Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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Publication date
2018
Document Version
Other version
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PERIOPERATIVE CONTINUATION OF METFORMIN DOES NOT IMPROVE GLYCAEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES; A RANDOMISED CONTROLLED TRIAL.

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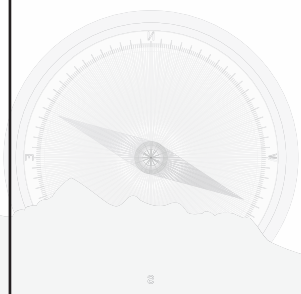
Diabetes, Obesity and Metabolism. 2017 Sep 20
e-pub ahead of print



Abstract

Objective: Historically, metformin was withheld before surgery in fear of metformin associated lactic acidosis. Now, this risk is deemed low and guidelines move towards continuation of metformin. We hypothesised that continuing metformin perioperatively would lower postoperative serum glucose without an effect on plasma lactate.

Methods: We performed a single-blind multicentre randomised controlled trial in type 2 diabetes mellitus patients scheduled for non-cardiac surgery and continued (MF+) or withheld (MF–) metformin before surgery. Main outcome parameters were the differences in perioperative plasma glucose and lactate levels.

Results: We randomised 70 patients (37 MF+ group and 33 MF– group) with type 2 diabetes mellitus. Postoperative glucose levels were similar between groups (8.2 ± 1.8 (MF+) vs. 8.3 ± 2.3 mmol l^{-1} (MF–), p=0.95) Although preoperative lactate levels were slightly higher in the MF+ group compared to the MF– group (1.5 vs. 1.2 mmol l^{-1}, p=0.02), the postoperative lactate levels were not significantly different (1.2 vs. 1.0 mmol l^{-1}, p=0.18).

Conclusion: Continuation of metformin during elective non-cardiac surgery does not improve glucose control or raise lactate levels to a clinically relevant degree.

Trial registry number: NTR5254 Nederlands Trial Register

Introduction

Historically, metformin was withheld before surgery in fear of metformin-associated lactic acidosis (MALA), a very rare, albeit severe, adverse reaction caused by hepatic gluconeogenesis and inhibition of mitochondrial respiration (1). However, a Cochrane review of 347 studies showed no increased risk of lactic acidosis in patients treated with metformin (2). While many guidelines still recommend withholding metformin preoperatively (3-5), others are moving towards continuing metformin, at least for patients without chronic renal failure undergoing minor surgery (6-7). However, there are no data on the possible benefit on glycaemic control after perioperative continuation of metformin. To test the hypothesis that continuing metformin perioperatively would lower pre- and postoperative glucose concentrations without causing a significant increase in plasma lactate, we randomised patients with type 2 diabetes to either continuation or withholding their metformin in the 24 hours before surgery.

Methods

This report is written in accordance with the revised recommendations of the CONSORT group for reporting randomised trials (8).

Study design

This was a randomised two-centre, single blind, parallel, clinical trial, with a 1:1 randomization, conducted in the Netherlands. The study was approved by the regional research ethics committee of the Academic Medical Centre (AMC) Amsterdam (NL51964.018.15) and was registered in the Nederlands Trial Register before start of enrolment (NTR5254). The study was conducted in accordance with the most recent version of the Declaration of Helsinki and good clinical practice guidelines.

Participants and setting

We screened patients scheduled for elective non-cardiac surgery at the AMC and the Medical Centre (MC) Slotervaart in Amsterdam between July 2015 and March 2016. We included adult (18 to 80 years) patients with diabetes mellitus type 2 taking metformin daily. Exclusion criteria were: insulin use, day case surgery, planned duration < 45 minutes, perioperative corticosteroid treatment, postoperative ICU stay, renal failure, severe liver disease, alcohol abuse, and pregnancy. Eligible subjects were contacted at least 24 hours before their preoperative consultation and written informed consent was obtained before inclusion.

Randomisation and intervention

Randomisation was performed using sequentially numbered, sealed, opaque envelopes and block randomization. Block sizes varied between two and ten and were generated by a random even number generator. Randomization was stratified for low (≤1000 mg) or high (>1000 mg) total daily metformin dose. Patients were randomised by an independent researcher who contacted all patients to explain their respective treatment group and instructed not to disclose this to their medical staff. Randomization remained blinded to all other researchers until completion of the trial. Patients in the MF– group were instructed to withhold their metformin dose 24 hours before surgery. In the MF+ group, patients were instructed to continue their usual dose of metformin, including on the morning of surgery. All other anti-hyperglycaemic agents were stopped on the morning of surgery, and only restarted after first oral intake after surgery.

Measurements and anaesthetic management

Type of anaesthesia and medication used was left to the discretion of the anaesthesiologist except for perioperative corticosteroid treatment, which was to be avoided. Fasting plasma glucose and lactate were measured on the day of surgery, two hours after the end of surgery and on the first postoperative day, by blood gas analysis (ABL90 FLEX analyser, Radiometer, Brønshøj, Denmark). Hyperglycaemia was corrected using a sliding scale insulin algorithm (table 1). After 30 days, all patients were interviewed by telephone call and medical charts were reviewed to assess postoperative complications and length of hospital stay.

Table 1. Sliding scale insulin algorithm

Glucose measurement	Insulin 1st bolus	If glucose increases after 1st bolus	If glucose increases after 2nd bolus
> 10 mmol l^{-1}	2 IU	4 IU	6 IU
> 12 mmol l^{-1}	4 IU	6 IU	8 IU
> 14 mmol l^{-1}	6 IU	8 IU	10 IU
> 16 mmol l^{-1}	8 IU	10 IU	12 IU
> 18 mmol l^{-1}	Contact research physician		
< 4.0 mmol l^{-1}	Give 250 mg glucose iv, measure again after 10 minutes and contact research physician		

Outcome measures

The primary outcome was the between-group difference in mean glucose concentration two hours postoperatively, when glucose concentrations reach their maximum after surgery(9,10).

Secondary outcomes were the difference in fasting glucose before and at day 1 after surgery, lactate levels before, two hours and one day after surgery, amount of insulin administered during surgery, occurrence of mild (<4 mmol l^{-1}) and severe hypoglycaemia (<2.3 mmol l^{-1}), length of hospital stay and number of complications within 30 days after surgery.

Sample size and statistical analysis

With a reported postoperative glucose of 10 mmol l^{-1} and a standard deviation of 2.2 mmol l^{-1} (11), a minimum group size of 34 was needed to be able to detect a difference in blood glucose concentration of 1.5 mmol l^{-1} with a power of 80% and a significance level of 5%. Dropouts were to be replaced.

Analyses were based on the intention-to-treat principle, using SPSS (IBM, version 23). Between group differences in plasma glucose, lactate and length of hospital stay were compared using a student t-test or Mann-Whitney U test, depending on the distribution of data. Equality of variance was tested using Levene's test. Normality was assessed visually with histogram plots and tested using the Shapiro-Wilk test. Differences in postoperative complications within 30 days after surgery were assessed using a $\chi 2$ test.

Results

From July 2015 to March 2016, 93 patients were assessed for eligibility. Of them, 23 were excluded before randomization: four withdrew consent; four met exclusion criteria at full assessment; and operations were rescheduled for fifteen patients. Of the remaining 70 subjects, 37 patients were randomly allocated to the metformin MF+ group and 33 patients to the MF– group.

All patients reported compliance with the intervention. Seven patients received dexamethasone intraoperatively despite the study protocol: four patients (10.8%) in the MF+ group, three patients (9.1%) in the MF– group. These patients were included in the intention-to-treat analysis.

Baseline characteristics are displayed in Table 2 and were comparable between groups, including type 2 diabetes duration, HbA1c level before surgery, and mean metformin dose, which ranged from 500 to 3000 mg daily in both groups. Most of the participating patients were enrolled in the MC Slotervaart (87.1%), and nearly half of the patients had laparoscopic gastric bypass surgery (45.7%).

Table 2. Baseline characteristics of the patients

	MF+ (n=37)	MF- (n=33)
Age (years)	59 (11)	59 (11)
Female sex	19 (51%)	20 (60%)
Caucasian	35 (95%)	29 (88%)
Other	2 (5%)	4 (12%)
Body Mass Index (BMI, kg m^{-2})	33.5 (7.4)	33.8 (6.8)
Surgery duration (min)	64 (36)	67 (42)
History of type 2 diabetes (years)	7.3 (5.4)	4.9 (3.6)
Anti-hyperglycemic agents	11 (30%)	10 (30%)
Metformin only	25 (68%)	23 (70%)
Metformin and Sulfonylurea	11 (30%)	10 (30%)
Metformin and GLP-1-R agonist	3 (8%)	1 (3%)
Metformin dose (mg)	1464 (786)	1325 (752)
HbA1c (%)	6.6 (0.8)	6.3 (0.9)
HbA1c (mmol mol^{-1})	49 (9)	45 (10)
ASA II	20 (54%)	21 (64%)
ASA III	17 (46%)	12 (36%)
MC Slotervaart	33 (89%)	28 (85%)
AMC	4 (11%)	5 (15%)
Anesthesia		
General	32 (87%)	31 (94%)
Spinal	5 (13%)	2 (6%)

Data are presented as number (%) or mean (SD). GLP-1-R = Glucagon like peptide 1 receptor. ASA = American Society of Anesthesiologists physical status classification system.

All outcome measures are presented in Table 3. There was no difference in mean (±SD) postoperative blood glucose levels two hours after surgery, (8.2 ± 1.8 (MF+) vs. 8.3 ± 2.3

Table 3. Postoperative glucose, lactate, hospital stay and complications.

Outcome variable	MF+ (n=37)	MF- (n=33)	Difference & 95% CI	p-value
Blood glucose (mmol l^{-1})				
Preoperative	7.2 (1.5)	6.9 (1.3)	-0.2 (-0.9 – 0.5)	0.60
Postoperative, 2 hours	8.2 (1.8)	8.3 (2.3)	0.1 (-0.9 – 1.0)	0.95
Postoperative, 1 day	7.5 (1.6)	7.5 (1.4)	0 (-0.8 – 0.8)	0.96
Hypoglycemia (glucose < 4 mmol l^{-1})	1 (3%)	0 (0%)	-3% (-2.5% – 8%)	0.53
Hyperglycemia (glucose > 10 mmol l^{-1})	9 (24%)	9 (27%)	3% (-18% – 23%)	0.78
Lactate (mmol l^{-1})				
Preoperative	1.5 (1.2 – 1.8)	1.2 (1.0 – 1.5)	-0.3 (-0.6 – 0.0)	0.02
Postoperative, 2 hours	1.2 (0.9 – 1.6)	1.0 (0.8 – 1.4)	-0.2 (-0.5 – 0.1)	0.18
Postoperative, 1 day	1.1 (0.9 – 1.5)	1.3 (1.1 – 1.8)	0.2 (-0.2 – 0.6)	0.17
Hospital stay (days)	2.0 (2.0 – 3.0)	2.0 (2.0 – 3.0)	0.0 (-0.5 – 0.5)	0.83
Postoperative complications	4 (11%)	3 (9%)	-2% (-16% – 12%)	0.57

Data are presented as number (%), mean (SD) or median (IQR).

mmol l^{-1} (MF–), p=0.95 [difference (95% CI) 0.1 (-0.9 – 1.0 mmol l^{-1})). Glucose increased significantly in both groups during surgery; MF+ group (mean before surgery 6.8 ± 1.5 mmol l^{-1} vs. 8.2 ± 1.8 mmol l^{-1} after surgery, p=0.004), MF– group (6.9 ± 1.3 vs. 8.3 ± 2.3 mmol l^{-1}, p=0.002). Median total insulin dose was zero units in both groups (range between 0 and 16 IU) and only 8 patients received insulin in the study period for a glucose concentration >10 mmol l^{-1} (4 patients in either group).

The preoperative median lactate levels were significantly higher in the MF+ group as compared to the MF– group (1.5 (1.2 – 1.8) vs. 1.2 (1.0 – 1.5) mmol l^{-1}, p= 0.02). After surgery, the difference between groups was not significant (1.2 (0.9 – 1.6) vs. 1.0 (0.8 – 1.4) mmol l^{-1}, p= 0.18). The highest measured lactate after surgery was 3.7 mmol l^{-1} which occurred in the MF– group, the maximum in the MF+ group was 2.3 mmol l^{-1}. Only one patient (MF+ group) suffered a mild hypoglycaemia (blood glucose of 3.8 mmol l^{-1}) 30 minutes before surgery and was treated with 250 mg glucose intravenously. Finally, there was no between group difference with regard to length of hospital stay or postoperative complications.

A per protocol analysis excluding all patients receiving glucocorticoids (7 cases) or having an operating time less than 45 minutes (21 cases) yielded similar results for all outcomes. Sub-analyses of patients taking multiple anti-hyperglycaemic agents versus only metformin, or between the low (≤1000 mg) and high (>1000 mg) metformin dose strata, yielded similar results for all outcomes.

Conclusions

We observed that continuing metformin had no effect on perioperative glycaemic control. Preoperative median lactate levels were mildly but significantly higher in the MF+ group, compared to the MF– group (1.5 vs. 1.2 mmol l^{-1}). However, the differences in lactate (0.3 mmol l^{-1} before surgery, and 0.2 mmol l^{-1} after surgery, respectively) can be regarded as clinically irrelevant, and no extremes in lactate levels were measured. This is in accordance with previous studies (12,13) and the Cochrane analysis that found no increased risk of lactic acidosis in type 2 diabetes patients treated with metformin (2).

This study has some limitations. First, we studied a relatively healthy patient population, with few major surgeries, which might have contributed to the lack of effect of our intervention. However, our inclusion and exclusion criteria were based on the literature and the manufacturer's instructions. Despite relatively short operating times (66 ± 39 minutes), we did observe a surgical stress response as a significant increase in glucose

concentrations from preoperative to postoperative. Secondly, although it was an exclusion criterion, seven patients received dexamethasone for postoperative nausea and vomiting prophylaxis. Nonetheless, a per protocol analysis yielded similar results for all outcomes. Future studies could focus on major surgery and a population with more co-morbidity. However, given the lack of effect on glycaemic control in our relatively healthy population, one would not expect much different effects on glycaemic control in other populations.

We found a between group difference in postoperative glucose of only 0.1 mmol l^{-1} (8.2 vs 8.3 mmol l^{-1}) with a 95% CI of -0.9 – 1.0 mmol l^{-1}. Therefore, subsequent confirmatory studies with larger sample size could potentially find glucose differences up to 1.0 mmol l^{-1}, the clinical relevance of which can be discussed.

In conclusion, this is the first study on continuation of metformin during elective non-cardiac surgery and it shows no improvement in glucose control after continuation of metformin. An associated slightly, but significantly higher plasma lactate when continuing metformin was not deemed clinically relevant. As such, the decision to continue or withhold metformin during surgery should not be based on its glucose lowering potential in the perioperative period.

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