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Thromboprophylaxis with single dose versus seven dose enoxaparin in intermediate risk postpartum women: A single blinded randomized control study

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Abstract
Venous thromboembolism is a life threatening condition, commonly affecting pregnant and puerperal women and requires thromboprophylaxis for prevention. There are no clear guidelines regarding duration of thromboprophylaxis in intermediate risk postpartum women. We have conducted a randomized control study to compare the efficacy of a single dose thromboprophylaxis with seven days regimen in a tertiary care hospital over one year. We selected 1280 intermediate risk postpartum patients and randomised into two groups. The study group was given a single dose and the control group received seven doses of Enoxaparin. Incidence of thromboembolism in both groups were analysed. Both groups were comparable in terms of risk factors. Deep vein thrombosis developed in 0.31% of the study population and 0.16% of the control group, showing a similar outcome. We concluded that single dose regime can be used as effectively as seven dose to reduce the occurrence of thromboembolism and its related morbidity and mortality in postpartum women.

Keywords: Single dose LMWH, thromboprophylaxis, intermediate risk, postpartum, venous thromboembolism

Introduction
Venous thromboembolism (VTE) is a life threatening phenomenon and when occurring in pregnancy, can have serious consequences. The pathophysiology of VTE in pregnancy appears to relate to the increased venous stasis noted during this period but other factors such as alterations in the balance of proteins of the coagulation and fibrinolytic systems have also been implicated [1-2-3-]. VTE is upto 10 times more common in pregnant than in nonpregnant women of a similar age**.** The risk per day of thromboembolism is actually greatest in the weeks following delivery as shown in one metaanalysis (0.23 per day during pregnancy & 0.83 during postpartum period) [4].There are a number of known risk factors, some inherited factors (thrombophilia) and some acquired factors specific to pregnancy like venous stasis, maternal age of ≥35 years, multiparity, instrument-assisted or Caesarean delivery, haemorrhage, pre-eclampsia, prolonged labour, obesity and prolonged immobilization [5].UK incidence of VTE in pregnancy & puerperium is 1-2/1000 [5-6]. The incidence of VTE in India, remains elusive due to lack of evidence based studies. In developing countries the estimated postsurgical DVT ranges from 0.15-1.35% [7]. It is also related with increased risk of pulmonary embolism, which is the leading cause of maternal death in the developed world [5]. The use of thromboprophylaxis is an effective measure to prevent VTE in general population as well as in pregnancy and after delivery. LMWH is the preferred mode of thromboprophylaxis as it is well supported by Cochrane review [8-9]. And does not require monitoring.

RCOG classifies the postnatal patients into three groups, high risk, intermediate risk and lower risk [5]. Mobilization & avoidance of dehydration is sufficient for lower risk group where as it requires six weeks postnatal prophylactic LMWH for high risk patients.

However, there is no scientific evidence about the duration of thromboprophylaxis in the intermediate risk group, only clinical recommendations. RCOG recommends ten days thromboprophylaxis for this group, whereas recommendations for South Africa and Australia suggest thromboprophylaxis for seven to ten days and five to fourteen days respectively [5-10-11]. There are studies which have found similar efficacies with different dosage regimes like five doses and seven doses [12-13-14]. For India, there is no standing recommendation regarding

Postpartum thromboprophylaxis at present. In a low resource setting, it is not cost effective to administer multiple doses of LMWH to all postpartum women with intermediate risk, mainly due to the increased number of patients and prolonged hospital stay. Therefore, keeping the low prevalence of VTE in mind, single dose thromboprophylaxis is a highly feasible option in these women. If it is proved to be equally efficacious to multiple dose regimen, it can be used as a viable alternative in reduction of incidence of VTE in a low resource and high demand set up like our institute, which has an annual delivery rate of more than 20000, and a forty percent emergency caesarean section rate.

We had selected seven dose recipients as the control population like the study by Blondon *et al.* because this duration of thromboprophylaxis conformed with different guidelines [10-11-12].We compared the effectiveness of one day Enoxaparin with seven days regimen for thromboprophylaxis in the intermediate risk group of postpartum patients in this randomized control study.

Materials and Methods

This was a prospective, single blinded, randomized control trial conducted in RG Kar Medical College & Hospital, Kolkata, West Bengal, India-a tertiary care medical college, for a period of one year.

Incidence of Thromboembolism in postpartum intermediate risk population is around 0.5% [15-16].

With thromboprophylaxis with LMWH, incidence of Thromboembolism reduces to 0.1% [8].

Power of study was taken to be 80%, therefore with 80% power, sample size (alpha=5%) was calculated to be 1280 (Binomial Proportion Test).

Hence, with Study: Control=1:1, 640 study population and 640 control population were selected.

All the participants were selected fulfilling following inclusion and exclusion criteria. Informed consent was obtained from individual participants.

Inclusion Criteria

Any one of the following:

1. All Emergency Caesarean sections
2. Asymptomatic thrombophilia.
3. Obesity (BMI >40)
4. Prolonged hospital admission
5. Any associated medical disorder (Heart disease, Diabetes Mellitus, Systemic Lupus Erythematosus, Inflammatory conditions, Sickle cell disease, Cancer)

Or,

Any two of the following risk factors:

1. Age > 35years
2. Obesity (BMI>30)
3. Parity 3 or higher
4. Smoker
5. Elective Caesarean section
6. Preeclampsia
7. Mid cavity rotational operative delivery
8. Prolonged labour>24 hours
9. PPH>1 litre or blood transfusion

Exclusion Criteria

1. Any previous VTE
2. Thrombophilia + previous recurrent VTE
3. Active post partum bleeding
4. Platelet count less than 1 lakh / cumm
5. Severe renal disease (GFR<30 ml/min /1.73 sq.m & abnormal 24 hrs creatinine clearance)
6. Severe liver diseas
7. Uncontrolled hypertension (SBP>200 mm Hg or DBP>120mm Hg)
8. Documented peptic ulcer within 6 weeks
9. Heparin, bisulfite, or fish allergy History of steroid use (one week or more)
10. History of heparin induced thrombocytopenia.
11. Efusal to give informed consent.
12. Refusal to give informed consent.

Computer generated, pretested random number table was used for randomization of the patients into control and study arms. We have used enoxaparin as the thromboprophylactic agent.

In Control Patients, Enoxaparin prefilled syringe was subcutaneously injected once daily for seven days. Doses of enoxaparin were based on weight. For thromboprophylaxis the booking or most recent weight was used to guide dosing.

Weight (kg)	Dosage of Enoxaparin
< 50 kg	20 mg daily
50–90 kg	40 mg daily
91–130 kg	60 mg daily
131–170 kg	80 mg daily

In Study patients, Enoxaparin was injected for one day subcutaneously and injection of distilled water was given subcutaneously for six days, dosage calculation being similar.

In both the groups, the first dose of LMWH was given as soon as possible after delivery after checking the eligibility criteria. LMWH was not given for six hours after use of spinal anaesthesia or after the epidural catheter was removed.

It was a single blinded study, as the patients only were blinded here.

Outcome Monitoring

A pre tested proforma was used for all the patients. They were clinically examined daily during rounds (Pulse, BP, Respiration rate, Temperature, SpO2 monitoring, Bleeding Per vaginum) on second day onwards up to seventh day. All the patients underwent colour Doppler study of deep venous system of both lower limbs to exclude deep venous thrombosis (DVT) and Chest X-ray on seventh day or earlier.They were again followed up at six weeks.

Aim of our study was to compare efficacy of single dose LMWH as compared to seven days LMWH in postpartum thromboprophylaxis of intermediate risk patients.Outcome measures were incidence of deep venous thrombosis and pulmonary thromboembolism. A comparative analysis between the two groups was done with regard to these parameters.

After primary data collection and recording details of obstetric history, age, parity, gestational age assessment, blood pressure, mode of delivery, maternal complications etc, Statistical analysis was done by SPSS software using Students independent t-test and Chi-square test with Yates correction where applicable. The null hypothesis taken was “Single dose Enoxaparin therapy is less efficacious than seven dose Enoxaparin therapy”. P value less than 0.05 was considered to indicate a statistically significant difference.

Results

There were 1280 patients who were included in the study after checking the eligibility criteria. There were randomized in two

groups each of 640 women. Both groups were comparable in reference to maternal age. Mean age of study group was 24.6±2.17 years and of control group was 24.2±1.93 years, which were statistically comparable. (p=0.0824)

Table 1: Distribution of women on the basis of obstetrical parameters

Parameter		Study (n=640)	Control(n=640)	Chi Squared	DF	P value
Gestational Age Mean ± SD (weeks)		38.2±1.62	38.1±1.66	-	-	0.5859
Gravida	Primigravida	368(57.5%)	344(53.75%)	1.674	1	0.1957
	Multigravida	272(42.5%)	296(46.25%)			
BMI	<30	520(81.25%)	536(83.75%)	1.218	1	0.26
	≥30	120(18.75%)	104(16.25%)			
Pregnancy Induced Hypertension	Yes	168(26.25%)	152(23.75%)	0.938	1	0.3329
	No	472(73.75%)	488(76.25%)			

Both groups were comparable in terms of gestational age. 57.5% of study group and 53.75% of control group were primigravida, which was statistically insignificant (p=0.1957.) Regarding BMI, 18.75% of study women and 16.25% of control women were of BMI≥ 30, which showed no difference in the distribution of obesity among these two groups (p=0.26). About one fourth of women of each group were hypertensive (26.25% and 23.75% respectively; p=0.3329) (Table 1)

Table 2: Distribution of women on the basis of obstetrical outcomes

Parameter		Study(640)	Control (640)	Chi Squared	DF	P value
Duration of Labour	<24 hrs	440 (68.75%)	424 (66.25%)	0.801	1	0.3707
	≥24 hrs	200 (31.25%)	216 (33.75%)			
Outcome	Emergency LSCS	328 (51.25%)	344 (53.75%)	2.269	3	0.519
	Elective LSCS	80 (12.5%)	88 (13.75%)			
	Normal Delivery	120 (18.75%)	112 (17.5%)			
	Instrumental Vaginal Delivery	112 (17.5%)	96 (15%)			

Table 2 shows labour duration and obstetrical outcome. Both groups were comparable in terms of duration of labour with 31.25% of study women and 33.75% of control women having prolonged labour (Duration ≥ 24 hrs). Emergency LSCS was the most common mode of delivery in both groups (51.25% and 53.75%) respectively. These two groups were also comparable in terms of the other mode of deliveries (Elective LSCS, Normal Delivery & Instrumental Vaginal Delivery). (P= 0.519)

Table 3: Distribution of women on the basis of incidence of DVT/PE

Parameter		Study (640)	Control (640)	Chi Squared	DF	P value
DVT	DVT	2 (0.31%)	1 (0.16%)	0.000 (Yates Correction)	1	1.000
	No DVT	638 (99.69%)	639 (99.84 %)			
Pulmonary Embolism	Yes	1 (0.16 %)	1 (0.16 %)	0.000 (Yates Correction)	1	1.000
	No	639 (99.84 %)	639 (99.84 %)			

Table 3 shows the outcome of both groups in terms of DVT and pulmonary embolism (PE). We found only two cases of DVT in the study group. Out of these two, one was asymptomatic and was diagnosed by routine ultrasound having a unilateral calf vein thrombosis. We detected the venous thrombus in other case with ultrasound only after she developed difficulty in breathing and PE was clinically suspected and diagnosis supported by ancillary investigations on the second postoperative (emergency LSCS) day. It was found to be a case of Iliofemoral DVT. In the control population, one women was diagnosed with DVT (unilateral calf vein thrombosis) on the 5th postoperative day when she was complaining of pain and swelling in left calf. She was started on therapeutic dose of LMWH. She never developed PE. One patient of the control group developed pulmonary embolism on the first postoperative day. We could not locate any venous thrombus by Doppler ultrasound in this case. Both the cases of PE were urgently shifted to intensive care unit, therapeutic dose of LMWH was started and they were put on ventilator support. There was no maternal mortality in our study.

Discussion

The use of thromboprophylaxis is an important measure to prevent VTE and its dire consequences in pregnancy and postpartum period. There is difference of opinion among the different guidelines regarding thromboprophylaxis of the intermediate risk postpartum patients, where as they all agree regarding thromboprophylaxis of high risk and low risk patients [5-10-11].

The evaluation of low doses of LMWH is important not only for its cost effectiveness but also the compliance of patient. So, to find out the efficacy of a single dose LMWH compared to seven doses, we randomized 1280 intermediate risk patients into study and control groups. We analyzed the presence of known risk factors like age, multiparity, obesity, hypertension, prolonged labour in both the groups and there were no statistically significant differences. Caesarean delivery increases the risk of VTE because it involves pelvic surgery that may last >30 minutes [17]. In the present study 408 and 432 pregnancies were terminated by Caesarean section (both elective and emergency) in study and control groups respectively, which were comparable. The incidence of caesarean section is comparatively more in our study population, a total of 840 out of 1280 i.e. 65.6% as we have only taken the intermediate risk population.

There were concerns regarding incidence of VTE in postpartum women, Specially after caesarean section. In a study by W. Sia *et al.* the incidence of deep vein thrombosis in women undergoing cesarean delivery was 0.5% whereas

Jacobsen *et al.* found in their study that symptomatic pulmonary embolism after elective cesarean section was 0.47% [15-16].There were systematic review of studies which showed prevalence of VTE in 0.86% of this population [18]. All these studies were without any thromboprophylaxis.

There have been a number of studies in postpartum women which shows the effectiveness of thromboprophylaxis but the consensus of doses of LMWH for prophylaxis in intermediate risk postpartum women is variable in different studies [12-13-14]. A study by M. Blondon *et al.* had shown incidence of VTE of 0.15-0.22% in post caesarean women with thromboprophylaxis for 7 days [12]. Cavazza S *et al.* showed that overall incidence of DVT in postpartum women was 0.2% after thromoboprophylaxis [17]. The incidence of VTE was 0.154% in a study who compare two regimes (5 days and 10 days of Bemiparin) after caesarean section [14].

Burrows *et al*. had found occurrence of deep vein thrombosis was 1.3% after thromboprophylaxis which is much higher than in the patients who had not received thromboprophylaxis [13].

Here in our study, population comprised only of intermediate risk group and we found 0.31% of study group and 0.16% of control group had deep vein thrombosis after thromboprophylaxis which is comparable with the results of previous studies [12-14-17].

Hence the effectiveness of thromboprophylaxis had already been proven by different studies and also there was no statistically significant difference between the different doses of LMWH used [14].This is also true for our study.

Incidence of pulmonary embolism was 0.16% in both the groups as one out of each group was diagnosed with PE. The incidence of pulmonary embolism is reported to be higher after caesarean section than after vaginal delivery, by a factor of 2.5 to 20, and the incidence of fatal pulmonary embolism by a factor of ten [19]. Hence prophylaxis of venous thromboembolism is of paramount importance.

A major percentage of thromboembolism are clinically silent. Symptomatic events are merely the tip of the iceberg. In our study one out of two cases of DVT was asymptomatic and was a case of calf vein thrombosis. The case of pulmonary embolism in study group was also found associated with silent DVT. Ultrasound cannot detect DVT in 50% cases of PE, which was true for our case also, where we could not localise the thrombus in PE in the control group, as we had only ultrasound as the imaging tool [20]. The limitation of our study was that it was a single blinded study. Biases were minimized, but not completely abolished. Diagnostic tools of DVT were limited. Our setting being of low resource, CT Pulmonary Angiogram (CTPA) and VQ Scan were not available for diagnosis of pulmonary embolism.

Conclusion

This single blinded randomised control trial showed that in postpartum intermediate risk population, a single dose of LMWH is equally effective as seven doses for thromboprophylaxis to prevent the occurrence of VTE. Further randomized control trials are although needed in similar settings to validate meaningful conclusion. However, in a low resource set up in developing countries where the facilities of laboratory investigations or treatment cost are limited, and prolonged hospital stays are a burden on the health care system, single dose enoxaparin for thromboprophylaxis will be suitable for wide application in the intermediate risk population and helpful for safe motherhood.

Conflict of interest

The authors declare that they have no conflict of interest.

Informed consent

Informed consent was obtained from individual participants included in the study

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Ethical approval

The study was approved by the Institutional Ethics Committee, R G Kar Medical College.

References

1. Blann AD, Lip GY; Venous thromboembolism. BMJ. 2006; 332(7535):215-9.
2. Lockshin MD, Venous thromboembolism during pregnancy. Engl N Med J. 1996; 335(24):1847.
3. Acog Practice Bulletin Clinical Management Guidelines for Obstetrics-Gynecologists Number 84, August, 2007.
4. Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and leg of presentation. Obstet Gynecol Surv.1999; 54:265-71.
5. Royal College of Obstetricians and Gynaecologists. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium. Green-top Guideline No. 37a. April, 2015.
6. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. Ann Intern Med. 2005; 143:697-706.
7. Lee LH, Gallus A, Jindal R, Wang C. Incidence of venous thrombembolism in Asian population: A Systematic Review. Thromb Haemost. 2017; 117(12):2243-2260.
8. Bain E, Wilson A, Tooher R, Gates S, Davis LJ, Middleton P. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database of Systematic Reviews, Issue. Art. No.: CD001689, 2014; (2)
9. Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. Cochrane Database of Systematic Reviews, Issue Art. No: CD007557, 2017; (4).
10. Schapkaitz E, de Jong P R, Jacobson B F, Büller H R. Recommendations for thromboprophylaxis in obstetrics and gynaecology. Afr S Obstet J Gynaecol. 2018; 24(1):27-31.
11. South Australian Perinatal Practice Guideline. Thromboprophylaxis and Thromboembolic Disease in Pregnancy.
12. Blondon M, Perrier A, Nendaz M, Thromboprophylaxis with low-molecular-weight heparin after cesarean delivery-A decision analysis. Thromb Haemost. 2010; 103(1):129-37.
13. Robert F. Burrows, Eng Ganb T, Alexander Gallusc S, Euan Wallacea M, Elizabeth. Burrows A, A randomised double-blind placebo controlled trial of low molecular weight heparin as prophylaxis in preventing venous thrombolic events after caesarean section: a pilot study.

British Journal of Obstetrics and Gynaecology. 2001; 108:835-839.
14. Milagros Cruz *et al*. Postcesarean Thromboprophylaxis with Two Different Regimens of Bemiparin. Obstetrics and Gynecology International. December; Article ID 548327, 6 pages doi:10.1155/2011/548327, 2011.
15. Winnie W. Sia, Raymond O. Powrie The incidence of deep vein thrombosis in women undergoing cesarean delivery. Thrombosis Research. January. 2009; 123(3):550-555.
16. Anne Flem Jacobsen *et al*. Deep vein thrombosis after elective caesarean section. Thrombosis Research, 113(5):283-288
17. Stefania Cavazza, Maria Pia Rainaldi, Angelina Adduci, Gualtiero Palareti. Thromboprophylaxis following cesarean delivery: One site prospective pilot study to evaluate the application of a risk score model. Thrombosis Research. 2012; 129(1):28-31
18. Ian A. Greer, Catherine Nelson Piercy Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005; 106(2):401407.
19. Paul E. Marik, Lauren A. Plante. Venous Thromboembolic Disease and Pregnancy. N Engl J Med. 2008; 359:2025-33
20. Kirsten van Langevelde, Alexandr Sramek. Finding the origin of pulmonary emboli with a total-body magnetic resonance direct thrombus imaging technique. Haematologica. 2013; 98(2):309-315