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Original Article

Safety and efficacy of thromboprophylaxis using enoxaparin sodium after cesarean section: A multi-center study in Japan

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ABSTRACT

Objective: Pulmonary embolism (PE) is the leading cause of maternal death in developed countries, and the prevention of venous thromboembolism (VTE) is a pivotal part of current obstetric care. This study evaluated the safety and efficacy of enoxaparin sodium for thromboprophylaxis after cesarean section (C/S), and analyzed the risk factors associated with VTE.

Materials and methods: One hundred and forty-three women deemed to be at high risk of postoperative deep vein thrombosis (DVT) were enrolled between January 2011 and May 2012 in seven institutions in Japan. Subcutaneous administration of enoxaparin 4000 units/d was initiated 24–36 hours after C/S for 5 days. Adverse events, based on the Common Terminology Criteria for Adverse Events, Version 4, were recorded. The diagnoses of PE and DVT were made on clinical signs. Venous ultrasonography in the lower extremities was performed in 102 patients. The association between VTE and various risk factors was evaluated using univariate analysis.

Results: There were 10 (7.0%) Grade 1 adverse events: elevated aspartate aminotransferase or alanine aminotransferase levels in eight patients, chest pain in one patient, and subcutaneous hematoma in one patient. No patients showed clinical signs of PE and/or DVT. Among 102 patients who underwent venous ultrasonography, thrombus was detected in unilateral soleus veins in four (3.9%) patients. A body mass index (BMI) $\geq$ 25 kg/m^2 before pregnancy was associated with asymptomatic DVT.

Conclusion: The current study demonstrates the safety and efficacy of enoxaparin for thromboprophylaxis after C/S. Further studies are required to determine the best method of preventing asymptomatic DVT.

Introduction

Pulmonary thromboembolism (PTE) is the leading cause of maternal death in Japan and the developed world [1–3]. Deep vein thrombosis (DVT), a major risk factor for PTE, may develop during pregnancy and puerperium, especially after cesarean section (C/S) [1–8]. The incidence of PTE after C/S is 0.06% and that of DVT after C/S is 0.04% among the general population in Japan. After C/S, women are estimated to have 22- and five-times higher risks of PTE and DVT, respectively, than those after transvaginal delivery [2]. The rate of C/S has been increasing steadily over the past decades in developed countries, including Japan [2]. Consequently, prevention of venous thromboembolism (VTE) after C/S has become a pivotal

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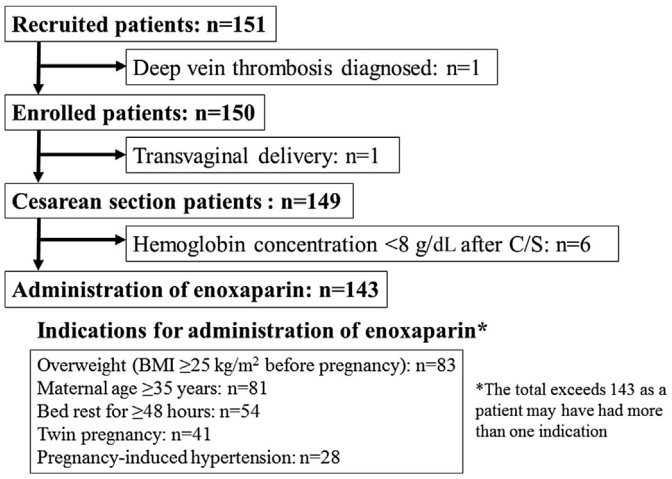

Fig. 1. Study participants. BMI = body mass index.

part of current obstetric practice that aims to further reduce the incidence of maternal pregnancy-related death.

Low-molecular-weight heparin (LMWH) is widely used as an agent for prevention of VTE after C/S in patients with risk factors, such as thrombophilia or being overweight [4,5]. Many investigators have reported that LMWH is a safe means of providing thromboprophylaxis after C/S [8–12]. Enoxaparin sodium was only recently granted a license in Japan for thromboprophylaxis and there have been few evaluations of its safety in pregnant Japanese women [11]. The efficacy of enoxaparin sodium has been established in a series of studies that used the clinical signs of VTE after major surgery [10,13,14]. However, the incidence of asymptomatic DVT and its risk factors have not yet been studied in women receiving thromboprophylaxis with enoxaparin sodium after C/S.

This study aims to establish the safety and efficacy of enoxaparin sodium for thromboprophylaxis after C/S in women at a known risk of developing VTE based on clinical and laboratory signs. The efficacy of enoxaparin sodium by detection of asymptomatic DVT using venous ultrasonography is evaluated. The risk factors associated with VTE, including asymptomatic DVT in Japanese women undergoing C/S were determined.

Materials and methods

Study population

Participants included 151 Japanese women who fulfilled the inclusion criteria (i.e., were considered to be at high risk of DVT), but did not meet an exclusion criterion (Table 1) in seven institutions in Japan (Iizuka Hospital, Fukuoka University Hospital, Yamaguchi Red Cross Hospital, Kitakyushu Municipal Hospital, National Kyushu Medical Center, Kyushu Kosei Nenkin Hospital, and Oita Prefectural Hospital). The study protocol was approved by the Institutional Review Boards of all hospitals and written consent was obtained from all participants. Patients were recruited at 34–36 weeks' gestation between January 2011 and May 2012. After excluding one patient in whom preexisting DVT was diagnosed, 150 patients were enrolled in this study. Seven patients were further excluded, including one who delivered transvaginally and six who were anemic (serum hemoglobin concentration < 8 g/dL after C/S). The remaining 143 patients were analyzed for evaluation of the safety and efficacy of enoxaparin sodium based on clinical and laboratory signs (Fig. 1). For evaluation of asymptomatic DVT, 102 out of 143 participants were examined in three hospitals where venous ultrasonography of the lower extremities was available. In the 143 participants, the median maternal age was 36.0 years (range 22–49 years) and 53 women were primiparous. The median gestational age at C/S was 38 weeks (range, 34–41 weeks) and 46 patients had emergency C/S performed. The indications for C/S were previous C/S (n = 52), twin pregnancy (n = 39), malpresentation (n = 12), deterioration of preeclampsia (n = 10), nonreassuring fetal status (n = 9), placenta previa (n = 7), arrest of labor (n = 5), myomectomy before pregnancy (n = 4), the presence of myoma uteri causing cephalopelvic disproportion (n = 4), and obesity (n = 1). The indications for enoxaparin administration were as follows: overweight, defined as a BMI ≥25 kg/m^2 before pregnancy (n = 83); maternal age ≥ 35 years (n = 81); bed rest for ≥ 48 hours before C/S (e.g., because of threatened preterm delivery or placenta previa) (n = 54); twin pregnancy (n = 41); and hypertensive disorders of pregnancy with systolic blood pressure of ≥160 mmHg and/or diastolic blood pressure of ≥110 mmHg, including preeclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and gestational hypertension (n = 28). The total number of indications is greater than the number in the cohort because some women had more than one indication.

Study protocol

A total of 4000 units of enoxaparin sodium were administered subcutaneously 24–36 hours after C/S, twice daily for 4 further days, and once on the 6th postoperative day (Fig. 2). In 133 patients in whom a continuous epidural infusion had been used for

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
Participants met all criteria listed below:
Written consent to participate in the study
Maternal age ≥ 20 y
Body weight ≥ 40 kg
Normal complete blood count & vital organ function, including the following:
(1) White blood cell count ≥ 4000/mm^3
(2) Neutrophil count ≥ 2000/mm^3
(3) Platelet count ≥ 100,000/mm^3
(4) Hemoglobin concentrations ≥ 8 g/dL
(5) Serum aspartate aminotransferase & alanine aminotransferase concentrations < 2.5 times the in-house normal value
(6) Total bilirubin concentrations ≤ 2.0 mg/dL
(7) Creatinine clearance ≥ 70 ml/min
(8) Peripheral oxygen saturation ≥ 90%
Participants met at least one of the criteria listed below:
History of venous thromboembolism
Presence or suspicion of thromboembolism
Family history of thromboembolism
Advanced maternal age (≥ 35 y)
Body mass index ≥ 25 kg/m^2 before pregnancy
Bed rest for ≥ 48 hours before cesarean section (e.g., for threatened preterm delivery, placenta previa)
Twin pregnancy
Hypertensive disorders of pregnancy (preeclampsia, chronic hypertension, preeclampsia on chronic hypertension, & gestational hypertension) with systolic blood pressure ≥ 160 &/or diastolic blood pressure ≥ 110 mmHg)
Marked varices in the lower extremities
Paralysis of the lower extremities
Exclusion criteria
History of allergy to heparin or heparin derivatives
History of heparin-induced thrombocytopenia
History of cerebral hemorrhage
Liver dysfunction (Child–Pugh classification > Grade A)
Clinical signs of bacterial endocarditis
Clinical signs of venous thromboembolism
Hemorrhage (intra-abdominal, retroperitoneal, intracranial, or in other vital organs)