Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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THE EFFICACY OF CONTINUOUS INTRAVENOUS GLUCOSE MONITORING ON PERIOPERATIVE GLYCAEMIC CONTROL, A RANDOMISED CONTROLLED STUDY.

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Abstract

Background: Continuous Glucose Monitoring (CGM) via arterial or central venous sampling has been investigated in the operating theatre to improve perioperative glycaemic control. We investigated the efficacy of perioperative CGM via peripheral intravenous sampling in patients with diabetes mellitus (DM) compared to standard care.

Methods: Patients with DM type 2 undergoing major abdominal or cardiothoracic surgery were randomised to CGM (M-ON) or standard care (M-OFF) . All patients were treated according to the same routine anti-hyperglycaemic algorithm with a blood glucose target range of 4 – 10 mmol l^{-1}. Main outcome measure was difference in median glucose 1 hour postoperatively, assessed by point-of-care (POC) measurements. Secondary outcome measures included percentage of glucose measurements in target range, as well as CGM sensor accuracy.

Results: We included 36 patients. There was no significant difference in postoperative median glucose 1 hour after surgery (M-ON 8.5 mmol l^{-1} (IQR 6.8 – 10.3) vs. M-OFF 9.3 mmol l^{-1} (IQR 8.3 – 10.5), p=0.504). There was no difference in proportion of POC measurements in target range (75% vs. 67%, p=0.56). The Mean Absolute Relative Difference compared to plasma glucose was 7.8% (IQR 5.5 – 10.4). We experienced technical problems with the CGM in 9 patients (24%).

Conclusions: Intravenous CGM did not improve glycaemic control in patients with DM2 undergoing major surgery when targeting for glucose between 4 – 10 mmol l^{-1}. Although the accuracy of the CGM was acceptable, sampling at the peripheral intravenous site was associated with frequent technical failure.

Trial registry number: NTR5009, www.trialregister.nl

Introduction

Perioperative hyperglycaemia is commonly encountered in patients with diabetes mellitus (DM) and is associated with postoperative complications (1-3). In the general surgical population with DM, a postoperative glucose reduction on the ward from 9.7 mmol l^{-1} to 8.7 mmol l^{-1} significantly decreased the occurrence of postoperative complications and admissions to the intensive care unit (ICU) (4).

Proper treatment of perioperative hyperglycaemia has proven difficult (5); glucose management requires staff commitment and a substantial time investment, and compliance with perioperative glucose measurements is problematic (5-7). Furthermore, justified fear for inducing hypoglycaemia with insulin therapy might limit proper treatment of hyperglycaemia (8, 9).

When glucose can be monitored accurately with a continuous glucose monitor (CGM) during the perioperative treatment, hyperglycaemia and hypoglycaemia might be detected early and treated more promptly and aggressively.

Over the past decade, several CGM's have been tested in the perioperative phase, both subcutaneous and intravenous sensors (10-13). The accuracy of subcutaneous CGM's was moderate and proved technically challenging in the perioperative period (13,14). The accuracy of intravenous CGM's, inserted through a central venous line, was reported to be good, with a mean absolute relative difference (MARD) ranging from 5.6% to 7.5% (12,15). However, as not all patients require central venous access for perioperative management, a CGM via a peripheral intravenous line would be more suitable and less invasive.

The objective of the present study was to evaluate whether the use of a CGM inserted via a peripheral intravenous line would lead to improved glycaemic control in the perioperative period when compared to standard point of care measurements. We hypothesised that the availability of CGM data intraoperatively would lead to a lower glucose value one hour postoperatively.

Methods

Design and patients

The study protocol was approved by the medical ethical committee of the Academic Medical Centre and performed in accordance with the declaration of Helsinki. All patients

included in the study provided written informed consent. The study was registered with the Dutch national trial register, number NTR5009, (www.trialregister.nl). We included patients from January to May 2015.

We performed this randomised controlled study in the Academic Medical Centre in Amsterdam, the Netherlands. All eligible patients received written information at least one week prior to surgery. One day prior to surgery, written informed consent was obtained. We included patients scheduled for major cardiothoracic or abdominal surgery, diagnosed with type 2 DM, aged between 18 and 85 years. We excluded patients scheduled for total pancreatectomy, with an allergy for heparin or with a history of heparin-induced thrombocytopenia.

Study device

We used the Glucoclear© (Edwards Lifesciences SA, Breda, The Netherlands) as peripheral intravenous CGM. For a detailed description of this CGM, we refer to the publication of Faubert and colleagues (16). In brief, the Glucoclear© uses the glucose oxidase technique to measure glucose. For every measurement, 40 microliter of blood is aspirated into the catheter with the sensor inside. Afterwards the system flushes the blood back into the bloodstream of the patient together with reference fluid. The reference fluid has a known glucose concentration and is used for auto-calibration every 5 minutes. The reference fluid contains heparin in a concentration of 2 IU ml^{-1} and a maximum of 6 IU hr^{-1} of heparin is administered to the patient.

Study procedures

On the morning of surgery, patients were randomised to either the use of a CGM (M-ON group) or standard care (M-OFF Group). Figure 1 shows the study flow chart. We used opaque envelopes for randomization, with stratification for cardiothoracic and abdominal procedures. The patients and physicians were not blinded for the treatment arm. After induction, a 20 gauge peripheral intravenous line was inserted into a large vein in the upper or lower extremity of all patients. The CGM sensor was inserted through this dedicated intravenous line, both in the M-ON and M-OFF group. No other intravenous lines were placed in the respective extremity. Twenty minutes after insertion, the first glucose value became available on the screen. The CGM was removed when patients returned to the ward or on the morning after surgery when patients were still in the intensive care unit. Thirty days postoperatively, the occurrence of postoperative complications (transfusion, repeat surgery, readmission, infection etc.) was evaluated by chart review using the Dindo-Clavien grading system (17). Postoperative wound infections were scored according to the definition of Centre for Disease Control (18).

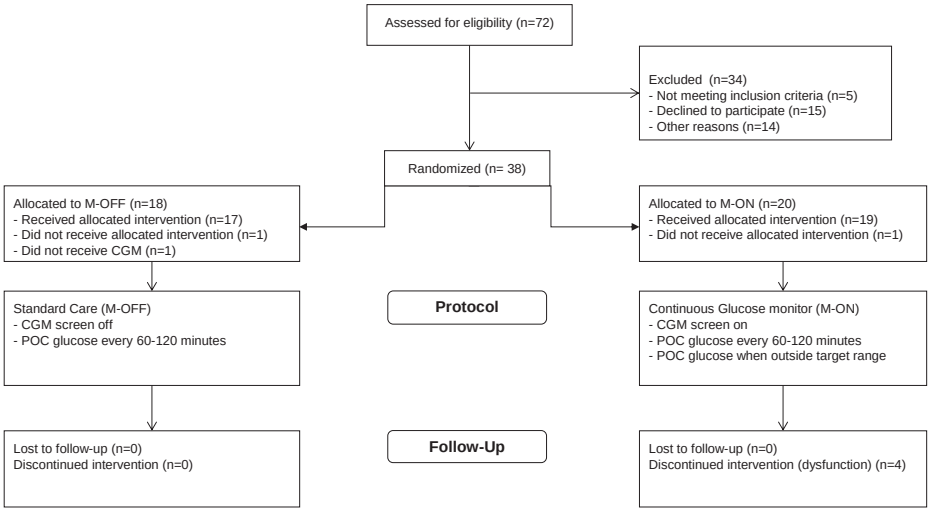

Figure 1. Flow chart of the study

All patients were treated according to local protocol. Patients treated with insulin at home received 50% of their long acting insulin the night before surgery. On the morning of surgery, a glucose 5% drip combined with 1/8 of their total daily insulin dose was started at 83 ml hr^{-1} and continued during surgery. Patients treated with oral glucose lowering medication did not take their tablets on the morning of surgery. The target range for all patients was 4 – 10 mmol l^{-1}. Hypoglycaemia was treated with a glucose bolus of 4g or 50g for a glucose value < 4 mmol l^{-1} or < 2.3 mmol l^{-1}, respectively. Hyperglycaemia, (glucose > 10 mmol l^{-1}) was treated with an intravenous bolus of insulin according to the algorithm given in table 1.

Table 1. Intravenous insulin treatment algorithm

Glucose (mmol l^{-1})	Novorapid iv. Bolus (IU)
4-10	-
1**0-12**	2
12-14	4
14-16	6
>16	8

Iv: intravenous. *Contact physician

For patients in the M-ON group, a glucose value was visible on the screen during the intra- and early postoperative period. As a safety check, point of care (POC) arterial blood glucose (RAPIDlab 1265, Siemens Healthcare, the Hague, the Netherlands) was measured every 60-120 minutes, or when glucose values given by CGM were above or

below target range. The CGM value was used to guide treatment in the hyperglycaemic range, unless the difference between POC and CGM value was > 1 mmol l^{-1}. The POC value was used to guide treatment in the hypoglycaemic range. When an insulin bolus was administered to the patient, 30 minutes were allowed before the next insulin bolus could be administered if glucose remained >10 mmol l^{-1} on CGM.

For patients in the M-OFF group, the screen of the CGM was turned black and all alarms were silenced. POC glucose was measured every 60-120 minutes.

Outcome measures and statistical analyses

The primary outcome of this study was the between group difference in median POC glucose 1 hour after surgery calculated with ANCOVA, correcting for preoperative fasting POC glucose. Patients with failing sensors were included in this analysis. As secondary outcomes of glycaemic control, we calculated the between group differences of percentage of measurements in target range, both for CGM and POC measurements, with the Mann-Whitney U test. Failing sensors were excluded from the CGM analysis. Furthermore, the between group difference in intraoperative use of insulin was calculated and analysed using the Mann-Whitney U test. The between group difference in occurrence of postoperative complications was calculated and tested for significance using the Chi Square test. Furthermore, the occurrence of hypoglycaemic events (glucose < 4 mmol l^{-1}) was assessed.

As sensor specific secondary outcome measures, overall mean absolute relative difference (MARD) in the lower glycaemic (glucose < 4 mmol l^{-1}), normoglycaemic (glucose 4–10 mmol l^{-1}) and hyperglycaemic (glucose > 10 mmol l^{-1}) range were calculated (using POC measurements as reference), irrespective of randomization. The MARD during cardiopulmonary bypass was also calculated. The MARD was calculated as ((mean CGM value – mean POC) / mean POC) for all data and excluding failing sensor data. In addition, a Clarke error grid and Bland-Altman plot were plotted including all sensor data. A Clarke error grid plots the glucose values of the CGM against the glucose values of the POC measurements. The grid is divided into zone A to E. At least 95% of the points should be in zone A and a maximum of 5% in zone B to be considered accurate (13,19). Points in zone C to E are not acceptable, as this will lead to overtreatment without immediate consequences (zone C), lack of treatment (zone D) or inverse treatment (zone E). A Bland-Altman plot analyses the difference of POC – CGM against POC glucose, to assess any bias of the sensor (20). In addition, we assessed the rate of sensor failure as secondary outcome.

Sensor failure was defined as missing sensor data for more than 50% of the intraoperative or postoperative period or when the difference with POC measurements on 2 subsequent time points was > 2.5 mmol l^{-1}. Furthermore, for the Glucoclear©, dislocation

of the sensor outside the bloodstream might occur leading to a subcutaneous depot of reference fluid due to flushing. This depot can subsequently be sampled by the sensor, leading to erroneous glucose levels of 5.5–6 mmol l^{-1} on the monitor. We recorded the number of times the intravenous cannula had to be replaced due to one of the above-mentioned reasons.

For the power calculation, an 1 mmol l^{-1} difference in mean glucose was deemed clinically significant as this resulted in a relevant decrease in postoperative complications in a previous study (4). Assuming a power of 80%, a significance level of 5% and a dropout rate of 10%, we needed 18 patients per group to detect this difference of 1 mmol l^{-1} with a standard deviation (SD) of 1 mmol l^{-1} between groups. Statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

We assessed 72 patients for eligibility, of which 38 patients were randomised. Due to logistic reasons, two patients did not participate in the study and one patient in the M-OFF group did not receive a sensor, but was included in the analyses. We included 36 patients in the final analyses (figure 1). Patient characteristics are shown in table 2.

Table 2. Patient characteristics

	M-ON (n=19)	M-OFF (n=17)
Male, n (%)	15 (79%)	11 (65%)
Age, mean (SD)	64.1 (10.1) years	66.9 (11.5) years
BMI, mean (SD)	27.6 (5.1) kg/m^2	25.6 (3.9) kg/m^2
ASA		
- **II, n (%)**	5 (26%)	6 (35%)
- **III, n (%)**	14 (74%)	11 (65%)
Procedure		
- **Major abdominal, n (%)**	7 (37%)	8 (47%)
- **Cardiothoracic, n (%)**	12 (63%)	9 (53%)
Duration of surgery, mean (SD)	287 (94) minutes	215 (72) minutes
Diabetes duration, mean (SD)	7.1 (7.3) years	11.7 (9.0) years
Diabetes medication		
- **Insulin, n (%)**	5 (26%)	9 (53%)
- **OAD, n (%)**	15 (79%)	14 (82%)
Fasting blood glucose, median (IQR)	7.7 mmol l^{-1} (6.3-8.6)	8.3 mmol l^{-1} (7.3-9.6)

Number (n), standard deviation (SD), Body Mass Index (BMI), American Society of Anesthesiology Classification (ASA), interquartile range (IQR), oral antidiabetic medication (OAD)

Postoperative median glucose was 8.5 mmol l^{-1} (IQR 6.8 – 10.3) in the M-ON group and 9.3 mmol l^{-1} (IQR 8.3 – 10.5) in the M-OFF group (p=0.504). There was no difference in pre- and postoperative glucose between cardiac and abdominal surgery subgroups.

In the M-ON group, 93% (IQR 71 – 100) of the CGM measurements were in target range, compared to 72% (IQR 41 – 96) in the M-OFF group (p=0.09). The proportion of POC measurements in target range was 75% (IQR 46 – 100) in the M-ON group and 67% (IQR 27 – 100) in the M-OFF group (p=0.56), respectively. Six patients (32%) in the M-ON group were treated with insulin during surgery, with a median of 8 units (IQR 4.5 – 12.5). This was comparable to the M-OFF group, in which 8 patients (47%) were treated with insulin, with a median of 6 units (IQR 2.5 – 7.5, p=0.29).

During the study, we observed 4 hypoglycaemic readings on the CGM, which were not confirmed by POC measurements. There was one hypoglycaemic POC measurement of 3.9 mmol l^{-1}, which was not detected by the GCM. There was no difference in the occurrence of postoperative complications between the two groups (data not shown).

Nine of the 37 sensors (24.3%) met the criteria for sensor failure; two sensors due to missing data, three sensors due to a large difference between CGM and POC glucose and four sensors were excluded based on both criteria. Two sensors of the M-ON group with missing data on the monitor had to be replaced during the procedure.

The overall median MARD was 7.8% (IQR 5.5 – 10.4) including all sensor data and 7.6% (IQR 4.4 – 9.2) for the measurements without sensor failure. The median MARD during cardiopulmonary bypass was 5.7% (IQR 3.5 – 10.7). The MARD for the normal- and hyperglycaemic range is shown in table 3. The Bland-Altman plot showed a sensor bias of -0.77 mmol l^{-1} (figure 2).

Table 3. Sensor accuracy

	All Sensors (n=37)	Excluding failing sensors (n=28)
MARD Overall (%)	7.8 (5.5 – 10.4)	7.6 (4.4 – 9.2)
MARD Normoglycemia (%)	7.2 (4.8 – 9.7)	6.8 (4.2 – 9.1)
MARD Hyperglycemia (%)	8.7 (5.5 – 13.6)	8.5 (5.1 – 11.0)
MARD CPB (%)	5.7 (3.5 – 10.7)	5.1 (3.4 – 8.3)

Data reported are median (IQR). MARD: mean absolute relative difference. CPB: Cardiopulmonary bypass

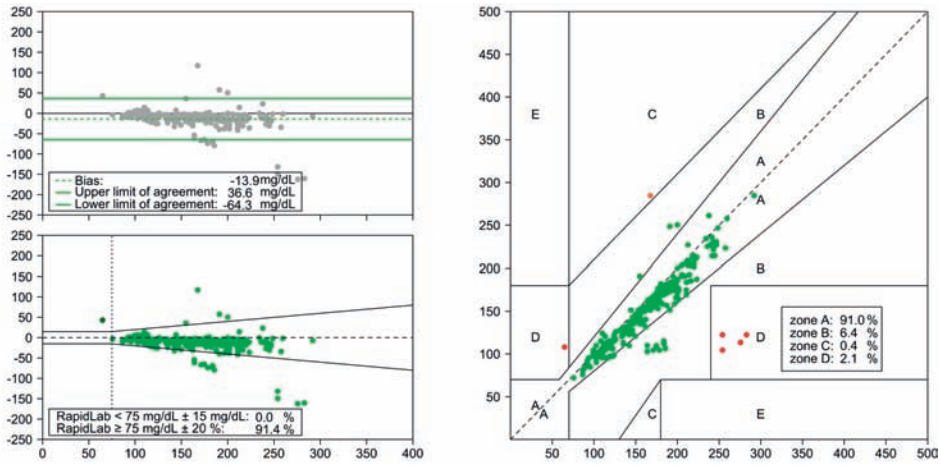

Figure 2. Bland Altman plot, glucose prediction error grid and Clark error grid
The left upper panel the Bland–Altman plot. The POC glucose is plotted on the x-axis, and the difference between CGM and POC measurements is plotted on the y-axis. The dotted line represents the mean difference; the upper and lower continuous lines represent the mean difference plus or minus 1.96 times the SD of the difference. The lower panel is a glucose prediction error grid. The x-axis and y-axis represent POC glucose and the difference between CGM and POC as mentioned above. The continuous lines represent the 15% margin of error for glucose < 75mg dl^{-1} and 20% margin of error for glucose > 75mg dl^{-1}. CGM, continuous glucose monitoring; POC, point of care.
Right panel is the Clark error grid. The POC glucose is plotted on the x-axis, the CGM glucose is plotted on the y-axis. Zone A represents a good level of agreement; zone B represents a moderate level of agreement. Points in zone C to E are not acceptable, as this will lead to overtreatment without immediate consequences (zone C), lack of treatment (zone D) or inverse treatment (zone E).

Discussion

Intraoperative glucose management with a CGM did not improve glycaemic control compared to hourly POC measurements in this randomised clinical trial. Mean postoperative glucose was comparable and within target range in both groups; 8.5 and 9.3 mmol l^{-1} in the M-ON and M-OFF group, respectively. Although literature suggests that patients are often discharged from the recovery room with postoperative hyperglycaemia (4, 11), perioperative glycaemic control seemed to be fairly well regulated in both groups.

The benefit of a CGM compared to standard care has been evaluated in several acute care settings. In patients admitted to the ICU, use of a CGM did not result in an improvement in time in target range compared to standard care (21,22). Holzinger et al. did, however, find significantly less hypoglycaemic events with the use of a CGM, while Boom et al. could not confirm this reduction in hypoglycaemic events (21,22). Kopecky

et al. studied cardiac surgery patients admitted to the ICU, but also could not establish a difference in time in target range between CGM and standard care (23). All three studies used the same treatment algorithm for glycaemic control in both the CGM and standard care group. A study in 20 patients admitted to the acute coronary care unit of our hospital showed that glycaemic control significantly improved when using a CGM plus insulin pump compared to standard care. However, the treatment algorithm in the CGM group differed from the standard care group (24). In the present study both groups were treated according to the same algorithm, where CGM did not improve the time in target range. This suggests that the combination of a more aggressive treatment algorithm and a continuous glucose monitor might be needed to improve glycaemic control in an acute setting, while it is also possible that a more aggressive treatment algorithm alone might be able to achieve this.

Furthermore, the optimal target range for perioperative glycaemic control remains unknown. Current guidelines recommend keeping blood glucose < 10 mmol l^{-1} (25). Stricter glycaemic control did not result in a reduction of postoperative complications in patients with DM after cardiac surgery (9,26,27). However, subgroup analysis showed a reduction of complications in patients without DM when targeting for glucose < 8.0 mmol l^{-1} (27). Additionally, for patients undergoing abdominal surgery a glucose < 8.0 mmol l^{-1} might be beneficial, but we are still awaiting randomised data on the optimal target range in this group (2,4). For the current target range of 4 – 10 mmol l^{-1}, perioperative CGM does not seem to be imperative. However, this might change when targeting for a more stricter glycaemic range (21).

The target of hourly glucose measurements is almost never met in clinical practice (7). Therefore, a CGM, in theory, could help reduce the workload of frequent blood withdrawals and more awareness for perioperative blood glucose values. During our study, almost 25% of the sensors failed and their data could not be used during or after surgery. Although this is an improvement compared to the previously reported 66% with subcutaneous sensors, 25% of system failure is still unacceptably high (13). Trouble shooting in the M-ON group took more time than expected and did not result in a reduction of workload for the anaesthetic team. However, this might primarily be due to the peripheral sampling site and not the device itself.

Patients appeared to be at risk for hyperglycaemia, as the CGM could display false-low glucose readings in case of dislodgement from the bloodstream, which happened in 7 (19%) of the patients and caused 2.5% of the paired measurements to be in zone C and D of the Clark error grid. A complicating factor was that verification of intravenous placement of the sensor was not always possible during surgery, as the insertion site

was often covered by the surgical drapes. Sampling from a peripheral vein appeared to be troublesome. However, sampling through a central venous line can also be accompanied by operational problems (15).

The average MARD of sensors used in the perioperative period ranged from 12.3 to 14.6% for subcutaneous and from 5.6 to 9.2% for intravenous and arterial sensors (12,13,28,29). The Glucoclear© was reported to have a MARD of 5.04% in healthy subjects and 5.05% in ICU patients (7). We found this to be 7.8% in our cohort of surgical patients in the perioperative period. Thus, when the CGM does work, it has acceptable accuracy. The MARD during cardiopulmonary bypass (CPB) was even better (5.7%), possibly due to the high doses of heparin these patients received before they were connected to CPB. The feasibility of CGM during CPB has been demonstrated before (30,31).

A limitation of the study is the sample size. The results of CGM measurements in target range (M-ON 93% vs. M-OFF 72%, p=0.09) suggest a trend towards better glycaemic control in the M-ON group and thus raising the possibility that this study is underpowered. However, the possible trend toward better glycaemic control in the M-ON group was much smaller with POC measurements (M-ON 75% vs. M-OFF 67%, p=0.56) and the amount of insulin used was comparable in both groups.

Conclusion

Intravenous CGM did not improve glycaemic control in patients with DM2 undergoing major surgery when targeting for glucose between 4 – 10 mmol l^{-1}. Although the accuracy of the CGM is acceptable, sampling at the peripheral intravenous site was associated with a high rate of technical failure.

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