Closed-Loop Insulin Delivery in Adults with Well-Controlled Type 1 Diabetes: A Free-Living Day-and-Night Randomised Crossover Study

L. Bally[1, 2, 3*], H. Thabit[1, 2*], H. Kojzar[4], J.K. Mader[4], J. Qerimi-Hyseni[4], S. Hartnell[2], M Tauschmann[1, 5], J.M. Allen[1, 5], M.E. Wilinska[1, 5], T. R. Pieber[4], M. L. Evans[1, 2], R. Hovorka[1, 5]

[1]Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom
[2]Department of Diabetes & Endocrinology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
[3]Department of Diabetes, Endocrinology, Clinical Nutrition & Metabolism, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[4]Department of Internal Medicine, Division of Endocrinology & Diabetology, Medical University of Graz, Graz, Austria
[5]Department of Paediatrics, University of Cambridge, Cambridge, United Kingdom

Introduction

Tight glycaemic control remains a predisposing factor to hypoglycaemia which is associated with increased morbidity and mortality in type 1 diabetes[1,2]. Closed-loop insulin delivery has the potential to further improve glycaemic control whilst reducing the hypoglycaemia burden[3].

In a four-week open-label prospective two-centre randomised crossover study, we evaluated the efficacy, safety and utility of unsupervised day-and-night closed-loop insulin delivery in type 1 adults with HbA1c below 7.5%, compared to usual insulin therapy under free-living conditions.

Methods

- Adults with type 1 diabetes were recruited from Addenbrooke's Hospital Cambridge (UK) and University of Graz (Austria).
- Training on study insulin pump and continuous glucose monitoring (CGM) was followed by 2-4 weeks of run-in for familiarisation with study devices and compliance assessment.
- Participants were randomised to day-and-night hybrid closed-loop system or usual pump therapy, followed by 2-4 weeks washout period and then the other intervention for 4 weeks.
- During the control period, the display of the study CGM was blinded. Participants were allowed to use their own glucose monitoring devices (continuous or flash glucose monitoring) if it was part of their pre-study usual care.
- Closed-loop utilised a model-predictive-control algorithm to direct insulin delivery.
- Primary outcome: % of time when sensor glucose was in target range (3.9-10.0mmol/l). Analyses were by intention to treat.

Results

	N=29
Gender (F/M)	**15/14**
Age (years)	**41 ± 13**
Weight (kg)	**72.9 ± 13.0**
BMI (kg/m^2)	**25.1 ± 3.0**
HbA1c (%)	**6.9 ± 0.5**
HbA1c (mmol/mol)	**51.7 ± 4.8**
Duration of diabetes (years)	**24 ± 12**
Duration on pump (years)	**6 ± 4**
Total daily insulin (U/kg/day)	**0.5 ± 0.1**
Baseline glucose sensor use, N [%]	
No prior glucose sensor use	**18 [62%]**
Real-time continuous glucose monitoring	**5 [17%]**
Flash glucose monitoring	**6 [21%]**

Table 1. Baseline characteristics. Data are presented as mean ± SD, unless specified otherwise.

- Baseline characteristics of randomised participants are shown in Table 1.
- Of the 29 randomised participants, 17% used real-time CGM and 21% used flash glucose monitoring as part of their usual care.

Results

- Closed-loop increased % of time when glucose was in target range by 11 percentage points, compared to control period (p<0.001), see Table 2.
- Closed-loop reduced the proportion of times spent hypoglycaemic and burden of hypoglycaemia (p<0.001).
- Lower mean glucose during closed-loop was achieved without changing the total daily insulin delivery (p=0.36).
- All measures of glycaemic variability were significantly lower in the closed-loop period than in the control period (p<0.001).
- Participant use of closed-loop was high (90% of time, 95% CI 78 to 89). The majority (76%) agreed that less time was spent on diabetes self-management during closed-loop.
- No episodes of serious adverse events occurred.

	Closed-loop (n=29)	Control (n=28)	Paired difference or paired ratio (95% CI)	p value
Time spent at glucose level (%)				
3.9 to 10 mmol/l	**76.2 (6.4)**	**65.6 (8.1)**	**10.5 (7.6 to 13.4)**	**<0.001**
>10 mmol/l	**20.4 (6.3)**	**27.4 (9.6)**	**-6.9 (-10.2 to -3.5)**	**<0.001**
< 3.9 mmol/l	**2.9 (2.3 to 4.0)**	**5.3 (3.5 to 10.0)**	**0.50 (0.41 to 0.63)**	**<0.001**
<3.5 mmol/l	**1.3 (0.8 to 2.3)**	**3.4 (1.9 to 7.2)**	**0.35 (0.26 to 0.47)**	**<0.001**
<2.8 mmol/l	**0.3 (0.1 to 0.5)**	**1.0 (0.5 to 2.6)**	**0.24 (0.14 to 0.41)**	**<0.001**
AUC< 3.5 mmol/l (mmol/l x min)	**9.1 (3.7 to 18.2)**	**26.7 (13.1 to 65.5)**	**0.27 (0.18 to 0.41)**	**<0.001**
Mean glucose (mmol/l)	**7.9 (0.5)**	**8.3 (0.9)**	**-0.4 (-0.7 to -0.1)**	**0.023**
SD of glucose (mmol/l)	**2.8 (0.4)**	**3.3 (0.5)**	**-0.5 (-0.7 to -0.3)**	**<0.001**
CV of glucose (%)	**35.3 (3.0)**	**40.3 (5.1)**	**-5.0 (-7.1 to -3.0)**	**<0.001**
CV of glucose between days (%)	**12.8 (3.3)**	**20.2 (4.6)**	**-7.5 (-9.7 to -5.3)**	**<0.001**

Table 2. Overall day-and-night glucose control during closed-loop and control periods based on sensor glucose measurements. Data are mean (SD) or median (IQR)

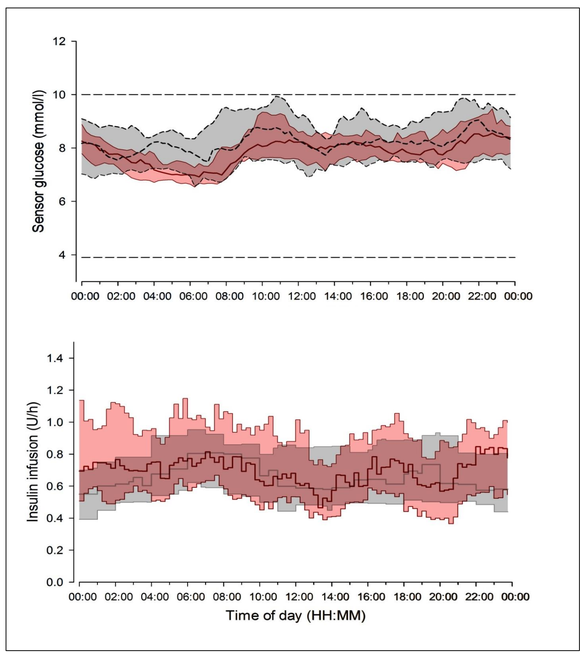

Figure 1. Median and IQR of sensor glucose (top) and insulin delivery (bottom).

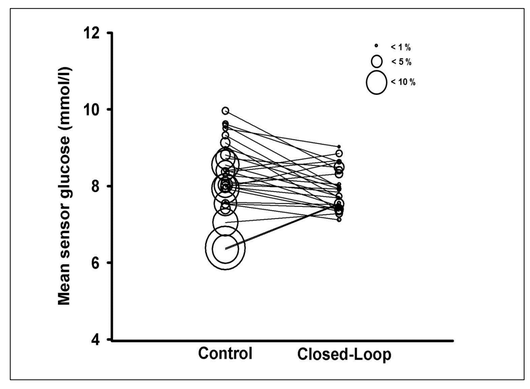

Figure 2. Individual values of mean sensor glucose and % of time spent with glucose concentration below 3.5mmol/l.

Conclusions

Use of day-and-night hybrid closed-loop insulin delivery under unsupervised, free-living conditions for 4 weeks in adults with type 1 diabetes and HbA1c below 7.5% is safe, well tolerated, improves glucose control, and reduces hypoglycaemia burden. Larger and longer studies are warranted.

References:
1. Khunti K et al, Diabetes Care 2015; 38(2): 316-22
2. UK Hypoglycaemia Study Group, Diabetologia 2007; 50(6): 1140-7
3. Thabit H et al. Diabetologia 2016; 59(9): 1795-805

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