Safety of Enoxaparin used as Thromboprophylaxis in Pregnant Females with Mechanical Prosthetic Valves: 7 Year Prospective Study

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ABSTRACT

Introduction: Pregnancy is a hypercoagulative state. Pregnancy after mechanical heart valve implantation is risky for mother and child because of adverse effects of anticoagulants as well as aggravation of existing heart pathology and deranged function of the heart. Risks include maternal heart failure, valve thrombosis as well as arrhythmias and endocarditis. Unfortunately, there is no consensus among doctors regarding the choice of anticoagulant nor are there controlled clinical trials to provide guidelines for effective antithrombotic therapy. We have undertaken this study of using Low Molecular heparin with dosage adjustment of the drug during pregnancy with an aim for safe pregnancy and delivery in women with mechanical prosthetic valve. We will also assess the foetal outcome after delivery in these patients.

Material and methods: This was a prospective observational study starting from 1st July 2013 to 30th June 2020 in pregnant females with mechanical prosthetic valves who were anticoagulated with LMWH injection till delivery. This study was conducted at Hi-Tech Medical College & Hospital, Rourkela. Our study consisted of 30 pregnant females with mechanical prosthetic valves either with mitral/aortic or both. Out of 30 females, 22 had prosthetic mitral valves, 6 had prosthetic aortic valves and 2 had both mitral and aortic valves. 22 of these patients were referred from maternity out patients department and 8 came from cardiac OPD. Written informed consent was obtained prior to our study from each pregnant female.

Results: There was 1 maternal mortality in the sample of 30, there was 1 case of valvular thrombosis, 3 had haematuria for less than 48 hours, 2 had spotting per vaginum and 1 had purpuric spots over the skin.

Conclusion: Our study showed that Inj. LMWH can be safely administered to pregnant females with MPHV during pregnancy with a dose adjustment to maintain anti Xa level between 1.0Unit/ml 1.2unit/ml.

Keywords: MPHV (Mechanical Prosthetic Heart Valve), LMWH (Low Molecular Weight Heparin), UFH (Un fractionated heparin).

INTRODUCTION

Physiologically pregnancy is associated with many circulating changes once there is a pre-existing cardiac problem. Pregnancy can increase the cardiac output beyond the physiological range, can retain excessive Na and water leading to volume expansion and reductions in systemic vascular resistance and systemic blood pressure.[1] Pregnancy is also a hyper coagulable state[2], and thrombo-embolic risk is higher in pregnancy.[3] Risks in pregnancy with MPHV is compounded with aggravation of maternal heart dysfunction and adverse effects of anticoagulants. Potential risks during pregnancy with MPHV are maternal heart failure, infective endocarditis, arrhythmias and maternal death.[4] MPHV are preferred to bio prosthetic valves because bio prosthetic valves get deformed and there are significant structural deformities particularly during pregnancy.[5] In contrast, mechanical prosthetic valves are associated with risk of increased thrombogenicity and require anticoagulant prophylaxis.[6] Greater thrombogenicity was observed with older generation prosthetic valves as compared to new generation prosthetic valves like St Jude's Medical & Medtronic valves.[7] Prophylactic anticoagulation is required in all pregnant females with mechanical prosthetic heart valves.[8,9] Warfarin was being used as the preferred anticoagulant for years but is associated with foetal embryopathy.[4] When the dose of Warfarin is more than 5mg/day, the chances of embryopathy in the form of facial dysmorphism, hypoplasia of nasal bridge, laryngo malacia and congenital heart disease occur in more than 5% of children born to mother on Warfarin therapy during the 1st semester of pregnancy. This incidence is much less when the dose is less than 5mg/day.

LMWH has got a molecular weight of less than 10,000 Daltons. LMWH exerts its action by inhibiting the action of the activated factor X(Factor Xa). LMWH has generated interest basing on two factors; their safety and as they do not cross the blood brain barrier the foetal embryogenecity is least. LMWH has caused rare incidents of thrombo cytopinia as compared to UFH. LMWH caused less incidence of osteoporosis.[10] LMWH does not cross the placental barrier and hence safe in pregnancy both for mother and foetus.[11,12] While monitoring for anti Xa activity, peak activity is measured after 3 to 4 hours of injecting LMWH subcutaneously. Reports of thrombosis of heart valves in pregnancy with

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MPHV resulted in a warning by the manufacturer for its use in such cases.[13] Subsequently, many other studies[14,15,16] refuted this opinion and stated that out of 3 options, Warfarin, UFH and LMWH, the last one is the safest. The 8th American College of Chest Physicians guidelines recommended the use of LMWH to achieve a peak anti Xa level of 1unit/ml as a treatment option.[17] This study was carried out to determine the safety of LMWH in pregnant females with MPHV after making a dose adjustment to maintain a peak anti Xa value between 1unit/ml to 1.2unit/ml. The key outcomes measured were maternal mortality, major bleeding and thrombosis. We also noted down presence of any embryogenic defect in the foetus after delivery.

MATERIAL AND METHODS

The study was carried out at Hi-Tech Medical College & Hospital, Rourkela, Odisha wef 1st july 2013 to 30th June 2020. Total number of patients qualified for the study was 30. The women in our study were between 20 to 38 years of age with MPHV either a mitral or aortic or dual(both mitral and aortic) valves. Some of these cases were referred from hospitals in the near vicinity and some were from the adjacent states of Jharkhand and Chhattisgarh.

All these patients were on warfarin which was prescribed in their ante natal clinic or by cardiologists/physicians before conception for prophylactic treatment.

An informed consent was taken in written form and prior approval from the ethical committee was taken before including these pregnant females in our study. Ethical clearance for this study was granted by the ethical committee of Hi-Tech Medical College & Hospital, Rourkela, Odisha.

Exclusion Criteria: Women with NYHA Class III, Class IV group, infective endocarditis, history of repeated haemolysis like sickle cell disease which is very much prevalent in our region or known thrombolytic state were excluded from our study. Also we excluded from our study anyone who was absent for one week after initiating the study and females who did not have minimum of 14 days of LMWH. We also excluded subjects who developed thrombocytopenia during the study. We also excluded subjects who were on NSAIDs, steroids and other thrombolytics.

Our subjects were admitted as soon as they were observed to have pregnancy with MPHV. In the hospital they were administered Inj LMWH 1mg/kg of body weight twice a day for 7 days and after teaching them how to administer injections subcutaneously they were discharged from the hospital. During this period the dose of Enoxaparin was adjusted to achieve a level of anti Xa value of 1unit/ml to 1.2units/ml. These females were advised to attend our clinics once in a fortnight till 32nd week of gestation and then weekly thereafter. Anti Xa values showing a lesser value of 1unit/ml was up titrated by 10mg/dose of LMWH to achieve anti Xa level 1unit/ml to 1.2unit/ml. Values showing anti Xa level of more than 1.2units/ml where administered 10mg lesser dose to achieve anti Xa level between 1unit/ml to 1.2units/ml. Major bleeding was defined as any bleeding which resulted in loss of blood resulting in drop of Heamoblobin concentration by more than 2gm/dl. as any bleeding requiring transfusion of 2 or more units of blood. Bleeding which did not come in this criteria was defined as minor.

RESULTS

Initially we had taken up 42 pregnant females but 12 were excluded from the final sample as 4 were lost during follow up and 2 did not fulfill the criteria of at least 14 day treatment with LMWH before delivery and 2 could not afford cost of treatment. 2 females developed thrombocytopenia and 2 developed NYHA class IV heart failure. All females were given Inj. LMWH at a dose of 1mg/kg of body weight by subcutaneous injection twice daily. Dose was adjusted to keep the 3 hour post dose anti Xa level between 1.0unit/ml to 1.2unit/ml.

Occurrence of Prosthetic valve thrombosis, bleeding and maternal mortality were observed with prophylactic use of low molecular weight heparin. So in the final stage of study we had 30 patients who could complete the entire period of our study.

Table 1 illustrates all informations about all the patients included in our study. This table also illustrates the duration of anticoagulation and type of mechanical prosthetic valve implanted in our patients. In our group we had 10 primigravidas and 20 multigravidas. All the patients were in NYHA Class I or II group. 10 patients were implanted with double valve replacement and 20 had single valve replacement. The average age of our patient was 24.6 years(median age 29 years). The average duration of Enoxaparin administration was 9 weeks and total duration of Enoxaparin administration was 270 weeks in a combined manner in all patients. 4 patients did not receive any anticoagulant prior to reporting for our study(Patient 3,8,9,11).

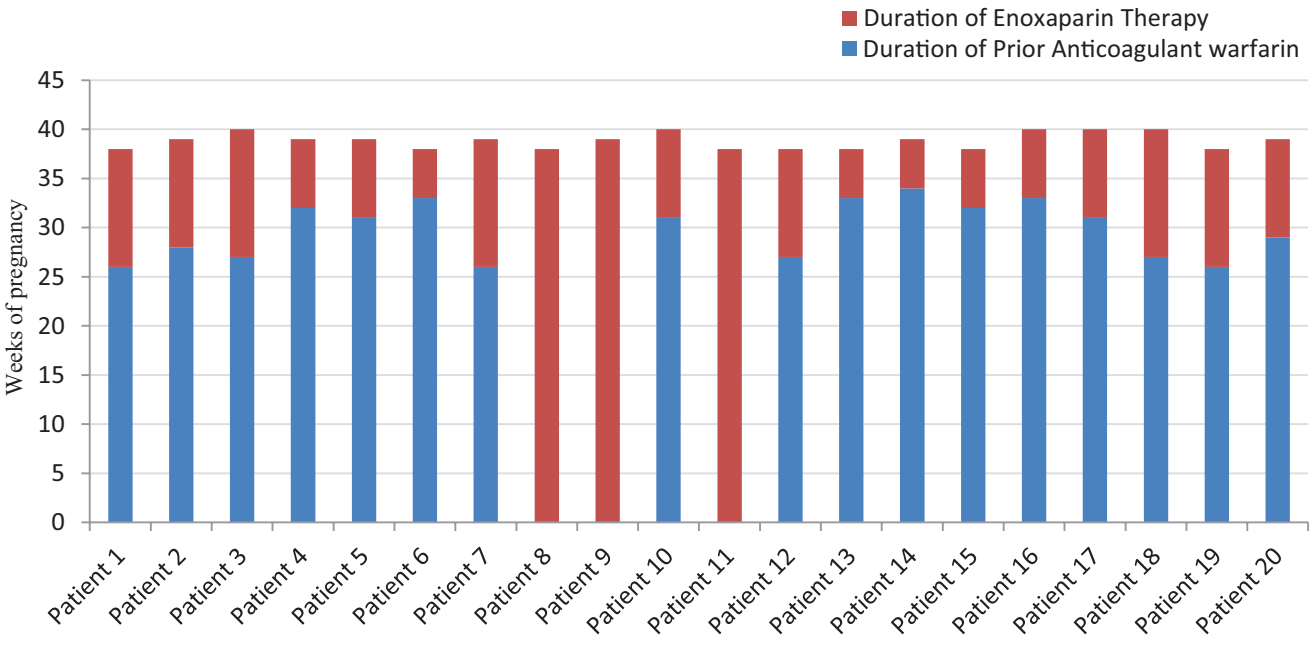
Table 2 depicts adverse outcomes in our patients. Maternal morbidity was expressed as minor bleeding, major bleeding, post parturition haemorrhage, cardiac or obstetrics complications. 1 patient had post partum haemorrhage where Hb level dropped from 12gm% to 9gm% and she was transfused 2units of blood. 3 patients developed itching at the injection site which subsided on application of anti histaminic ointment. 2 patients had dyspnea and were subjected to xray of chest and Echocardiography which were normal. They had bilateral crepitations which subsided with 10mg of IV Furosemide. 2 patients developed purpuric spots of more than 10 number and their anti Xa level was more than 1.5units/ml. The dose of Enoxaparin was reduced by 10mg and within 7 days there was relief and anti Xa level came down to 1.2units/ml. 2 patients epistaxis requiring nasal package and epistaxis subsided within 24 hours. Anti Xa level in these 2 cases were 1.7units/ml and 1.8units/ml respectively and downgrading the dose of Enoxaparin by 10mg/dose brought down the level to 1.1units/ml after 14 days. We lost 1 case at 34th week of gestation due to pneumonia (klebsiella) and Acute Respiratory Distress Syndrome. Although her anti Xa level was normal and she was on ventilator support, we lost her after 5 days of treatment. 2 patients had minor spotting with a passage of a few drops of blood which subsided within

Serial no	Age (years)	Weight	Parity	Type of MPHV	Prior Anticoagulation	Duration of Adjusted dose of Enoxaprin
1	23	62	Primi	MVR Medtronic	Warfarin1-26	27-38
2	27	57	Multi	MVR Medtronic	Warfarin28	29-39
3	32	67	Multi	MVR St Jude	No Warfarin1-27	28-40
4	37	72	Multi	AVR MVR Medtronic	Warfarin32	32-37 Mortality due to pneumonia
5	28	59	Multi	AVR MVR Medtronic	Warfarin31	32-39
6	21	57	Primi	MVR Medtronic	Warfarin33	34-38
7	26	67	Multi	MVR St Jude	Warfarin26	27-39
8	24	70	Primi	MVR Medtronic	No Warfarin1-31	32-38
9	29	67	Multi	MVR St Jude	No Warfarin1-29	30-39
10	37	71	Multi	MVR	Warfarin31	32-40
11	28	63	Primi	MVR Medtronic	No Warfarin1-30	30-38
12	24	67	Primi	MVR St Jude	Warfarin 27	28-38
13	19	54	Primi	AVR MVR Medtronic	Warfarin 33	34-38
14	20	59	Primi	MVR St Jude	Warfarin 34	35-39
15	23	61	Primi	MVR St Jude	Warfarin 32	33-38
16	26	67	Multi	MVR Medtronic	Warfarin 33	34-40
17	29	70	Multi	AVR MVR St Jude	Warfarin 31	32-40
18	33	72	Multi	MVR Medtronic	Warfarin 27	28-40
19	25	63	Primi	MVR Medtronic	Warfarin 26	27-38
20	23	57	Primi	MVR St Jude	Warfarin 29	30-39

Table-1: Data of all patients with baseline information & duration of anticoagulation.

Patient no.	Valve type	Bleeding	Cardiac/ obstructive/other morbidities	Maternal Mortality
4	DVR			Mortality due to pneumonia
7	MVR	Epistaxis		
10	AVR	PPH		
11	AVR		Dyspnoea bilateral lung crepitation	
14	AVR	Epistaxis		
18	MVR		Dyspnoea bilateral lung crepitation	
22	MVR	Minor spotting		
27	MVR	Minor Spotting		

Table-2: Maternal morbidity & mortality



Patient no. 8,9 & 11 did not receive any anticoagulant for 32,30 & 30 weeks of pregnancy respectively

Figure-1: Duration of Enoxaparin and prior anticoagulant.

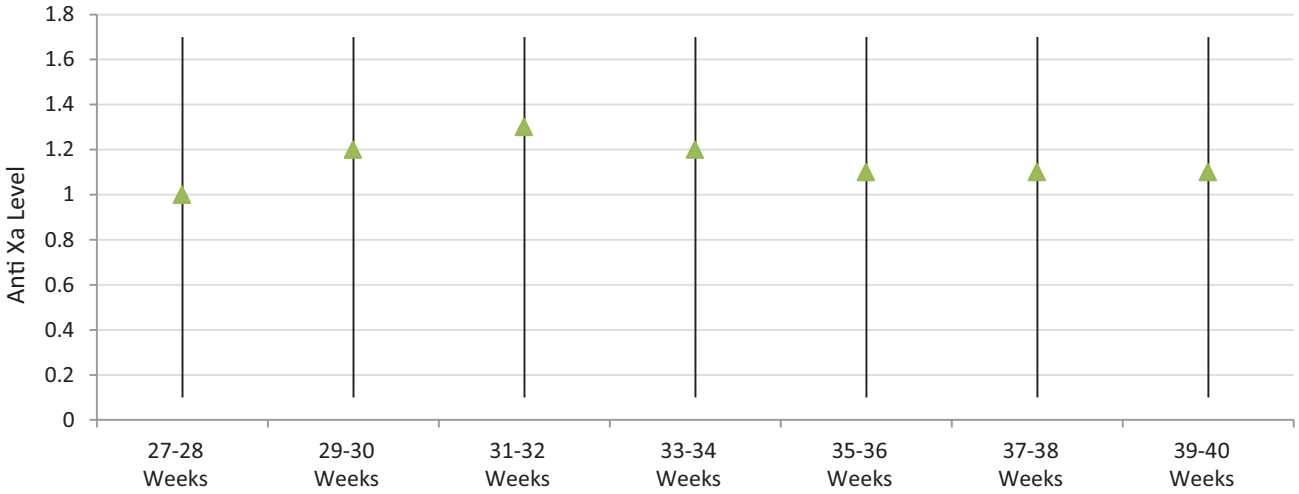


Figure-2: Showing Anti Xa level as per weeks of pregnancy.

48 hours. We encountered mild thrombocytopenia, platelet count <90,000/cmm after 14 days of treatment with 1 patient and on repetition of the platelet counts after 3 days of it was 1,40,000/cmm of blood. In this case the anti Xa level was normal. We did not encounter any vertebral osteoporosis on bone deximetry in any patients.

Figure 1 depicts duration of adjusted dose of Enoxaparin after presentation of the patients to us and other anticoagulation duration before presentation to our study.

Figure 2 depicts the average anti Xa reading after presentation to us with 95% CI. We maintained a level of anti Xa level of 1unit/ml to 1.2units/ml throughout the pregnancy in all the patients in our study.

DISCUSSION

The management of pregnancy in patients with MPHV is problematic and there is no guideline for optimal antithrombotic therapy. The 8th American College of Chest Physician(ACCP) guidelines recommend the use of LMWH in pregnancy with MPHV keeping anti Xa value between 1unit/ml to 1.2units/ml.[17] A review of 75 women with MPHV who were treated with inj. LMWH during pregnancy was published by Oram et al reported 8.6% valvular thrombosis.[18] Although rate of valvular thrombosis was unacceptably high in these patients as it is associated with maternal & foetal morbidity and mortality. There was a pattern which was noticed in this study where it was evident that dose of LMWH was inadequate resulting in a sub therapeutic anti Xa level. To mitigate this flaw we strictly maintained an anti Xa level between 1unit/ml to 1.2 units/ml throughout pregnancy in accordance with 8th ACCP guidelines.[17]

There have been reports of failure of subcutaneous injections of UFH to prevent thromboembolism in pregnant females with MPHV.[18,19,20] Reports of massive pulmonary oedema secondary to thrombosis of MPHV in pregnant females was made by some authors.[21] FDA in 2002 made a warning that LMWH was not recommended in pregnant females with PMHV.[22] Subsequently, clinical cardiology consensur report cleared this concept.[14,23]

Our data of safety of Enoxaparin in adjusted dose in pregnancy with MPHV was supported by groups from London and Auckland. Risks of thrombosis was more in older generation mitral valves as compared with new generation of St Jude And Medtronic Bileaflet Mitral Valves.[24] All the patients on our group were replaced with new generation MPHV. We maintained a strict level of anticoagulation with constant vigil to keep the anti Xa level between 1unit/ml to 1.2units/ml. Prophylactic Antithrombosis with LMWH is efficacious and is associated with least mortality as reported by Chan et al.[25] Until head to head trials are done with warfarin it is suggested LMWH to be a safe option to prevent maternal mortality and certainly to prevent foetal embryopathy. Use of LMWH in pregnany with MPHV is quite recent practice and it is expected that with many more studies lights can be thrown as to the safety of Enoxaparin as an antithrombotic prophylaxis in pregnancy with MPHV.

CONCLUSION

Our study comprising of 30 patients with MPHV who received Enoxaparin Injection during a seven year prospective study seem to be a study with small number of patients. But it clearly proves the safety of Enoxaparin as far as maternal morbidity and mortality are concerned provided a strict level of anti Xa level is maintained. The treatment with Inj. Enoxaparin was expensive and combined efforts of cardiologists, physicians and gynecologists are required for such type of treatment to be successful. Careful selection of cases is required prior to the treatment and women with significant bleeding tendency and haemoglopathies should be excluded from this treatment.

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