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Lowering blood glucose during hip surgery does not influence coagulation activation

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ABSTRACT

Background: Hyperglycaemia during and after hip surgery is associated with coagulation activation and an increased risk of venous thromboembolism. Whether lowering of glucose levels during hip surgery diminishes coagulation activation is unknown. We investigated the efficacy of the human GLP-1 analogue liraglutide to lower glucose during and after hip surgery and studied its influence on coagulation activation.
Methods: A total of 37 obese subjects who underwent hip surgery were randomized to subcutaneous liraglutide or placebo for 4 consecutive days, starting one day prior to surgery. Glucose levels and coagulation indices at three fixed time-points (pre-operative, 2 h post-operative and 3 days post-operative) were measured.
Results: Liraglutide reduced glucose at day three post-surgery (median glucose (IQR) liraglutide 5.5 (5.2–5.7) vs. placebo 5.8 (5.5–6.2); difference 0.3 mmol/L, $P = 0.04$). Changes in 6 out of 8 coagulation indices studied did not differ between the two groups. Only D-dimer levels were significantly lower in the liraglutide group at day three post-surgery and FVIII levels were significantly higher in the liraglutide group 2 h post-surgery.
Conclusion: Although the human GLP-1 analogue liraglutide moderately reduced post-operative blood glucose levels in non-diabetic and prediabetic obese patients undergoing elective hip surgery, no changes were observed with respect to coagulation activation.

1. Introduction

Patients undergoing hip surgery have a risk to develop postoperative venous thromboembolism (VTE). It is estimated that symptomatic VTE occurs in approximately 0.5 to 2.0% of patients, even if adequate thromboprophylaxis is provided [1,2]. While the procedure-related tissue damage is the major activator of coagulation, several risk factors, such as postoperative immobilization, increasing age and high body mass index, have been associated with a higher incidence of VTE [3]. In addition, we have recently shown that post-surgical 'stress-induced' hyperglycaemia in patients undergoing elective hip surgery is associated with an increased risk for symptomatic VTE, independent of diabetes mellitus and other confounders [4].

That surgery itself can precipitate acute hyperglycaemia, or 'stress hyperglycaemia', is well known and appears to be due to alteration of endogenous hormone production and metabolites [5]. Growing evidence supports the hypothesis that 'stress hyperglycaemia' leads to a hypercoagulable and hypofibrinolytic state [6]. In experimental settings as well as in patients with diabetes, hyperglycaemia contributes to coagulation activation and downregulation of fibrinolytic activity, as demonstrated by increased levels of several procoagulant factors, such as thrombin–antithrombin (TAT) complexes, soluble tissue factor, fibrinogen, von Willebrand (vWF), factor VII, factor VIII and decreased levels of antifibrinolytic factors (plasminogen activator inhibitor-1 (PAI-1)) [7–9]. Moreover, hip surgery in patients without diabetes mellitus has been shown to induce hyperglycaemia peaking the days after the procedure, which was followed by a rise of factor VIII, vWF and prothrombin fragment 1 + 2 (F1 + 2) [10].

In diabetic patients, the effect of hyperglycaemia on coagulation seems to be modifiable, as improvement of glycaemic control among

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these patients led to downregulation of coagulation activation [11,12]. Whether establishing glycaemic control during hip surgery will influence the coagulation activation is unknown.

Insulin therapy is the most widely used method to induce glycaemic control. However, insulin therapy is time consuming and is accompanied by an increased risk of hypoglycaemia, which is related to serious morbidity [13]. The human glucagon-like peptide-1 (GLP-1) analogue liraglutide is an alternative glucose lowering agent which acts in a glucose-dependent manner, i.e. it stimulates insulin secretion only when blood glucose levels are above normal. Consequently, it has negligible risk of hypoglycaemia [14]. In the current study we aimed to investigate the efficacy of the human GLP-1 analogue liraglutide to lower glucose during and after hip surgery and its influence on coagulation activation.

2. Matherials and methods

2.1. Study design and participants

This was a randomized, double-blind, placebo-controlled trial performed at the orthopaedic department of a teaching hospital (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands) involving 37 patients. Participants were recruited between August 2012 and September 2013. Inclusion criteria were: men and women between 18 and 75 years of age, scheduled for elective hip surgery, dabigatran used as anticoagulant drug after surgery and signed informed consent. Exclusion criteria were: type 1 or type 2 diabetes mellitus, use of oral corticosteroids, use of Vitamin K antagonists, known coagulation disorders, known active cancer, a history of chronic pancreatitis or idiopathic acute pancreatitis, impaired liver function (defined as alanine aminotransferase (ALAT) 2.5 times upper normal limit) or renal function (defined as serum-creatinine 133 μmol/L for males and 115 μmol/L for females), females of child bearing potential who are pregnant or breast-feeding and spinal anaesthesia. The study protocol was approved by the institutional review board (medical ethical committee of the Academic Medical Center, Amsterdam and Onze Lieve Vrouwe Gasthuis, Amsterdam). All participants provided written informed consent. This trial is registered at the Dutch trial register, www.trialregister.nl, number NTR3547.

2.2. Study procedures

Participants were randomized to receive either liraglutide or matching placebo by block randomisation (block size was 4) via a pre-generated fixed list with successive numbered treatment options. Both participants and investigators were blinded to treatment assignment. Treatment with liraglutide (0.6 mg) or placebo started one day prior to surgery. Participants underwent dose escalation to 1.2 mg/day at the day of surgery until day 3 post-operative. Liraglutide (6.0 mg/mL) and placebo were provided in identical FlexPen® devices (Novo Nordisk A/S, Bagsværd, Denmark) and were given by subcutaneous injection in the abdomen at 5 pm daily. Adverse events were recorded daily by study personnel. The total planned treatment period was 4 days. All participants received general anaesthesia and identical anti-emetic prophylaxis (droperidol 0.625 mg during induction, granisetron 1 mg post-operatively). None of the subjects received corticosteroids. Venous blood samples for laboratory tests were taken at 3 fixed points in time (before induction of anaesthesia, 2 h after the end of surgery and three days post-operative. All blood samples were taken by venapuncture in the fasting state. In all participants, 220 mg dabigatran once-daily in the morning starting from the day after surgery was given as thromboprophylaxis. All subjects were allowed to resume their daily diet when they were transferred to the surgical ward.

2.3. Outcome measures

The primary outcome was the difference in glucose at day 3 post-surgery between the study groups. Secondary outcomes were the difference in coagulation indices at day 3 post-surgery and included prothrombin fragment 1 + 2 (F1 + 2), thrombin–antithrombin complex (TAT), plasmin–alpha2-antiplasmin complex (PAP), D-dimer, coagulation factor VIII (FVIII), von Willebrand factor (vWF), antithrombin (AT) and plasminogen activator inhibitor-1 (PAI-1).

2.4. Laboratory assessments

All blood samples were centrifuged within 1 h at 1500 g at 4 °C for 10 min, plasma was separated (separated plasma of citrate samples was centrifuged again for 10 min) and stored immediately at −70 °C. Plasma glucose concentrations were measured with a glucose hexokinase method (Roche/Hitachi, Indianapolis, USA). D-dimer, factor VIII activity and AT were measured on an automated coagulation analyser (Siemens BCS-XP system) using protocols and reagents from the manufacturer (Siemens Healthcare Diagnostics, Marburg, Germany). Antigen levels of vWF were assayed by ELISA using antigens from DAKO (Heverlee, Belgium). F1 + 2 and TAT were determined by ELISA from Siemens Healthcare Diagnostics, PAI-1 was determined by ELISA from BioMed and PAP was determined by ELISA from DRG diagnostica (Marburg, Germany).

2.5. Statistical analysis

The study was powered to detect a difference (± SD) of 1.0 ± 0.8 mmol/L in glucose three days post-surgery between the two study groups. This difference was based on a 2 mmol/L increase in glucose level in a prior study [10] and an expected 50% reduction in glucose with use of liraglutide. Taking into account a drop-out rate of 10%, the sample size calculation indicated that 18 patients per group were needed in order to detect the effect on glucose between the two study groups with 80% power and an alpha level of 0.05. Analyses were based on the intention-to-treat principle. Data of the patients who were withdrawn from the study before day three post-surgery were used for the analyses as far as possible. Results are expressed as percentages for categorical variables, mean and standard deviation (SD) for continuous normally distributed variables, and median and interquartile range (IQR) for continuous non-normally distributed variables. Groups were compared by using Fisher's Exact test, Student's *t* test or Mann Whitney rank-sum test where appropriate. Primary and secondary outcomes were analysed by use of the Mann Whitney rank-sum test. In addition, mixed between-within ANOVA analyses were performed to assess the treatment effect over time. A secondary analysis was performed to assess the influence of surgery-induced stress on coagulation. Data from the placebo group were used to assess equality of the laboratory parameters at three time points using the Friedman test. Where the Friedman test resulted in statistical significance, subsequent tests were performed using the Wilcoxon Signed rank test. All analyses were performed using PASW statistics software version 20.0 (SPSS Inc, Chicago, IL, USA); a *P*-value of <0.05 was considered statistically significant.

3. Results

In total, 37 patients were randomized and 36 received study medication in the trial. Thirty-two patients completed the trial (Fig. 1). One patient withdrew informed consent prior to start of treatment and was replaced. Two patients in the liraglutide group withdrew from the study due to adverse events (moderate/severe nausea, starting at the dose of 1.2 mg/day). Furthermore, in each study-group one patient discontinued the study due to non-compliance with the protocol (not willing to undergo blood sampling). Baseline characteristics are summarized in Table 1. More women were randomized to the placebo group, which did not reach statistical significance. Most patients included in the trial were overweight (average BMI of 28 kg/m^2).