First Look at Control-IQ: A New-Generation Automated Insulin Delivery System

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OBJECTIVE

To pilot test a new closed-loop control technology to validate it for a further large clinical trial.

RESEARCH DESIGN AND METHODS

The t:slim X2 insulin pump with Control-IQ Technology (Tandem Diabetes Care) includes a Dexcom G6 sensor and a closed-loop algorithm implemented in the pump that *1*) automates insulin correction boluses, *2*) has a dedicated hypoglycemia safety system, and *3*) gradually intensifies control overnight, aiming for blood glucose levels of approximately 100–120 mg/dL every morning.

RESULTS

Five patients with type 1 diabetes (mean age 52.8 years, 2/3 male/female, mean A1C 6.5%) used Control-IQ in an outpatient setting (hotel) for approximately 37 h. During the closed loop, mean glucose was 129 mg/dL (135/121 mg/dL during the day/night), time within target range 70–180 mg/dL was 87% (82%/94% during the day/night), and time <60 mg/dL was 1.1% (2.0%/0.0% during the day/night).

CONCLUSIONS

Following this pilot trial, Control-IQ was deployed in several studies, including the large-scale National Institutes of Health International Diabetes Closed-Loop (iDCL) Trial.

In July 2016, *Diabetes Care* published a symposium that was exclusively dedicated to outpatient studies of automated insulin delivery done with portable artificial pancreas (AP) systems (1–5), including trials at patients' homes lasting a month or more (1–4) and studies in young children (5). In the past 2 years, the AP transitioned from research to clinical practice with long-term AP use and challenging exercise studies (6–9). A pivotal trial was completed of the first commercial hybrid AP system—the Medtronic 670G, which automatically modulates basal rate but does not automate insulin correction boluses (6)—and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) invested in four large projects intended to bring AP systems to market (9). The focus of this pilot study was to test a new AP system using a well-established control algorithm implemented in a new platform, prior to launching large-scale outpatient clinical trials.

RESEARCH DESIGN AND METHODS

An investigational device exemption was approved by the U.S. Food and Drug Administration (FDA) (IDE #G170255), and then the study was approved by the

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University of Virginia Institutional Review Board and registered on ClinicalTrials.gov (reg. no. NCT03368937). The major eligibility criteria included *1*) clinical diagnosis of type 1 diabetes treated with insulin for at least 1 year, *2*) use of an insulin pump for at least 6 months, *3*) age 18 to <75 years, *4*) A1C <10.5%, and *5*) total daily insulin dose at least 10 units/day and ≤100 units/day. Subject participation included *1*) signing informed consent and having a screening visit, *2*) an active 36- to 48-h session in an outpatient supervised setting (hotel) using the Control-IQ system (described below), and *3*) an assessment of participants' impression of the AP system using a technology acceptance questionnaire. The study had predefined criteria for success that included time in target range 70–180 mg/dL of at least 72 ± 5%, median time <70 mg/dL no more than 5%, and connectivity in closed-loop control and continuous glucose monitoring (CGM) of at least 80%. These criteria were defined for regulatory purposes and had to be met in order to proceed with subsequent larger-scale investigations. In addition, there were several predefined challenges to the system with intentional disconnections by study staff to test the system recovery (e.g., CGM sensor change, intentional loss of connectivity with pump). Those intentional times of loss of connectivity were not included in the analysis.

Artificial Pancreas System

The Tandem t:slim X2 insulin pump with Control-IQ Technology (Tandem Diabetes Care, San Diego, CA) uses a G6 CGM sensor (see photo in Supplementary Data) and is a third-generation descendant of the mobile DiAs (Diabetes Assistant) system developed at the University of Virginia (UVA) in 2011 (10). DiAs used a smartphone to run AP algorithms and transmit CGM and insulin delivery data in real time to the cloud (10,11). During 2012–2013, DiAs enabled the first outpatient trials of mobile AP (12–14), and since then it has been in use in a number of clinical studies (2,3,5,7,8). The second generation of DiAs—inControl, developed by TypeZero Technologies, Inc.—is a mobile AP system that was used and tested extensively in several clinical trials, including long-term large-scale studies of mobile AP (e.g., ClinicalTrials.gov reg. nos. NCT02679287, NCT02844517, and NCT02985866). While preserving the same AP algorithm, Control-IQ took a step forward by implementing the algorithm in the t:slim X2 insulin pump. The distinguishing features of this algorithm include *1*) automated insulin correction boluses administered using CGM-based patient state estimation; *2*) a dedicated hypoglycemia safety system that attenuates smoothly, or discontinues, insulin delivery using CGM and insulin-on-board information; and *3*) gradually intensified control overnight, sliding the algorithm target down to achieve blood glucose levels of approximately 100–120 mg/dL by the morning.

RESULTS

Five patients with type 1 diabetes, mean age 52.8 years, two male and three female, mean A1C 6.5%, and mean daily insulin dose 0.43 units/kg, were recruited and completed the pilot testing of Control-IQ. All patients participated simultaneously, on a single weekend. The total duration of system use was 185.2 h (37.0 h per patient) with closed-loop control enabled, excluding periods of intentional disconnections by staff. In terms of system connectivity, the CGM signal was available 94.4% of the time and closed loop was running without interruption 98.4% of the time.

Table 1 presents the glycemic outcomes during the study, computed from CGM data as recommended by the recent International Consensus on Use of CGM (15), when Control-IQ was active: the percent time in the target range (TIR) of 70–180 mg/dL was 82% on average during the day and 94% overnight, with minimal time spent in the hypoglycemic range <54 mg/dL (0.7% median time). The intersubject variability of the TIR was low: by subject, overall TIR was 76%, 82%, 91%, 92%, and 94%, i.e., control of over 75% in target range was achieved for all participants, with a median coefficient of variation of 27% (21% overnight). The control was better (but not statistically superior) overnight,

Table 1—Outcomes of Control-IQ use

Glycemic outcomes of Control-IQ use

Metric	Overall	Daytime	Nighttime
Mean glucose, mg/dL	129	135	121
Coefficient of variation, % (median)	27	27	21
% time <54 mg/dL (median)	0.7	0.0	0.0
% time <60 mg/dL (median)	1.1	2.0	0.0
% time <70 mg/dL (median)	2.9	4.1	1.0
% time in range 70–180 mg/dL (mean)	87	82	94
% time >180 mg/dL (median)	4.7	7.5	5.7
% time >250 mg/dL (median)	0.0	0.0	0.0
% time >300 mg/dL (median)	0.0	0.0	0.0

Participants' impression of Control-IQ use

Question (1 = lowest rating to 5 = highest rating)	Average score
How easy to use was the device? (1 = Not at all to 5 = Extremely)	5.0
How useful in managing your diabetes was the device? (1 = Not at all to 5 = Extremely)	4.8
How much did you trust the device? (1 = Not at all to 5 = Extremely)	5.0
I had greater peace of mind while wearing the device. (1 = Strongly disagree to 5 = Strongly agree)	4.8
It will be hard to give up the device once the study is over. (1 = Strongly disagree to 5 = Strongly agree)	5.0

which is consistent with the Control-IQ algorithm design. Results were similar when the entire study period was analyzed (mean TIR 86% overall, mean glucose 130 mg/dL, and median time <70 mg/dL 2.8%). Participants completed technology acceptance questionnaires at the end of the trial, and five selected questions, which were answered on a scale of 1–5, are presented in Table 1. Participant answers were overwhelmingly positive. There were no adverse effects or significant device issues during the study.

CONCLUSIONS

To be ultimately established and accepted as a viable treatment of diabetes, AP systems need to prove their safety and efficacy in large clinical trials in a person's natural environment. Here, we present the first data from the new Control-IQ system, which was tested in a pilot study prior to its inclusion in subsequent larger clinical trials. The system met the predefined criteria for success in this small study of well-controlled individuals with type 1 diabetes; therefore, its use in subsequent studies was approved by the FDA.

Control-IQ is the next generation of the UVA AP system, which in its mobile (DiAs and inControl) implementations has logged at least 15,000 days of outpatient use to date by more than 450 people with T1D. Most DiAs and inControl studies were multicenter, including research sites in the U.S., Europe, Israel, and Argentina, which ensured external validity of the data (2,3,5,7,8,13,14). The same control algorithm was used with three sensors (Dexcom G4, G5, G6), two insulin pumps (Roche, Tandem), implemented in mobile AP based on a smartphone, and now embedded in an insulin pump (Tandem t:slim X2 with Control-IQ). The distinct features of the algorithm (automated correction boluses, hypoglycemia prevention, and overnight intensified control) have remained unchanged through several generations of hardware implementations.

Since the completion of this pilot trial, Control-IQ was used in a recent multicenter winter-sport study of 48 adolescents and children ages 6 years and up skiing in Virginia, California, and Colorado (ClinicalTrials.gov reg. no. NCT03369067) and is now included in UVA's Project Nightlight (ClinicalTrials.gov reg. no. NCT02679287) and in Protocol 3 of the multicenter International Diabetes Closed-Loop (iDCL) Trial funded by NIDDK (NCT03563313). Thus, as intended, this pilot study opened the field for subsequent large-scale investigations. In particular, the iDCL Trial will be using the new Dexcom G6 sensor, recently approved by the FDA to work without fingerstick calibration, which should contribute to further acceptance of this new technology by patients and health care providers.

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Duality of Interest. S.B. reports material support provided to UVA from Tandem Diabetes Care, Roche Diagnostics, and Dexcom. B.K. has patents related to the study technology managed by the UVA Licensing & Ventures Group, had speaking engagements for Dexcom, and received material support (to UVA) from Tandem Diabetes Care, Roche Diagnostics, and Dexcom. At the time of acceptance of this manuscript, B.K. was also a shareholder and board member of TypeZero Technologies, Inc. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. S.B designed and conducted the trial and wrote the manuscript. D.R. performed the data analysis and reviewed and edited the manuscript. E.E. conducted the trial and reviewed and edited the manuscript. B.K. obtained funding, assisted in the design of the trial, and wrote the manuscript. S.B. 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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