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ORIGINAL ARTICLE

Prophylactic Low Molecular Weight Heparin Improving Perinatal Outcome in Non-thrombophilic Placental-Mediated Complications

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Abstract

Objective To study the role of low molecular weight heparin (LMWH) in perinatal outcome.

Methods A randomized, case control study was conducted at Safdarjang hospital, New Delhi. Patients were recruited from Sept. 2011 to May 2013 and were followed up till delivery. Thirty cases and controls were enrolled which comprised non-thrombophilic patients with previous history of preeclampsia, fetal growth restriction, abruption, and stillbirth (>20 weeks). Study group received daily single dose of LMWH depending upon the weight, subcutaneously; it was started before 15 weeks of gestation and continued up to 36 weeks. Nursery/NICU admission, APGAR score at 0 and 5 min, birth weight, gestational age at delivery, mode of delivery were observed among the interventional and control groups.

Result There was substantial reduction (80 %) in nursery/NICU admission. The mean gestational age and birth

weight of the cases were observed to be higher as compared to those of control (38.05 ± 2.02 vs. 37.58 ± 2.06 weeks and 2770 ± 400 vs. 2530 ± 0.533 g).
Conclusion Prophylactic LMWH before 15 weeks of gestation improved the perinatal outcome in non-thrombophilic pregnant women.

Keywords Low molecular weight heparin · Placental-mediated complication · Perinatal outcome · APGAR · NICU

Introduction

During the first half of human pregnancy, uteroplacental arteries undergo a series of pregnancy-specific changes that reduce the maternal blood flow resistance and increase the uteroplacental perfusion, to help meet the fetal requirement. Reduced endovascular trophoblast invasion and uteroplacental artery remodeling are the key pathologic features of Intra-uterine growth restriction (IUGR) and preeclampsia. Placental thrombosis also leads to severe pregnancy complications mainly preeclampsia, abruption which contributes to poor perinatal outcome [1–4]. These pregnancy-related complications leads to poor APGAR score, birth asphyxia, increase in operative deliveries and NICU admission, and also grave complications, such as Fetal Growth restriction (FGR) and stillbirth. These complications occur due to placental vascular thrombosis which decreases placental perfusion [5–7]. Several studies have reported these placental-mediated complications even in patients without thrombophilia [8].

Pathological examination of placenta in pre-eclamptic patients has revealed placental infarct and sclerotic narrowing of arteries and arterioles. Sclerosis of arterioles can cause FGR, stillbirth, and poor fetal and perinatal prognosis. Fetal growth restriction is the 2nd most common cause of perinatal mortality after prematurity [9, 10]. Prevalence of IUGR is 8 % among general population [11]. Placental dysfunction and abnormal placentation are the most frequent etiologies of IUGR. Up to thirty-five percent of still births have no explanation. More than half of stillbirths are associated with IUGR [11]. They usually occur due to poor attachment and abnormal vascularization of placenta.

As thrombosis in the uteroplacental circulation is frequently observed in placental-mediated pregnancy complications [12] and since pregnancy is a prothrombotic condition, anticoagulation represents a good preventive option. LMWH treatment has been suggested for pregnant women with previous history of adverse pregnancy outcomes and who were diagnosed as thrombophilic. Since placental vasculopathy is similar for both thrombophilic and non-thrombophilic patients [5–7], LMWH can prevent pregnancy complication and thus improve perinatal outcome. LMWH prevents thrombosis, stimulates angiogenesis, and increases vascular permeability [13]. It also inhibits proliferation of vascular smooth muscles [14] which helps in adequate perfusion to fetus through placenta, thus improving the perinatal outcome. Only a few studies have been reported till date and none of them has been done on the Indian population to see the effect of LMWH on perinatal outcome. So the present study was specifically designed to see the effect of LMWH on perinatal outcome in non-thrombophilic pregnant women.

Materials and Methods

The present study was a randomized, prospective case-control study conducted at the Department of Obstetrics and Gynaecology, V.M.M.C & Safdarjang Hospital, New Delhi. Patients were recruited from September 2011 to May 2013 and followed up till delivery.

Inclusion Criteria

- Women of age group ≥18 years.
- History (h/o) of severe preeclampsia in previous pregnancy defined as high blood pressure (two separate readings taken at least 6 h apart of 140/90 or more) and 300 mg of protein in a 24-h urine sample (proteinuria), and severe preeclampsia is diagnosed when BP is over 160/110 and proteinuria >3 g.
- OR h/o fetal growth restriction in previous pregnancy defined as weight below the 10th percentile for its gestational age.
- OR h/o severe placental abruption.
- OR h/o stillbirth after 20 weeks in previous pregnancy.
- Gestational age <14 weeks.
- Thrombophilia screen—negative (including)
  - Anticardiolipin antibody
  - Lupus anticoagulant
  - β 2 glycoprotein
  - protein C and protein S
  - Leiden actor V
  - Anti-thrombin III

Exclusion Criteria

- Multiple pregnancy.
- History of losses due to anatomic, chromosomal, endocrine, or immunological causes.
- H/O arterial or venous thrombosis or thrombophilic disorder.

- Women were already known to have anti-phospholipid antibody.
- Previous h/o infertility (≥3 early miscarriage).
- Maternal HIV, cytomegalovirus virus, toxoplasma virus.
- Allergy to heparin or LMWH.
- H/O diabetes, hyperthyroidism, chronic renal insufficiency.

Pregnant women with history of placental-mediated complication were screened for thrombophilia and those who fulfilled the inclusion criteria were included. All females were given a serial number and randomization was done using random number table, and were then labeled as cases and controls. Ethical clearance was obtained from the ethical committee of V.M.M.C & Safdarjang Hospital. Out of 60 pregnant females, 30 women were included in the study group and rest 30 were labeled as control.

The females in the study group received LMWH (Enoxaparin Sodium) depending upon their body weight (<50 kg = 20 mg; 50–90 = 40 mg and >90 kg = 60 mg) subcutaneously; it was started before 15 weeks of gestation and continued up to 36 weeks. Since during the placental development, invasion of trophoblastic cells leads to formation of low resistance vessel in placenta which completes by the end of the first trimester of pregnancy (~12–13 weeks). Hence, if LMWH is started in <15 weeks, it provides adequate trophoblastic invasion and hence better perinatal outcome. Full blood count and coagulation profile were performed at 7–10 days after commencement of treatment and then repeated at 28 and 36 weeks. Monthly ultrasound scan was done to assess the fetal growth and placental maturity. Trimester wise Doppler was done to assess uteroplacental blood flow by studying resistance index and pulsatility index in uterine and umbilical artery. All cases and control were given intensive antepartum, intrapartum, and postpartum care in the hospital and perinatal outcome was observed.

All the data were recorded in a master chart and were analyzed using the SPSS version 16.0. Student's '*t*' test and Chi-square test was used to compare data. Fisher's exact test and Mann–Whitney tests were used.

Observation

- Less than 7 % babies in the intervention group required nursery/NICU support while 30 % babies in the control group had to be admitted in nursery.
- Majority (86.6 %) of babies in the study group had good APGAR score of 8 at 0 min, while 6.6 % had APGAR ≤7 and 9. In contrast, in the control group, one-third neonates had APGAR ≤7 and only 63.3 % had APGAR score of 8 while none had APGAR >9. At 5 min, all the babies of study group had score of >9 while the corresponding figure was 76.6 % in the control group.
- Mean birth weight of babies in the study group was higher, 2773 ± 400 g, in contrast to 2530 ± 533 g in the control group.
- Mean gestational age was 38.05 ± 2.02 weeks and 37.58 ± 2.06 weeks, respectively, in case and control groups.
- Eighty percent of babies were delivered normally while 16.7 % were delivered by cesarean section (LSCS) and 3.3 % had assisted vaginal delivery. The corresponding figures in controls are 60, 33.3, and 6.7 %, respectively.

Discussion

While including cases and controls in the study, care was taken to ensure that both the groups were comparable in terms of placental-mediated complications and thrombophilia screen negative (Table 1). Babies of the interventional group required lesser nursery or NICU care. A decrease of 77.6 % in nursery or NICU admission was observed between two groups. Rey et al. [12] also noticed a decline of 34.6 % in their study.

There was no statistical difference in the mean gestational age of delivery between the two groups in the present study (38.05 ± 2.02 vs. 37.58 ± 2.06 weeks). Similarly, Rey et al. [8] in his study did not find any difference in gestational age between cases and controls. However, Mello et al. [15] observed gestational age of delivery to be 37 weeks. Kupferminc et al. [16] also noticed a higher gestational age of delivery in the study group.

In the present study, birth weight was found to be statistically significant in the study group as compared to that in control (2770 ± 400 v/s 2530 ± 530 g). Similar observations were drawn by Mello et al. (2001–2002), Kupferminc et al., and Rey et al.

At 0 min, 86.6 % of babies in the study group had good APGAR score of 8 while 6.6 % had APGAR score of 9. While in the control group, 63.3 % of babies had APGAR of 8 and 33.3 % of babies had APGAR score of <7. In the study group, APGAR reached 9 in all babies, while only 76.6 % of babies in the control group had APGAR score of 9 at 5 min. It denoted that APGAR was also affected in a positive way by the administration of LMWH in women with previous placental-mediated complications. Hence the perinatal morbidity is less (Table 2).

The effectiveness of LMWH may be the result not only of its antithrombotic effect but also of its other properties. LMWH promotes the differentiation and invasion of the trophoblast in vivo [17, 18], prevents monocyte adhesion to

Table 1 Adverse outcomes in the study and control groups before treatment

	Cases $n = 30$	Control $n = 30$	p value
Stillbirth n (%)	14 (46.7 %)	14 (46.7 %)	NS
Preeclampsia mild n (%)	0 (0 %)	1 (3.3 %)	NS
Preeclampsia severe n (%)	11 (36 %)	14 (46.6 %)	NS
Abruption n (%)	7 (23.3 %)	6 (20 %)	NS
IUGR n (%)	11 (36.7 %)	14 (46.7 %)	NS

Table 2 Comparative analysis of perinatal outcome in cases and control

	Cases	Contol	p value
NICU/nursery admission	6.7 %	30 %	0.02
APGAR at 0 min			
<7	6.6 %	33.3	0.04
>8	86.6 %	63.3	
APGAR at 5 min			
<7	0 %	6.6	0.3
>9	76.6 %	6.6	
Mode of delivery			
Normal vaginal	80 %	60 %	0.2
Instrumental	3.3 %	6.7 %	
Cesarean section	16.7 %	33.3 %	
Mean birth weight (g)	2773 ± 400	2530 ± 500	0.03
Mean gestational age (week)	38.05	37.58	0.3

Table 3 Comparative analysis of perinatal outcome of different studies

	Mello et al. (2001–2002) Italy $n = 80$		Rey et al. (2000–2007) Canada $n = 72$		Kupferminc et al. (2003–2007) Israel $n = 116$		Singh et al. (2011–2013) India $n = 60$	
	Cases	Control	Cases	Control	Cases	Control	Cases	Control
NICU/nursery admission n (%)	–	–	6 (11.5)	9 (17.6)	–	–	2 (6.7)	9 (30)
Gestational age of delivery (weeks)	37	34	36.2	35.8	38.1	35.3	38	37.5
Birth weight (g)	3080	2380	2993	2923	2970	2267	2770	2530

activated endothelium [19], and inhibits tumor necrosis factor-α-induced leukocyte rolling [20]. These drugs decrease vascular resistance in vitro [21] and in vivo [15–22]. Therefore, LMWH may act by improving placental development as well as by inhibiting reactive pathways involved in Pre-eclampsia (PET) and Small for Gestation Age (SGA). Hence, LMWH improved uteroplacental blood flow and thus improving perinatal outcome. The indicators are decreased nursery and NICU care, higher weight gain in the case group, and higher APGAR score in the population receiving LMWH. Similarly, gestational age of delivery was observed to be higher in the case group. The incidence of LSCS was lower; majority of the babies in the interventional group were delivered by normal vaginal delivery. In contrast, Rey et al. [12] observed only 52.7 % of the cases had vaginal delivery (Table 3).

Conclusion

- Decreased nursery or NICU admission of babies in the interventional group.

- Higher mean gestational age at delivery (38.05 ± 2.02 weeks) in the LMWH group.
- No preterm delivery occurred in the study group.
- Babies of the study group had higher birth weight.
- Since the cost of treatment is very high and LMWH has to be administered daily, it requires approximately 300 daily subcutaneous injections over the whole gestational period. Thus, it is a good alternative to patients who can afford it or when treatment is subsidized.

Compliance with ethical requirement and conflict of interest Ethical Clearance was obtained from Ethical Committee of V.M.M.C and Safdarjang Hospital. Written informed consent was taken from all participants written in their own language. The authors report no conflicts of interest.

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