

Hip surgery sequentially induces stress hyperglycaemia and activates coagulation

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ABSTRACT

Background: A frequent complication of orthopaedic procedures is venous thromboembolism (VTE). Hyperglycaemia has been shown to activate the coagulation system and is associated with postoperative morbidity and mortality. Therefore, we hypothesised that glucose levels increase during orthopaedic surgery and are associated with an activation of the coagulation system.

Methods: Nine adult patients undergoing elective hip replacement were included. Venous blood samples were taken before, during and after surgery. Plasma glucose levels, factor VIII clotting activity (fVIII:c), von Willebrand ristocetin cofactor activity, von Willebrand factor antigen and prothrombin fragment 1+2 were measured.

Results: Immediately after induction of anaesthesia, plasma glucose levels started to increase until the second day postoperatively (peak 8.0 mmol/l). After seven weeks glucose values had returned to baseline (6.1 mmol/l), $p < 0.001$ with ANOVA. All coagulation parameters increased during surgery, subsequent to the rise in glucose. The change in mean FVIII:c and von Willebrand ristocetin cofactor activity was significantly correlated with mean glucose values.

Conclusions: These observations indicate that total hip replacement surgery causes an increase in glucose levels that precedes the proportional rise of the measured coagulation parameters. This suggests a possible role of glucose in the activation of the coagulation system during hip surgery.

KEYWORDS

Coagulation activation, orthopaedic surgery, stress hyperglycaemia

INTRODUCTION

A frequent complication of surgical procedures is venous thromboembolism (VTE), manifesting as deep venous thrombosis or pulmonary embolism.¹ Especially

after orthopaedic surgery the incidence of postoperative symptomatic VTE is high, occurring in 1.5 to 10% of the patients despite adequate anticoagulant prophylaxis.² Risk factors for the development of VTE after surgery include underlying malignancy and advanced age.² In an experimental setting, hyperglycaemia has been shown to activate the coagulation system in healthy volunteers, in particular by stimulating the tissue factor pathway.^{3,4} This is of interest since hyperglycaemia in response to surgery is a common finding.^{5,7} Counter-regulatory hormone action initiated by the surgical trauma can induce 'stress hyperglycaemia', even without known diabetes mellitus.⁸ Recently, preoperative hyperglycaemia has been identified as a risk factor for pulmonary embolism, independent of diabetes mellitus.⁹ Thus, we hypothesised that glucose levels increase during orthopaedic surgery and may contribute and therefore be related to an activation of the coagulation system.

MATERIALS AND METHODS

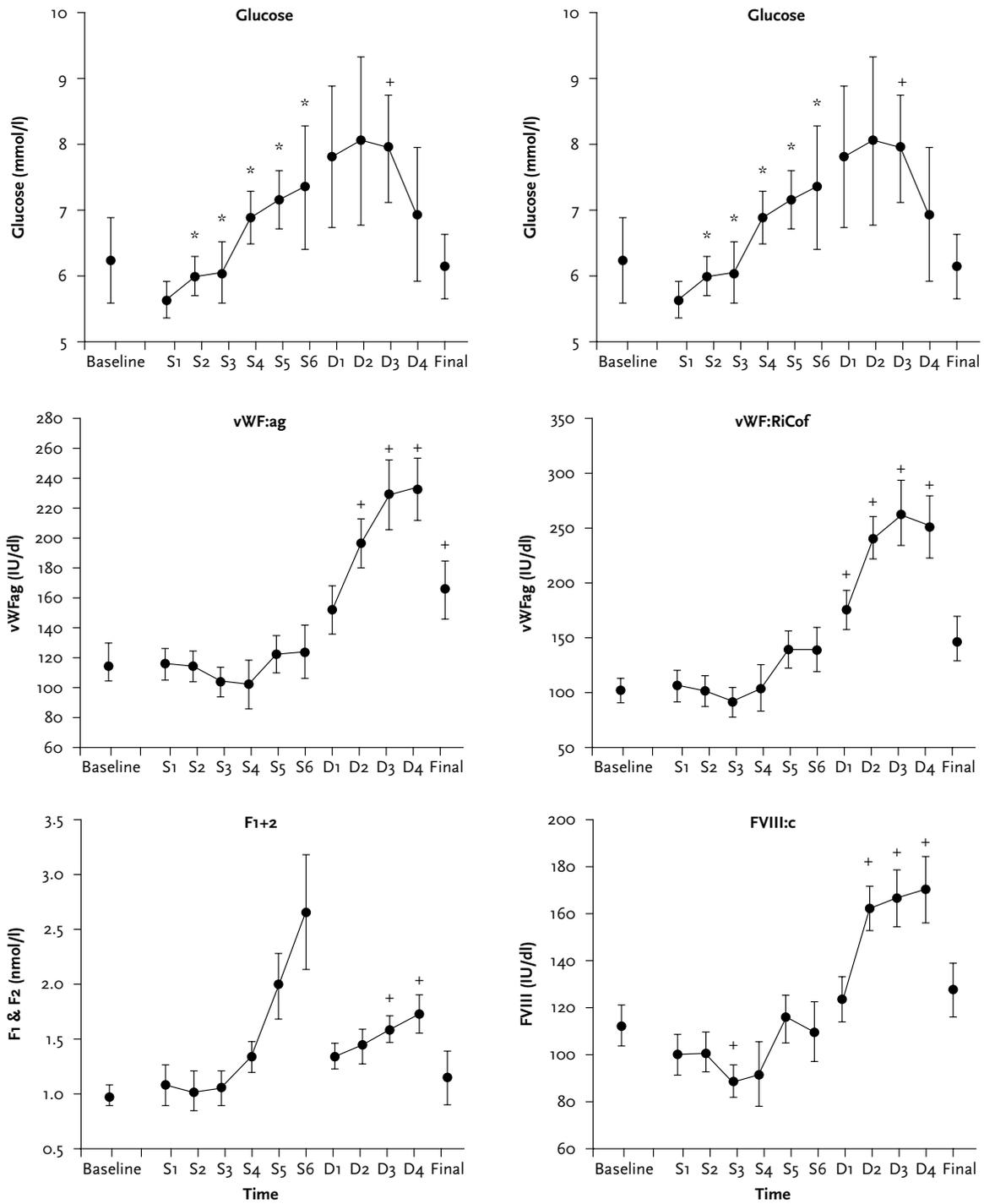
Study design and population

We performed an observational study, assessing the correlation between perioperative changes in plasma glucose levels and a number of coagulation parameters. Adult patients undergoing elective hip replacement surgery were recruited from the Department of Orthopaedic Surgery at the Academic Medical Centre, University of Amsterdam, the Netherlands. Exclusion criteria were: previous VTE, revision hip replacement, use of β -blockers, known diabetes mellitus, inability or unwillingness to give written informed consent, and inability to be followed up. The study was approved by the Medical Ethics Commission of the Academic Medical Centre, University of Amsterdam and written informed consent was obtained from each patient.

Data collection

Clinical data including date of birth, sex, height, weight, blood and indication for hip replacement were recorded. Venous blood samples were taken at 14 set points in time (*figure 1*).

Figure 1. Mean perioperative and postoperative glucose levels (2 upper graphs are identical) and coagulation parameters with 95% CI + $p < 0.05$ as compared with baseline, * $p < 0.05$ as compared with S1 (glucose fasting samples only)



Sampling time points

Baseline (n=9)	Baseline: surgery - 1 day	S6 (n=8)	2 hours after surgery
S1 (n=7)	Before induction	D1 (n=9)	Surgery + 1 day
S2 (n=8)	After induction	D2 (n=7)	Surgery + 2 days
S3 (n=8)	After skin incision	D3 (n=9)	Surgery + 3 days
S4 (n=8)	After placing cup	D4 (n=7)	Surgery + 4 days
S5 (n=8)	After placing prosthesis	Final (n=9)	Surgery + 49 days

Repeated measurements ANOVA: $p < 0.001$ for glucose, vWF:ag, vWF:RiCof, F1+2 and FVIII:c.

The samples on the day of surgery were taken in the fasting state. The samples on the other days (non-fasting) were taken between 8 and 10 am to exclude the influence of circadian fluctuations on the haemostatic parameters.

Laboratory determinations

Blood was collected in ice-cooled tubes of 2.7 ml containing 0.109 M trisodium citrate, which were centrifuged within one hour. The citrate samples were centrifuged at 3000 rpm at 4°C for 20 minutes and the separated plasma again at 4000 rpm and 4°C for five minutes and stored immediately at -80°C. Plasma glucose was measured using the HK/G-6PD method (Roche/Hitachi, Basel, Switzerland) and corrected for the 10% dilution with sodium citrate. Factor VIII clotting activity (FVIII:c) and von Willebrand ristocetin cofactor activity (vWF:RiCof) assays were performed on an automated coagulation analyser (Behring Coagulation System) with reagents and protocols from the manufacturer (Dade Behring, Marburg, Germany), and are expressed as a percentage of reference activity. Measurements of prothrombin fragment 1+2 (F1+2) (Dade Behring, Marburg, Germany) and von Willebrand factor antigen (vWF:Ag) (antibodies from Dako, Glostrup, Denmark) were performed by ELISA.

Statistical analyses

Mean glucose levels perioperatively and during surgery were plotted against time. Sequential glucose values were analysed with the repeated measurements ANOVA. For the ANOVA analyses, missing values per patient were linearly interpolated. Post-hoc testing was performed using the paired t-test with Holm's sequential Bonferroni correction, comparing the non-fasting samples with the baseline mean glucose values and the fasting samples with the pre-induction sample. To assess the correlation between mean glucose levels and mean FVIII:c, vWF:Ag, vWB:RiCof, F1+2 values we calculated the correlation coefficient. Correlation was considered relevant in case of $r > 0.5$. The level of significance was $p < 0.05$.

RESULTS

During the study period 17 patients scheduled for elective hip replacement surgery were evaluated. Nine patients met the inclusion criteria and provided written informed consent. The investigated cohort included five males and four females with a mean age of 63 years (SD 22 years) and mean BMI of 27.7 kg/m² (SD 2.8). Indication for hip surgery was coxarthrosis in seven patients, one case of idiopathic femur head necrosis and prednisone-induced femur head necrosis in one patient. This last subject had stopped taking prednisone two years before inclusion in this study. Low-molecular-weight heparin (LMWH), starting the day before surgery, was used as thromboprophylaxis in five patients. One patient started LMWH the day after surgery and three patients used oral anticoagulants.

Glucose values

Mean plasma glucose levels and the number of successful samples per time point are depicted in *figure 1* and *table 1*. The repeated measurements ANOVA for all sequential glucose samples was $p < 0.001$. Missing values are due to occlusion of the intravenous sampling catheter during surgery. Mean plasma glucose levels changed significantly during surgery as compared with pre-induction. Directly after induction of anaesthesia glucose levels increased from 5.6 to 6.0 mmol/l ($p = 0.002$). Two hours after surgery, glucose levels were still significantly increased as compared with pre-induction (7.3 mmol/l, $p = 0.01$). Postoperatively non-fasting glucose levels peaked at the second postoperative day and remained increased up to the 4th day after surgery as compared with baseline non-fasting mean glucose values. After seven weeks, non-fasting glucose levels returned to baseline values.

Coagulation factors

The mean levels of FVIII:c, vWF:Ag, vWF:RiCof and F1+2 are presented in *table 1*. All values increased significantly during surgery. FVIII:c and F1+2 returned to baseline

Table 1. Mean levels of glucose and coagulation parameters per time point, displayed with mean \pm SD

Time		Glucose (mmol/l)	F1+2 (nmol/l)	vWF:Ag (IU/dl)	vWB:RiCof (IU/dl)	FVIII:c (IU/dl)
Surgery - 1 day	Baseline	6.2 (\pm 1.0)	1.0 (\pm 0.3)	116.8 (\pm 37.2)	101.8 (\pm 34.3)	113.1 (\pm 25.3)
Before induction	S1	5.6 (\pm 0.4)	1.1 (\pm 0.5)	115.4 (\pm 27.5)	105.4 (\pm 36.7)	100.9 (\pm 23.7)
After induction	S2	6.0 (\pm 0.4)	1.0 (\pm 0.5)	114.0 (\pm 29.0)	101.0 (\pm 35.2)	101.0 (\pm 24.8)
After skin incision	S3	6.0 (\pm 0.7)	1.0 (\pm 0.4)	103.6 (\pm 28.2)	91.1 (\pm 39.6)	89.3 (\pm 19.0)
After placing cup	S4	6.9 (\pm 0.6)	1.3 (\pm 0.4)	102.1 (\pm 46.2)	104.5 (\pm 59.8)	92.5 (\pm 38.4)
After placing prosthesis	S5	7.2 (\pm 0.6)	2.0 (\pm 0.8)	122.0 (\pm 34.8)	140.4 (\pm 47.4)	116.3 (\pm 28.8)
2 hours after surgery	S6	7.3 (\pm 1.4)	2.6 (\pm 1.5)	123.6 (\pm 50.0)	138.6 (\pm 58.6)	110.4 (\pm 36.6)
Surgery + 1 day	D1	7.8 (\pm 1.7)	1.3 (\pm 0.4)	151.4 (\pm 48.4)	175.9 (\pm 54.6)	124.3 (\pm 28.7)
Surgery + 2 days	D2	8.0 (\pm 1.7)	1.4 (\pm 0.4)	195.4 (\pm 42.8)	240.6 (\pm 52.1)	163.3 (\pm 24.5)
Surgery + 3 days	D3	7.9 (\pm 1.2)	1.6 (\pm 0.4)	228.0 (\pm 69.3)	264.0 (\pm 87.8)	167.7 (\pm 37.0)
Surgery + 4 days	D4	6.9 (\pm 1.4)	1.7 (\pm 0.5)	231.4 (\pm 54.7)	250.6 (\pm 71.2)	171.3 (\pm 37.0)
Surgery + 49 days	Final	6.1 (\pm 0.8)	1.1 (\pm 0.7)	164.6 (\pm 57.9)	149.2 (\pm 62.7)	128.4 (\pm 35.2)

values seven weeks after surgery. However, vWF:Ag and vWF:RiCof remained elevated. In *figure 1* the increase in mean levels of coagulation factors per time point are shown. In contrast with the steep increase in glucose levels after placement of the prosthesis cup (S4), vWF:Ag, vWF:RiCof and FVIII:c levels somewhat lagged behind the glucose pattern. Both FVIII:c ($r=0.69$, $p=0.03$) and vWF:RiCof ($r=0.69$, $p=0.006$) were significantly correlated with the mean glucose levels. Correlation coefficients of F1+2 ($r=0.58$, $p=0.07$) and vWF:Ag ($r=0.59$, $p=0.06$) had borderline significance.

DISCUSSION

In this observational study, we have demonstrated how plasma glucose levels increase in response to hip replacement surgery. Following this rise in glucose, FVIII:c, vWF:Ag, vWF:RiCof and F1+2 levels also increased. These changes in mean glucose levels and mean levels of coagulation parameters during hip replacement surgery were closely correlated. All measured parameters remained elevated for several days up to seven weeks postoperatively. The link between glucose increase and activation of the coagulation system has been established before. Stegenga and co-workers showed in clamp studies that hyperglycaemia leads to upregulation of coagulation parameters in healthy volunteers, measured by soluble tissue factor and thrombin-antithrombin complexes.³ Furthermore, exposure to prolonged hyperglycaemia (diabetes mellitus) is an established risk factor for VTE.¹⁰ Coagulation activation by hyperglycaemia may be explained by mechanisms such as glycocalyx damage, non-enzymatic glycation, or the development of increased oxidative stress.^{10,11} From the present study we cannot conclude whether increasing glucose levels directly activates the coagulation system. Activation of coagulation could be due to other causes such as vascular damage and bleeding induced by the surgery. However, it is of interest to note that the rise in glucose levels precedes the increase in the measured coagulation parameters and is closely correlated with these parameters. Our study was limited by the small sample size ($n=9$). This was therefore a pilot study, to determine whether hip surgery does indeed cause hyperglycaemia and whether this is associated with activation of the coagulation system. To investigate the direct influence of perioperative glucose levels on coagulation parameters, a randomised controlled trial is needed, comparing an intervention group in which normoglycaemia is maintained with untreated controls, as in our study population. A consideration in interpreting the results is the possible lowering of coagulation parameters in response to the use of thromboprophylaxis and anticoagulants, especially the use of oral anticoagulants in three patients and the

influence on F1F2. However, one would have expected an even larger increase in the coagulation parameters when no anticoagulants or thromboprophylaxis were used, and this is therefore not likely to have biased the results.

Glucose values were measured both fasting (preoperatively) and non-fasting (perioperatively). In the analyses we have attempted to overcome this limitation by comparing the non-fasting samples to the baseline mean glucose values and the fasting samples with the pre-induction sample. It should also be noted that the medium in which the blood was collected, trisodium citrate, is not the medium of choice for glucose measurements. We have, however, corrected for the dilution factor. In addition, samples were stored in ice-cooled tubes which were centrifuged immediately. This limits possible glycolysis.

In conclusion, our observations indicate that total hip replacement surgery causes glucose levels to increase, prior to a rise in the concentration of the measured coagulation parameters. This suggests a possible role of glucose in the activation of the coagulation system during hip surgery. Confirmation of this observation in interventional studies is needed.

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