Perioperative hyperglycaemia and its treatment in patients with diabetes mellitus

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PERI-OPERATIVE MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS UNDERGOING NON-CARDIAC SURGERY USING LIRAGLUTIDE, GLUCOSE-INSULIN-POTASSIUM INFUSION OR INTRAVENOUS INSULIN BOLUS REGIMENS: A RANDOMISED CONTROLLED TRIAL.

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Abstract

Objective: In this multicentre randomised controlled trial, we investigated three intra-operative treatment strategies to lower glucose and reduce the need for rescue insulin in patients with DM type 2 undergoing non-cardiac surgery.

Methods: Patients were randomised to premedication with liraglutide (Liraglutide), an infusion with glucose-insulin-potassium (Insulin infusion) or an insulin bolus regimen (Insulin bolus), all with rescue insulin as needed, targeting for glucose < 8.0 mmol l^{-1}. The main outcome was the between group difference in median glucose one hour after surgery. Secondary outcomes included insulin requirements, incidence of hypoglycaemia and postoperative complications.

Results: We analysed 150 patients according to the intention to treat principle. Median plasma glucose one hour postoperatively was slightly lower in the Liraglutide group compared to the Insulin infusion and Insulin bolus groups, Liraglutide: 6.6 mmol l^{-1} (IQR 5.6 – 7.7), Insulin infusion: 7.5 mmol l^{-1} (IQR 6.4 – 8.3, p=0.026) and Insulin bolus: 7.6 mmol l^{-1} (IQR 6.4 – 8.9, p=0.006). In the Liraglutide group, 48% received a corrective bolus of insulin, as compared to 74% and 72% in the Insulin infusion and Insulin bolus group, respectively (p=0.014). The incidence of hypoglycaemia and postoperative complications did not differ between the groups. The incidence of preoperative nausea was increased in the Liraglutide group (12.8% versus 0%, p=0.007).

Conclusion: An insulin infusion or intravenous insulin bolus regimen led to comparable glycaemic control with a similar rate in rescue boluses. The pre-operative administration of liraglutide stabilised peri-operative plasma glucose levels and reduced peri-operative insulin requirements, at the expense of increased pre-operative nausea rates.

Introduction

The prevalence of diabetes mellitus is increasing in patients presenting for surgery (1-3) and peri-operative glycaemic management in those patients can be challenging (4). A recent meta-analysis showed that a peri-operative glucose target < 8.3 mmol.l^{-1} reduced surgical site infections, but at the cost of an increased risk of peri-operative hypoglycaemia (5). Despite the importance of peri-operative glucose control, glucose targets are almost never met (4).

During the peri-operative period, established treatment strategies are predominantly insulin-based (6-10). Insulin acts rapdily, can be administered as bolus or as continuous infusion, and is easily adjusted. However, due to interpatient variation in insulin resistance, the magnitude of its effect is unpredictable (11). A glucose-insulin-potassium infusion is an established treatment strategy and together with intravenous (i.v.) and subcutaneous (s.c.) insulin bolus regimens ('sliding scale') a wide range of treatment options are available (2,6,8). Despite years of experience with peri-operative insulin administration, the optimal treatment is still unknown. To lower the risk of hypoglycaemia but at the same time prevent hyperglycaemia, a strategy which reduces insulin requirements and lowers glucose values would be optimal.

Over recent years, glucagon-like peptide-1 (GLP-1) agonists have been included in guidelines for the outpatient management of diabetes mellitus (12). GLP-1 agonists stimulate pancreatic insulin secretion and reduce glucagon secretion in a glucose-dependent manner, with a low risk of inducing hypoglycaemia (13). They have proven effective in lowering postoperative blood glucose levels and could potentially be of value in the peri-operative period (14).

Our objective was to investigate three peri-operative treatment strategies in patients with type 2 diabetes mellitus undergoing non-cardiac surgery; namely, to compare the effects of a GLP-1 agonist (liraglutide), glucose-insulin-potassium infusion and i.v. insulin bolus regimen on glucose levels and the need for rescue insulin therapy.

Methods

The study protocol was approved by the medical ethical committee of the Academic Medical Centre Amsterdam and was conducted in accordance with the declaration of Helsinki and Good Clinical Practice guidelines (15). The study was registered at https://ClinicalTrials.gov/ and all included patients provided written informed consent.

A detailed description of the protocol of this study was published at the start of the trial (16). In summary, we conducted a multicentre open-label randomised controlled trial, that studied patients with type 2 diabetes mellitus, aged 18 to 75 years, who were scheduled for non-cardiac in-patient surgery. We did not study patients with the following conditions: use of corticosteroids; insulin use > than 1 IU (international unit) per kilogram bodyweight; use of GLP-1 agonists; renal impairment (serum-creatinine ≥ 133 μmol.l^{-1} for males and ≥ 115 μmol.l^{-1} for females); planned bowel surgery; emergency surgical procedures; or planned postoperative intensive care unit admission. Recent data have suggested that GLP-1 agonists are safe in patients with liver disease (17); therefore, the exclusion criterion of liver failure was omitted during the trial after approval of the ethical committee.

Patients were randomised via a web-based randomisation program to one of three treatment groups, with stratification for preoperative insulin use (TENALEA Clinical Trial Data Management System). We used block randomisation with random block sizes of three to twelve patients. Patients, care-givers and researchers were not blinded for the allocated treatment group. Patients were randomly allocated to either premedication with liraglutide (Liraglutide group), peri-operative glucose-insulin-potassium infusion (Insulin infusion group) or peri-operative i.v. insulin bolus regimen (Insulin bolus group).

Patients in the Liraglutide group received 0.6 mg liraglutide s.c. the night before surgery and 1.2 mg liraglutide s.c on the morning of surgery. After proper instruction, liraglutide was self-administered by the patient. The concentration of liraglutide peaks 8 h after s.c. injection, with a half-life of approximately 13 h (18). Patients in the Insulin infusion group received a glucose-insulin-potassium infusion, which was started 30 min before surgery until 4 h after surgery. The glucose-insulin-potassium infusion consisted of glucose 5% 500ml with 10 mmol potassium and insulin. The dose of insulin was calculated according to the following formula: Insulin dose = (fasting glucose in mmol.l^{-1} – 7) / (200 / body-weight in kg) + 8 [8]. This formula was chosen to account for peripheral insulin resistance in the overweight. The infusion was started at 83 ml.h^{-1}. Patients in the Insulin bolus group received 50% of their own morning dose of long-acting insulin (if applicable). In all groups, glucose lowering medication and short-acting insulin was withheld on the morning of surgery and long-acting insulin dose was reduced by 50% the night before surgery. All patients received hourly capillary glucose measurements, starting 30 min before surgery until 4 h after surgery. When plasma glucose was > 8.0 mmol.l^{-1} a bolus of intravenous insulin was administered according to the study algorithm until 4 h postoperatively (16). The anaesthetic team was instructed not to use dexamethasone for postoperative nausea and vomiting (PONV) prophylaxis. Postoperative hyperglycaemia at the ward was treated according to the hospital protocol by the attending physician at the ward. Patient follow-up was done via chart review and a telephone call 30 days after surgery.

In the peri-operative period, glucose peaks in the first hour after surgery and is, therefore, a good measure of the overall peri-operative glucose control (19,20). Preventing this peak is likely to facilitate glucose management postoperatively. Therefore, the primary outcome of the study was the difference in median plasma glucose between the liraglutide, insulin infusion and insulin bolus groups 1 h postoperatively. Secondary outcomes were: the differences in insulin requirements during surgery and the first 4 h postoperatively; the mean absolute glucose change as a measure of glucose variability between the three groups; and the differences in plasma glucose values 1 hour pre-operatively, 4 h postoperatively and 24 h postoperatively. The difference in adverse events (i.e. hypoglycaemia, hypo- and hyperkalaemia, postoperative nausea and vomiting and postoperative complications) was also assessed. Nausea was scored using an 11-point numeric rating scale (NRS), where 0=no nausea and 10=worst imaginable nausea (21). Severe nausea was defined as a NRS > 4. We measured three composite adverse event endpoints: major complications (e.g. sepsis); minor complications (e.g. cystitis); and diabetic-related complications (e.g. adjustment of diabetes medication).

A reduction of 1 mmol l^{-1} in postoperative glucose values was associated with a decrease in postoperative complications in the RABBIT-2 trial, which compared two insulin regimens (22). We hypothesised that if we were able to prevent the first hyperglycaemic peak, this would translate into better glucose management at the ward. Therefore, sample size calculation was aimed to establish a difference of 1 mmol l^{-1} between the treatment groups. We initially we planned to recruit 315 patients in a 1:1:1 ratio. Due to unexpected slow enrolment of patients in the study, we requested termination of the study at 150 patients after three years of recruitment, which was approved by the local ethical committee. The adjustment to 150 patients was based on a power calculation with a 1:2 (GLP-1:insulin) ratio, power of 80% and a significance level of 5%, in order to detect a difference of 1 mmol.l^{-1} in glucose levels between the groups (assuming mean (SD) glucose levels 8.7 (1.7) mmol.l^{-1} and 9.7 (2.4) mmol.l^{-1}). Ultimately we performed the analyses in the original 1:1:1 ratio.

Statistical analyses were performed with IBM SPSS (V23.0) (SPSS Inc., Chicago, IL, USA). All patients that were randomly allocated and had received study medication were included in the safety population; all patients that were randomly allocated, had received study medication, underwent surgery and had a postoperative glucose measurement were included in the intention-to-treat population. The primary outcome, as well as insulin- and glucose-related outcomes were analysed in the intention to treat population. The composite endpoints of postoperative complications and PONV were analysed in the safety population. A per-protocol analysis was performed excluding patients with a protocol violation in the form of peri-operative use of dexamethasone. The difference

in blood glucose values was assessed with the Kruskal-Wallis test with further testing between groups with a Mann Whitney-U test. The mean absolute glucose in $mmol.l^{-1}.h^{-1}$ was calculated by the sum of the absolute glucose difference of the capillary samples divided by the time over which the samples were taken (23). The difference in the number of adverse events was analysed with the Chi-square test. In case of multiple comparisons, we checked for possible false positive results using the Benjamin and Hochberg approach for multiple comparisons (24).

Results

Between February 2014 and January 2017, 154 patients were included in the safety-population and 150 patients were included in the intention to treat population (Fig. 1). The main reason for exclusion was renal impairment. There was a protocol violation in thirteen patients, who received dexamethasone during surgery. Reasons for dexamethasone administration included prevention of postoperative oedema, refractory hypotension and suspected allergic reaction in the peri-operative period. These patients were included in the intention-to-treat analyses and excluded in the per protocol analy-

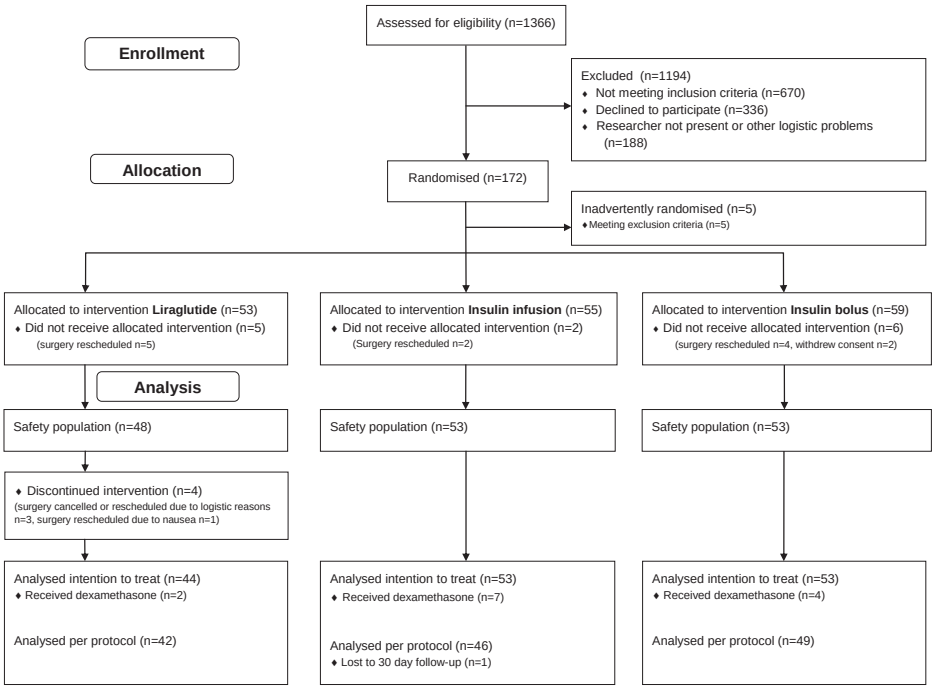

Figure 1. Consort flow diagram of study

ses. The second dose of liraglutide was omitted in three patients due to complaints of nausea. These patients were included in the intention-to-treat analysis.

The patient characteristics are shown in Table 1. The surgical specialties were as follows: urology (n=28); orthopaedics (n=28); gynaecology (n=23); general surgery (n=17); vascular surgery (n=9); plastic surgery (n=11); neurosurgery (n=8); otolaryngology (n=11); and other (n=14). These specialities were evenly distributed between the treatment groups.

Table 1. Preoperative patient characteristics of patients receiving liraglutide, a GIK infusion or an insulin bolus regimen during the study. Data is given as mean (sd), n (%) or median (IQR [range]).

	Liraglutide (N=44)	**Insulin infusion (N=53)**	**Insulin bolus (N=53)**
Male/Female	20/24	23/30	28/25
Age (years)	61.8 (8.8)	61.8 (8.1)	60.5 (8.6)
BMI (kg/m2)	29.1 (26.0 – 32.5 [21.1 – 42.7])	27.8 (26.4 – 34.6 [18.6 – 42.3])	28.6 (26.0 – 31.4 [17.6 – 51.4])
ASA (II/III)	32/12	38/15	36/17
History of:			
Myocardial infarction	4 (9.1)	4 (7.5)	7 (13.2)
Obstructive lung disease	5 (11.4)	10 (18.9)	12 (22.6)
Hypertension	25 (56.8)	36 (67.9)	30 (56.6)
Malignancy	6 (13.6)	12 (22.6)	10 (18.9)
DM history			
Duration of DM (years)	5.0 (3.0 – 10.0 [0.8 – 28])	5.0 (3.0 – 11.5 [0.5 – 30.0])	8.0 (4.8 – 13.0 [0.5 – 22.0])
Treated with diet	0	1 (1.9)	0
Treated with OAD	35 (79.5)	40 (75.5)	42 (79.2)
Treated with insulin	3 (6.7)	3 (5.7)	1 (1.9)
Treated with OAD and insulin	6 (13.6)	9 (17)	10 (18)
Total daily insulin dose (IU)	41 (33 – 55 [10 – 68])	41 (30-64 [8 – 114])	50 (32 – 60 [20 – 112])
HbA1c (%) (mmol/mol)	6.8 (6.3 – 7.7 [5.4 – 11.9]) 51 (45 – 61 [36 – 107])	6.7 (6.1 – 7.4 [5.3 – 9.7]) 50 (44 – 58 [34 – 83])	7.1 (6.6 – 7.8 [5.4 – 13.5]) 54 (49 – 62 [36 – 124])
Surgery			
AMC/DIAK/OLVG	22/14/8	37/10/6	39/8/6
Duration of surgery (min.)	78 (52 – 125 [11 – 367])	88 (63 – 131 [7 – 675])	81 (43 – 145 [18 – 558])
General anaesthesia	35 (79.5)	47 (88.7)	45 (84.9)
Spinal anaesthesia	7 (15.9)	4 (7.6)	6 (11.3)

(ASA) American Association of Anesthesiology; (DM) diabetes mellitus; (OAD) oral glucose lowering drugs; (AMC) Academic Medical Centre; (DIAK) Diakonessenhuis; (OLVG) Onze Lieve Vrouwe Gasthuis

The peri-operative plasma glucose values are shown in Table 2. At 1 h postoperatively, median (IQR [range]) plasma glucose was lower in the Liraglutide group compared to the Insulin infusion and Insulin bolus groups (6.6 (5.6-7.7 [4.2-13.5]) mmol.l^{-1} vs. 7.5 (6.4-8.3 [3.9-16.6]) mmol.l^{-1} (p=0.026) and 7.6 (6.4-8.9 [4.7-13.2]) mmol.l^{-1}) (p=0.006), respectively).

Table 2. Perioperative glucose levels. Data is given in mmol l^{-1}. Median (IQR [Range]).

	Liraglutide (n=44)	Insulin infusion (n=53)	Insulin bolus (n=53)	p-value
1 hour preoperatively	7.1 (5.7 – 8.7 [4.7 – 21.2])	7.0 (6.4 – 8.7 [3.6 – 13.8])	8.2 (6.3 – 9.4 [4.8 – 15.3])	.143
1 hour postoperatively	6.6 (5.6 –7.7 [4.2 – 13.5])	7.5 (6.4 – 8.3 [3.9 – 16.6])	7.6 (6.4 – 8.9 [4.7 – 13.2])	.015*
4 hours postoperatively	6.5 (5.0 – 7.6 [4.1 – 9.5])	6.7 (5.6 – 8.6 [3.5 – 13.1])	7.3 (5.9 – 8.4 [4.4 – 11.7])	.073
1 day postoperatively	7.7 (6.6 – 10.0 [4.7 – 17.9])	7.9 (6.8 – 10.0 [4.4 – 19.8])	8.8 (7.0 – 11.5 [5.0 – 14.7])	.166

*liraglutide vs. insulin infusion p=0.045; liraglutide vs. insulin bolus p=0.010.

Peri-operative insulin requirements were significantly lower in the Liraglutide group as compared to patients in the Insulin infusion and Insulin bolus groups (Table 3). Fewer patients in the Liraglutide group required rescue insulin bolus doses compared to the Insulin infusion and Insulin bolus groups. Furthermore, mean absolute glucose (IQR [range]) was more stable in the Liraglutide group compared to the Insulin infusion and Insulin bolus groups (0.7 (0.4-0.9 [0.1-5.8]) mmol.l^{-1}.h^{-1} vs. 1.0 (0.6-1.3 [0.2-4.2]) (p=0.006) and 0.8 (0.6-1.2 [0.0-3.3]) (p=0.09) respectively).

Table 3. Insulin requirements and adverse glycaemic events. Data is given as median (IQR [range]) or n (%).

	Liraglutide (n=44)	Insulin infusion (n=53)	Insulin bolus (n=53)	p
Total perioperative insulin dosage (IU)	0 (0 – 6 [0 – 61])	10 (7 – 18 [0 – 38])	5 (0 – 16 [0 – 36])	<.001*
Patients receiving rescue insulin bolus	21 (48)	39 (74)	38 (72)	.014
Bolus insulin dosage (IU)	0 (0 – 6 [0 – 61])	3 (0 – 11 [0 – 22])	5 (.0 – 15 [0 – 36])	.031†
No. of insulin bolus	0 (0 – 2 [0 – 10])	1 (0 – 3 [0 – 6])	2 (0 – 4 [0 – 7])	.018‡
Severe Hypoglycaemia < 2.3 mmol l^{-1}	0	0	0	-
Mild Hypoglycaemia < 4.0 mmol l^{-1}	1 (2.3)	4 (7.5)	1 (1.9)	.260
Hyperglycaemia > 10 mmol l^{-1}	16 (36.4)	18 (34)	24 (45.3)	.456
Hypokalaemia < 3.5 mmol l^{-1}	2 (4.5)	6 (11.3)	8 (15.1)	.241
Hyperkalaemia > 5.0 mmol l^{-1}	3 (6.8)	6 (11.3)	6 (11.3)	.705

*infusion vs. bolus p=.006 ; bolus vs. liraglutide p=.005 ; infusion vs. liraglutide p<001. † bolus vs. liraglutide p=.013 ; infusion vs. liraglutide p=.044. ‡ bolus vs. liraglutide p=.008 ; infusion vs. liraglutide p=.033.

Six patients had pre-operative nausea in the Liraglutide group, of which two had severe nausea (NRS > 4), compared to no patients in the Insulin infusion and Insulin bolus groups (p=0.007). There was no difference in the incidence of postoperative nausea, which was reported by seven patients in the Liraglutide group (of which four had severe nausea), seven patients in the Insulin infusion group (five had severe nausea) and four patients in the Insulin bolus group, (two of which scored this as severe) (nausea p=0.72, severe nausea p=0.48).

There was no difference in the number of patients having a postoperative complication between the Liraglutide, Insulin infusion and Insulin bolus groups (major complications: seven vs. eight vs. nine, respectively (p=0.94); minor complications: 14 vs. 19 vs. 19, respectively (p=0.69)). One patient died of multi-organ failure after liver surgery in the Insulin infusion group. There were no cases of pancreatitis during the study.

Peri-operative diabetic-related complications occurred in eight patients in the Liraglutide group, three patients in the Insulin infusion group and six patients in the Insulin bolus group (p=0.22). All multiple comparisons were re-analysed using the Benjamin and Hochberg approach for false discovery rate. This revealed no false discoveries in our analyses as presented above when using the significance level of 0.05.

Discussion

We investigated three strategies to optimise peri-operative glucose concentrations in patients with type 2 diabetes mellitus undergoing non-cardiac surgery. Our results showed that all groups had comparable median plasma glucose levels 1 h postoperatively. There was no difference in efficacy when comparing glucose-insulin-potassium infusion to an i.v. insulin bolus regime. Patients receiving liraglutide, however, had a reduction in insulin requirements when compared to those managed with an insulin infusion or insulin boluses, without an increased risk of hypoglycaemia.

Good peri-operative glycaemic control achieved with less corrective boluses of insulin translates into a reduced workload for anaesthesists and nursing staff during the peri-operative period. In the Insulin infusion and Insulin bolus groups, a comparable amount of patients needed rescue insulin boluses in order to stay in target range, which implies that the use of a glucose-insulin-potassium infusion offers no advantages over insulin rescue boluses; this was also found in a previous study in insulin-naive patients (25).

The use of liraglutide in the peri-operative period limits the use of insulin. Insulin is regarded as high-risk medication according to standards of the Joint Commission International and reducing the need for insulin could reduce potential medication errors (26). The use of an i.v. infusion of a GLP-1 agonist has been shown to reduce insulin requirements by 45% (27). We were able to demonstrate a comparable effect with a commercially available compound.

Consistent with our expectations we found a low rate of mild hypoglycaemic events in both the Liraglutide and Insulin bolus groups, witha slightly higher rate in the Insulin infusion group. Similar numbers of hypoglycaemic events (1-2%) are reported in studies targeting blood glucose levels < 10 mmol.l^{-1}, but this increases to 14.8% when lower targets are pursued (glucose < 6.5 mmol.l^{-1}) (28,29). A study targeting postoperative glucose < 7.8 mmol.l^{-1} using a combination of insulin and incretin treatment had a comparable low rate (2%) of mild hypoglycaemic events (30). Thus, rescue i.v. insulin or incretin use in the peri-operative period does not increase the risk of hypoglycaemic events when aiming for a glucose target < 8.0 mmol.l^{-1}.

In this study, we did not find a difference in postoperative complications, while we did find a 0.8-0.9 mmol l^{-1} difference in plasma glucose levels. Apart from the longer treatment period (9 days) in the RABBIT 2 trial (22), this discrepancy could be due to several reasons; although the Insulin infusion and Insulin bolus groups had higher plasma glucose values than the Liraglutide group, we were able to prevent the first hyperglycaemic peak after surgery in all three treatment groups (glucose< 8.0 mmol l^{-1}). This study was designed and powered to detect a difference in plasma glucose, not complications, as the prevention of this first hyperglycaemic peak could, in theory, facilitate better glycaemic management at the ward. In clinical practice, i.v. insulin boluses and a continuous insulin infusion are discontinued on return to the ward, whereas liraglutide could be safely administered without additional monitoring. Therefore, future studies are needed to investigate whether continuing liraglutide treatment on the ward reduces postoperative complications.

During the study patients received two increasing doses of liraglutide. A well-known adverse-effect of GLP-1 agonists is nausea and vomiting. In total, 15% of the patients receiving liraglutide complained of nausea and vomiting before surgery, which is consistent with the literature (31). In one patient, surgery was rescheduled due to extreme nausea and vomiting after the second dose of liraglutide; for three other patients, surgery was rescheduled due to logistic reasons not related to the study protocol. Postoperatively, no difference in nausea and vomiting was seen between the Liraglutide group and the Insulin infusion and Insulin bolus groups. The emetic effects of anaesthe-

sia probably outweighed the effects of the earlier liraglutide administration. We found similar results in patients without diabetes receiving liraglutide while undergoing surgery (32). To minimise these adverse-effects, peri-operative liraglutide treatment could be combined with standard anti-emetic treatment, or GLP-1 treatment could be started after induction of anaesthesia.

This study does have some limitations. This was the first study to look at efficacy of a commercially available GLP-1 agonist in patients with diabetes undergoing non-cardiac surgery. However, it was an open label trial, thus patients, care givers and researchers were aware of group allocation. Furthermore, we did not include patients who underwent bowel surgery due to the gastrointestinal side-effects of liraglutide. This was also the main reason for the slow patient recruitment. However, another study has shown the feasibility of GLP-1 treatment in patients undergoing abdominal surgery (14). Patients gave written informed consent when they were admitted to the hospital, usually on the afternoon prior to surgery. Consequently, this study lacks a proper baseline fasting glucose for all patients, as liraglutide treatment was initiated on the afternoon before surgery. However, HbA1c values were comparable between the three groups. Although this trial was stopped prematurely, due to lower dispersion of glucose values than anticipated in the Liraglutide group, the post hoc power calculation was adequate and we were able to demonstrate a statistically significant effect for our primary endpoint.

In conclusion, the use of a glucose-insulin-potassium infusion or an i.v. insulin bolus regimen leads to comparable glycaemic control with a similar rate of rescue insulin boluses. The pre-operative administration of liraglutide stabilises peri-operative plasma glucose levels and reduces insulin requirements, making this strategy an interesting option for diabetic management during non-cardiac surgery.

References

1. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE Unrecognized diabetes among hospitalized patients. Diabetes Care 1998; 21: 246-9.
2. Robertshaw HJ, Hall GM Diabetes mellitus: anaesthetic management. Anaesthesia 2006; 61: 1187-90.
3. Shaw JE, Sicree RA, Zimmet PZ Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87: 4-14.
4. Ley SC FR, Bossenroth E, Schlack WS, Preckel B Datenlage zur perioperativen Diabetesbetreuung in einem universitatsklinikum. Diabetologe 2008; 4: 13-9.
5. 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.
6. Hemmerling TM, Schmid MC, Schmidt J, Kern S, Jacobi KE Comparison of a continuous glucose-insulin-potassium infusion versus intermittent bolus application of insulin on perioperative glucose control and hormone status in insulin-treated type 2 diabetics. J Clin Anesth 2001; 13: 293-300.
7. Ljungqvist O, Nygren J, Soop M, Thorell A Metabolic perioperative management: novel concepts. Curr Opin Crit Care 2005; 11: 295-9.
8. Thomas DJ, Platt HS, Alberti KG Insulin-dependent diabetes during the peri-operative period. An assessment of continuous glucose-insulin-potassium infusion, and traditional treatment. Anaesthesia 1984; 39: 629-37.
9. McCall AL Insulin therapy and hypoglycemia. Endocrinol Metab Clin North Am 2012; 41: 57-87.
10. Nauck MA A critical analysis of the clinical use of incretin-based therapies: The benefits by far outweigh the potential risks. Diabetes Care 2013; 36: 2126-32.
11. Meneghini LF Perioperative management of diabetes: translating evidence into practice. Cleve Clin J Med 2009; 76 Suppl 4: S53-9.
12. Meier JJ, Weyhe D, Michaely M, et al. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. Crit Care Med 2004; 32: 848-51.
13. World Medical A World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191-4.
14. Polderman JA, Houweling PL, Hollmann MW, DeVries JH, Preckel B, Hermanides J Study protocol of a randomised controlled trial comparing perioperative intravenous insulin, GIK or GLP-1 treatment in diabetes-PILGRIM trial. BMC Anesthesiol 2014; 14: 91.
15. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016; 387: 679-90.
16. Hermanides J, Huijgen R, Henny CP, et al. Hip surgery sequentially induces stress hyperglycaemia and activates coagulation. Neth J Med 2009; 67: 226-9.
17. Polderman JA, Hollmann MW, DeVries JH, Preckel B, Hermanides J Perioperative Hyperglycemia and Glucose Variability in Gynecologic Laparotomies. J Diabetes Sci Technol 2015; 10: 145-50.
18. 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: 256-61.
19. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH Glucose variability is associated with intensive care unit mortality. Crit Care Med 2010; 38: 838-42.

20. Raucoules-Aime M, Labib Y, Levraut J, Gastaud P, Dolisi C, Grimaud D Use of i.v. insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery. Br J Anaesth 1996; 76: 198-202.
21. Joint Commission International. Joint commission International accreditation standards for hospitals (5th edition). https://www.jointcommissioninternational.org/assets/3/7/Hospital-5E-Standards-Only-Mar2014.pdf (accessed 2017 Mar 17 2017)
22. Sokos GG, Bolukoglu H, German J, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. Am J Cardiol 2007; 100: 824-9.
23. Abdelmalak BB, Bonilla A, Mascha EJ, et al. Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial. Br J Anaesth 2013; 111: 209-21.
24. Cao SG, Ren JA, Shen B, Chen D, Zhou YB, Li JS Intensive versus conventional insulin therapy in type 2 diabetes patients undergoing D2 gastrectomy for gastric cancer: a randomized controlled trial. World J Surg 2011; 35: 85-92.
25. Umpierrez GE, Gianchandani R, Smiley D, et al. Safety and efficacy of sitagliptin therapy for the inpatient management of general medicine and surgery patients with type 2 diabetes: a pilot, randomized, controlled study. Diabetes Care 2013; 36: 3430-5.
26. Sun F, Yu K, Yang Z, et al. Impact of GLP-1 receptor agonists on major gastrointestinal disorders for type 2 diabetes mellitus: a mixed treatment comparison meta-analysis. Exp Diabetes Res 2012; 2012: 230624.
27. Sechterberger MK, Hermanides J, Poolman RW, et al. Lowering blood glucose during hip surgery does not influence coagulation activation. BBA Clin 2015; 3: 227-32.