



A comparison of the safety of two different enoxaparin doses for thromboprophylaxis following cesarean section

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Abstract

Enoxaparin, from the low molecular weight heparin group, is used as thromboprophylaxis in patients with risk factors following caesarean section. The aim of this study was to investigate the effect of enoxaparin doses on the formation of deep vein thrombosis (DVT), wound site infection (WSI), wound site hematoma (WSH) and hemogram results of patients on the 10th postoperative day. A retrospective examination was made of the files of patients who had undergone a caesarean section operation and been administered enoxaparin as postpartum thromboprophylaxis for 10 days postoperatively. Two groups were formed of 16 patients who received enoxaparin at dose of 60mg/day and 25 patients who received 40mg/day. The groups were compared in respect of age, weight, gravida, gestational week at the time of operation, the leukocyte (Wbc), hemoglobin (Hb), and platelet (Plt) values on postoperative days 1 and 10, and the development of DVT, WSI, and WSH on postoperative day 10. The development of WSI and WSH was determined to be significantly higher in the group that received 60mg/day enoxaparin than in the group that received 40mg/day ($p=0.007$, $p=0.008$). With the use of 60mg/day enoxaparin, no change was observed in the Wbc and Hb values on the postoperative 10th day compared to the 1st day ($p=0.128$, $p=0.947$), and a significant reduction was determined in Plt values ($p=0.014$). With an increase in the dose of enoxaparin used as thromboprophylaxis following caesarean section in patients with risk factors, there was seen to be an increase in the formation of WSI and WSH. Compared to a dose of 40mg/day, the use of 60mg/day enoxaparin reduced serum Wbc, did not change Hb, and increased Plt values. Dose adjustment should be made for the drug used as caesarean postoperative thromboprophylaxis in patients with indications, taking the side-effects of enoxaparin into consideration.

Keywords: caesarean, deep vein thrombosis, enoxaparin, hemogram, wound site infection-hematoma

1. Introduction

The likelihood of thromboembolism developing in pregnant females is 4-5-fold greater than in non-pregnant females. Thromboembolic events in pregnancy are venous in 80% of cases, and prevalence is 0.5-2.0 per 1000 pregnancies (1). Deep vein thrombosis (DVT) is seen in 75% of pregnancy-related venous thromboembolism (VTE), and pulmonary embolism (PE) in 20-25% (2). The VTE risk is greater in the postpartum period, and especially in the first two postpartum weeks (3). In a meta-analysis of the relationship between caesarean delivery and VTE, caesarean section delivery was reported to be an independent risk factor for VTE, and the estimated incidence of VTE was 0.003% which was seen to be a 4-fold increase compared with vaginal delivery (4).

While the leading cause of maternal death is hemorrhage in developing countries, thromboembolic diseases are among the leading causes in developed countries (5). Due to the high prevalence of thromboembolism in pregnancy and the postpartum period, and the severity of the outcomes, the treatment and prophylaxis of this disease have a very important place in antenatal care (6, 7). A national guideline has been established in Turkey, based on the RCOG

guidelines, for the determination of pregnant patients at moderate-high risk of thromboembolism (8, 9).

Various agents are used in postpartum thromboprophylaxis. The most used drug group is low molecular weight heparin (LMWH), but this may have side-effects such as bleeding and hematoma (10). Enoxaparin is a widely used LMWH (11). The aim of this study was to investigate deep vein thrombosis (DVT), wound site infection (WSI), wound site hematoma (WSH) and hemogram results on the 10th postoperative day of patients administered 40mg/day or 60mg/day enoxaparin according to the risk classification following caesarean section operation.

2. Materials and Methods

This retrospective study included 41 female patients who underwent caesarean delivery and then received postpartum thromboprophylaxis of enoxaparin for 10 days between January 2019 and January 2021 in the Obstetrics and Gynaecology Clinic of Turhal State Hospital. All the patients were aged 18-36 years and had no comorbidities. Two groups were formed of 16 patients who received enoxaparin at a dose of 60mg/day and 25 patients who received 40mg/day.

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Patients were excluded from the study if they had an allergy to heparin or heparin derivatives, liver failure, or any findings of perioperative bleeding (intraabdominal, retroperitoneal, and intracranial). As Turhal State Hospital is a second level healthcare institution, patients with a known high risk of thrombophilia, a history of VTE, a mechanical heart valve, heart failure, active systemic lupus erythematosus, or active inflammatory bowel disease, were transferred to a tertiary level healthcare institution. The study was approved by the Local Ethics Committee of Gaziosmanpaşa University with no: 21-KAEK-070.

All the patients underwent caesarean operation by the same surgeon. The operations were conducted under spinal or general anesthesia. The abdomen was entered with a Pfannenstiel caesarean-type incision, and the uterus was opened with a transverse incision. In all the operations, the uterus was sutured in a single layer after the procedure. At mean 8 hours postoperatively, the patients were mobilized and thromboprophylaxis was started at the postoperative 12th hour. In the postnatal period, prophylactic enoxaparin was administered for 10 days to patients with ≥ 2 points (apart from those with a history of VTE or high-risk thrombophilia) in the VTE risk factors according to the “management guidelines for venous thromboembolism in pregnancy” published by the Republic of Turkey Ministry of Health in 2017 (12) (Fig. 1).

Enoxaparin was administered as a single dose of 40mg/day to patients <90 kg body weight and at 60 mg/day to those weighing >90 kg. A record was made for each patient of age, weight, gravida, gestational week, and postoperative first day hemogram results. The patients were discharged after 48 hours at the earliest and were called for follow up at postoperative 10 days. The development of DVT-PE, the presence of wound site infection or hematoma, and hemogram results were recorded. All these data were compared between the two groups of patients who received 60mg/day enoxaparin and those who received 40 mg/day. The changes in the hemogram from postoperative day 1 to day 10 were also compared between the groups.

Statistical Analysis: Data obtained in the study were analyzed statistically using SPSS vn. 20.0 software (Statistical Package for Social Sciences Chicago, IL, USA). Descriptive statistics were stated as mean \pm standard deviation (SD) values for continuous variables and as number (n) and percentage (%) for categorical values. In the paired group comparisons, the Independent Samples t-test, Mann Whitney U-test, or the Chi-Square test were used. A value of $p < 0.05$ was accepted as statistically significant.

3. Results

Evaluation was made of a total of 41 females applied with enoxaparin following caesarean section delivery, as 25 patients who received 40mg/day and 16 patients who received 60 mg/day. The mean age of the patients was 27.20 \pm 4.76

years in the 40mg/day enoxaparin group and 26.25 \pm 4.49 years in the 60mg/day group ($p=0.451$). No difference was determined between the groups in respect of gestational week at the time of caesarean operation and gravida ($p=0.882$, $p=0.754$).

Table 1. Comparison of the groups administered enoxaparin 40 mg/day and enoxaparin 60 mg/day for thromboprophylaxis after cesarean section

	Enoxaparin 40 mg/day (n=25)	Enoxaparin 60 mg/day (n=16)	p
Age (years)	27.20 \pm 4.76	26.25 \pm 4.49	0.451
Gravidity	2(1-3)	2(1-3)	0.754
Maternal weight (kg)	77.68 \pm 8.47	98.75 \pm 7.03	<0.001*
Gestational week	38 (34-41)	39 (34-40)	0.882
Wbc in po. 1 st day($10^3/\mu\text{L}$)	8.79 \pm 2.96	8.21 \pm 3.41	0.385
Wbc in po. 10 th day($10^3/\mu\text{L}$)	8.29 \pm 3.9	9.14 \pm 3.21	0.302
Hb in po. 1 st day(g/dL)	11.79 \pm 1.15	11.49 \pm 1.67	0.862
Hb in po. 10 th day(g/dL)	11.04 \pm 0.97	11.05 \pm 1.43	0.715
Plt in po. 1 st day($10^3/\mu\text{L}$)	259.92 \pm 55.34	264.19 \pm 58.47	0.904
Plt in po. 10 th day($10^3/\mu\text{L}$)	203.16 \pm 61.53	171.75 \pm 39.69	0.316
IIS	2 (8)	7 (43.75)	0.007*
HIS	0	4 (25)	0.008*
DVT	0	1 (6.25)	0.236

Variables presented as mean \pm sd and number (%). Wbc= white blood cell, Hb= hemoglobin, Plt= platelet, po.=postoperative, IIS= Infection in the incision site, HIS= Hematoma under the incision site, DVT= Deep Vein Thrombosis

The development of WSI and WSH was determined to be significantly lower in the group that received 40mg/day enoxaparin than in the group that received 60mg/day ($p=0.007$, $p=0.008$). In the comparison of the Wbc, Hb, and Plt values on the postoperative 1st and 10th days, no statistically significant difference was determined between the groups ($p=0.385$, $p=0.302$, $p=0.864$, $p=0.715$, $p=0.904$, $p=0.316$) (Table 1).

From postoperative day 1 to postoperative day 10, there was a decrease of 56.76 \pm 55.61 $10^3/\mu\text{L}$ in the serum Plt value in the 40 mg/day enoxaparin group and a decrease of 92.44 \pm 48.53 $10^3/\mu\text{L}$ in the 60 mg/day enoxaparin group. The change in Plt was statistically significant between the groups ($p=0.014$).

From postoperative day 1 to postoperative day 10, there was a decrease of 0.5 \pm 4.04 $10^3/\mu\text{L}$ in the serum WBC value in the 40 mg/day enoxaparin group and an increase of 0.92 \pm 3.27 $10^3/\mu\text{L}$ in the 60 mg/day enoxaparin group, and the difference between the groups was not statistically significant ($p=0.128$). From postoperative day 1 to postoperative day 10, there was a decrease of 0.75 \pm 1.70 g/dL in the serum Hb value in the 40 mg/day enoxaparin group and a decrease of 0.43 \pm 2.06 g/dL in the 60 mg/day enoxaparin group. The change in Hb was not statistically significant between the groups ($p=0.947$) (Table 2).

Table 2. Comparison of the changes in Wbc, Hb and Plt levels of groups from postoperative 1st to postoperative 10th days

	Enoxaparin 40 mg/day (n=25)	Enoxaparin 60 mg/day (n=16)	p value
Wbc (10 ³ /µL)	0.5± 4.04	-0.92 ±3.27	0.128
Hb(g/dL)	0.75 ± 1.70	0.43 ± 2.06	0.947
Plt(10 ³ /µL)	56.76 ± 55.61	92.44 ± 48.53	0.014*

Variables presented as mean ±sd and number (%). Wbc= white blood cell, Hb= hemoglobin, Plt= platelet

4. Discussion

Within a two-year period, 41 patients who had undergone caesarean section operation in the single centre of the Obstetrics and Gynaecology Clinic of Turhal State Hospital received enoxaparin as postpartum thromboprophylaxis according to the “guidelines for the management of venous thromboembolism in pregnancy” published by the Republic of Turkey Ministry of Health in 2017. Of these patients, 16, weighing <90 kg received enoxaparin at a dose of 40mg/day and 25, weighing >90kg received 60 mg/day. The results of this study showed that with an increase in enoxaparin dose, there was an increase in the formation of WSI and WSH. Compared to enoxaparin at a dose of 40mg/day, with the use of 60mg/day, no change was observed in the serum WBC and Hb values, and a reduction was seen in Plt values.

During pregnancy, the risk of DVT or PE is approximately 0.1%, and this rate is 3-4 folds higher than in non-pregnant women of the same age (13). During the pregnancy and for 6-8 weeks postpartum, the DVT risk increases 5-6-fold. The frequency of DVT in pregnancy is 0.05%-1.8% and in pregnant patients who have a caesarean delivery, this rate increases to 2.2%-3% (14). Previous studies in literature have shown the efficacy of postpartum thromboprophylaxis (15). In a review of international guidelines, it was reported that LMWH administered for one week postpartum reduced the likelihood of DVT development by 70% (3). Caesarean section delivery increases the risk of venous thromboembolism 2-fold. Nevertheless, this risk for a healthy woman with no risk factors is still low (1/1000) (1). In the current study, PE was not observed in any patient, and DVT developed in only one patient. Due to the low numbers, no significant relationship could be determined between enoxaparin dose and DVT development.

LMWH may have side-effects such as bleeding and hematoma (16). Thrombocytopenia and osteoporosis are rarely seen side-effects caused by heparin (17). In a previous observational study, the likelihood of severe hemorrhage associated with LMWH was reported to be 0.3%-1.1% (18-20). In another study, it was calculated that to prevent each DVT, treatment with LMWH would cause two major hemorrhages, seven wound hematoma, and six transfusion cases (3, 21). In contrast, Watanabe et al. reported that enoxaparin started immediately after caesarean did not

increase the incidence of hemorrhagic complications and showed that of 131 cases, there was only one case of potential incision hematoma, and no change was recorded in hemoglobin (22). In the current study, of the 25 patients who received 40mg/day enoxaparin, WSI developed in two patients and no cases of WSH or DVT were observed.

In heparin-related thrombocytopenia, although the risk changes according to the form used, there is a risk of thrombocytopenia associated with all heparin preparations. Therefore, whatever type of heparin is used, the thrombocyte count of all patients using heparin should be monitored closely for at least 5-14 days after starting treatment (5, 23). This causes hypercoagulopathy, which is observed in platelet IgG antibody activation (24). In the current study, a significant reduction was seen in the Plt values from the first to the tenth day.

The selection of an appropriate and safe dose of enoxaparin is clinically important for obese women as this patient population is at high risk of developing DVT and hemorrhage after giving birth (25, 26). Of the 16 patients who received 60mg/day enoxaparin in the current study, WSI developed in 7, WSH in 4, and DVT in 1. The frequent occurrence of WSI was attributed to maternal excess weight.

There were some limitations to this study, primarily the retrospective design, and that patient data were gathered from the available patient follow-up forms and then analyzed. The low number of patients in each group may have been the reason that significant results were not obtained in the comparisons of some parameters. Therefore, there is a need for further prospective studies with a greater number of patients.

In conclusion, the Republic of Turkey Ministry of Health has set a target of the application of postpartum thromboprophylaxis to at least 50% of patients undergoing caesarean section delivery. The administration of enoxaparin at doses of 40mg/day and 60mg/day to pregnant patients at moderate – high risk of thromboembolism is effective and safe, but the side-effects of enoxaparin must not be overlooked. For patients with indications after caesarean delivery, there should be good dose adjustment of enoxaparin to be used as thromboprophylaxis.

Conflict of interest

None to declare.

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