Perioperative Fully Closed-Loop Insulin Delivery in Patients Undergoing Elective Surgery: An Open-Label, Randomized Controlled Trial

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OBJECTIVE

Perioperative management of glucose levels remains challenging. We aimed to assess whether fully closed-loop subcutaneous insulin delivery would improve glycemic control compared with standard insulin therapy in insulin-requiring patients undergoing elective surgery.

RESEARCH DESIGN AND METHODS

We performed a single-center, open-label, randomized controlled trial. Patients with diabetes (other than type 1) undergoing elective surgery were recruited from various surgical units and randomly assigned using a minimization schedule (stratified by HbA_{1c} and daily insulin dose) to fully closed-loop insulin delivery with fast-acting insulin aspart (closed-loop group) or standard insulin therapy according to local clinical practice (control group). Study treatment was administered from hospital admission to discharge (for a maximum of 20 days). The primary end point was the proportion of time with sensor glucose in the target range (5.6–10.0 mmol/L).

RESULTS

Forty-five patients were enrolled and assigned to the closed-loop ($n = 23$) or the control ($n = 22$) group. One patient (closed-loop group) withdrew from the study before surgery and was not analyzed. Participants underwent abdominal (57%), vascular (23%), orthopedic (9%), neuro (9%), or thoracic (2%) surgery. The mean proportion of time that sensor glucose was in the target range was 76.7 ± 10.1% in the closed-loop and 54.7 ± 20.8% in the control group (mean difference 22.0 percentage points [95% CI 11.9; 32.0%]; $P < 0.001$). No episodes of severe hypoglycemia (<3.0 mmol/L) or hyperglycemia with ketonemia or any study-related adverse events occurred in either group.

CONCLUSIONS

In the context of mixed elective surgery, the use of fully closed-loop subcutaneous insulin delivery improves glucose control without a higher risk of hypoglycemia.

Hyperglycemia is particularly frequent in the perioperative period, with prevalence estimates ranging from 20 to 80%, depending on the type of surgery (1,2). The

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high frequency is explained by the surgical stress that results in an increase of catabolic hormones inducing insulin resistance and compromising β-cell function (3). Observational and prospective randomized studies have shown that perioperative hyperglycemia is associated with increased rates of morbidity and mortality (4–6). Perioperative hyperglycemia is also known to increase hospital costs and readmission rates (7). Thus, there is a universal consensus that perioperative hyperglycemia should be treated with insulin once glucose levels are >10.0 mmol/L (8,9). However, striving for more stringent glycemic goals increased the risk of iatrogenic hypoglycemia in previous studies using standard therapeutic approaches (10,11).

Perioperative glucose management requires frequent blood glucose monitoring and insulin adjustments to accommodate the highly variable insulin requirements caused by surgical stress changes in nutritional status and prescribed medication (e.g., vasopressors, glucocorticoids). Implementation in the perioperative period is further complicated by the need to coordinate clinical care among various staff teams (e.g., surgeons, anesthesiologists, ward physicians) and care settings (e.g., transitions from operating room to the postanesthesia care unit and general wards) (12).

We have previously reported the concept of fully automated subcutaneous closed-loop insulin delivery (also known as the artificial pancreas) to address the unmet need of improving glucose control without increasing the risk of hypoglycemia and to streamline clinical staff workflow (13). The closed-loop approach involves communication of real-time glucose data provided by a continuous glucose monitoring (CGM) device to a control algorithm, which autonomously modulates insulin delivery in response to sensor glucose levels. In previous work, we have demonstrated that fully automated closed-loop insulin delivery in noncritically ill patients outside early perioperative care is efficacious and safe. In addition, it achieves superior glucose control over standard insulin therapy, including in challenging groups such as those requiring nutrition support and/or hemodialysis (13–15).

In the perioperative context, the fully closed-loop approach has so far only been adopted using the STG-55 or its precursor device made by Nikkiso, which is available exclusively in Japan. The system relies on continuous intravenous (IV) glucose measurements, drawing 2 mL of blood per hour while modulating an IV insulin and dextrose infusion. Although glycemic benefits were convincingly shown (16,17), the system's invasiveness, substantial blood requirements, and complexity restrict its use to a transient period of time (e.g., 48 h) and intensive care settings only. Thus, fully closed-loop insulin delivery using the subcutaneous route for both glucose sensing and insulin delivery may offer a more pragmatic approach for perioperative glucose management.

In this article, we report the results of a single-center, randomized, open-label trial assessing the efficacy of fully closed-loop insulin delivery in patients with diabetes other than type 1 who require insulin while undergoing elective surgery at a tertiary hospital. We hypothesized that perioperative closed-loop insulin delivery compared with standard insulin therapy would improve glycemic control without increasing the risk of hypoglycemia from hospital admission to discharge.

RESEARCH DESIGN AND METHODS

Study Design and Participants

In this single-center, open-label, randomized controlled trial, participants were recruited during preadmission appointments at University Hospital of Bern. We included patients with type 2 or other forms of non–type 1 diabetes aged ≥18 years, planned for elective surgery of ≥2 h duration expected to require insulin perioperatively and to stay for ≥72 h in the hospital. Exclusion criteria were type 1 diabetes, pregnancy, breastfeeding, any physical or psychological condition likely to interfere with the conduct of the trial or the interpretation of the results, and incapacity to give informed consent. Full inclusion and exclusion criteria are available in the Supplementary Material. Eligible candidates were identified through elective surgery plans and direct referrals by local surgeons. Written informed consent was obtained from participants during the preadmission appointment, before the start of study-related procedures. The study protocol was approved by the local research ethics committee (Ethics Committee Bern, Switzerland, approval number 2020-01024). The safety of the trial was overseen by a local study monitor. The trial was done in accordance with the principles of the Declaration of Helsinki. The full trial protocol is available in the Supplementary Material.

Randomization and Masking

Eligible participants were randomly allocated (1:1) to either fully closed-loop subcutaneous insulin delivery with fast-acting insulin aspart (closed-loop group) or standard insulin therapy according to modus operandi of responsible clinical care teams (control group). Group allocation was done using the minimization method (18), implemented in the randomization software MinimPy (19) to balance between group characteristics as follows: glycated hemoglobin A_{1c} (HbA_{1c}) (<7.5 or ≥7.5%) and total daily insulin dose (<50 or ≥50 units). The allocation was performed after recruitment by the investigator. This study was open label, but the CGM receiver in the control group masked the sensor glucose values to blind the participant, investigators, and ward staff.

Procedures

At enrollment, participant demographics and medical history, body weight and height, comorbidity burden, antidiabetic medication, and details of the planned surgery (including day of hospital admission) were recorded, and HbA_{1c} was measured if not performed within ≤3 months. Devices were installed upon hospital admission by the study team and continued for a maximum of 20 days or until hospital discharge. In the closed-loop group, this included the discontinuation of the participants' usual insulin therapy and sulfonylurea medication, if prescribed. All other antidiabetic medications were continued as per prescription of the anesthesiologists. A subcutaneous cannula was inserted by the investigator in the abdomen or upper arm for delivery of fast-acting insulin aspart (Fiasp; Novo Nordisk, Bagsværd, Denmark) by a study pump (Dana Diabecare RS; SOOIL, Gyeonggi-do, South Korea). A subcutaneous real-time CGM sensor (Dexcom G6; Dexcom, San Diego, CA), which performed with satisfactory accuracy in previous inpatient studies (20, 21), was placed on the upper arm or abdomen. The pump was controlled by the CamAPS HX closed-loop application (CamDiab Ltd., Cambridge, U.K.), which resided on an unlocked Android

phone and received sensor glucose data from a Dexcom G6 transmitter. Using the Cambridge adaptive model predictive control algorithm (version 0.3.71, HX variant), insulin infusion was modulated every 8–12 min in response to sensor glucose data. The CamAPS HX system controls glucose levels fully autonomously without the need for manual input to manage meals or nutrition support. Sensor glucose and insulin data were automatically uploaded to the Diasend/Glooko data management platform (https://diasend.com//en). The control algorithm was initialized using the participant's weight and estimated total daily insulin dose. The nominal glucose target was set to the default of 5.8 or 7.0 mmol/L on the basis of individual circumstances. The low-glucose alert was used per the default setting (3.1 mmol/L). When sensor glucose was unavailable during warmup or for other technical reasons, hourly arterial blood glucose was entered by the study team without interruptions to closed-loop insulin delivery. In the control group, a masked CGM sensor (Dexcom G6) was inserted at hospital admission and maintained throughout the study duration for the assessment of glucose outcomes. None of the study-related activities interrupted or specified clinical workflows of perioperative care.

Outcomes

The primary outcome was the proportion of time the sensor glucose concentration was in the target glucose range of 5.6–10.0 mmol/L from the first to the last sensor reading. Secondary outcomes comprised time with sensor glucose below target range (<5.6 mmol/L), proportion of time in hyperglycemia (>10.0 and >20.0 mmol/L) and hypoglycemia (<3.9 and <3.0 mmol/L), and mean sensor glucose and glucose variability (defined as the SD and coefficient of variation of sensor glucose). The proportion of time the sensor glucose concentration was in the range of 3.9–10.0 mmol/L was calculated to align with the consensus recommendations for CGM and reporting in clinical trials (22). Safety outcomes included severe hypoglycemia (<2.2 mmol/L) and clinically significant hyperglycemia (>20.0 mmol/L) with ketonemia (β-hydroxybutyrate >1.0 mmol/L), as well as other adverse events related to the study procedures.

Sample Size Calculation

This was a proof-of-concept study in which we planned for up to 40 patients with at least 48 h of data. This sample size was determined to have a power of 80% to detect a clinically significant between-group difference in the primary outcome of 20 percentage points with the use of a two-sided *t* test and an α level of 0.05. Since previous inpatient studies might not provide reliable information about the SD of the primary end point in the perioperative setting, an SD of 30% for the primary outcome was used for the power calculation.

Statistical Analysis

We analyzed efficacy and safety data according to the intention-to-treat principle. We calculated outcomes and performed statistical analyses with R (version 4.0.2). The unpaired Welch *t* test was used to compare means of variables conforming to normality assumptions, while the Mann-Whitney *U* test was used otherwise. The proportion of time sensor glucose was in target range (primary outcome) was compared using the unpaired Welch's *t* test. Mean difference and 95% CIs between the interventions (or median of the differences corresponding to the Hodges-Lehmann estimate and its 95% CI in cases of nonparametric testing) are reported for all prespecified outcomes. We tabulated the number of device and safety events in each trial group and compared the proportion of participants with events in each group with the Fisher exact test. We report values as mean ± SD or median (25^{th}; 75^{th} percentile), unless stated otherwise. Reported *P* values correspond to two-tailed tests. $P < 0.05$ was considered statistically significant.

RESULTS

From 23 September 2020 to 20 August 2021, 72 participants were approached for enrollment, of whom 45 were eligible and consented. Twenty-three were randomly assigned to the closed-loop group and 22 to the control group (Supplementary Material). Five participants had <48 h of data. One participant of the closed-loop group withdrew from the study because of perceived discomfort with wearing the study device while waiting for the postponed surgery. Due to the withdrawal before surgery, data from this participant were not included in the analysis. Four of 44 participants experienced an earlier discharge than expected and, thus, provided <48 h of sensor glucose data. Underlying reasons were quick recovery (two in the closed-loop group and one in the control group) and terminated surgery because of metastasized disease and transition to palliative care (one participant in the control group). Nineteen and 20 participants in the closed-loop and control groups, respectively, were discharged before the maximum study duration of 20 days. The Consolidated Standards of Reporting Trials flow diagram is shown in the Supplementary Material.

The baseline characteristics of the closed-loop and control groups are shown in Table 1. Mean age was 67.3 ± 15.0 years in the closed-loop group and 69.6 ± 9.6 years in the control group, of whom 45.4% and 22.7%, respectively, were female. In both groups, abdominal surgery was the predominant type of elective surgery (54.5 and 59.1% in closed-loop and control groups, respectively). Presurgery HbA_{1c} was 7.5 ± 1.8% (58.0 ± 19.7 mmol/mol) in the closed-loop group and 7.6 ± 1.9% (60.0 ± 20.8 mmol/mol) in the control group. The mean Charlson Comorbidity Index, length of hospital stay and surgical complications (classified according to standardized definitions [23]), and American College of Surgeons preoperative risk assessment for perioperative complications (24) did not significantly differ between groups (Table 1 and Supplementary Material).

The study duration, defined as the period from the first sensor reading after admission until the last sensor reading, was similar between groups (8.4 ± 5.0 days in the closed-loop group and 9.4 ± 6.0 days in the control group; *P* = 0.558). Closed-loop was suspended in four participants because of transient stays in the intensive care unit in two, decision of a clinical team to temporarily use IV insulin for glucose control after a surgical revision in one, and a magnetic resonance examination (bridged with 4 units of insulin detemir) in one. The time with suspension of closed-loop insulin delivery ranged from 8 to 97 h. Sensor glucose data were available for 99.2% (25^{th}; 75^{th} percentile 97.9; 99.9) of the study period in the closed-loop group and 99.0% (98.2; 100.0) in the control group. Closed-loop therapy was

Table 1—Baseline characteristics

	Closed-loop group	Control group
Patients, *n*	22	22
Age (years)	67.3 ± 15.0	69.6 ± 9.6
Female sex	45.4	22.7
BMI (kg/m^2)	30.8 ± 7.8	29.4 ± 3.7
HbA_{1c}		
%	7.5 ± 1.8	7.6 ± 1.9
mmol/mol	58.0 ± 19.7	60.0 ± 54.5
Diabetes duration (years)*	12.2 ± 10.5	8.2 ± 6.3
Duration of insulin therapy (years)**	4.4 ± 5.6	4.0 ± 4.9
Glucose-lowering therapy at enrollment (%)		
Basal insulin therapy	18.2	31.8
Basal-bolus insulin therapy	27.3	31.8
Insulin naïve	54.5	36.4
Metformin	59.1	59.1
Gliptins	27.3	13.6
GLP-1RA	13.6	9.1
SGLT inhibitors	13.6	18.2
Sulfonylurea	9.1	0.0
Charlson comorbidity index	7.3 ± 3.8	8.0 ± 3.2
ACS risk of complications (%)	20.1 ± 13.1	22.7 ± 8.8
Surgical discipline (%)		
Abdominal surgery	54.5	59.1
Neurosurgery	4.5	13.6
Orthopedic surgery	13.6	4.5
Thoracic surgery	4.5	0
Vascular surgery	22.7	22.7

Data are mean ± SD or %. ACS, American College of Surgeons; GLP-1RA, glucagon-like peptide 1 receptor agonist; SGLT, sodium–glucose cotransporter. *n = 21 per group (data from two participants are missing). **Insulin-naïve patients are not considered.

operational for 99.6% (98.8; 100.0) of the study duration and for 100.0% (99.1; 100.0) of the time when sensor glucose data were available.

Surgery was performed on the day of admission in 10 participants (45.5%) of the closed-loop group and 10 (45.5%) of the control group; all other participants were admitted on the day before surgery. Eight participants (36.4%) of the closed-loop group and one (4.5%) of the control group received preoperative oral carboloading (1–4 h before admission). Mean duration of surgery was 257 ± 129 min in the closed-loop group and 267 ± 111 min in the control group (P = 0.528). During surgery, three closed-loop participants (13.6%) required IV insulin for the treatment of hyperkalemia, whereas 13 control participants (59.1%) received IV insulin for glucose control. The proportion of participants receiving glucocorticoids intraoperatively was 63.6% in the closed-loop group and 72.7% in the control group (Supplementary Material).

In the postoperative period, control participants were mostly treated with subcutaneous insulin, but 36.4% transiently received IV insulin during their stay on the ward. Delivery of nutrition support parenteral and/or enteral was 36.4 and 31.8% of participants in the closed-loop and control groups, respectively. The proportion of participants receiving postoperative glucocorticoids was 13.6% in both groups. Length of hospital stay was 9.5 days (25^{th}; 75^{th} percentile 5.0; 15.3) in the closed-loop group and 9.4 days (4.8; 13.0) in the control group. Occurrence of surgical complications (assessed using the Clavien-Dindo classification) did not significantly differ between the groups (Supplementary Material).

The proportion of time that sensor glucose concentration was in the target range (5.6–10.0 mmol/L; primary outcome) was 22.0 percentage points (95% CI 11.9; 32.0) higher in the closed-loop group than in the control group (76.7 ± 10.1 vs. 54.7 ± 20.8%; $P < 0.001$) (Table 2). Mean sensor glucose concentration was significantly lower in the closed-loop group than in the control group (8.0 ± 0.7 vs. 9.4 ± 2.5 mmol/L) (Table 2). Glycemic variability during closed-loop therapy, as measured by the SD of sensor glucose measurement, was significantly lower compared with conventional insulin therapy (2.1 ± 0.4 vs. 2.6 ± 0.8 mmol/L; P = 0.011) (Table 2). The coefficient of variation of sensor glucose was 24.4 ± 3.9% during closed-loop insulin therapy and 28.5 ± 7.1% with conventional insulin therapy (P = 0.149). The proportion of time spent at sensor glucose concentrations above the target range (>10.0 mmol/L) was significantly lower in the closed-loop than in the control group (15.4 ± 8.4 vs. 33.9 ± 26.4%; P = 0.004), but the time spent below the target range (<5.6 mmol/L) did not differ significantly between groups (P = 0.257) (Table 2). The proportion of time spent with concentrations <3.9, <3.0, and >20.0 mmol/L were low and not significantly different between groups (Table 2). Total daily insulin dose delivered did not differ significantly between groups (P = 0.226) (Table 2). Averaged 24-h profiles of sensor glucose and insulin delivery data are illustrated in Fig. 1. Mean daily sensor glucose values over the first 8 days of the study are shown in Fig. 2.

The proportion of time that overnight (00:00–06:00 h) and daytime (06:00–00:00 h) sensor glucose concentrations were in the target range was significantly higher in the closed-loop group than in the control group (overnight difference 21.4 percentage points [95% CI 10.2; 32.8 ($P < 0.001$)]; daytime difference 21.5 percentage points [10.1; 32.8 ($P < 0.001$)]). Mean sensor glucose was significantly lower in the closed-loop group than in the control group during the overnight and daytime periods (Supplementary Material). SD of sensor glucose during the overnight and daytime periods was significantly lower in the closed-loop group than in the control group. No significant differences between groups were observed for the coefficient of variation of sensor glucose. Measures of hypoglycemia did not significantly differ between groups (Supplementary Material).

No episodes of severe hypoglycemia or significant hyperglycemia with ketonemia

Table 2—Primary and secondary outcomes

	Closed-loop group (n = 22)	Control group (n = 22)	Group difference	95% CI	P
Primary outcome					
Percent time with sensor glucose in target range (5.6–10.0 mmol/L)	76.7 ± 10.1	54.7 ± 20.8	22.0	11.9; 32.0	<0.001
Secondary outcomes					
Percent time with sensor glucose level (mmol/L)					
3.9–10.0	84.2 ± 8.6	64.3 ± 25.4	19.9	8.2; 31.7	0.002
<5.6	6.4 (3.3; 9.0)	6.3 (1.5; 14.5)	0.3	−4.9; 3.2	0.953
<3.9	0.2 (0.0; 0.6)	0.0 (0.0; 0.6)	0.0	−0.03; 0.3	0.422
<3.0	0.0 (0.0; 0.01)	0.0 (0.0; 0.0)	0.0	0.0; 0.0	0.890
>10.0	15.4 ± 8.4	33.9 ± 26.4	−18.5	−30.7; −6.4	0.004
>20.0	0.0 (0.0; 0.0)	0.0 (0.0; 0.3)	0.0	−0.14; 0.0	0.071
Mean sensor glucose levels (mmol/L)	8.0 ± 0.7	9.4 ± 2.5	−1.4	−2.5; −0.2	0.025
SD sensor glucose levels (mmol/L)	2.1 ± 0.4	2.6 ± 0.8	−0.5	−0.9; −0.1	0.011
CV sensor glucose levels (%)	25.4 ± 3.9	28.5 ± 7.1	−3.1	−6.0; 1.0	0.149
Total daily insulin dose (IU)	27.1 ± 14.2	21.4 ± 16.7	5.7	−3.7; 15.2	0.226

Data are mean ± SD or median (25th; 75th percentile). P values were computed using Welch t test or Wilcoxon rank sum test. The 95% CI is the difference in the location parameters (difference in means or Hodges-Lehman estimator). CV, coefficient of variation.

occurred in either group. One severe adverse event (cardiac arrest) unrelated to the study procedures occurred in one control participant (Table 3). Device deficiencies occurred in six participants in the closed-loop group and two in the control group. The most common device deficiency was intraoperative malfunction of the CGM device, which in three cases resulted in premature sensor failure requiring replacement.

CONCLUSIONS

In this randomized controlled trial, we compared the glycemic efficacy and safety of fully closed-loop subcutaneous insulin delivery with standard insulin therapy in mixed elective surgery patients with diabetes other than type 1 from hospital admission until discharge or a maximum of 20 days. We observed that fully closed-loop insulin delivery significantly improved glycemic control by increasing the time spent in the glycemic target range and lowering mean sensor glucose. Improved glycemic control was notably achieved without increasing the risk of hypoglycemia.

The glycemic benefits shown by this study provide evidence that the fully automated closed-loop approach has the potential to substantially improve glucose management during a complex metabolic situation caused by surgical stress and use of glucocorticoids, vasopressors, and nutritional support. Enrolled participants underwent a wide range of surgical interventions with various postsurgical procedures and needs. The consistent benefit of the closed-loop treatment underscores its wide applicability due to its adaptive design for personalized treatment.

Compared with our previous inpatient fully closed-loop studies using the same model predictive algorithm and primary outcome measure (i.e., percent time with sensor glucose between 5.6 and 10.0 mmol/L), the closed-loop approach in the current study achieved an even higher proportion of time spent in the target range (77 vs. 66 [13] and 68% [14]). In these previous studies, the fully closed-loop system was started during the course of the hospital stay (not upon admission) and enrolled a mixed medical and surgical population. Of note, the control group in the present study showed a higher proportion of time spent in the glucose target range compared with those of the previous studies (55 vs. 36 and 42%, respectively). We can only speculate on the underlying reasons, but the relatively high use of IV insulin in the control group of the present study may have resulted in a higher level of surveillance and therapeutic adjustments, and overall oral food intake may have been lower than in previous studies.

Of note, this was a proof-of-concept study and not powered to show potential differences in clinical outcomes such as length of stay or postoperative complications in previous studies. Whether improved glucose control due to fully closed-loop insulin delivery may translate into improved clinical outcomes will have to be investigated in trials with larger sample sizes. The previously published Randomized Study of Basal-Bolus Insulin Therapy 2 Surgery (RABBIT 2 Surgery) in general surgery patients with type 2 diabetes demonstrated that more intensive glucose control (basal-bolus insulin therapy, n = 104) compared with less stringent control (sliding scale insulin [SSI] therapy, n = 107) resulted in significantly reduced hospital complications (composite of wound infection, pneumonia, bacteremia, and respiratory and acute renal failure) (4). The mean blood glucose levels in more intensively versus less stringently controlled patients were similar to mean sensor glucose levels in the basal bolus vs. SSI group study (e.g., 8.1 vs. 9.5 mmol/L). Conversely, the average total insulin use in the RABBIT 2 Surgery study differed significantly between groups (33.4 vs. 12.3 units/day), whereas no such between-group difference in insulin delivery was found in the basal bolus vs. SSI group study. Finally, better glucose control in the RABBIT 2 Surgery study came at a cost of a higher risk of mild hypoglycemia (29 vs. 5% of participants experienced blood glucose levels <3.9 mmol/L), which could be avoided using a fully closed-loop approach as done in the basal bolus vs. SSI group study. Benefits of improved perioperative glucose control on postoperative complications were also demonstrated in two meta-analyses (25,26). Both analyses only considered randomized controlled trials, with the first focusing on surgical site infections and the second evaluating various postoperative

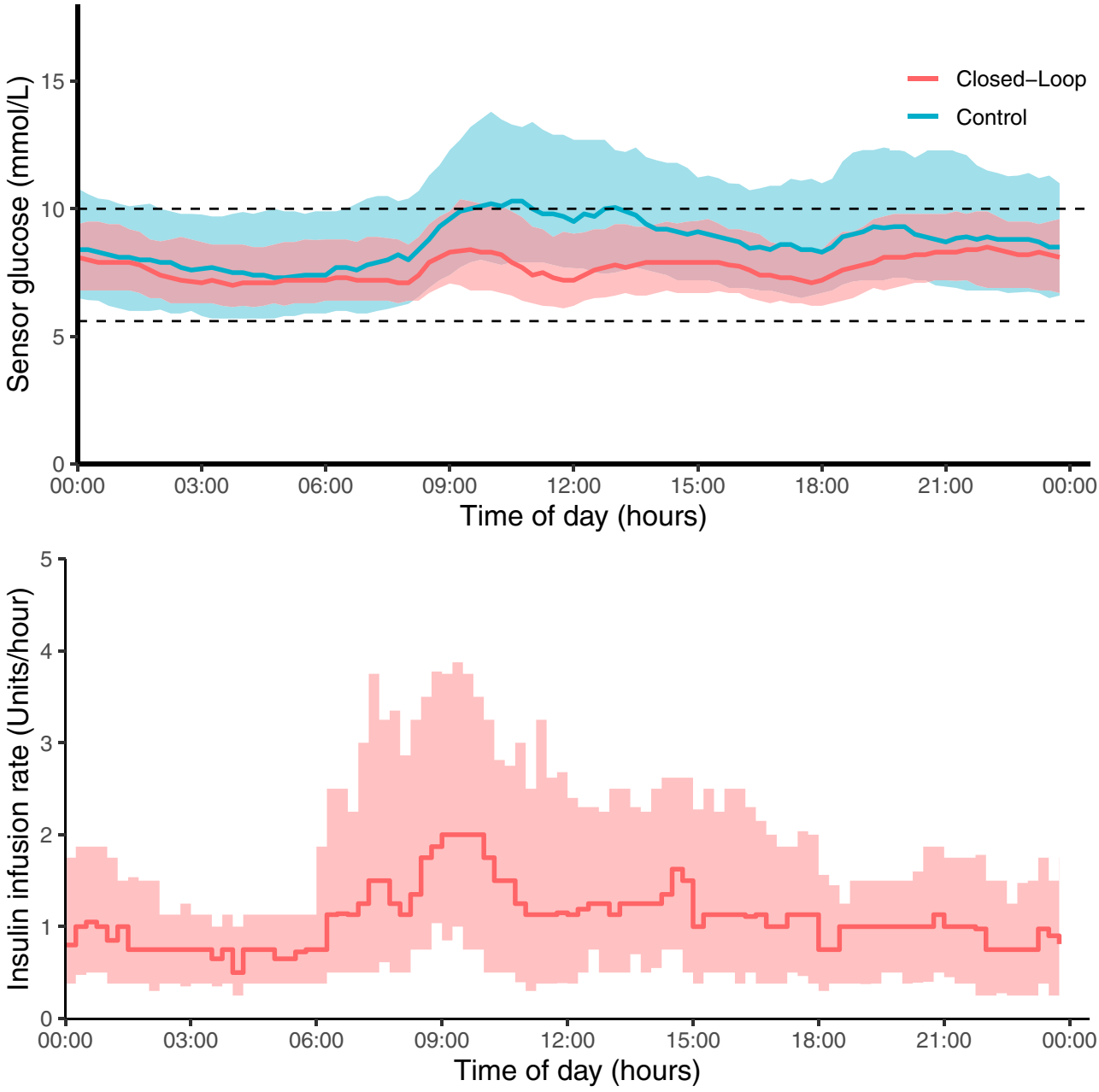

Figure 1—Sensor glucose concentration and insulin delivery profiles. Top: sensor glucose in a 24 h representation during closed-loop and control intervention. The target glucose range is 5.6–10.0 mmol/L. Bottom: algorithm-directed insulin delivery during closed-loop intervention. Solid lines indicate medians and shaded areas indicate the interquartile range.

complications. Authors concluded that intensive glucose control resulted in a lower risk of surgical site infections, overall postoperative infectious complications, atrial fibrillation, and renal failure, as well as shorter length of stay in the intensive care unit and hospital. However, in both analyses, intensive glucose control was again shown to increase the risk of hypoglycemia. It is well established that episodes of hypoglycemia should be avoided because they can potentially result in cardiac arrhythmias, neurocognitive dysfunction, longer intensive care unit stay, and even death (27,28). Since the closed-loop approach yielded significantly better glucose control without increasing the risk of hypoglycemia, future work will need to determine whether *1*) this emerging treatment modality can translate into improved perioperative patient outcomes and *2*) identify specific patient groups in whom such efforts are of particular relevance.

Apart from providing a tangible treatment option, the presented fully closed-loop approach, which uses the subcutaneous route for both glucose sensing and insulin delivery, provides additional insights into the ongoing debate regarding the use of IV or subcutaneous insulin. Our findings support the notion that satisfactory control can be achieved using subcutaneous insulin delivery, even in patients with complex needs. The fully closed-loop subcutaneous insulin approach, therefore, fits well into the call for pragmatic glucose management in light of the coronavirus disease 2019 pandemic, which requires economical use of staff resources and minimization of patient interactions (29). Although the high staff

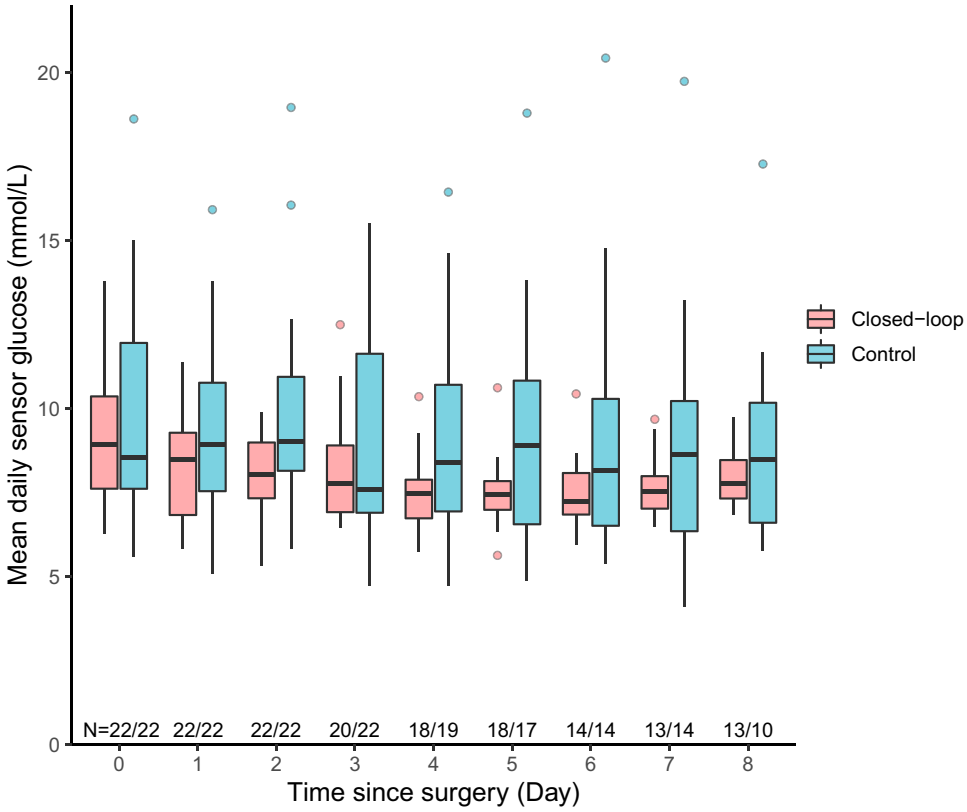

Figure 2—Time course of mean daily sensor glucose after surgery for the closed-loop group and the control group. Box-and-whisker plots show median values (solid line), interquartile range (box outline), spread of data points without outliers (whiskers), and outliers identified as measurements beyond 1.5 * interquartile range (symbols). N corresponds to the number of participants at the respective time points and included in the calculation. Data after day 8 are not shown because of the low number of participants after this time.

costs of IV insulin delivery (30) can be reduced through the use of a previously published fully closed-loop system combining IV insulin delivery with subcutaneous glucose sensing (31), IV insulin delivery is often not feasible outside the intensive care environment because of lower staffing levels and safety concerns (32,33).

We acknowledge some limitations of the current study. The study was conducted at a single center only with a limited sample size. In addition, hospital staff were not involved in the management of study devices, precluding any statements regarding its compatibility with daily clinical and operational workflows.

In conclusion, we have shown that fully closed-loop insulin delivery allows for effective and safe perioperative glycemic management in patients undergoing elective surgery. To support the wider adoption of fully closed-loop insulin therapy in the perioperative setting, future research is required to assess whether closed-loop glycemic control can translate into improved clinical outcomes and increased cost-effectiveness.

Table 3—Safety and device issues

	Closed-loop group, *n*	Control group, *n*
Severe hypoglycemic events (plasma glucose <2.2 mmol/L)	0	0
Significant hyperglycemic events*	0	0
Serious adverse events	0	1†
Adverse device effects	0	0
Other adverse events	3	1
Device deficiencies	6	2

*Defined as plasma glucose >20.0 mmol/L with ketonemia (β-hydoxybutyrate >1.0 mmol/L). †Non–study-related (non–ST-elevated myocardial infarction). Nonserious adverse events included hyperkalemic episodes requiring insulin correction in patients with end-stage renal disease and postoperative edema.

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Company representatives had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Duality of Interest. M.E.W. reports receiving license fees from B. Braun and patents related to the closed-loop field and being a consultant

at CamDiab Ltd. R.H. reports receiving speaker honoraria from Eli Lilly, Dexcom, and Novo Nordisk; license fees from B. Braun and Medtronic; consulting fees from Abbott Diabetes Care, patents related to the closed-loop field with the University of Cambridge (Glucose Monitoring and Control Using Multi-Model Approach, patent no. CA2702345C) and the University of Cambridge and Abbott Diabetes Care (Methods for Reducing False Hypoglycaemia Alarm Occurrence During Closed-Loop, patent no. US9579456B2), being director and stockholder at CamDiab Ltd., and having a leadership/fiduciary role for Advanced Technologies & Treatments for Diabetes. A.P.V. reports advisory board fees from MSD. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. D.H., S.S., J.R., D.S., L.C., S.W., A.K., G.J.K., D.P.G., A.R., K.A.S., G.B., B.G., A.P.V., and L.B. were responsible for screening and enrollment of participants, arranged informed consent from the participants, and provided patient care. D.H., C.T.N., M.E.W., R.H., and A.P.V. contributed to the data analysis, including the statistical analyses. D.H., R.H., A.P.V., and L.B. codesigned the study. D.H. and L.B. wrote the report. L.B. designed and coordinated the study. All authors contributed to the interpretation of the results, critically reviewed the report, and approved the submission of the final manuscript. D.H. and L.B. 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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References

1. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010;33:1783–1788
2. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125:1007–1021
3. Thorell A, Efendic S, Gutniak M, Häggmark T, Ljungqvist O. Insulin resistance after abdominal surgery. Br J Surg 1994;81:59–63
4. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011;34:256–261
5. Kotagal M, Symons RG, Hirsch IB, et al.; SCOAP-CERTAIN Collaborative. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015;261:97–103
6. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki E, Flum D. Importance of perioperative glycemic control in general surgery: a report from the Surgical Care and Outcomes Assessment Program. Ann Surg 2013;257:8–14
7. Buehler L, Fayfman M, Alexopoulos AS, et al. The impact of hyperglycemia and obesity on hospitalization costs and clinical outcome in general surgery patients. J Diabetes Complications 2015;29:1177–1182
8. Pasquel FJ, Lansang MC, Dhatariya K, Umpierrez GE. Management of diabetes and hyperglycaemia in the hospital. Lancet Diabetes Endocrinol 2021;9:174–188
9. American Diabetes Association. 15. Diabetes Care in the Hospital: *Standards of Medical Care in Diabetes-2021*. Diabetes Care 2021;44(Suppl. 1):S211–S220
10. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
11. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
12. Kitch BT, Cooper JB, Zapol WM, et al. Handoffs causing patient harm: a survey of medical and surgical house staff. Jt Comm J Qual Patient Saf 2008;34:563–570
13. Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. N Engl J Med 2018;379:547–556
14. Boughton CK, Bally L, Martignoni F, et al. Fully closed-loop insulin delivery in inpatients receiving nutritional support: a two-centre, open-label, randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:368–377
15. Bally L, Gubler P, Thabit H, et al. Fully closed-loop insulin delivery improves glucose control of inpatients with type 2 diabetes receiving hemodialysis. Kidney Int 2019;96:593–596
16. Okabayashi T, Nishimori I, Yamashita K, et al. Continuous postoperative blood glucose monitoring and control by artificial pancreas in patients having pancreatic resection: a prospective randomized clinical trial. Arch Surg 2009;144:933–937
17. Okabayashi T, Nishimori I, Maeda H, Yamashita K, Yatabe T, Hanazaki K. Effect of intensive insulin therapy using a closed-loop glycemic control system in hepatic resection patients: a prospective randomized clinical trial. Diabetes Care 2009;32:1425–1427
18. Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials. a review. Control Clin Trials 2002;23:662–674
19. Saghaei M. An overview of randomization and minimization programs for randomized clinical trials. J Med Signals Sens 2011;1:55–61
20. Davis GM, Spanakis EK, Migdal AL, et al. Accuracy of Dexcom G6 continuous glucose monitoring in non-critically ill hospitalized patients with diabetes. Diabetes Care 2021;44:1641–1646
21. Tripyla A, Herzig D, Joachim D, et al. Performance of a factory-calibrated, real-time continuous glucose monitoring system during elective abdominal surgery. Diabetes Obes Metab 2020;22:1678–1682
22. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603
23. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213
24. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. J Am Coll Surg 2013;217:833–842.e1–3
25. de Vries FE, Gans SL, Solomkin JS, et al. Meta-analysis of lower perioperative blood glucose target levels for reduction of surgical-site infection. Br J Surg 2017;104:e95–e105
26. Jiang J, Li S, Zhao Y, et al. Intensive glucose control during the perioperative period for diabetic patients undergoing surgery: an updated systematic review and meta-analysis. J Clin Anesth 2021;75:110504
27. Finfer S, Heritier S; NICE Study Management Committee and SUGAR Study Executive Committee. The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study: statistical analysis plan. Crit Care Resusc 2009;11:46–57
28. Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007;146:233–243
29. Korytkowski M, Antinori-Lent K, Drincic A, et al. A pragmatic approach to inpatient diabetes management during the COVID-19 pandemic. J Clin Endocrinol Metab 2020;105:dgaa342
30. Aragon D. Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. Am J Crit Care 2006;15:370–377
31. Leelarathna L, English SW, Thabit H, et al. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. Crit Care 2013;17:R159
32. Koscal LJ, Weeda ER, Matuskowitz AJ, Weant KA. Intravenous insulin for the management of non-emergent hyperglycemia in the emergency department. Am J Emerg Med 2021;45:335–339
33. van Steen SC, Rijkenberg S, van der Voort PHJ, DeVries JH. The association of intravenous insulin and glucose infusion with intensive care unit and hospital mortality: a retrospective study. Ann Intensive Care 2019;9:29