

RESEARCH DESIGN AND METHODS

We conducted a multinational, open-label, randomized crossover study. Children (age 1–7 years) with T1D received treatment for two 4-month periods in random order, comparing HCL with sensor augmented pump (control). At baseline and after each treatment period, caregivers were invited to complete World Health Organization–Five Well-Being Index, Hypoglycemia Fear Survey, and Epworth Sleepiness Scale questionnaires.

RESULTS

Caregivers of 74 children (mean ± SD age 5 ± 2 years and baseline $HbA1_c$ 7.3 ± 0.7%; 42% female) participated. Results revealed significantly lower scores for hypoglycemia fear ($P < 0.001$) and higher scores for well-being ($P < 0.001$) after HCL treatment. A trend toward a reduction in sleepiness score was observed ($P = 0.09$).

CONCLUSIONS

Our results suggest better well-being and less hypoglycemia fear in caregivers of very young children with T1D on CamAPS FX HCL.

Type 1 diabetes (T1D) management in very young children is challenging for their caregivers (1). Age-specific characteristics add to the complexity of daily diabetes management (2,3). Attempting to meet treatment targets requires persistent efforts, but not meeting targets may have lifelong consequences for a child's brain function, health, comorbidities, and life expectancy (4–6). Caregivers are often conflicted about recommended glucose targets and fear of hypoglycemia (7), leading to sleep deprivation (8) and poorer caregiver well-being (9).

We recently reported significantly improved metabolic control without increased hypoglycemia when using the CamAPS FX hybrid closed-loop (HCL) system in this population (10). To analyze the impact of HCL on caregivers' well-being, fear of

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hypoglycemia, and sleepiness, we invited them to answer a set of validated questionnaires.

RESEARCH DESIGN AND METHODS

We conducted an open-label, international, multicenter, randomized two-period crossover study, which compared HCL insulin delivery via the CamAPS FX algorithm (CamDiab, Ltd., Cambridge, U.K.) with sensor augmented pump (SAP) delivery in children age 1 to 7 years who had T1D for at least 6 months and had received pump therapy for at least 3 months before enrollment. Duration was 16 weeks for both study arms in a free-living setting. Throughout the entire study, a Dana Diabecare RS insulin pump (Sooil, Seoul, South Korea) and Dexcom G6 sensor (Dexcom, San Diego, CA) communicated wirelessly with an unlocked smartphone, with or without the CamAPS FX algorithm. Bolus administration was performed through children's smartphones. The follower option allowed caregivers to receive the glucose values in real time on their own smartphones. Ethical approval was obtained from all participating centers. The main caregiver of each child was invited to complete validated questionnaires at baseline and the end of each treatment period. A secure link was sent to the caregiver to complete questionnaires online.

Measures

The Hypoglycemia Fear Survey (HFS) for caregivers of young children with T1D (11) measures caregivers' behavior and worry related to hypoglycemia fear; 26 items are scored on a 5-point Likert scale (1 never to 5 always). Scores for HFS-worry and HFS-behavior subscales (with 15 and 11 items, respectively; score range 26–130) can be computed in addition to the total HFS score, with higher scores reflecting higher levels of hypoglycemia fear.

The Epworth Sleepiness Scale (ESS) (12) measures caregiver daytime sleepiness and dozing; eight items are scored on a 4-point Likert scale (0 would never doze to 3 high chance of dozing; score range 0–24), with total scores >9 suggesting excessive sleepiness.

The World Health Organization–Five Well-Being Index (WHO-5) questionnaire (13) documents caregivers' perceived well-being. It includes five items, with item scores ranging from 5 (all the time) to 0 (at no time), multiplied by 4 to create a percentage scale from 0 to 100%. The threshold for relevant clinical change is 10 points (14).

Statistical Analysis

Descriptive statistics (means and SDs) for measures are provided for each treatment period. To assess the treatment effect, linear mixed model analyses were conducted, with treatment as a fixed factor and site as a random factor. Missing data were not imputed but dealt with in the linear mixed model approach by using maximum likelihood estimates. The model accounted for correlated data from the same participant. Nominal (uncorrected) P values were adjusted for multiple comparisons using the Benjamini-Hochberg adaptive false discovery rate procedure.

RESULTS

Caregivers of the 74 randomly assigned children (mean ± SD age 5 ± 2 years; 42% female) were included. A summary of questionnaire outcomes is provided in Table 1.

Hypoglycemia Fear

HFS scores indicated that caregivers expressed both worry and behavioral action in relation to hypoglycemia fear. The total score was mostly affected by reported behavior rather than worry. Caregivers reported significantly lower fear of hypoglycemia (total HFS score) after the HCL treatment period than after SAP treatment. More specifically, after adjusting for baseline, the mean difference for the total score was -5 (95% CI -9, -2; $P < 0.001$) in favor of HCL (Table 1). The lower levels of HFS total score were related to lower levels of both behavior (-2; 95% CI -3, -1; $P < 0.006$) and worry subscales (-3; 95% CI -6, -1; $P < 0.001$) after HCL treatment.

Daytime Sleepiness

Results of the linear model analysis did not indicate that caregivers' reported sleepiness differed in relation to the treatment used. Although the adjusted mean ESS score (95% CI -2, 1; $P = 0.09$) was slightly lower after HCL than after SAP, this difference was not statistically significant (Table 1). At baseline, 24.7% scored >9, suggesting excessive sleepiness. After HCL and SAP, only 16.4% and 23.5%, respectively, scored >9.

WHO-5

Caregivers reported higher levels of well-being after using HCL treatment than after using SAP treatment. The adjusted mean difference of eight (95% CI 3, 16; $P < 0.001$) was statistically significant (Table 1). At baseline, 11% of caregivers scored <50, whereas after HCL and SAP, 7.5% and 16.4%, respectively, did so. The differences in WHO-5 score were apparent for each individual item (for all items, raw mean item scores were highest after HCL); this was most notable for the item "I woke up feeling fresh and rested," with a mean score at baseline and after SAP of 2.9 and a mean score after HCL of 3.5.

CONCLUSIONS

The results of this randomized crossover study in very young children with T1D show that the impact of HCL in this population goes beyond improved metabolic control and has a significant effect on caregivers' hypoglycemia fear and

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Table 1—Descriptive statistics for measures for different treatment arms

	Baseline (N = 74)	HCL period (n = 73)[a]	SAP period (N = 74)	Adjusted mean difference (95% CI)	P[b]
HFS total score[c]	72.4 (14.9)	64.6 (12.6)	68.9 (12.7)	−5 (−9, −2)	<0.001
HFS-behavior subscale score[d]	35.4 (5.9)	33.4 (5.8)	34.9 (6.6)	−2 (−3, −1)	0.006
HFS-worry subscale score[c]	36.9 (11.2)	31.2 (8.7)	34.2 (9.2)	−3 (−6, −1)	<0.001
ESS total score[e]	6.1 (4.1)	5.6 (3.8)	6.5 (4.3)	−1 (−2, 1)	0.09
WHO-5 total score[d]	69.3 (16.6)	75.0 (17.8)	66.6 (18.4)	8 (3, 16)	<0.001

[a]Excludes one participant randomly assigned to SAP period first, who dropped out before HCL period. [b]Based on linear mixed model adjusting for measurement point (fixed effect) and treatment center (random effect and accounting for correlated data from same participant). Nominal (uncorrected) P values were adjusted for multiple comparisons using Benjamini-Hochberg adaptive false discovery rate procedure. [c]Questionnaire or subscale score missing for n = 1 participant at baseline, n = 6 participants in HCL arm, and n = 8 participants in SAP arm. [d]Questionnaire or subscale score missing for n = 1 participant at baseline, n = 6 participants in HCL arm, and n = 7 participants in SAP arm. [e]Questionnaire or subscale score missing for n = 1 participant at baseline, n = 6 participants in HCL arm, and n = 6 participants in SAP arm.

perceived well-being; for sleepiness, a trend was observed, although not significant. The effects persisted when including only those caregivers with a complete data set in the analyses. Furthermore, when comparing baseline with the two treatment arms, fewer caregivers scored in the critical range for WHO-5 and ESS after HCL compared with baseline and SAP. Our results complement the qualitative data for a subset of the caregivers (n = 30) (15). In interviews, caregivers indicated that the access to remote surveillance was an important feature, because it enabled them to monitor the children's glucose levels from a distance. This surveillance allowed them to still feel close by and confident about glucose control in the children. Because remote surveillance was used during both treatment periods, it may have contributed to caregivers' ability to sleep and explain, at least partially, the lack of significant difference in sleepiness. Although several factors may contribute to caregivers' well-being, we considered only those factors directly related to diabetes care. It should be noted that the study was conducted between 2018 and 2020. This means that some data were collected at a time when caregivers were experiencing stress associated with the direct and indirect effects of COVID-19, and this may have affected, for example, their well-being. The randomized crossover design with control for baseline enables control for several sources of systematic error. As such, the design ensures that possible effects can be attributed to a specific treatment (i.e., use of HCL vs. SAP). Furthermore, the study was conducted in a multicenter and international collaborative setting. Findings can therefore be generalized more easily to other settings.

On the basis of these initial results, HCL systems should be considered as first-line treatment in very young children with T1D to ensure the best possible short- and long-term outcomes for both children and their caregivers.

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Duality of Interest. M.E.W. is a consultant at CamDiab, Ltd., and reports patents related to closed loop. C.d.B. has received speaker honoraria from MiniMed Medtronic and has been a member of its European Psychology and e-Learning Advisory Boards. U.S. has received speaker honoraria from MiniMed Medtronic. E.F.-R. reports having received speaker honoraria from MiniMed Medtronic and Eli Lilly and serving on advisory boards for Eli Lilly. J.K.M. is a shareholder in Decide Clinical Software, Ltd.; a member of the advisory boards of Boehringer Ingelheim, Eli Lilly, Medtronic, Prediktor AS, Roche Diabetes Care, and Sanofi; and has received speaker honoraria from Abbott Diabetes Care, AstraZeneca, Dexcom, Eli Lilly, NovoNordisk AS, Roche Diabetes Care, Servier, and Takeda. T.M.K. has received speaker honoraria from MiniMed Medtronic, Roche, and Eli Lilly and consulted for Sanofi-Aventis. B.R.-M. reports having received speaker honoraria from Abbott, MiniMed Medtronic, Eli Lilly, Roche, Menarini, and Novo Nordisk and serving on advisory boards for Eli Lilly. S.E.H. declares speaker honoraria from Eli Lilly, Sanofi, Pfizer, Vertex, Medtronic, and Omnipod/Insulet. F.M.C. has received speaking fees from Abbott, Medtronic, Eli Lilly, and Novo Nordisk. C.B. reports receiving grant support from Tandem Diabetes Care and consulting for CamDiab, Ltd. J.W. reports receiving speaker honoraria from Ypsomed. R.H. reports receiving speaker honoraria from Eli Lilly, Dexcom, and Novo Nordisk; receiving license and/or consultancy fees from B. Braun and Abbott Diabetes Care; holding patents related to closed loop; and being a director at CamDiab, Ltd. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. C.d.B., A.Tha., M.E.W., E.F.-R., T.M.K., B.R.-M., S.E.H., F.M.C., J.Y., J.M.A., C.B., J.K.M., and R.H. codesigned the study. C.d.B., A.Tha., E.F.-R., T.M.K., B.R.-M., S.E.H., and F.M.C. were the lead clinical investigators. C.d.B., U.S., J.W., E.F.-R., T.M.K., B.R.-M., S.E.H., F.M.C., J.Y., M.F., A.Thi., J.M.A., and C.B. screened and enrolled participants, provided patient care, and/or took study samples. L.E.B., C.K., and I.M.P.C. carried out or supported data analysis, including the statistical analyses. J.S. supported study setup and randomization. J.L. conducted the qualitative psychological evaluation. S.R. conducted cost utility analysis. All authors critically reviewed the manuscript before publication and contributed to the interpretation of the results. C.d.B. and I.M.P.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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