Original Article

Role of Enoxaparin to Improve Obstetrical Outcome in Patients with IUGR and Oligohydramnios

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Abstract

Objective: To assess the role of enoxaparin to improve obstetrical outcome in patients with IUGR and oligohydramnios.

Study design: Randomized Controlled Trial study.

Setting and duration: Study was conducted at Department of obstetrics and gynecology, Aziz Fatimah Hospital, Faisalabad, from April 2017 to September 2018.

Methods: After taking approval from hospital ethical committee, a total of 104 pregnant women, 52 in each group were enrolled. Group A received Enoxaparin along with standard treatment and group B only standard treatment. All the patients were followed up two weekly till 28 weeks of gestation, on every visit all the patients had ultrasonographic measurement of amount of liquor, growth scans along with prothrombin time and platelet counts. After 28 weeks of gestation every patient was followed up every week.

Results: The mean maternal age in Enoxaparin group was 27.54 ± 3.74 years and 28.46 ± 3.49 years in Standard treatment group. The mean gestational age (37.65 ± 0.76 vs. 36.95 ± 0.84 weeks) in Enoxaparin group was significantly (p-value < 0.05) higher as compared to Standard treatment group. The rate of miscarriages significantly (p-value < 0.05) lesser in Enoxaparin group (11.54% vs. 38.46%) as compared to Standard treatment group. In Enoxaparin group the incidence of preeclampsia was (8.69% vs. 43.75%, p-value < 0.05) lesser as compared to Standard treatment group. Preterm deliveries (15.22% vs. 25%) and preeclampsia rate (8.69 vs. 43.75%, P < 0.05) was significantly lower in Enoxaparin group.

Conclusion: Low molecular weight heparin along with aspirin have shown high live birth rate, less chances of miscarriage, preeclampsia, preterm delivery and prematurity as compared to aspirin group only, in patients with IUGR and oligohydramnios.

Keywords: Enoxaparin, Obstetric outcome, IUGR, Oligohydramnios.

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Introduction

Pregnancy is natural process of a woman's life, but it is accompanied by many hazards for fetus and mother. The pregnancy associated with oligohydramnios is one of the most important causes of fetal growth restriction. This complication is quite common in both developed and developing countries being a major contributor towards the infant morbidity and mortality. The amniotic fluid and its quantity is very important for development and survival of the fetus. Amniotic fluid is produced soon after the amniotic sac is formed at about 12 days after conception. Mother's circulation provides the basis for production of amniotic fluid at the start and then primary substance for this is provided by the

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fetal urine around the 20th week of gestation. Too low level of amniotic fluid is termed as oligohydramnios and too high level is called polyhydramnios. [1,2]

Amniotic fluid which surrounds developing fetus in amniotic sac provides several benefits to the fetus. Despite decades of investigations, the regulation of amniotic fluid volume and composition remains incompletely understood. Amnion is metabolically active, and help in maintaining the amniotic fluid homeostasis by involving in transportation of solute and water. This also facilitate in production of bioactive compounds like vasoactive peptides, cytokines and growth factors. So, amnion regulates the blood flow and chorionic vessel tone. [3,4]

Amniotic fluid plays a major role in the fetal growth and development of fetus. It provides a medium, in which the fetus can readily move, cushions the fetus against possible injuries and helps maintain an even temperature. The abnormalities of the fluid volume can thus interfere directly with fetal development or may be an indirect sign of underlying disorder.[5] Oligohydramnios is a frequent finding in a hypertensive woman with intrauterine growth restriction. Causes of second trimester olighydramnios are the same as for the third and include fetal urinary tract anomalies, rupture of membranes and placental insufficiency. The decrease in amniotic fluid volume increases the incidence of perinatal mortality. The incidence of major congenital anomalies and IUGR also increases considerably with decrease in volume of amniotic fluid. [6]

There are many pregnancy related complications like preeclampsia, oligohydramnios, IUGR, recurrent pregnancy loss that are major contributors for perinatal morbidity and mortality. Some studies have suggested that these complications are integrated with placental insufficiency. Inappropriate coagulation activation is one of the major causes of this insufficiency. On the basis of this relationship, it has been postulated that anticoagulant therapy like low molecular weight heparin and enoxaparin has very good results in reducing the incidence of these complications. [7]

The prophylactic use of low molecular weight heparin has given excellent results in terms of improvement in perinatal outcome in conditions like recurrent miscarriages, APS and thrombophilias. [8,9] Low molecular weight heparin is now considered as a better choice in comparison to unfractionated heparin due to its lesser side effects like haemorrhagic disorders, thrombocytopenia, allergic reactions and osteoporosis during the pregnancy. Also, it does not have any teratogenic side effect. [10]

This present study was planned with the objective to find the role of Enoxaparin in improving the pregnancy outcome in women having IUGR and oligohydramnios in our population.

Methodology

This randomized controlled trial study was started by taking approval from hospital ethics committee. All the pregnant women with unexplained IUGR and oligohydramnios referred or visiting for the treatment to the OPD of Obstetrics and Gynecology department, Aziz Fatimah hospital, Faisalabad were recruited for the study. A total of 104 pregnant women were enrolled for the study by non-probability consecutive sampling and was randomly divided into two equal groups of 52 each by lottery method. Group A was the treatment group in which Enoxaparin (40 mg subcutaneously/day) along with standard treatment (Aspirin, 75 mg once daily orally) was given and in group B only standard treatment based on aspirin was given. The sample size was calculated by WHO sample size calculator with 5% level of significance, 90% power of test and rates of live birth of 91% in enoxaparin group and 65% in standard treatment group.[11] All the women included in the study were briefly described about the objective and methodology of the study and informed written consent was taken.

All the patients were interviewed about their medical, personal, obstetrical and family history. The women presenting with pre-eclampsia, chronic medical disorders, ruptured membrane, congenital anomalies of the fetus, anti-phospholipid syndrome, Diabetes Mellitus or thyroid disorders or cardiac diseases, by doing appropriate investigations related to each disorder, were excluded from the study.

All the patients were followed up two weekly till 28 weeks of gestation, on every visit all the patients had ultrasonographic measurement of amount of liquor, growth scans along with prothrombin time and

platelet counts. After 28 weeks of gestation every patient was advised to visit every week and, on every follow up visit, growth scan and umbilical artery doppler were done. The fetuses were also monitored by umbilical artery Doppler flow systolic/diastolic ratio at each visit, which was also normal, i.e., <2.6. All these patients were tried to deliver at term with normal vaginal root but in the situation of emergency and elective caesarian section, LMWH was stopped 24 hours prior to surgery. All the neonates were kept in intensive care unit for 24 hours, to observe for any side effect or complication.

All the collected data was entered and analyzed with SPSS v. 21. Descriptive statistics were used to calculate mean with standard deviation for numerical data and frequencies along with percentages for categorical data. Independent sample t-test and Chi-square tests were applied to compare quantitative and qualitative variables between both groups. P-value < 0.05 was considered significant.

Results

In this randomized controlled trial study, a total of 104 patients were included. In group A, Enoxaparin was used and in group B standard treatment was given to the pregnant women. In Enoxaparin group mean maternal age was 27.54 ± 3.74 years and in Standard treatment group the mean age was 28.46 ± 3.49 years with no significant (p-value > 0.05) difference between two groups. The mean gestational age (37.65 ± 0.76) in Enoxaparin group was significantly (p-value < 0.05) higher as compared to Standard treatment group in which the mean gestational age was 36.95 ± 0.84 weeks. Previous pregnancy rate was not different (p-value > 0.05) in both groups with mean values of (3.65 ± 2.18 vs 4.36 ± 1.85, p-value > 0.05). The mean value of previous abortions in Enoxaparin group was 1.38 ± 0.45 as compared with 1.26 ± 0.58 in Standard treatment group with no statistically significant (p-value > 0.05) difference in both groups.

The comparison of rate of miscarriages between both groups showed that in Enoxaparin group the rate of miscarriages was significantly (p-value < 0.05) lesser (11.54% vs. 38.46%) as compared to Standard treatment group as elaborated in table I.

According to the results the rate of preeclampsia was significantly less in women who were using Enoxaparin as compared to women who were in Standard treatment group in which the rate of preeclampsia was very high. In Enoxaparin group the incidence of preeclampsia was 8.69% as compared to Standard treatment group in which the incidence of 43.75% was noted. The difference in incidence rate of preeclampsia was highly significant.

There was no significant (p-value > 0.05) difference in preterm delivery rate between Enoxaparin group (15.22%) and Standard treatment group (25.0%). The rate of prematurity was significantly higher in Standard treatment group (56.25% vs. 28.26%, p-value < 0.05) as compared to Enoxaparin group. There was no any significant difference in mode of delivery of both groups. The rate of live birth was significantly (p-value < 0.05) higher (88.46%) in Enoxaparin group as compared to (65.39%) in Standard treatment group. The results of this study also showed that the mean value of birth weight of the babies in Enoxaparin group was significantly (p-value < 0.05) higher (3.32 ± 0.412) kg as compared

Table I: Comparison of demographic characteristics of both groups

characteristics	Enoxaparin Group (n=52)		Standard treatment group (n=52)		P-value
Maternal age of the participants					
Mean, SD	27.54	3.74	28.46	3.49	0.196
Gestational age					
Mean, SD	37.65	0.76	36.95	0.84	0.000
Previous pregnancies					
Mean, SD	3.65	2.18	4.36	1.85	0.076
Previous abortions					
Mean, SD	1.38	0.45	1.26	0.58	0.241
Miscarriages					
Yes	6	11.54%	20	38.46%	0.001
No	46	88.46%	32	65.39%	

to (2.86 ± 0.518) kg in Standard treatment group as given in table II.

Discussion

Low molecular weight heparin is being used in different pregnancy related diseases like thromboembolic disease. It has improved the outcome not only in prophylactic use in patients having thrombophilia but also in patients with complications accompanying thromboembolic disease. The use of LMWH has also shown tremendous results in patients with pregnancy related complications like recurrent pregnancy loss, preeclampsia, abruptio placentae, intrauterine growth restriction and intrauterine fetal death. The use of LMWH has some advantages over unfractionated heparin because it has longer duration of action and more predictable response. It has also the advantage of better compliance due to once daily subcutaneous administration. The mechanism of action of LMWH include reduction in inflammation, inhibition of complement activation and enhancing the implantation. [12]

Most common causes of maternal and perinatal morbidity and mortality are preeclampsia and fetal growth restriction. The prediction of these conditions is poor in current clinical practice and risk of these conditions cannot be gauged in a good manner. Most commonly previous clinical history is used as a tool for prediction of preeclampsia and fetal growth restriction. Some strategies like use of aspirin or calcium has been demonstrated to reduce the risk of pregnancy related complications but these strategies have not given promising results. A considerable amount of evidence is available which support the use of LMWH with higher benefits. [13]

In this present study the mean maternal age in Enoxaparin group was 27.54 ± 3.74 years with no significant (p-value > 0.05) difference from Standard treatment group having 28.46 ± 3.49 years. The mean gestational age (37.65 ± 0.76 vs. 36.95 ± 0.84 weeks) in Enoxaparin group was significantly (p-value < 0.05) higher as compared to Standard treatment group. Previous pregnancy rate (3.65 ± 2.18 vs 4.36 ± 1.85, p-value > 0.05) and previous abortions rate (1.38 ± 0.45 vs. 1.26 ± 0.58) was not different (p-value > 0.05) in both groups.

A very common complication of pregnancy is oligohydramnios, accompanied with fetal growth restriction and other diseases related to this condition. This is a major cause of morbidity and mortality among infants worldwide. Severe oligohydramnios in second trimester is very threatening for fetus, because the perinatal mortality rate is high up to 90% among women having this condition. The most severe complication of oligohydramnios is pulmonary hypoplasia. Currently,

Table II: Comparison of maternal complications between both groups

Complications	Enoxaparin Group (n=46)		Standard treatment group (n=32)		P-value
	Frequency	Percentage	Frequency	Percentage	
Preeclampsia					
Yes	4	8.69%	14	43.75%	0.000
No	42	91.31%	18	56.25%	
Preterm delivery					
Yes	7	15.22%	8	25.0%	0.281
No	39	84.78%	24	75.0%	
Prematurity					
Yes	13	28.26%	18	56.25%	0.013
No	33	71.74%	14	43.75%	
Mode of Delivery					
Normal	11	21.11%	18	34.62%	0.126
Cesarean Section	41	78.45%	34	61.54%	
Live births					
Yes	46	88.46%	32	65.39%	0.001
No	6	11.54%	20	38.46%	
Birth Weight of the babies					
Mean, SD	3.32	0.412	2.86	0.518	0.000

obstetricians are looking for some modalities of treatment such as maternal hydration, amnioinfusion, transabdominal amnioinfusion prior to labor induction but whether routine antepartum or intrapartum treatment will improve outcome remains to be discovered. [14, 15]

The rate of miscarriages in this present study was significantly (p-value < 0.05) lesser in Enoxaparin group (11.54% vs. 38.46%) as compared to Standard treatment group. Similarly, in Enoxaparin group the incidence of preeclampsia was 8.69% significantly (p-value < 0.05) lesser as compared to Standard treatment group in which the incidence of 43.75% was noted. Analysis of the data revealed statistically significant difference between the treatment Groups in terms of live birth rate (88.46%) versus 65.39%); p = 0.001), the mean gestational age at delivery (37.65±0.76 versus 36.95± 0.84 weeks; p =0.000) and the mean birth weight (3.32± 0.412 versus 2.86 ±0.518 kg; p =0.000). The results are in agreement with previous studies like in studies of Mohamad KAA and Saccone G. [11, 16]

Preterm deliveries were experienced by 15.22% of women in Enoxaparin group compared with 25% in Standard treatment group. The rate of preeclampsia was significantly lower in Enoxaparin group (8.69%) than in Standard treatment group (43.75%); (P =0.000). These results are comparable to other studies. [17, 18]

In patients presenting with placental insufficiency, the use of low molecular weight heparin has given significantly improved results as compared to other managements. Studies have shown encouraging results which support to the idea that the use of LMWH in patients having intrauterine growth restriction (IUGR) and oligohydramnios can improve the pregnancy outcome considerably. The use of LMWH has also given wonderful results in patients of IUGR and oligohydramnios, which are caused by other reasons than APS and thrombophilia. [19]

Prophylactic LMWH use in patients with adverse pregnancy outcome due to severe IUGR and oligohydramnios because of chronic hypertension with superimposed gestational hypertension also gives good results. No side-effects with LMWH were observed in any of the participants in this present study and no other studies in the literature have revealed any side effect. [20, 21]

Conclusion

Low molecular weight heparin along with aspirin have shown high live birth rate, less chances of miscarriage, preeclampsia, preterm delivery and prematurity as compared to aspirin group only. This combination may promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation. Low molecular weight heparin has definitive role in patients with adverse pregnancy outcome due to IUGR and oligohydramnios

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