Safety and Efficacy of 24-h Closed-Loop Insulin Delivery in Well-Controlled Pregnant Women With Type 1 Diabetes

A randomized crossover case series

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OBJECTIVE—To evaluate the safety and efficacy of closed-loop insulin delivery in well-controlled pregnant women with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII).

RESEARCH DESIGN AND METHODS—A total of 12 women with type 1 diabetes (aged 32.9 years, diabetes duration 17.6 years, BMI 27.1 kg/m^2, and HbA_{1c} 6.4%) were randomly allocated to closed-loop or conventional CSII. They performed normal daily activities (standardized meals, snacks, and exercise) for 24 h on two occasions at 19 and 23 weeks' gestation. Plasma glucose time in target (63–140 mg/dL) and time spent hypoglycemic were calculated.

RESULTS—Plasma glucose time in target was comparable for closed-loop and conventional CSII (median [interquartile range]: 81 [59–87] vs. 81% [54–90]; $P = 0.75$). Less time was spent hypoglycemic (<45 mg/dL [0.0 vs. 0.3%]; $P = 0.04$), with a lower low blood glucose index (2.4 [0.9–3.5] vs. 3.3 [1.9–5.1]; $P = 0.03$), during closed-loop insulin delivery.

CONCLUSIONS—Closed-loop insulin delivery was as effective as conventional CSII, with less time spent in extreme hypoglycemia.

Diabetes Care 34:2527–2529, 2011

There is strong evidence that avoidance of hyperglycemia is key to improved pregnancy outcomes in type 1 diabetes. Currently, the price to pay for tight glucose control is increased risk of severe hypoglycemia, causing significant maternal morbidity (seizures, road-traffic accidents, and death) (1). Despite the increased use of insulin pumps and fast-acting insulin analogs, continuous glucose monitoring (CGM) highlights the prevalence of hypoglycemia exposure (3 h per day at <70 mg/dL and 1 h per day at <50 mg/dL) during pregnancy (2). Although the neonatal consequences of maternal hypoglycemia are unclear, it is accepted that the benefits of tight glycemic control must be balanced against the potential risk of hypoglycemia (3).

Closed-loop systems use computerized algorithms to link insulin delivery with CGM glucose levels in real time, aiming to more closely approximate normal glucose concentrations. Overnight studies in children and adults indicate the potential for reduced nocturnal hypoglycemia (4,5). We previously documented the effectiveness of overnight closed-loop deliver in early- and late-gestation type 1 diabetic pregnancy, with 84–100% time in target without nocturnal hypoglycemia during sedentary conditions (6). The aim of this study was to evaluate the safety and efficacy of 24-h closed-loop insulin delivery, incorporating normal daily activities and exercise.

RESEARCH DESIGN AND METHODS

From April 2010 to April 2011, 12 pregnant women with type 1 diabetes from two U.K. antenatal clinics (Addenbrooke's Hospital, Cambridge, U.K., and Kings College Hospital, London, U.K.) were recruited into a randomized crossover trial of closed-loop insulin delivery. The same study protocol comparing closed-loop and conventional continuous subcutaneous insulin infusion (CSII) was applied for two 24-h visits, separated by a 1- to 6-week interval. Study protocols were approved by the research ethics committee, and all participants provided written informed consent.

Study devices and procedures

A FreeStyle Navigator sensor (Abbott Diabetes Care, Alameda, CA) was inserted the day before each study. An intravenous sampling catheter and study pump (Animas 2020; Johnson & Johnson, New Brunswick, NJ) were inserted on arrival (1200 h). After lunch (50 g carbohydrate), an Actiheart physical activity energy expenditure (PAEE) monitor (CamNtech, Cambridge, U.K.) was attached (7). From 1400 h, venous samples were obtained every 15–30 min until the study ended at 1230 h on day 2. Plasma glucose concentrations were measured immediately (YSI 2300 STAT Plus Analyzer; Farnborough, U.K.), with plasma extracted for later insulin concentration

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Received 29 July 2011 and accepted 21 September 2011.
DOI: 10.2337/dc11-1430. Clinical trial reg. no. ISRCTN50385583, www.isrctn.org.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1430/-/DC1.

measurements by immunochemiluminometric assay (Invitron, Monmouth, U.K.).

Daily activities

Activities included three 20-min walks (1400, 1930, and 0900 h) and two 50-min sessions of brisk treadmill walking (1500 h on day 1 and 0930 h on day 2). Meal and snack choices were consistent between visits. Pre-exercise snacks were given according to capillary glucose measurements (15 g carbohydrate >108 mg/dL and 30 g carbohydrate ≤108 mg/dL). An additional 15-g carbohydrate snack was provided at 2100 h.

Insulin delivery

During closed-loop, basal insulin infusion rates were manually adjusted at 15-min intervals according to CGM glucose levels and the control algorithm advice. During conventional CSII, the women set temporary basal rates and used correction boluses according to capillary glucose measurements (7–10 per day). During both visits, insulin boluses were calculated by women according to capillary glucose levels, aiming for the National Institute for Health and Clinical Excellence (NICE)-recommended target glucose range of 63–140 mg/dL (8).

Hypoglycemia

Hypoglycemia was defined as plasma glucose levels ≤54 mg/dL with symptoms or ≤45 mg/dL without symptoms. Episodes were treated with 15 g oral carbohydrate (90 mL Lucozade Energy Original; GlaxoSmithKline, Middlesex, England, U.K.).

Statistical analysis

The primary outcome was plasma glucose time in target (63–140 mg/dL) from 1400 h on day 1 to 1230 h on day 2. Secondary outcomes were time spent above and below target, mean glucose concentration, glucose SD, and low blood glucose index (LBGI). The Wilcoxon signed rank test was used to compare paired measurements within an individual between closed-loop and CSII visits. Values are given as medians (interquartile ranges), unless otherwise stated. Analyses were conducted using SPSS version 15 (SPSS, Chicago, IL).

RESULTS—Participants (n = 12) had a median age of 32.9 years (30.4–36.7), diabetes duration of 17.6 years (8.0–27.3), CSII duration of 2.0 years (0.8–2.0), weight of 77.0 kg (68.5–84.6), BMI of 27.1 kg/m^2 (25.3–30.8), and HbA_{1c} of 6.4% (6.1–6.6). A total of 11 women started CSII preconception, and 7 were primaparous. Studies were performed at 19 weeks' (16–25) and 23 weeks' (20–28) gestation, with a between-visit interval of 27 days (17–34). The primary and secondary outcome data are shown in Table 1, with details of the glycemic control achieved shown in the Supplementary Data. There was comparable median [interquartile range] plasma glucose time in target between closed-loop and CSII visits (81 [59–88] vs. 81% [54–90]; P = 0.75).

Hypoglycemia

There were 13 hypoglycemic episodes (8 symptomatic and 5 asymptomatic) during closed-loop delivery versus 20 hypoglycemic episodes (17 symptomatic and 3 asymptomatic) during CSII, including 3 episodes below 36 mg/dL. During closed-loop delivery, the LBGI was lower (P = 0.03), with less time spent below 45 mg/dL (P = 0.04).

Overnight glucose control

The overnight plasma glucose time in target was strikingly high, with no differences

Table 1—*Primary and secondary outcomes during closed-loop and conventional CSII*

	Closed-loop delivery	CSII	*P*
Primary outcome			
Plasma glucose time in target			
Percentage of time in target (63–40 mg/dL)	81 (59–88)	81 (54–90)	0.75
Secondary outcomes			
Plasma glucose outcomes			
Mean plasma glucose (mg/dL)	108 (99–121)	104 (92–108)	0.35
SD of plasma glucose (mg/dL)	25.2 (23.4–37.8)	28.8 (25.2–41.4)	0.69
Hypoglycemia			
Percentage of time hypoglycemic <63 mg/dL	6.9 (1.3–12)	7.5 (3.6–18)	0.48
Percentage of time hypoglycemic ≤50 mg/dL	0.6 (0.0–2.1)	1.5 (0.0–2.7)	0.17
Percentage of time hypoglycemic ≤45 mg/dL	0.0 (0.0–0.2)	0.3 (0.0–1.5)	0.04
Symptomatic hypoglycemia	8	17	
Episodes >45–54 mg/dL	8	12	
Episodes >36–45 mg/dL	5	5	
Episodes <36 mg/dL	0	3	
LBGI*	2.4 (0.9–3.5)	3.3 (1.9–5.1)	0.03
Hyperglycemia			
Percentage of time hyperglycemic >140 mg/dL	14.0 (6.8–28)	6.7 (5.8–22)	0.75
Percentage of time hyperglycemic ≥180 mg/dL	0.2 (0.0–6.0)	0.0 (0.0–6.2)	0.78
High blood glucose index	0.8 (0.3–1.6)	0.4 (0.3–1.4)	0.81
PAEE (kJ/kg)	23.4 (19.7–27.0)	21.2 (19.0–22.1)	0.09
Insulin			
Insulin infusion (units/h)	0.7 (0.5–0.9)	0.8 (0.5–1.1)	0.35
SD insulin infusion rate	0.9 (0.5–1.0)	0.2 (0.2–0.5)	<0.001
Plasma insulin concentration	120 (101–146)	107 (82–145)	0.88

Data are median (interquartile range), unless otherwise indicated. *LBGI assessed the duration and extent of hypoglycemia.

between visits (95 [84–100] vs. 100% [64–100]). However, during conventional CSII, there was significantly less overnight time spent in target by CGM glucose measurements (98 [94–100] vs. 83% [50–100]; $P = 0.03$). There were no discrepancies between plasma and CGM measurements during any other time period.

CONCLUSIONS—In this cohort of pregnant women with tight glycemic control, closed-loop insulin delivery was as effective as conventional CSII but potentially safer because closed-loop delivery reduced the extent and duration of hypoglycemia.

Although there were fewer episodes of hypoglycemia, decreased LBGI, and less time spent below 45 mg/dL, closed-loop delivery could not prevent exercise-related hypoglycemia. Even algorithms incorporating glucagon cannot prevent exercise-related hypoglycemia if there is a rapid glucose reduction, increased insulin on board, or sensor inaccuracy (9,10).

The finding that overnight time in target measured by CGM, rather than plasma glucose, favors closed-loop delivery warrants additional consideration. Plasma glucose measurements are impractical for home studies, so establishing the optimal means of assessing overnight closed-loop delivery is important.

The strengths of this study include a robust crossover design, standardized meals, and physical activity to approximate a real-life setting. Limitations are the small sample size and that the system was not fully automated. The achievement of 100% overnight time in target provides support for the further investigation of closed-loop systems in pregnancy. Home testing over multiple nights now is required to determine whether the near-optimal overnight glucose control can be translated into longer-term real-life benefits.

Acknowledgments—This work was funded by a Diabetes UK project grant (BDA 07/003551). H.R.M. was funded by a National Institute for Health Research (NIHR) research fellowship (PDF/08/01/036). The research was conducted with support from the Juvenile Diabetes Research Foundation, Abbott Diabetes Care (FreeStyle Navigator continuous glucose monitors and sensors), the investigator-initiated study program of the Animas Corporation (Animas 2020 insulin pump), the Medical Research Council Center for Obesity and Related Metabolic Diseases, the NIHR Cambridge Biomedical Research Center, and Addenbrooke's Clinical Research Facility (Cambridge, U.K.). No funder had any role in the study design; data collection, analysis, and interpretation; or manuscript preparation. Ethical approval was received from the Essex 2 Research Ethics Committee (09/H0302/113).

H.R.M. has received honoraria for speaking engagements from Medtronic. S.A.A. has received consultancy and lecture fees from Medtronic, Roche, Novo Nordisk, Eli Lilly, and MDS. M.E.W. has received license fees from Becton Dickenson and has received patent applications. R.H. has received honoraria for speaking engagements from Medtronic, LifeScan, Novo Nordisk, Eli Lilly, Animas, and the Medtronic Advisory Panel; has received license fees from Becton Dickenson; and has received patent applications. No other potential conflicts of interest relevant to this article were reported.

H.R.M. designed and performed the study, interpreted and guaranteed the data, and drafted the manuscript. K.K. recruited participants, performed studies, analyzed and interpreted the data, and reviewed and edited the manuscript. D.E. performed studies and reviewed and edited the manuscript. J.M.A. and K.C. recruited participants and performed studies. M.B. performed studies and reviewed and edited the manuscript. D.S., D.B.D., M.N., M.E.W., and S.A.A. reviewed and edited the manuscript. R.H. designed the study, interpreted and guaranteed the data, and reviewed and edited the manuscript. All authors approved the final version of the manuscript.

The authors thank Helen Rogers (Kings College Hospital, London, U.K.) for the identification of potential participants; Laura Watson (Addenbrooke's Clinical Research Facility, Cambridge, U.K.) and Kate Westgate (University of Cambridge, Medical Research Council Epidemiology, Cambridge, U.K.) for Actiheart PAEE data; Angie Watts (University of Cambridge, Cambridge U.K.) for laboratory support; Dr. Stephen Luzio and colleagues (University of Swansea, Swansea, U.K.); and the generous support of all the participating women and their families and partners who assisted with child care duties.

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