Original Article

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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Summary

In this open-label multicentre randomised controlled trial, we investigated three peri-operative treatment strategies to lower glucose and reduce the need for rescue insulin in patients aged 18–75 years with type-2 diabetes mellitus undergoing non-cardiac surgery. Patients were randomly allocated using a web-based randomisation program to premedication with liraglutide (liraglutide group), glucose–insulin–potassium infusion (insulin infusion group) or insulin bolus regimen (insulin bolus group), targeting a glucose < 8.0 mmol.l^{-1}. The primary outcome was the between group difference in median glucose levels 1 h after surgery. We analysed 150 patients (liraglutide group n = 44, insulin infusion group n = 53, insulin bolus group n = 53) according to the intention-to-treat principle. Median (IQR [range]) plasma glucose 1 h postoperatively was lower in the liraglutide group compared with 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). The incidence of hypoglycaemia and postoperative complications did not differ between the groups. Six patients had pre-operative nausea in the liraglutide group, of which two had severe nausea, compared with no patients in the insulin infusion and insulin bolus groups (p = 0.007). 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.

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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 rapidly, can be administered as a bolus or as a continuous infusion, and is easily adjusted. However, due to inter-patient 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 insulin bolus regimens ('sliding scales'), a wide range of treatment options are available [2, 6, 8]. Despite years of experience with peri-operative insulin administration, the optimal regimen 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]. Glucagon-like peptide-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 potentially could 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 and was conducted in accordance with the declaration of Helsinki and Good Clinical Practice guidelines [15]. The study was registered 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 multi-centre open-label randomised controlled trial, that studied patients with type-2 diabetes mellitus, aged 18–75 years, who were scheduled for non-cardiac inpatient surgery. We did not study patients with the following conditions: use of corticosteroids; insulin use > 1 IU (international unit) per kilogram bodyweight; use of GLP-1 agonists; renal impairment (serum creatinine ≥ 133 μmol.l^{-1} for men and ≥ 115 μmol.l^{-1} for women); 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 by the ethical committee.

Patients were randomly allocated via a web-based randomisation program to one of three treatment groups, with stratification for pre-operative insulin use (TENALEA Clinical Trial Data Management System). Block randomisation was used with random block sizes of 3–12 patients. Patients, caregivers and researchers were not blinded to 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 subcutaneously the night before surgery and 1.2 mg liraglutide subcutaneously on the morning of surgery. After being taught how, liraglutide was self-administered by the patient. The concentration of liraglutide peaks 8 h after subcuaneous 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 500 ml glucose 5% insulin-based 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/bodyweight in kg) + 8 [8]. This formula was chosen to account for peripheral insulin resistance in the overweight patient. 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 were 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 i.v. insulin was administered according to the study algorithm [16]. The anaesthetic team was instructed not to use dexamethasone for postoperative nausea and vomiting (PONV) prophylaxis. Postoperative hyperglycaemia on the ward was treated according to the hospital protocol by the attending physician. Patient follow-up was 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 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 study groups 1 h postoperatively. Secondary outcomes were: difference in insulin requirements during surgery and the first 4 h postoperatively; mean absolute glucose change as a measure of glucose variability between the three groups; and difference in plasma glucose values 1 h pre-operatively, 4 h postoperatively and 24 h postoperatively. The difference in adverse events (i.e. hypoglycaemia, hypo- and hyperkalaemia, PONV 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 NRS > 4. We measured three composite adverse event end-points: 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 a recent 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 aimed to establish a difference of 1 mmol.l^{-1} between the treatment groups. We initially planned to recruit 315 patients in a 1:1:1 ratio. Due to unexpected slow enrolment, 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 who were randomly allocated and had received study medication were included in the safety population; all patients who were randomly allocated, 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 end-points of postoperative complications and PONV were analysed in the safety population. A per-protocol analysis was performed which did not include 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 13 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, but not in the per-protocol analyses. 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.

Baseline 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.

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 with the insulin infusion and insulin bolus groups p = 0.006.

Peri-operative insulin requirements were significantly lower in the liraglutide group compared with patients in the insulin infusion and insulin bolus groups (Table 3). Fewer patients in the liraglutide group required rescue insulin bolus doses compared with the insulin infusion and insulin bolus groups. Furthermore, change in mean absolute glucose (IQR [range]) was more stable in the liraglutide group compared with 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).

Six patients had pre-operative nausea in the liraglutide group, of which two had severe nausea

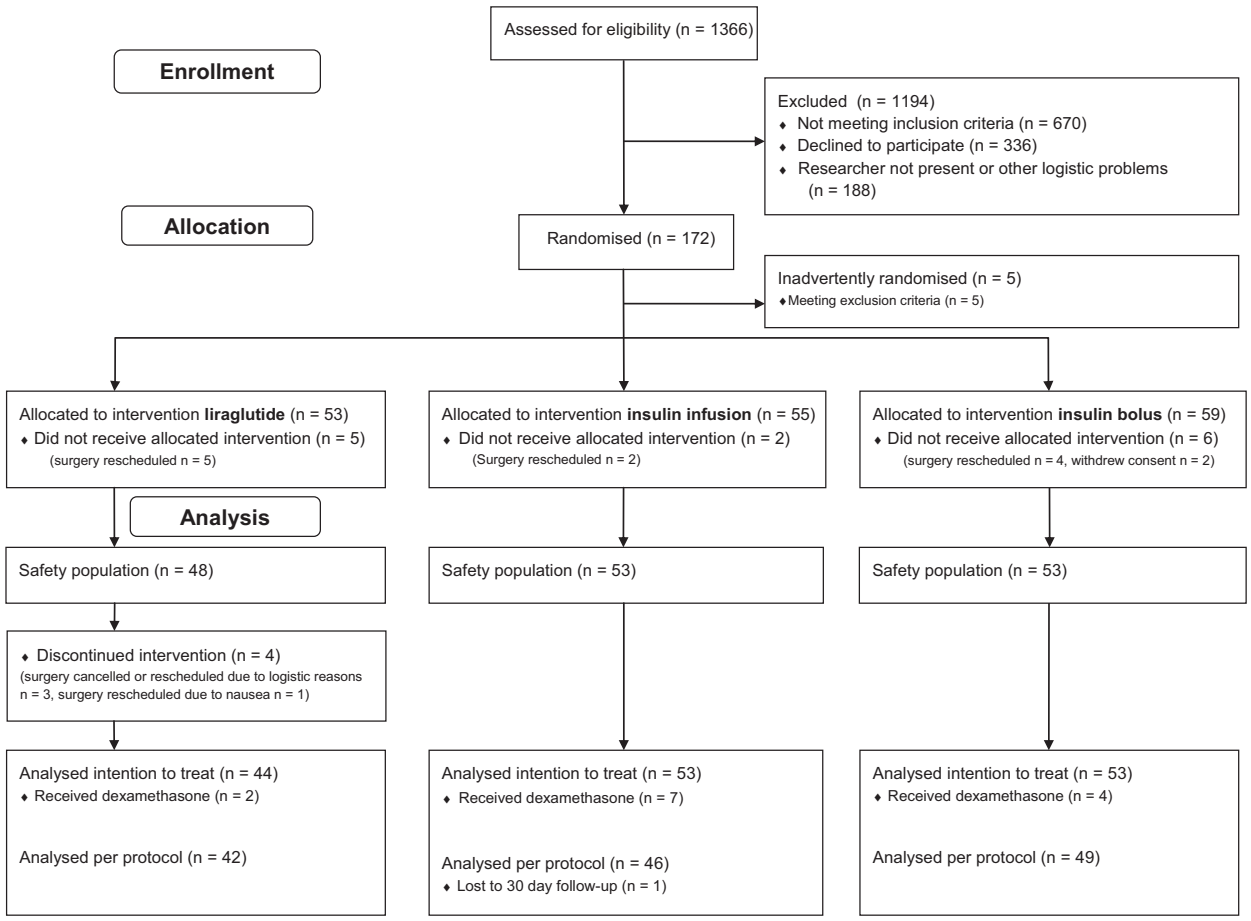

Figure 1 CONSORT flow diagram.

Table 1 Pre-operative patient characteristics of patients receiving liraglutide, glucose–insulin–potassium infusion or an insulin bolus regimen. Values are number, mean (SD) or median (IQR [range]).

	Liraglutide n = 44	Insulin infusion n = 53	Insulin bolus n = 53
Sex; male	20	23	28
Age; year	62.0 (8.8)	62.0 (8.1)	61.0 (8.6)
BMI; $kg.m^{-2}$	29 (26–33 [21–43])	28 (26–35 [19–42])	29 (26–31 [18–51])
ASA status (2/3)	32/12	38/15	36/17
History of			
Myocardial infarction	4	4	7
COPD	5	10	12
Hypertension	25	36	30
Malignancy	6	12	10
Duration of diabetes; y	5 (3–10 [1–28])	5 (3–12 [1–30])	8 (5–13 [1–22])
Diabetic treatment			
Diet	–	1	–
Oral agents	35	40	42
Insulin	3	3	1
Insulin and oral agents	6	9	10
Total daily insulin dose; IU	41 (33–55 [10–68])	41 (30–64 [8–114])	50 (32–60 [20–112])
HbA_{1c}; %	6.8 (6.3–7.7 [5.4–11.9])	6.7 (6.1–7.4 [5.3–9.7])	7.1 (6.6–7.8 [5.4–13.5])
HbA_{1c}; $mmol.mol^{-1}$	51 (45–61 [36–107])	50 (44–58 [34–83])	54 (49–62 [36–124])
Duration of surgery; min	78 (52–125 [11–367])	88 (63–131 [7–675])	81 (43–145 [18–558])
General anaesthesia	35	47	45
Spinal anaesthesia	7	4	6

COPD, chronic obstructive pulmonary disease; IU, international units.

Table 2 Peri-operative glucose levels. Values are median (IQR [range]).

	Liraglutide group n = 44	Insulin infusion group n = 53	Insulin bolus group n = 53	p value
Glucose 1 h pre-operatively; $mmol.l^{-1}$	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])	0.143
Glucose 1 h postoperatively; $mmol.l^{-1}$	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])	0.015*
Glucose 4 h postoperatively; $mmol.l^{-1}$	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])	0.073
Glucose 24 h postoperatively; $mmol.l^{-1}$	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])	0.166

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

(NRS > 4), compared with 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 whom 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 whom scored as severe) (nausea p = 0.72, severe nausea p = 0.48).

There was no difference in the number of patients who experienced 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) (see Supporting Information, Table S1a-c). 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.

Table 3 Insulin requirements and adverse glycaemic events. Values are median (IQR [range]) or number (proportion).

	Liraglutide n = 44	Insulin infusion n = 53	Insulin bolus n = 53	p value
Total peri-operative insulin dosage; IU	0 (0–6 [0–61])	10 (7–18 [0–38])	5 (0–16 [0–36])	< 0.001*
Patients receiving rescue insulin bolus	21 (48%)	39 (74%)	38 (72%)	0.014
Bolus insulin dosage; IU	0 (0–6 [0–61])	3 (0–11 [0–22])	5 (0–15 [0–36])	0.031†
Number of insulin boluses	0 (0–2 [0–10])	1 (0–3 [0–6])	2 (0–4 [0–7])	0.018‡
Severe hypoglycaemia < 2.3 mmol.l^{-1}	–	–	–	–
Mild hypoglycaemia < 4.0 mmol.l^{-1}	1 (2%)	4 (8%)	1 (2%)	0.260
Hyperglycaemia > 10 mmol.l^{-1}	16 (36%)	18 (34%)	24 (45%)	0.456
Hypokalaemia < 3.5 mmol.l^{-1}	2 (5%)	6 (11%)	8 (15%)	0.241
Hyperkalaemia > 5.0 mmol.l^{-1}	3 (7%)	6 (11%)	6 (11%)	0.705

*Insulin infusion group vs. Insulin bolus group p = 0.006; Insulin bolus group vs. Liraglutide group p = 0.005; Insulin infusion group vs. Liraglutide group p < 0.001.
†Insulin bolus group vs. Liraglutide group p = 0.013; Insulin infusion group vs. Liraglutide group p = 0.044.
‡Insulin bolus group vs. Liraglutide group p = 0.008; Insulin infusion group vs. Liraglutide group p = 0.033.

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 with an i.v. insulin bolus regime. Patients receiving liraglutide, however, had a reduction in insulin requirements when compared with 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 anaesthetists 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 the 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 potentially reduce 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, with a 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 post-operative complications, whereas we did find a 0.8–0.9 mmol.l^{-1} difference in plasma glucose levels. Apart from the longer treatment period (nine days) in a recent 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 on 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 anaesthesia 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 the 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, caregivers and researchers were aware of group allocation. Furthermore, we did not include patients who underwent bowel surgery due to the gastro-intestinal 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 before surgery. Consequently, this study lacks a proper baseline fasting glucose for all patients, as liraglutide treatment was initiated on the afternoon before surgery. However, HbA_{1c} 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 end-point.

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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1a. Composite end-point major complications.

Table S1b. Composite end-point minor complications.

Table S1c. Composite end-point diabetes-related complications.

