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COMPARISON OF EFFECTIVENESS OF ENOXAPARIN ON MATERNAL MORTALITY AND COSTAFTER ELECTIVE AND EMERGENCY CESAREAN SECTION

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A B S T R A C T

Objective: Cesarean sections (CS) are believed to be associated with greater risks of postpartum venous thromboembolism (VTE). VTE remains one of the main direct causes of maternal mortality in developed countries, largely due to pulmonary thromboembolism (PE) which is responsible for around 20% of maternal deaths. The present study aimed to comparison of enoxaparin use for elective and emergency cesarean section on maternal mortality and cost effective in our hospital.

Material and Method: This study was conducted with 200 patients who underwent emergent or elective cesarean section in Izmir Katip Celebi University Atatürk Education and Research Hospital Obstetrics and Gynecology Clinic between 01.01.2016 and 01.01.2017 after the recommendation for venous tromboembolism in pregnancy which published from the ministry of health's 'guideline for the management of risky pregnancies' in 2014. Enoxaparin was used to all patient for VTE prophylaxis in direction of recommendation the ministry of health's guidelines.

Results: 100 patiens were elective CS and 100 patients were emergency CS. All patients mean age was 29.43±5.71 years, mean gestational was 38.22±1.61 weeks. Body mass index (BMI) was 29.88±4.7 kg/m^2. There was no any venous thromboemboli and maternal mortality and morbidity in two groups. There were no statistically significant differences between the groups when compared to cost effectiveness.

Conclusion: This study shows safety and efficacy of enoxaparin for venous thromboprophylaxis after C/S. Although our study population are limited, but we agree with the recommendations of recent ministry of health's guidelines.

INTRODUCTION

Venous thromboembolism (VTE) is a leading cause of maternal morbidity and mortality in developed countries(1–3), largely due to pulmonary thromboembolism (PE) which is responsible for around 20% of maternal deaths(4). Cesarean section(CS) is the most common intraperitoneal surgical procedure in obstetric practice; accounting for about 10-35% of all deliveries(5,6). About a third of all women deliver by cesarean section (CS) in Europe and North American today(7). CS are associated with more VTE than vaginal deliveries (VD) in many but not all studies, and whether elective CS are associated with increased VTE risk remains debated(8). Many risk factors such as obesity, pre-eclampsia, and caesarean delivery following labour are relatively common(9-11). There are no randomised controlled trials of the prevention of thromboembolic disease in relationship to caesarean section. Post-caesarean thromboprophylaxis has been identified as a means of systemically reducing maternal mortality,(10) and in 2011 the American Congress of Obstetricians and Gynecologists (ACOG) supported the routine use of perioperative pneumatic compression devices during caesareans(11). Post-caesarean pharmacologic thromboprophylaxis may provide additional benefit to

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women at high risk for thromboembolism(12,13). However, guidelines from major societies such as the ACOG, the Royal College of Obstetricians and Gynaecologists (RCOG), and the American College of Chest Physicians (Chest) differ substantially in terms of criteria for identifying patients that should receive prophylaxis with unfractionated (UFH) or low-molecular weight heparin (LMWH). The Ministry of Health has recently published a national risk-based guideline for thromboprophylaxis for obstetricians and gynaecologists in Turkey (Turkish Public Health Agency and Department of Women's and Reproductive Health 2014) (14). The present study aimed to comparison of enoxaparin (LMWH) for elective and emergency caesarean section on maternal mortality and cost effectiveness according to our ministry of health's guideline.

MATERIALS AND METHODS

This study is conducted retrospectively with the participation of 200 patients who underwent emergent or elective cesarean section in Izmir Katip Celebi University Atatürk Education and Research Hospital Obstetrics and Gynecology Clinic between 01.11.2015 and 01.01.2016. All patients who underwent emergency cesarean section were treated with enoxaparin (Clexane ®) subcutane for venous thromboembolism prophylaxis in accordance with the recommendations of the Turkish Ministry of Health's Risky Pregnancy Management Guideline(14).Criteria specified in Table-1 were used in the selection of venous thromboembolism prophylaxis in patients undergoing elective cesarean section. The criteria specified in Table-2 were used for dosing of LMWH/AFH. The criteria outlined below were used for the duration of postpartum venous thromboembolism prophylaxis in all patients in line with the recommendation of the Risky Pregnancy Management Guideline.

Prophylactic LMWH / AFH therapy should be continued for six weeks at least seven days postpartum in pregnancies with existing three or more (excluding past VTE or thrombophilia) of the risk factors mentioned in Table-1.

All emergency caesarean sections should be given thromboprophylaxis with LMWH for seven days after the operation.

Thromboprophylaxis with LMWH should be given for seven days if there is one or more additional risk factors (greater than 35 years old, BMI> 30) after elective cesarean section.

The first LMWH / AFH dose should be given as soon as possible after the delivery has not been postpartum bleeding and sure that regional analgesia has not been administered. In the case of regional analgesia, LMWH / AFH should be given four hours after the application of the post-operative / epidural catheter.

The main purposeof the study is defined as to determine whether there are differences about maternal mortality(maternal death, venous pulmonary embolism) and costeffectiveness of enoxaparin between two groups.

Statistical Analysis

Statistical analysis of the data is performed by IBM SPSS Statics Version 20 package software. Pearson Chi-Square and Fisher's Exact tests were used to compare the cathegoric data between groups, İndependent Sample t tests were used to compare the continous data due to normal distrubution of data, Mann Whitney U were used to compare the continous data due to abnormal distrubution of data. $P<0.05$ is applied as statistically significant.

Table 1 Risk Factors

Time	Factors
	A. Previous venous thromboemboli
	B. Thrombophilia
	Inherited Antithrombin deficiency, Protein C deficiency, Protein S deficiency, Factor V Leiden, Prothrombin gene G20210ASubsequent acquisition
Known before	• Antiphospholipid syndrome
	• Pre-pregnancy or early gestational age over 35 years
	• Obesity (BMI>30kg/m^2)
	• Parity ≥3
	• Smoking
	• Significant varicose veins (symptomatic and / or on the knee or with phlebitis, edema and / or skin changes)
	• Paraplegia
	• Multiple pregnancy, assisted reproductive techniques
	• Preeclampsia
Obstetrics	• Cesarean section
	• Postpartum hemorrhage requiring transfusion(>1lt)
	• Prolonged labor, interventional birth
New onset / transient	Surgical intervention in pregnancy or puerperium (appendectomy, postnatal sterilization)
	• Hospitalization or immobilization (3 days and / or long bed rest)
Reversible	• Systemic infection (requiring hospital admission or use of antibiotics) (eg pneumonia, pyelonephritis, postpartum wound infection)
	• Long distance travel (> 4 hours)

Prophylactic LMWH / AFH administration should be considered for at least seven days postpartum in pregnancies with existing two or more (excluding past VTE or thrombophilia) of the risk factors mentioned in Table-1.

RESULTS

100 emergency cesarean sections and 100 elective cesarean sections were included in this study. Mean age was 29.43±5.71 years. Mean gestational was 38.22±1.61 weeks. Body mass index (BMI) was 29.88±4.7 kg/m^2. 16

patients (8%) underwent general anesthesia and 184 patients (92%) underwent regional anesthesia. Mean operation time was 46.3±10.71 minutes.

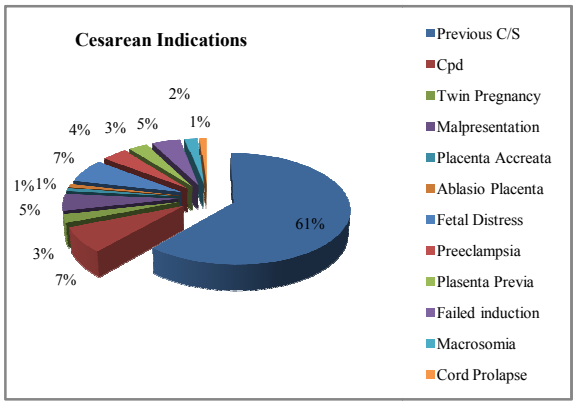
Table 2 Suggested Doses for Low Molecular Weight Heparin

Weight (kg)	Enoxaparin	Dalteparin	Tinzaparin
< 50	20 mg/day	2500 u/ day	3500 u/ day
50–90	40 mg/ day	5000 u/ day	4500 u/ day
91–130	60 mg/ day *	7500 u/ day *	7000 u/ day *
131–170	80 mg/ day *	10 000 u/ day *	9000 u/ day *
> 170	0.6 mg/kg/ day *	75 u/kg/ day *	75 u/kg/ day *
High prophylactic dose			
50-90 kg	40 mg 12 hours	5000 u 12 hours	4500 u 12 hours
Therapeutic Dose			
Antenatal	1 mg/kg/12 hours	100 u/kg/12 hours	175 u/kg/day
Postnatal	1.5 mg/kg/day	200 u/kg/day	175 u/kg/day
*** It can be given in divided doses.**			

Distribution demographic and clinical characteristics of cases have shown Table-3. Indications of cesarean section were presented Graphic-1.

Table 3 Distribution Demographic and Clinical Characteristics of Cases

Factors	Emergency cesarean section	Elective cesarean section
Age	28.14±6.05	30.72±5.07
Gravida	2.57±1.3	3.50±1.47
Parite	2.28±1.11	1.90±0.92
BMI(kg/m2)	29.55±5.08	30.20±4.35
Pre op hb(gr/dl)	11.47±1.55	11.36±1.44
Post op hb(gr/dl)	10.21±1.33	10.96±0.87
Duration of Enoxaparin (days)	12.25(7-42)	13.36(7-42)
Pre-op platelet (K/ul)	235290±70528.35	243350±77911.80
Post-op platelet (K/ul)	212570±63171.76	214670±63509.81
Gestational Age(Weeks)	38.28±1.87	38.16±1.36
Operation Time (minutes)	45.2±9.58	47.3±10.72
Cost (TL/$)	199.71±21.70/52.55±5.71	244.98±27.91/64.46±7.34
Hospital stay (days)	2.34±1.13	2.18±0.82



Graphic 1 Indications of Cesarean section

Cpd: Cephalopelvic disproportion

Obstetrical conditions and demographic risk factors for thromboembolism, such as maternal age ≥35 years (21.5%), obesity with BMI ≥30 kg/m^2 (43%), parity ≥3(18.5%)and pre-eclampsia (4%), were detected. There was no any venous thromboemboli and maternal mortality and morbidity in two grups. Cost of enoxaparin was 222.3±25 Turkish lira(TL)/58,5± 6,57 United states dollar($). Although there were no statistically significant differences between two groups when compared to operation time, hospital stay, amount of bleeding, thrombocytopenia, cost effectiveness of enoxaparin, duration of enoxaparin and dose of enoxaparin. But the cost was higher in elective group.

DISCUSSION

In this study, no serious advers effect were detected and we have not had any adverse effects from the administration of LMWH (bleeding, thrombocytopenia induced by LMWH). Today, thromboprophylaxis in the postpartum period still represents a unique opportunity to reduce maternal morbidity and perhaps mortality. In the United States, that the annual ~ 1.2 million CS would lead to about 3000-4000 postpartum VTE every year. However, thromboprophylaxis appears widely under-utilized in the US: it is prescribed in 25% of women after CS, mainly by compression stockings with <3% of heparin prescription. It is estimated that 75% of women after CS do not receive any prophylaxis in the postpartum(15). However, there is strong evidence supporting the efficiency of chemoprophylaxis with heparin in medical and surgical patients, and emerging evidence in the obstetrical setting(16).The American College of Obstetricians and Gynecologists suggests the use of pneumatic compression devices for all patients undergoing CS, and to consider adding heparin in case of additional risk factors(11). The American College of Chest Physicians recommends no thromboprophylaxis following CS in women without additional risk factors, and heparin in case of additional risk factors (17). The Royal College of Obstetricians and Gynecologists in the UK suggests the use of low molecular-weight heparin (LMWH) for 10 days after all CS except elective CS without additional risk factors(18).Why use low molecular weight heparin? There have been no randomised trials on the use of low molecular weight heparin antenatally in pregnancy nor post-operatively as proposed. A variety of randomised controlled trials have asssessed the use of low molecular weight heparin compared with standard heparin on the risk of thromboembolic disease following major abdominal surgery and the effect seems to be comparable in terms of their therapeutic efficacy(19). Our ministry of health's released new guideline recommending similar thromboprophylaxis strategies for postpartum patients(14). We prescribe enoxaparin (LMWH) in all emergency cesareans delivery unless there is a specific contraindication after ministry of health's guideline, we agree with the recommendations of recent ministry of health's guidelines, because we cannot know a priori whether another thrombosis risk factor will appear in puerperium (e.g., anaemia, infection, hypertension) or whether a longer rest period will be required (e.g., for postpuncture headache, infection).The prevalence of risk factors for VTE is rising,(20) with obesity, advanced maternal age, and major medical co-morbidities becoming increasingly common(21). In our study 43 patients were advanced maternal age(>35) and 86 patients were obese(BMI ≥30 kg/m2), there were no any medical co-

morbidities between grups. Maternal deaths in the UK from thromboembolism decreased by more than half, from 1.94 maternal deaths per 100 000 deliveries in 2003–2005 to 0.79 maternal deaths per 100 000 in 2006–2008(1). Guidelines from other countries including Sweden and Queensland, Australia, similarly advocate thromboembolism prophylaxis for women based on risk factors, resulting in a larger proportion of women receiving pharmacologic prophylaxis than recommended in the guidelines of the ACOG and chest (22,23). There are at least three randomised controlled trials in the field of orthopaedic surgery supporting the utility of low molecular weight heparin being started post-operatively (12-24 hours) (24,25). Our enoxaparin administration protocol was designed in accordance with new guidelines which states first dose should be given 4-6 hours after being sure there is no any bleeding after surgery. In the RCOG's report(26) it is noted that in 30% of patients the fatal pulmonary embolism occurred before seven days, whereby it could be argued that not providing prophylaxis beyond four to five days is leaving the group unprotected at the time of greatest risk. Our enoxaparin prophylaxis continues 7 days or 42 days whether depends on more additional risk factor according to new guideline(14). Low molecular weight heparin has been reported to have a very low rate of heparin-induced thrombocytopenia(27). In a review of papers using low molecular weight throughout pregnancy(28) encompassing 171 pregnancies, no cases of heparin thrombocytopenia were seen. In our study all women had post-operative haemoglobin and platelet assessments and there were no thrombocytopenia induced by LMWH between goups. There is limited data in the literature on the cost effectiveness of thromboprophlaxis, but studies from sweden suggest that thromboprophlaxis is cost effectiveness when true incidence of postoperative VTE exceeds 8-10%(29). In our study enoxaparin cost was similiar in two groups and it was about 222.3TL (58.5$).

In conclusion preventing postpartum VTE after CS may lead to an important reduction of it is associated with morbidity and mortality from a public health's perspective. This study shows safety and efficacy of enoxaparin for thromboprophylxis after CS. But our study population are limited. We feel that further observational studies and randomized trials are needed to define the efficacy and safety of thromboprophylaxis after CS.

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