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ORIGINAL ARTICLE

Use of thromboelastography to guide thromboprophylaxis after caesarean section

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ABSTRACT

Background: Thromboprophylaxis is commonly required following caesarean section. However the effect of thromboprophylactic dosages of subcutaneous heparin on coagulation is unknown because conventional laboratory tests are largely unaffected. The aim of this study was to determine if thromboelastography could detect and quantify the effect of unfractionated heparin on coagulation profile when given at the time of surgery.

Methods: Nineteen women undergoing elective caesarean section were recruited. Blood samples collected before and after administration of subcutaneous unfractionated heparin 7500 IU underwent thromboelastography using both plain and heparinase cuvettes. Anti-factor Xa levels were also measured.

Results: There was a significant difference in R times between plain and heparinase samples (-10.6%, $P = 0.0072$) indicating that thromboelastography could detect an effect of unfractionated heparin. Compared to baseline there were significant decreases of R times in plain (-20.4%, $P = 0.033$) and heparinase (-28.8%, $P = 0.0001$) samples despite the administration of unfractionated heparin. Anti-factor Xa levels were virtually undetectable (mean 0.01 U/mL).

Conclusion: Thromboelastography was able to detect and quantify the effect of unfractionated heparin on blood coagulability, an effect not detected by conventional laboratory tests. Thromboelastography demonstrated a pro-coagulant effect of surgery that was only partially mitigated by the use of unfractionated heparin. In this study, at a dose of 7500 IU subcutaneous unfractionated heparin appears to have little anticoagulant effect.

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Keywords: Obstetric anaesthesia; Thromboelastography; Thromboprophylaxis; Heparin; Caesarean section

Introduction

Thromboembolism continues to be a leading cause of direct maternal death in the UK and caesarean section (CS) is a well recognised risk factor.[1–3] Thromboprophylaxis using a combination of mechanical methods and heparin has become routine practice after CS.[4] Dosage requirements for heparin are known to increase during pregnancy[5–9] and higher doses are recommended for thromboprophylaxis compared to the non-pregnant population, although recommendations are not evidence-based.[10] In a hypercoagulable parturient undergoing CS, the effects of a thromboprophylactic dose of heparin on the clotting profile are unknown.

Thromboelastography (TEG®) is a ward-based monitor of whole blood coagulation. It has been used to demonstrate the coagulation changes during pregnancy that culminate in the hypercoagulable state known to exist at term. When blood is placed in an oscillating cuvette and allowed to clot, it couples a pin suspended within it. The shear modulus and elasticity of the clot is transmitted through the pin and produces a signature trace of clotting activity within 20–30 min.[11] Kaolin can be added as an activator to accelerate the process, while addition of a heparinase reagent abolishes heparin activity and allows review of the coagulation profile as if heparin were entirely absent. The tracing is characterised by four variables. The R value (reaction time) is the time in minutes from start to splitting of the graphical trace, and represents initial fibrin formation. The k value is the time in minutes from the end of the R time for the trace to reach an amplitude of 20 mm, and represents the speed of clot formation. The α angle is the slope of the TEG tracing from the end of R time to k time, is closely related to the k time and represents the

use of clotting factors, fibrinogen and platelets to promote fibrin build-up and cross-linking. The MA (maximum amplitude, measured in mm), represents clot strength and is a function of platelets and fibrin. A heparin effect can be measured by changes in the R time, k time and α angle.[12,13]

Low-molecular-weight heparin (LMWH) is the heparin of choice in the UK for thromboprophylaxis after CS,[10,14] and in our unit is started on the first post-operative night. For many years our unit has also administered unfractionated heparin (UH) 7500 IU subcutaneously after neuraxial anaesthesia and immediately before surgery on the basis that it might provide additional thromboprophylaxis during the high risk period of surgical immobility. We were not aware of this being routine practice in the US or UK, nor of any studies that might justify the approach, since the effect of this dose of UH on the clotting profile of parturients is unknown. The aim of this study was to use TEG to determine the effect and magnitude of UH on the coagulation profile, and hence allow re-evaluation of local practice.

Methods

The study was approved by the Local Research Ethics Committee. Following written informed consent, women of American Society of Anesthesiologists status I or II, undergoing elective CS at 37 or more weeks of gestation under neuraxial anaesthesia, with a singleton pregnancy and of low to moderate thromboembolic risk[10] were recruited. Patients classified as high risk for thromboembolic disease or receiving medication known to affect coagulation, those with a history of clotting disorder, preeclampsia, pregnancy-induced hypertension, diabetes, vascular problems, or presenting in active labour were excluded. Patients whose blood loss exceeded 1000 mL during CS, and hence who might develop coagulopathy secondary to haemorrhage or blood transfusion, were also excluded.

Each subject had two 16-gauge venous cannulae inserted, one in each arm. One cannula was reserved for blood sampling, and the other for routine clinical use. After the first sample was taken, an intravenous infusion of compound sodium lactate was started before neuraxial anaesthesia.

Following skin asepsis and local anaesthetic infiltration, a combined spinal-epidural (CSE) was performed using a needle-through-needle technique (16-Tuohy and 27-gauge Whitacre needles) at the L3–4 interspace. The epidural space was identified using loss-of-resistance to saline. Injection of intrathecal 0.5% hyperbaric bupivacaine with fentanyl at a dose determined by the attending anaesthetist was made via the spinal needle, after which an epidural catheter was passed and the patient positioned according to the preference of the anaesthetist. Routine standard monitoring was used. Once the neuraxial block was established, but before surgery, UH 7500 IU was administered subcutaneously into the thigh. Following surgery, epidural diamorphine 2.5 mg and rectal diclofenac 100 mg were given for post-operative analgesia. Routine patient care in the recovery ward included removal of the epidural catheter just before transfer to the postnatal ward, approximately 4 h after surgery.

Blood samples were drawn from the 16-gauge cannula; the first 5 mL was discarded and a 2-mL sample collected. The baseline sample was taken before anaesthesia (time 0) and analysed using a plain cuvette. Subsequent samples were taken at hourly intervals for 4 h and analysed using both plain and heparinase cuvettes to allow direct observation of the UH effect at each stage. 1 mL was placed into a vial containing kaolin (Haemoscope, Niles, IL, USA) and, after mixing by inversion 10 times, 360 μL kaolin-activated whole blood was pipetted into a plastic cuvette cup for analysis in a pre warmed (37 °C) and calibrated TEG® Haemostasis Analyser 5000 (Haemoscope, Niles, IL, USA). An additional 360 μL of activated blood was added to heparinase coated cuvettes as a control sample, used to demonstrate a patient-specific heparin effect. All samples were run in parallel. A heparin effect was defined as a kaolin TEG R time > 25% longer than the heparinase-modified TEG R time.[15]

Additional samples were taken at 2 and 4 h for anti-factor Xa levels and Activated Partial Thromboplastin Time (APTT). A volume of 4.5 mL of blood was placed in a tube containing trisodium citrate (BD Vacutainer 9NC 0.109 M) and were centrifuged in the laboratory within 1 h at 3000 rpm for 10 min at 4 °C. APTT and anti-factor Xa levels were measured immediately (Sysmex CA 7000UK Ltd).

Data collection included TEG parameters, age, weight, height, gestation, intraoperative blood loss and intravenous fluids received. Data are presented as mean (SD), median [interquartiles] and count as appropriate. Normal values for kaolin activated TEG variables in the non-pregnant population were defined as R time 4–8 min; α angle 47–74°; k time 3–6 min; and MA 54–72 mm.

Statistical analysis

Sample-size estimates suggested that 19 evaluable subjects would be required to find a nominal difference of 10% in R time using a conservative estimate of within-subject SD at 10% with 89% power, and would also have >90% power to detect as nominal significance a 10% difference in MA. Data analyses included repeated measures analysis of variance (RMANOVA), Bonferroni multiple comparison post-tests, paired Student's t tests and Wilcoxon matched-pairs tests as appropriate. Data