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Original Article OBSTETRICS & GYNECOLOGY

The effect of thromboembolic prophylaxis after cesarean section in patients with hypertensive disorders

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ABSTRACT

OBJECTIVE: This study aims to compare the effect of thromboembolic prophylaxis in patients diagnosed with hypertensive disorders of pregnancy undergoing cesarean section.

METHODS: Three hundred and eighty-six patients were included in the study. The patients were divided into groups according to the type of hypertensive disorders of pregnancy and whether thromboembolism prophylaxis was applied or not. The thromboembolic event incidence and other pregnancy outcomes were compared.

RESULTS: Nonadministration of thromboprophylaxis was recorded in 210 patients. Eleven patients had thromboembolic events (5%). Among 176 patients who received thromboprophylaxis, only two patients (1%) had a thromboembolic event ($p<0.05$).

CONCLUSION: There is an increased tendency to thromboembolism in pregnancy. The incidence increases in the presence of hypertension accompanying pregnancy. In our study, the importance of thromboembolism prophylaxis on peri-postnatal complications in patients with hypertensive disorders of pregnancy was emphasized.

Keywords: Anticoagulants; hypertensive disorders of pregnancy; prophylaxis; thromboembolism.

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Hypertension (HT) is the most common medical condition in pregnancy, and its incidence is 1/10 [1]. Hypertensive disorders during pregnancy include gestational HT (GHT) and preeclampsia. These are some of the leading causes of maternal and fetal morbidity and mortality in pregnancy [2]. If it is not diagnosed and treated in time, it may result in severe preeclampsia, eclampsia, or death [3].

Chronic HT is 1/3 of the hypertensive diseases of pregnancy, 2/3 of those are GHT and preeclampsia [4]. Approximately 2–8% of pregnancies worldwide result in preeclampsia. Preeclampsia is one of the most common causes of maternal deaths globally (10–15%) and responsible for more than 60,000 maternal deaths annually [5]. Preeclampsia is one of the main causes of maternal morbidity and mortality, perinatal deaths, preterm birth, and intrauterine growth retardation [6]. Preeclampsia affects kidney functions during pregnancy and increases the risk of chronic HT, chronic renal failure, and cardiovascular disease in the mother at later ages [7, 8]. HELLP (hemolysis, elevated liver enzymes, and low platelet) syndrome is a life-threatening form of preeclampsia and is seen in approximately 10–20% of severe preeclamptic pregnant women. High liver enzymes and thrombocytopenia were seen due to systemic end-organ damage and microangiopathic hemolysis in HELLP aids to diagnose as lab-

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oratory findings [9]. HT during pregnancy plays a vital role in cardiovascular diseases accompanied by maternal hemodynamic disorders [10]. The balance between procoagulant and anticoagulant proteins also changes during pregnancy and thrombogenic feature increases. Therefore venous thromboembolism (VTE) is a significant cause of morbidity and mortality in gynecology and obstetrics [11]. VTE occurs on an average of 1 in 1600 pregnancies. The risk of thromboembolism during pregnancy is 6 times higher than in the non-pregnancy period [12]. In the post-partum period, it is approximately 5 times higher than the antepartum period and 15–25 times more than non-pregnant women [13]. Therefore, the risk of thromboembolism during pregnancy and puerperal period in patients with preeclampsia are more exaggerated than those without preeclampsia [14].

The most widely used pharmacological agent for VTE prophylaxis is low-molecular-weight heparin (LMWH). LMWH acts by inactivating factor Xa [11]. Thromboprophylaxis with LMWH should be given to all women who undergo emergency cesarean section for 10 days after the operation. If there are one or more additional risk factors (such as age over 35, Body Kyla Index (BMI) >30) after elective cesarean, thromboprophylaxis with LMWH should be given for 10 days. All puerperal women who are morbidly obese (BMI> 40 kg/m^2) should be evaluated for prophylactic LMWH/unfractionated heparin administration for 10 days after birth [15].

The research question was "does pregnancy-induced HT is associated with a higher incidence of thromboembolic disease when not pharmacological prophylaxis was given postoperatively?". Therefore, we aimed to compare the development of thromboembolic events in patients with preeclampsia when thromboembolism prophylaxis is performed after cesarean section and not performed.

Highlight key points

- VTE is a significant cause of morbidity and mortality in gynecology and obstetrics.
- The risk of thromboembolism during pregnancy in patients with preeclampsia is more increased than those without preeclampsia.
- The prevalence of embolism and the duration of hospital stay may reduce with the thromboprophylaxis treatment after cesarean section in patients with hypertensive disorders.

MATERIALS AND METHODS

Following the Ethics Committee approval (date: January 05, 2018 and protocol no: 09.2018.003), the data of 386 cases undergoing cesarean section due to preeclampsia in our University Hospital between 2012 and 2018 were enrolled. Patients' age, number of pregnancies, gestational week, preeclampsia diagnosis time, blood pressure values both during hospital admission and a baseline value in the operating theater before cesarean section surgery, antihypertensive medication history, ultrasound findings, amount of proteinuria in urine tests, protein analysis in 24-h urine collection, the first laboratory values at admission, aspartate aminotransferase (AST), alanin aminotransferase (ALT), platelet count, hemoglobin, hematocrit, creatinine, blood urea nitrogen, albumin level, type of anesthesia, newborn's birth weight, and Appearance, Pulse, Grimace, Activity, and Respiration scores of the patients were recorded.

The incidence of thromboembolic event was recorded, and outcome analysis was performed.

LMWH was administered at a dose of 40 mg once a day for at least 10 days to patients who received thromboembolism prophylaxis after cesarean section. D-dimer test, bilateral lower extremity venous Doppler ultrasound, and pulmonary computerized tomography angiography were used to diagnose thromboembolic events. In the post-diagnosis treatment, LMWH was administered at a dose of 60 mg twice a day or 80 mg twice a day. The values of patients with and without thromboembolism prophylaxis after cesarean section were compared.

Statistical Analysis

IBM SPSS Statistics 22 program was used for the statistical analysis. One-way ANOVA test and Independent samples t-test were used for those who match the normal distribution of numerical data, Kruskal Wallis-H and Mann Whitney-U tests for those who did not and Chi-square test for examining the discrete variables. The results were evaluated at the 95% confidence interval and the significance level of $p<0.05$.

RESULTS

The data of 386 patients aged between 13 and 47 years (31.2±6.5 years) were analyzed. Preeclampsia was observed in 291 patients, eclampsia in 15 patients, chronic HT in 38 patients, and GHT in 42 patients. The patients were compared according to the type of gestational hypertensive disorder and whether they received thromboembolism prophylaxis after cesarean section.

Table 1. Blood pressure values

	Preeclampsia (n=291)	Eclampsia (n=15)	Chronic HT (n=38)	GHT (n=42)	p
Diastolic BP	93.61±16.64 (93)	100.8±17.66 (105)	96.55±13.36 (96.5)	88.93±13.07 (88.5)	0.012*[m]
Systolic BP	152.54±21.73	160.87±23.38	164.05±26.93	143.93±22.38	0.001*[b]

b: One-Way ANOVA test: Values were given as mean± standard deviation. m: Kruskal-Wallis H test: Values were given as mean± standard deviation. *: p<0.05: Statistically significant difference; HT: Hypertensin; BP: Blood pressure.

Table 2. Patient demographics

	Group 1 (n=210)	Group 2 (n=176)	p
Age (years)	30.91±6.8 (31)	31.6±6.12 (32)	0.269☐
BMI (kg/m²)	31.16±4.46 (30.95)	32.28±5.75 (30.90)	0.158☐
Protein (g)	2374±3129 (1089)	2128±2544 (1082)	0.887☐
Gestational age (weeks)	36+3	36+3	0.848☐
Hospital stay (day)	5.16±4.1 (4)	3.84±1.72 (3)	0.047*☐
ALT (U/L)	38.30±97.13 (13)	25.33±52.31 (13)	0.404☐
AST(U/L)	62.25±250.9 (21)	36.23±69.81 (20)	0.670☐
Hb (g/dL)	11.51±1.51 (11.6)	11.53±2.75 (11.5)	0.460☐
Htc (%)	34.49±4.40	34.23±4.29	0.564☐
Creatinine (µmol/L)	0.61±0.14 (0.60)	0.59±0.14 (0.57)	0.196☐
Seizure	9 (4.3%)	6 (3.4%)	0.858☐
Diabetes	8 (3.8%)	10 (5.7%)	0.531☐
Renal disease	5 (2.4%)	1 (0.6%)	0.226☐
Autoimmune	7 (3.4%)	21 (11.9%)	0.003*☐

s: Independent Samples t-test: Values were given as mean±standard deviation. m: Mann Whitney U test: Values were given as mean±standard deviation. k: Chi-square test: Values were given as frequency (percentage) *: p<0.05: Statistically significant difference; n: number; BMI: Body mass index; ALT: Alanine transaminase; AST: Aspartate transaminase; Hb: Hemoglobin; Htc: Hematocrit; µmol: Micromole; L: Liter.

According to the types of hypertensive disease, a statistically significant difference was observed in patients participating in the study, according to the mean age, BMI, proteinuria degree, gestational age, and duration of hospital stay (p<0.05). When the intergroup average age was evaluated, it was observed that it was significantly lower in the eclampsia group. While BMI was lowest in the preeclampsia group, it was highest in the GHT group. The proteinuria degree was the lowest (0) in the GHT group, whereas it was the highest in the eclampsia group. While the gestational age was the lowest in the chronic HT group, it was observed that it was the highest in the GHT group. In terms of hospital stay duration, it was observed that the GHT group was discharged earlier than the other groups, but the patients in the preeclampsia group were discharged later than the patients in the other group.

According to the types of hypertensive diseases of the patients, systolic and diastolic blood pressure values were significantly lower in the preeclampsia and GHT groups compared to the other groups (p<0.05) (Table 1).

According to the types of hypertensive disease in the groups, the number of patients with pulmonary embolism was not statistically significant. It was observed that the number of cases with pulmonary embolism was higher in the preeclampsia group, but it was not statistically significant.

Table 3. Pulmonary embolism presence and duration of hospital stay

	Group 1 (n=210)	Group 2 (n=176)	p
Pulmonary embolism	11 (5.2%)	2 (1.1%)	0.043*[k]

k: Chi-square test: Values were given as frequency (percentage); *: p<0.05: Intergroups statistically significant difference.

Table 4. Postoperative complications

	Group 1 (n=210)	Group 2 (n=176)	p
Postoperative blood product	21 (10%)	29 (16.5%)	0.083[k]
Postoperative arrhythmias	7 (3.3%)	11 (6.3%)	0.266[k]

k: Chi-square test: Values were given as frequency (percentage); *: p<0.05: Intergroups statistically significant difference.

Table 5. Postoperative findings in patients with embolism

	Embolism (-) (n=373)	Embolism (+) (n=13)	p
Arrhythmias	12(3.2%)	6(46.2%)	0.001*[k]
Hospital stay (day)	4.39±3.09 (3)	9.46±4.98(8)	0.001*[m]

k: Chi-square test: Values were given as frequency (percentage); m: Mann Whitney U test: Values were given as mean±standard deviation; *: p<0.05: Intergroups statistically significant difference.

The demographic data and laboratory measurements of the patients were comparable. ALT, AST, Hb, Hct, and Cre values did not show a statistically significant difference between the groups (Table 2).

Pulmonary embolism was observed with a significantly lower rate in patients using anticoagulants compared to patients who did not (Table 3).

In the patients included in the study, postoperative complications were observed to be statistically similar between the groups (Table 4).

Duration of hospital stay and arrhythmia rate were statistically significantly higher in patients with thromboembolism compared to patients without embolism (p<0.05) (Table 5).

Duration of hospital stay of patients who did not use anticoagulants and who had pulmonary embolism was significantly higher than patients without embolism (p<0.05).

DISCUSSION

Pregnancy complicated with preeclampsia and cesarean delivery are the conditions that create risk factors for thromboembolism. Our study compared the results of thromboprophylaxis with LMWH regarding embolic event development and postoperative complications in patients with the pregnancy-related hypertensive disorder and undergoing cesarean section between. We found that the prevalence of pulmonary embolism was lower in the thromboprophylaxis group, and the duration of hospital stay was also shorter. We observed that the prevalence of pulmonary embolism was not significantly affected by the type of hypertensive disease. The duration of hospital stay and the prevalence of arrhythmia were higher in patients with thromboembolism, but they had no clinical significance in terms of postoperative complications.

In the Acute Pulmonary Embolism Diagnosis and Treatment Guideline (ESC 2014), risk factors for thromboembolism were mentioned such as new-onset arrhythmias [16]. In our study, the duration of hospital stay and the prevalence of arrhythmia were significantly higher in patients with embolism than patients without embolism. These findings support that the duration of hospital stay is prolonged due to embolism and subsequent arrhythmia.

In terms of hospital stay duration, it was observed that the GHT group was discharged earlier than the other groups, but the patients in the preeclampsia group were discharged later than the patients in the other group. The reason for this is thought to be the higher rate of complications in patients with preeclampsia. In the study conducted by Egan et al. [13], the maternal systemic inflammatory response that develops against preeclampsia causes the coagulation system to be activated and clot formation. Therefore, the risk of VTE in pregnant women with preeclampsia is 5 times higher than normal pregnant women. Similarly, in our study, pulmonary embolism was more common in the preeclampsia group compared to other groups, but statistical significance was not found. The reason for this is that we compared preeclampsia with other type of hypertensive disorder of pregnancy, instead of normal pregnancy in our study.

Determining the amount of proteinuria in the 24-h urine collection is the current gold standard test since it represents circadian variability. When the amount of proteinuria was compared between the hypertensive groups, the amount of protein in the urine was significantly higher in the preeclampsia group than the other groups in our study. However, the presence of proteinuria is no longer a necessary diagnostic criterion for the diagnosis of preeclampsia. In case of absence of proteinuria thrombocytopenia, renal failure, impaired liver function tests, pulmonary edema, and the addition of any of the cerebral or visual findings together with new-onset HT also lead to the diagnosis of preeclampsia [17]. In a prospective study conducted by Silva et al. [18] in a tertiary obstetric center in Portugal, the 12-h test showed an acceptable sensitivity in detecting preeclampsia regardless of the collection time. We found similar results regarding the 12-h urine protein analysis.

While the gestational age was the lowest in the chronic HT group, it was observed that it was the highest in the GHT group. No statistically significant difference was observed regarding gestational age in patients who were and were not administered anticoagulant prophylaxis.

Obesity causes an increase for the risk of preeclampsia in pregnancy, gestational diabetes, stillbirth, post-term pregnancy, and cesarean delivery [19]. In our study, the age and BMI of pregnant women with chronic HT were significantly higher than those with the gestational hypertensive disorder. Parallel with our study, it was shown that higher maternal BMI was associated with higher complications of gestational hypertensive disorders and gestational diabetes [20]. In our study, no statistically significant difference was found between the groups in terms of increased BMI, which is thought to increase the complications in preeclampsia. Given these findings, it is concluded that the possible effect of BMI on the effectiveness of the anticoagulant treatment to prevent thromboembolic events is equally in both groups. Although the prevalence of severe preeclampsia was higher in patients not using anticoagulants than patients using anticoagulants, neither statistically significant difference was observed nor any important clinical results of the patients. However, this may have arisen due to the retrospective nature of our study and it could be accepted one of the major limitation of our study.

In the cohort study of Moussa et al. [21] including 2539 pregnant women, it was observed that the mean systolic blood pressure of pregnant women with superimposed preeclampsia was higher than pregnant women with chronic HT. However, it was not statistically significant, but the mean diastolic blood pressure was significantly higher in superimposed HT than chronic HT. This finding was statistically consistent with the diastolic blood pressure values in our study.

The findings of end-organ damage and systemic complications that can be seen in pregnancy-related hypertensive diseases were statistically similar between both groups. Rey et al. [22] also did not observe a statistically significant difference in the development of concomitant diseases such as gestational DM in pregnant women who underwent thromboprophylaxis.

Bain et al. [23] investigated the Cochrane Pregnancy and Birth group May 2009 records including 16 trials, put forwarded that evidence could be based on thromboprophylaxis recommendations in the early period after pregnancy and delivery was insufficient. On the other hand according to ESC Guidelines, if there were additional risk factors for thromboembolism in patients who gave birth by cesarean section, anticoagulant should be administered according to individual risk assessment [24]. In our study, we observed the beneficial effects of thromboprophylaxis in terms of maternal morbidity and mortality, predicting that thrombotic complications will increase in the patient group with hypertensive disorders during pregnancy.

In our study, the incidence of pulmonary embolism was lower in patients using anticoagulants than patients not using anticoagulants. To the best of our knowledge, limited studies observing the effect of thromboembolic prophylaxis on thromboembolic events were conducted in patients with hypertensive disorders during pregnancy. Therefore, there is a need for further studies to support our findings even with new-generation anticoagulant agents.

Conclusion

Pregnancy is a predisposing condition for thrombosis. Hypertensive disorders of pregnancy increase the frequency of thrombosis compared to normal pregnant women due to the vascular pathogenesis it creates. Thrombosis is an important condition that should be considered in terms of maternal mortality and morbidity that may develop later. In our clinic, thrombosis risk is minimized by performing thromboprophylaxis to all patients according to risk calculation. Hence, we aimed to reduce the duration of hospital stay and prevent complications such as deep-vein thrombosis and pulmonary embolism. In our retrospective study where we compared pregnant women with preeclampsia who underwent and did not undergo thromboprophylaxis after cesarean section, the incidence of pulmonary embolism was found to be significantly higher than in patients without thromboprophylaxis.

Ethics Committee Approval: The Marmara University Clinical Research Ethics Committee granted approval for this study (date: 05.01.2018, number: 09.2018.003).

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