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The effect on thrombin generation and anti-Xa levels of thromboprophylaxis dose adjustment in post-cesarean obese patients - A prospective cohort study

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ABSTRACT

Objective: To examine the laboratory anticoagulant effect of two thromboprophylactic low-molecular weight heparin (LMWH) regimens in post-cesarean obese patients.

Methods: A prospective cohort study, performed during 2017–2018 at a university hospital, of post-cesarean obese (> 90 kg) patients receiving 40 mg/day (n = 30) or 60 mg/day (n = 30) enoxaparin, and a control group of non-obese (n = 30) post-cesarean patients receiving 40 mg/day enoxaparin. Thrombin generation and anti-Xa were measured twice on the third postoperative day: prior to and 3.5–4 h following the third LMWH dose.

Results: Age, parity, weight and body mass index were comparable between the obese study groups. Compared to the control non-obese group, the 40 mg obese and 60 mg obese groups showed increased baseline thrombin generation: medians 491, 581, 571 nM, respectively (P = 0.001 and P = 0.04, respectively). At peak LMWH activity, thrombin generation was higher in the 40 mg than in the 60 mg obese and control groups: medians 2599, 2391, 2229 nM, respectively (P = 0.01 and P < 0.0001, respectively); and thrombin generation was comparable between the 60 mg obese and the control groups (P = 0.58). Similarly, a significantly lower proportion of patients in the 40 mg obese group (10%) had anti-Xa levels within the recommended prophylactic range (0.2–0.5 IU/mL) than in the other groups (P < 0.0001 for both comparisons).

Conclusion: As determined by thrombin generation and anti-Xa testing, post-cesarean obese patients have an increased procoagulant potential, which was diminished only in those receiving higher dosages of LMWH. These findings support the need for clinical evaluation of LMWH dose adjustment in this setting.

1. Introduction

Obesity is recognized as a global epidemic, due to its continually increasing incidence [1]. Obesity is an established risk factor for thrombotic complications due to multifactorial mechanisms including platelet activation, elevated levels of fibrinogen, coagulation factors VIII, IX, XI and XII, and impaired fibrinolysis [2]. As pregnancy is marked by an increased hypercoagulable state [3], obese pregnant women are at particularly high risk for venous thromboembolism (VTE) events [4–7], the latter are a leading cause of maternal morbidity and mortality [8]. This elevated thrombotic risk is most pronounced in the postpartum period, particularly following a cesarean section delivery [9,10].

Low-molecular weight heparin (LMWH) is the most widely used anticoagulant agent during pregnancy and the postpartum period. Nevertheless, there is no consensus regarding the optimal thromboprophylaxis regimen for preventing the occurrence of postpartum VTE among obese parturients. This is highlighted by the wide variability in recommendations espoused by professional society guidelines [11–13]. Moreover, the role of LMWH dose adjustment in parturients with extreme body weight is inconclusive [11–13]. In non-pregnant women, the demonstration that obesity may significantly reduce LMWH

Abbreviations: EBL, estimated blood loss; eGFR, estimated glomerular filtration rate; ETP, endogenous thrombotic potential; BMI, body mass index; LMWH, low-molecular weight heparin; VTE, venous thromboembolism

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bioavailability due to changes in distribution volume and renal clearance [14] raises concern regarding adequate dosing in obese parturients.

LMWH activity is commonly assessed by plasma anti-Xa activity. However, this measure is limited in its capacity to reflect the efficacy of VTE prevention [14], particularly among pregnant women, in whom LMWH renal clearance is accelerated [15]. In-vitro thrombin generation is a well-accepted tool for assessing the procoagulant potential of plasma; and thus, may quantify the composite global effects of the multiple parameters of the coagulation system [16,17]. Moreover, enhanced thrombin generation was found to correlate with VTE occurrence [18–20].

We aimed to compare the effect of two dosing regimens of LMWH thromboprophylaxis on thrombin generation and anti-Xa levels in post-cesarean obese women patients.

2. Materials and methods

2.1. Patients

This clinical trial was designed as a prospective cohort study. Obese patients (booking body weight > 90 kg and body mass index [BMI] > 30 kg/m^2) with singleton pregnancies who underwent cesarean delivery (before/during labor) from June 2017 to March 2018 at our medical center, and who were treated with postpartum thromboprophylaxis were assessed consecutively for eligibility to participate. Those eligible were invited to participate following their informed consent. We enrolled two study groups of post-cesarean obese patients; one group was receiving LMWH in the form of 40 mg/day enoxaparin and the other group 60 mg/day enoxaparin. Non-obese parturients who underwent cesarean section for whom 40 mg/day enoxaparin was prescribed for postpartum thromboprophylaxis, served as the control group for the laboratory analysis performed. Exclusion criteria for the study and control groups were: multifetal gestation, age < 18 years, personal or family history of VTE or thrombophilia, known bleeding disorders, recent thrombotic or bleeding events, thrombocytopenia (< 100 × 10^9/L), hepatic or renal failure, current or recent (< 7 days) use of any antiplatelet therapy or anticoagulants, body weight > 130 kg, active infection, current smoking and contraindication to anticoagulant therapy.

2.2. VTE prophylaxis

Routine prophylaxis among obese patients undergoing cesarean section included the application of a thigh-length pneumatic compression device at the time of surgery, and until the patient recovered normal mobility; and early ambulation, within the first few hours following the procedure. In addition, according to our local institutional protocol, anticoagulation prophylaxis is recommended for all obese patients (body weight > 90 kg) who undergo cesarean delivery, starting 8–12 h following surgery. Based on recommendations of the Royal College of Obstetricians and Gynaecologists (RCOG) [13], our protocol also suggests that dose adjustment (> 0.5 mg/kg) may be considered according to patients' body weight - 40 mg/day of enoxaparin in those < 90 kg, 60 mg/day in those > 90 kg–≤ 130 kg and 80 mg/day in those > 130 kg. The decision as to whether to adjust the dose of enoxaparin is at the discretion of the attending physician. Among non-obese post-cesarean patients, thromboprophylaxis is administered in the presence of at least one additional risk factor (e.g. age > 35 years, parity > 3, gross varicose veins, preeclampsia, immobilization, prolonged labor).

2.3. Data collection

Blood samples were taken at 2 successive time points at the third postoperative day and tested for thrombin generation and anti-Xa levels: (1) at baseline, 24 h after the second enoxaparin dose and prior to the injection of the third enoxaparin dose; to obtain heparin free plasma and to preclude the effect of prophylactic anticoagulation therapy; and (2) at time to peak plasma concentrations, 3.5–4 h following the injection of the third enoxaparin dose. Blood samples were collected from an antecubital vein, by using a 23-gauge needle without stasis. For coagulation assays, blood was collected in vacutainer tubes containing trisodium citrate (final concentration 0.32%) (Becton Dickinson and Company, Franklin Lakes, NJ, United States). All analyses were performed immediately, except for the thrombin generation assay, which was carried out using platelet poor plasma samples stored at −80 °C. In addition to the laboratory evaluation performed, the following data were extracted from the medical records for each participant: current maternal age, anthropometric parameters, parity, pregnancy-associated hypertensive disorders, gestational diabetes mellitus, the setting of cesarean delivery (elective vs. during labor), the type of anesthesia (general vs. neuroaxial), preoperative and postoperative (at postoperative day 1) blood count results (hemoglobin, hematocrit), estimated blood loss (EBL), bleeding events and the need for reoperation. EBL was estimated using the formula: 85 × Current weight (kg) × [Preoperative hematocrit (%) − Postoperative hematocrit (%)]/Preoperative hematocrit (%) [21]. For each patient, the estimated glomerular filtration rate (eGFR) was calculated based on the Cockcroft and Gault formula using patient adjusted body weight: [0.85 × (140-age) × Adjusted body weight (kg)]/[72 × Serum creatinine × 0.0113]. Adjusted body weight was calculated as [15 × (Height [m])^2] + [0.4 × Current weight (kg)]. Institutional Review Board approval was obtained for the study from the Hadassah Medical Center Ethical Committee and written informed consent was obtained from all the participants.

2.4. Laboratory investigations

2.4.1. Thrombin generation assay

Thrombin generation was measured in duplicate using a commercially available fluorogenic assay kit (Technothrombin®, Vienna, Austria) on a fully automated coagulation analyser (Ceveron®, Alpha, Technoclone, Vienna, Austria). Briefly, coagulation is initiated through the addition of tissue factor (3 pM) and phospholipids (3 μM). The concentration of thrombin is measured in platelet-poor plasma with a fluorescent peptide substrate, which is cleaved by thrombin to release a fluorophore. The rate of thrombin generation is measured over time, resulting in a thrombin formation curve. The following parameters of thrombin activity were recorded: (a) peak thrombin generation: the maximal concentration of thrombin formed (nM); and (b) endogenous thrombin potential (ETP), which equals the area under the curve, and represents the total amount of thrombin generated (nM).

2.4.2. LMWH anti-Xa assay

Plasma anti-Xa levels were measured using HemosIL®Liquid Anti Xa Kit (Instrumentation Laboratory, United States), performed on an ACL TOP 500 coagulometer (Instrumentation Laboratory, United States). Target prophylactic anti-Xa range was defined as 0.2–0.5 IU/mL [22].

2.5. Statistical analysis

Patient characteristics are described as proportions for categorical variables and as medians and interquartile ranges for continuous variables. Significant differences between subgroups were assessed using the chi-square test and Fisher's exact test for categorical variables, while the Mann-Whitney *U* test was used for continuous variables. Correlations were calculated by the Spearman test with the correspondent ρ_s and *P* values. A univariate regression model was applied to all clinical and laboratory parameters. A 2-sided *P*-value < 0.05 indicated statistical significance. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 22, IBM Corp,