Original Article

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

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ARTICLE INFO

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) ≥ 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.

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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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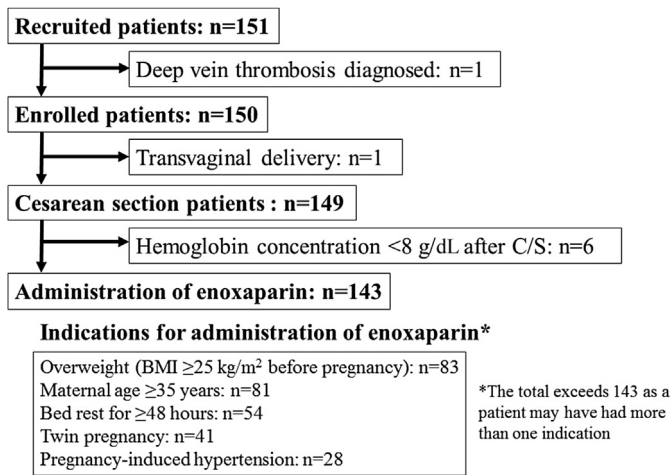E-mail address: ty-obgyn@cis.fukuoka-u.ac.jp (T. Yoshizato).

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 ($n = 10$), non-reassuring 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 $\geq$25 kg/m^2 before pregnancy ($n = 83$); maternal age $\geq$ 35 years ($n = 81$); bed rest for $\geq$ 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 $\geq$160 mmHg and/or diastolic blood pressure of $\geq$110 mmHg, including preeclampsia, chronic hypertension, preeclampsia superimposed on chronic hypertension, and gestational hypertension ($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 $\geq$ 20 y |
| Body weight $\geq$ 40 kg |
| Normal complete blood count & vital organ function, including the following: |
| (1) White blood cell count $\geq$ 4000/mm^3 |
| (2) Neutrophil count $\geq$ 2000/mm^3 |
| (3) Platelet count $\geq$ 100,000/mm^3 |
| (4) Hemoglobin concentrations $\geq$ 8 g/dL |
| (5) Serum aspartate aminotransferase & alanine aminotransferase concentrations < 2.5 times the in-house normal value |
| (6) Total bilirubin concentrations $\leq$ 2.0 mg/dL |
| (7) Creatinine clearance $\geq$ 70 ml/min |
| (8) Peripheral oxygen saturation $\geq$ 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 ($\geq$ 35 y) |
| Body mass index $\geq$ 25 kg/m^2 before pregnancy |
| Bed rest for $\geq$ 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 $\geq$ 160 &/or diastolic blood pressure $\geq$ 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) |
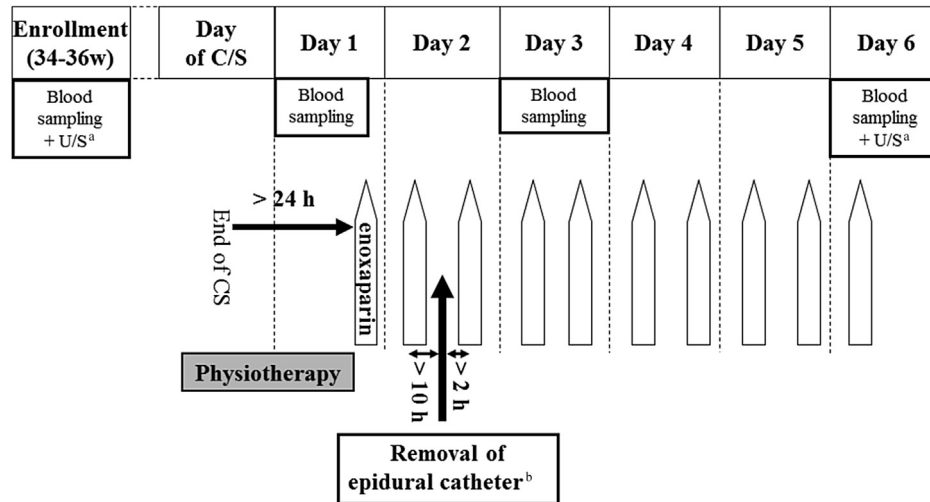
Fig. 2. Study protocol. [a] Venus ultrasound (U/S) examinations were undertaken in 102 cases. [b] If epidural anesthesia had been used for perioperative pain control. C/S = cesarean section.

postoperative pain relief, the catheter was removed 10 hours before or 2 hours after the administration of enoxaparin sodium. In all patients, additional prophylactic measures to prevent DVT, including compression stockings and/or intermittent compression of the lower extremities during and after C/S, were used. Venous blood specimens were obtained for complete blood count, serum biochemistry, and coagulation assays. A physical examination was undertaken to detect DVT and pulmonary embolism (PE). Peripheral oxygen saturation (SpO$_2$) was measured on postoperative Day 1 (before the administration of enoxaparin sodium) and on Day 3 and Day 6. Venous ultrasonography of the lower extremities, including the calf veins, was examined in 102 of the 143 participants at 34–36 weeks' gestation and at 6 days after C/S by experienced sonographers according to a standard protocol [15].

Parameters for evaluation of safety and efficacy of enoxaparin sodium

Adverse events were evaluated based on the Common Terminology Criteria for Adverse Events, Version 4. The efficacy of enoxaparin sodium for prevention of DVT was assessed by clinical examination or venous sonography, and for prevention of PE, by clinical examination. Univariate analysis was used to assess risk factors in women who were diagnosed with venous thrombosis.

Statistical analysis

Statistical analyses were performed using the Mann–Whitney U test and Chi-square test for assessment of risk factors associated with VTE. IBM SPSS statistics (Version 22; IBM, Armonk, NY, USA) was used for analysis. Statistical significance was defined as $p < 0.05$.

Results

Ten women in the cohort of 143 (7.0%) experienced Grade 1 adverse events as follows: elevated aspartate aminotransferase or alanine aminotransferase levels greater than the upper limit of normal and less than three times the upper limit of normal in eight patients; chest pain (i.e., mild pain) in one patient, and subcutaneous hemorrhage (i.e., minimal bleeding was identified on clinical examination; intervention not indicated) in one patient. No patients developed adverse events of Grade 2 or higher. The patient

with chest pain reported transient symptoms on the 3rd postoperative day, blood pressure, heart rate, SpO$_2$, and electrocardiogram were normal. The patient with subcutaneous hemorrhage was one of 19 patients in whom a subcutaneous surgical drain was placed. A 2 cm × 3 cm hematoma was detected on ultrasonography after removal of the drain on the 3rd postoperative day and enoxaparin sodium was discontinued. There was no incidence of epidural hematoma in the 133 patients in whom an epidural catheter had been placed.

No patients developed clinical signs of DVT or PE. Among the 102 women who underwent venous ultrasonography, none had thrombus before C/S; new thrombus was detected in four patients (3.9%). All of the thrombi were detected in unilateral soleus veins (2 on the right and 2 on the left). In these four patients, possible causes of thrombophilia, such as antithrombin III deficiency, protein C deficiency, protein S deficiency, and antiphospholipid syndrome, were excluded at a follow-up appointment 1 month or later postpartum.

The factors associated with asymptomatic DVT were examined. The only factor significantly associated with asymptomatic DVT was being overweight (BMI $\geq$ 25 kg/m^2 before pregnancy; Table 2). Factors that did not reach statistical significance were advanced maternal age $\geq$ 35 years ($n = 3$), prolonged bed rest $\geq$ 48 hours ($n = 3$), and twin pregnancy ($n = 2$).

Discussion

In this study, no serious adverse events of Grade 2 or higher were reported or detected. In the one patient reporting chest pain, symptoms were transient, and heart rate, SpO$_2$, and electrocardiogram remained normal. This woman did not undergo computed tomography pulmonary angiography to exclude PE. Therefore, nonlife threatening PE cannot be completely ruled out because SpO$_2$, blood pressure, and heart rate could be normal in a relatively young and healthy woman with a small PE. In the patient with subcutaneous hemorrhage, the hematoma was detected by ultrasonography after removal of the surgical drain, but no clinical signs were evident. Whether the hematoma was related to administration of enoxaparin sodium, or placement or removal of the subcutaneous drain is unknown. The study findings are broadly comparable with other reports in which Japanese women received enoxaparin sodium after C/S according to a similar protocol [11].

Table 2
Effect of potential risk factors on the incidence of deep vein thrombosis.

Parameters	DVT	nonDVT	p
	(n = 4)	(n = 98)	
Indications (clinical background)			
Maternal age (y)	36.0 (34—41)	36.0 (22—49)	0.489
Body mass index	28.5 (22.9—29.4)	24.5 (19.2—43.6)	0.049
No. of patients with prolonged bed rest	3 (75.0)	47 (48.0)	0.290
No. of patients with twin pregnancy	2 (50.0)	31 (31.0)	0.433
Parameters related to cesarean section			
No. of patients requiring emergency cesarean section	2 (50.0)	34 (34.6)	0.547
Duration of surgery (min)	56.5 (33—88)	62 (22—195)	0.476
Blood loss (mL)	1,045 (710—1817)	790 (272—2745)	0.375
Parameters related to administration of enoxaparin			
Interval between cesarean section & enoxaparin administration (h)	30.5 (28—31)	31.0 (20—46)	0.476
Postoperative data			
D-dimer levels (μg/mL)			
Before cesarean section	2.2 (1.1—7.0)	3.0 (0.2—10.8)	0.622
Postoperative Day 1	11.6 (4.9—16.7)	7.0 (1.6—50.3)	0.141
Postoperative Day 3	3.3 (2.6—8.3)	2.0 (0.8—19.5)	0.129
Postoperative Day 6	3.6 (2.9—7.3)	2.0 (0.7—20.9)	0.077

Data are presented as n (%) or median (range).
DVT = deep vein thrombosis.

Currently there are no reported incidences of DVT in women receiving thromboprophylaxis using unfractionated heparin or LMWH after C/S. This study found that the incidence of asymptomatic DVT among women at high risk of VTE was 3.9%. Two previous studies reported that symptomatic DVT was detected in 0.04% and 0.5% of patients [6,16]. The patients in these two studies were randomly selected populations in which thromboprophylaxis was not administered. The incidence of DVT is likely to be affected by the population studied, the thromboprophylaxis protocol used, and the timing and method of ultrasound examination. Nevertheless, no cases of thrombophilia among the four women diagnosed with asymptomatic DVT were detected by this study. In the 102 patients in whom no DVT was detected by ultrasonography before C/S, all of the deep veins in the lower extremities, including the calf muscle veins, were examined 6 days after C/S when the course of enoxaparin had finished. In the four cases of asymptomatic DVT, thrombus was only detected in unilateral soleus veins. The pathophysiological significance of soleus vein thrombosis is not fully understood, because only 20% of calf muscle vein thromboses propagate to the proximal veins, which carry a higher risk for PE [17—19].

Our enoxaparin administration protocol was designed in accordance with the standard indication in Japan, which states that the first dose should be given 24—36 hours after surgery. Development of this guidance was informed using data from Japanese patients who had undergone orthopedic surgery, after which patients may be immobile for some time. By contrast, women who have undergone C/S are likely to be healthier, younger, and more active than those who have undergone orthopedic surgery. Most thrombi develop within 24 hours of C/S, and symptoms related to VTE are likely to occur by the 3rd postoperative day [17,20]. Although there were no significant differences in the interval between C/S and the administration of enoxaparin sodium in women with and without DVT, future studies should focus on the optimum time that administration of LMWH should commence.

In the current study, the only significant risk factor associated with DVT was being overweight. Whether being overweight itself was a risk factor, or whether the dose of LMWH was not sufficient for the overweight patients' body mass is unclear. Logically, heavier women should receive higher doses of enoxaparin sodium, but the appropriate dose for body weight has not yet been determined. Other risk factors, including advanced maternal age, prolonged bed rest, and twin pregnancy, were not significant, but study findings suggest that patients with multiple risk factors were more likely to develop asymptomatic DVT. According to the VTE prevention guidelines in the United States [4] and the United Kingdom [21], but not Japan [3], patients with multiple risk factors are good candidates for prophylactic LMWH. In these cases, more frequent use of LMWH may be considered and the efficacy of such an approach should also be established.

The incidence of VTE, including asymptomatic DVT that was detected by ultrasonography in the low risk population after C/S without thromboprophylaxis, was 0—0.8% in five previous reports in which the sample sizes were small, ranging between 59 and 194 [16,20,22—24]. In three studies in which the number of participants was less than 100, no DVT was detected [22—24]. To date, no clinical trials have evaluated the incidence of VTE, including asymptomatic DVT, after C/S in the known at-risk population with thromboprophylaxis using LMWH. Therefore, in this study, a sample size of > 100 was determined *a priori*. The limitations of this study are that the sample size was relatively small and the study design was not a randomized control study.

This study shows the safety and efficacy of enoxaparin for thromboprophylaxis after C/S. However, four cases of asymptomatic DVT were reported. Further studies on the prevention of asymptomatic DVT, a potential risk factor for clinical VTE, are needed.

Conflicts of interest

The authors have no conflicts of interest relevant to this article. The views expressed in this article are the authors own and not an official position of the institution.

Acknowledgments

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