Role of low Molecular Weight of Heparin in Preventing Severe Preeclampsia

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ABSTRACT

Background: This condition is known as preeclampsia, which is characterized by new-onset hypertension after twenty weeks of gestation with indications of organ damage; the potential maternal and neonatal consequences of preeclampsia are considerable.

Aim of the work: The study's goal is to determine the function and efficiency of low molecular weight heparin in avoiding severe preeclampsia.

Patients and methods: The study is randomized, interventional study and carried out on cases of high risk of pre-eclampsia at obstetrics, gynecology department al-azhar university hospitals. Our study was done on one hundred participants of high risk of pre-eclampsia separate into 2 groups; Group 1 (study group): in accordance with standard regimen, 50 patients got low molecular weight heparin. Group 2 (control group): contain 50 cases had received usual regimen only.

Results: The current results show statistically significant differences between groups according to patient's clinical improvement, APGAR score and NICU admission with more improvement in patients who received low molecular weight heparin in accordance with usual regimen when it compared to other group which contain cases received usual regimen only (control group).

Conclusion: low molecular weight heparin is effective in preventing development of severe preeclampsia in patients with mild preeclampsia on expectant management of this resulting in less maternal, fetal and neonatal morbidity and mortality.

Keywords: *fetal; outcomes ; neonatal; preeclampsia; severity.*

INTRODUCTION

Preeclampsia is life threating multisystem vascular disorder with prevalence ranges from 5 to 8 % of pregnancies. It is the most common reason of perinatal and maternal morbidity and mortality affecting 8.5 million pregnancies worldwide, accounting for over 70 000 maternal deaths and 500 000 infant deaths annually. [1]

According to studies the complement system has major role in the preeclampsia pathogenesis, as complement system over activation or deficient regulation increase circulating anaphylatoxins and deposition of complement factors in the placenta leads to dysfunction of placental. HELLP syndrome (increased liver enzymes, hemolysis, and low platelets), placental abruption, severe renal failure, and pulmonary edema are all consequences of preeclampsia that can lead to eclampsia .[2]

Heparins are the drug of choice in pregnant women because it doesn't pass through the placenta and has a favorable maternal safety profile with a low risk of major bleeding, unfractionated heparin (UFH) and lowmolecular-weight heparin (LMWH) are major types of heparin. By binding anti thrombin, all heparins function as antithrombotic factors, preventing active coagulation factors from causing blood clotting (factors IIa, VIIa-TF, IXa, Xa, and XIa). In pregnant women, LMWH is the preferable. [3]

LMWH is safe in pregnant women without maternal or fetal side effects or major bleeding episodes.[4]

LMWH's potential to prevent preeclampsia is unclear at this time. There is evidence to support the use of low-molecular-weight heparin (LMWH) as a maternal vasodilator and endothelial enhancer, as well as an anti-compartment effect (C5a).[5]

Low-molecular-weight heparin has been shown in earlier trials to lower the incidence of venous thromboembolism and placenta-mediated pregnancy problems in pregnant women with thrombophilia who are at high risk of difficulties.

The study's goal is to determine the function and effectiveness of low molecular weight heparin in avoiding severe preeclampsia.

PATIENTS AND METHODS

This study was a randomized interventional study carried out at El Hussein University Hospital and Sidi Salem central Hospital from November 2020 to November 2021 for 100 female patients with mild pre-eclampsia

Sample size: This study was based on McLaughlin et al study, .'s [6] Epi Info STATCALC was used to determine the sample size based on the following assumptions: - A power of 80percent and a two-sided confidence level of 95%. The computed odds ratio is 1.115, with a 5percent margin of error. From the Epi-Info output, the ultimate maximum sample size was 96. To account for any drop-out instances during follow-up, the sample size was expanded to 100 cases.

Inclusion Criteria for study group: Pregnant patients ≥ 21 years old, more than 28 weeks gestation up to 36 weeks gestation (as documented by ultrasound) with mild pre-eclampsia.

Exclusion Criteria for groups: Patient less than 21 years old or greater than 40 years old, patients with severe pre-eclampsia, allergy to heparins, history of gastrointestinal or genitourinary bleeding and thrombocytopenia related to heparin use.

Methods: cases were exposed to:

Complete history was taking: Personal history like: name, age, marital state, address, menstrual history especially last menstrual period, present history: of chronic diseases and medication, past history of HTN, DM, family history of similar condition or diabetes, history of allergy to any medication and surgical history of operation, laparoscopic interference.

Examination:

General examination: Monitoring of the body's vital signs (blood pressure, temperature, heart rate, respiratory rate), Signs of (Pallor, Cyanosis, Jaundice, and Lymph node enlargement) and weight, Height, BMI and lower limb edema.

Abdominal and local clinical examination: Abdominal inspection: For detection of: Scars, abdominal distension, caput medusa, striae (stretch marks), abnormal masses indicating hernia according to the location and ecchymosis indicating internal hemorrhage. Abdominal palpation: Light palpation of the abdomen: For detection of: Tenderness, rebound tenderness and guarding. Deep palpation of the abdomen for detection of deeper masses. Abdominal percussion: Percussion was used to assess the size of the liver by applying percussion downward from the lung to the liver, and then the bowel. Abdominal auscultation

Vulvar Examination: Fundamental examinations of the vulvar area include the assessment of basic development, symmetry, and hair quality and growth distribution, as well as the detection of skin abnormalities, swelling, ulcerations, and the presence of growths such as external genital warts (EGW).

Vaginal Examination: The urethral aperture, the Skene glands, any discharge, soreness, or erythema, as well as any eversion or prolapse of the meatus, are all checked during the urethral examination. Bimanual Examination: was to define the size and nature of the uterus and the presence or absence of adnexal masses.

Laboratory study: Complete blood picture (CBC): hemoglobin concentration (Hb %), red blood cells (RBCs), white blood cells (WBCs), platelet count. Renal function test: serum creatinine, blood urea and urine analysis. Liver Test Profile: Serum aspirtate and alanene amino transferases (AST and ALT), serum albumen, serum biliruben, serum gamma-glutamyl transferase (GGT), (SGOT), (SGPT), prothrombin time and international normalized ratio (INR). Protein in urine, uric acid and 24h albumin in urine.

Ultrasound: To exclude cases of oligohydramnios and any other abnormalities and to assess gestational age, Doppler studies and biophysical profile.

Procedure: All 100 patients were undergone expectant management of mild preeclampsia which include: Bed rest, anti HTN drugs and fluid or not

Patients were divided into 2 groups: Study group: 50 cases received low molecular Weight heparin clexane 40mg once a day (Manufactured by Sanofi India Ltd) in addition to usual regimen. Control group: 50 cases received usual regimen.

Antenatal follow up:

Maternal: Daily follow up: Blood pressure: Temperature: We used mercury thermometer under septic condition to obtain temperature. Pulse: Assess pulse rate, rhythm, volume, equality. Detection the degree of Lower limb edema. Detection of fits and chest pulmonary edema

Weekly follow up: complete blood count: Hb, hematocrit: increased, RBCs count, MCV, MCH, MCHC : microcytic hemolytic anemia and platelets: thrombocytopenia in severe cases. Renal function test: serum creatinine, blood urea and urine analysis. Liver Test Profile, Protein in urine, uric acid and 24h albumin in urine and body mass index

Fundus examination: by palpation at the midpoint between the umbilicus and the pubic symphysis for detection of the fundal height which correlate to the gestation age. Weekly observation and documentation of Weight gain. Ultrasound and Doppler ultrasound: to assess fetal gross and fetal wellbeing. Observation of development of fits. Asking for symptoms of severe preeclampsia: Headache, nausea, epigastric pain and blurred vision

Outcome: 1ry outcome: Period of treatment, severity of pre-eclampsia, and number of patients proceeded to severe preeclampsia and termination of pregnancy. 2ry outcome: Apgar score, entering ICU and mortality and morbidity of the mother

Ethical Consideration: Study protocol had been submitted for approval by Institutional Review Board, Al-Azhar University. Informed verbal consent had been obtained from each participant sharing in the study.

Statistical Analysis: Using IBM SPSS software package version 20.0, we examined the collected data. (IBM Corp., Armonk, New York,) (2) Numbers and percentages were used to describe qualitative data. Kolmogorov-Smirnov tests were employed to determine whether or not the distribution of data was normal. We used range (lowest and highest values), mean, and standard deviation for describing our quantitative data. The significance of the findings was evaluated at a 5% level of significance. Tests performed included: Chi-square test: For categorical data, comparing two groups is done using the Chi-square test. In the case of typically quantifiable variables, the student t-test may be used to compare the results of two groups under investigation. Analyzing unusually quantifiable characteristics in order to compare two study groups

RESULTS

	Group (A) (n=50)	Group (B) (n=50)	t	P Value
Age				
Min.-Max.	21-37	22-41	1.719	0.089
Mean± S.D	29.12±4.507	30.84±5.452		
Previous CS	26(52.0%)	24(49.0%)	0.090	0.842
History of Preeclampsia	12(24.0%)	8(16.3%)	0.904	0.454
Weight	82.16±8.625	81.36±7.912	U= 1184.50	0.651
Height	170.36±7.013	170.52±7.587	U= 1225.50	0.866
BMI	28.32±4.013	28.12±3.567	t= 0.255	0.800

U: Mann-Whitney test
t: T-Student test
p: p-value for comparisons between the two groups investigated
*: Statistically important at P <0.05
Table 1: Comparison among two groups as regard to patient's demographic data
According to the demographic characteristics of the patients, Table 1 revealed no statistically important change among groups.

Laboratory investigations	Group (A) (n=50)	Group (B) (n=50)	Test of Sig.	P Value
Hb				
Before	11.67±1.403	11.45±1.386	t= 0.789	0.432
After	11.70±1.228	11.26±1.385	U= 1013.00	0.102
Platelet				
Before	152.12±23.904	159.92±32.069	t= 1.379	0.171
After	154.82±21.854	162.10±32.382	U= 1093.00	0.279
AST				
Before	41.90±9.215	40.66±10.849	t= 0.539	0.156
After	40.82±10.372	38.28±11.535	U= 1080.00	0.241
ALT				
Before	50.60±12.449	50.18±10.800	U= 1220.50	0.839
After	50.54±10.670	53.74±10.962	t= 1.479	0.142
Creatinine				
Before	0.86±0.177	0.86±0.110	U= 1242.50	0.958
After	0.87±0.159	0.85±0.105	U= 1126.0	0.382
INR				
Before	1.06±0.238	1.13±0.272	U= 1051.00	0.167
After	1.03±0.232	1.10±0.280	U= 1073.50	0.220
Uric Acid				
Before	4.88±0.873	4.88±0.787	U= 1229.50	0.888
After	5.15±0.827	5.06±0.822	U= 1171.50	0.588

U: Mann-Whitney test
t: T-Student test
p: p-value for comparisons among the two groups investigated
*: Statistically important at P <0.05
Table 2: Comparison among two groups as regard to patient's laboratory investigations at start of study
Table (2) showed no statistically significant differences between groups according to patient's laboratory investigations.

Outcome	Group (A) (n=50)		Group (B) (n=50)		P Value
	No.	%	No.	%	
Complete 37 weeks	17	34.0	11	22.4	0.265
Severe preeclampsia	28	56.0	17	34.0	0.044*
Fetal distress	18	36.0	16	32.7	0.833
Termination due to other cause (PROM)	2	4.0	3	6.1	0.678

p: p-value for comparisons among the two groups investigated

*: Statistically important at P <0.05

Table 3: Comparison between two groups as regard to patient's Outcome

Table (3) showed statistically significant differences between groups according to patients with severe preeclampsia.

Clinical improvement	Group (A) (n=47)		Group (B) (n=41)		P Value
	No.	%	No.	%	
No	27	57.4	33	80.5	0.024*
Yes	20	42.6	8	19.5	
Total	47	100	41	100	

p: p-value for comparisons among the two groups investigated

*: Statistically important at P <0.05

Table 4: Comparison between two groups as regard to patient's Clinical improvement

Table (4) showed statistically significant differences between groups according to patients clinical improvement with more improvement in group (A) when it compare to group (B).

APGAR score	Group (A) (n=47)	Group (B) (n=41)	P Value
1 min	5.82±1.859	4.38±1.817	<0.001*
5 min	6.68±1.362	5.04±1.702	<0.001*

p: p-value for comparisons among the two groups investigated

*: Statistically important at P <0.05

Table 5: Comparison between two groups as regard to patient's APGAR score

Table (5) showed statistically significant differences between groups according to patients APGAR score with more improvement in group (A) when it compare to group (B).

NICU admission	Group (A) (n=47)		Group (B) (n=41)		P Value
	No.	%	No.	%	
No	36	76.6	21	51.2	0.015*
Yes	11	23.4	20	48.8	
Total	47	100	41	100	

p: p-value for comparisons among the two groups investigated

*: Statistically important at P <0.05

Table 6: Comparison between two groups as regard to patient's NICU admission

Table (6) showed statistically significant differences between groups according to patients NICU admission with more improvement in group (A) when it compares to group (B).
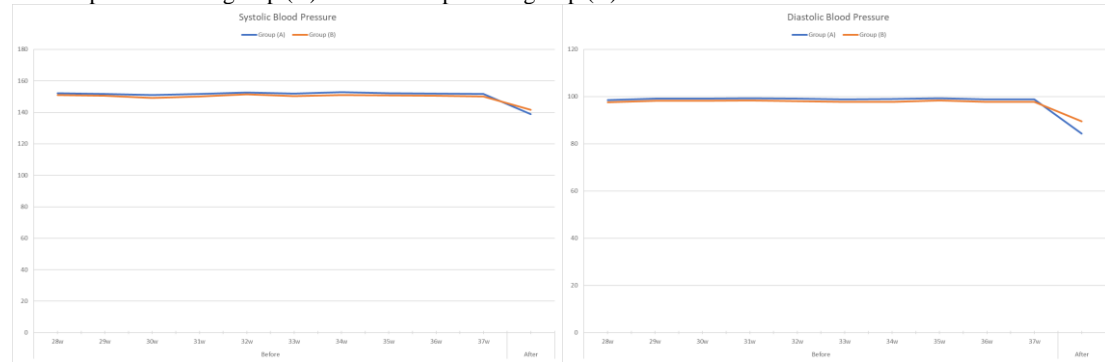

Fig. 1: Comparing two groups in terms of patient blood pressure

Figure (1) show statistically significant differences between groups according to patients blood pressure after treatment was stable in group (A) while in group (B) had to be worth when it compare to group (A).(Table (6); Figure (1))

DISCUSSION

A common explanation for why low molecular weight heparin is effective is that it has an anticoagulant effect within the placenta. This is true even though major trials did not include evaluations of the placenta after delivery and improved outcomes were observed in at-risk women who did not have demonstrable bleeding disorders. [7]

Low molecular weight heparin's impact in avoiding severe preeclampsia will be examined in this study.

This is a randomized, interventional research that was done in the obstetrics and gynecology departments of the Al-Azhar University hospitals on women who were at high risk of pre-eclampsia.

One hundred women at high risk of pre-eclampsia were split into two groups for our study: In the first group, 50 patients got low molecular weight heparin in addition to their regular treatment. A total of 50 patients in Group 2 (the control group) were given a standard treatment regimen.

Pregnant women over or equal the age of 18 years who are less than 16 weeks pregnant (as determined by ultrasound) and have at least one of the preeclampsia risk factors. Analysis of data had been done using SPSS.

Age, patient measures, fetal biometry, and laboratory tests had no statistically significant impact on the comparisons between groups in our study.

On the other hand, our results were shown that there are statistically significant differences between groups according to patients' blood pressure after treatment, patient's clinical improvement, APGAR score and NICU admission.

Regarding age, patients who received low molecular Weight heparin in addition to usual regimen was ranged between 21-37 years with mean 29.12±4.507 years while in cases received usual regimen only was ranged between 22-41 years with mean 30.84±5.452 years. There was no statistically important change between groups regarding age (P=0.089). Similar data had been recorded by Staff et al., [8].

Regarding weight, there was no statistically important change among the studied groups (p=0.651), patients who received low molecular weight heparin in addition to usual regimen were with weight mean 82.16±8.625 k.g, and also in cases received usual regimen only The mean weight was 81.36±7.912 k.g.

Patients who received low molecular weight heparin had a weight range of 80.09±5.12 kilograms, which is in agreement with the findings of De Vries et al., [9].

There was no statistically significant difference in height between the groups investigated (p=0.866). In a group of patients receiving low molecular weight heparin in addition to their regular treatment, the average height was 170.36±7.013 centimeters. As well as 170.527.587 cm in those that got simply a standard treatment. Staff et al. [8] have previously published similar findings,

Mean systolic blood pressure before treatment was 152.10±3.655 in the group of patients who got low molecular weight heparin in addition to their standard regimen. Cases that got only the normal treatment (p=0.201) were 150.90±4.482. Patients who got low molecular weight heparin in addition to their normal regimen had diastolic blood pressure mean of 98.50±2.315. And the regular regimen was given to 97.60±3.071 of the patients (p<0.156).

A study by Baldus et al., [10] also found that LMWH considerably decreased blood pressure in both mothers and babies, as well as the resistance of the uterine arteries, suggesting that the drug may help to "normalize" the blood pressure of pregnant women and the blood flow of the placenta. An unfractionated heparin treatment should be used in individuals with known coronary artery disease. Showed an increase in the bioavailability of nitric oxide (NO) through increasing flow-dependent endothelial vasodilation acetylcholine-induced dilatation of the forearm blood vessels and alterations in blood flow

There was no statistical change in hemoglobin levels among the groups examined for this study. Patients who got low molecular weight heparin in addition to their standard medication had an average hemoglobin level of 11.67±1.403 before starting treatment. And 11.45±1.386 among those who got only the standard treatment (p=0.432). In the group of patients who got low molecular weight heparin in addition to their normal regimen, the mean Hb was 11.70±1.228.

P=0.102, while only 11.26±1.385 among those who got the regular regimen exclusively.

Preeclampsia prevention by low molecular heparin is based on its wide-ranging biologic effects, which might enhance and normalize both placental function and maternal hemodynamics, as described by McLaughlin et al., [11]; Rodger et al., [12].

There was no statistically significant difference in Platelet counts across the groups that were examined. In the group of patients who got low molecular weight heparin in addition to their regular regimen, the mean platelet count was 152.12±23.904. 159.92±32.069 patients got just the standard treatment (p=0.171). In the group of patients who got low molecular weight heparin in addition to their regular regimen, the mean platelet count was 154.82±21.854. Furthermore, 162.10±32.382 were seen in patients who received only the standard regimen (p=0.279)...

Villa et al. [13] found that low molecular weight heparin reduced platelet aggregation, which in turn reduced the risk of thrombosis in patients.

In terms of AST, no statistically significant differences were seen across the groups examined. In a group of patients receiving low molecular weight heparin in addition to their regular prescription, the mean AST was 41.90±9.215 before therapy. And 40.66±10.849 among those who got only the regular treatment (p=0.156). As a result of therapy, the mean AST in the group of patients who got low molecular weight heparin in addition to their normal regimen was 40.82±10.372. Compared to 38.28±11.535 in those who got only the standard regimen (p=0.241).

Laskin et al. [14] found the opposite: that low molecular weight heparins, similar to the more common form of the drug used in clinical trials, are likely to cause harm to hepatocytes, which might explain why patients often have elevated levels of blood enzymes while on treatment. Animal studies have shown that this damage can be replicated.

Regarding international normalized ratio (INR), there was no statistically significant difference between the studied groups. Before treatment the mean INR was 1.06±0.238 in group of patients who received low molecular weight heparin in addition to usual regimen. And 1.13±0.272 in cases received usual regimen only (p=0.167). While after treatment the mean INR was 1.03±0.232 in group of patients who received low molecular weight heparin in addition to usual regimen. And 1.10±0.280 in cases received usual regimen only (p=0.220).

However, according to Espinoza et al., [15] it's possible that patients using low molecular weight heparin and warfarin will have an incorrect INR reading from the point-of-care device; as a result, patients should have their INRs tested in the laboratory using the normal reference technique.

When it comes to clinical improvement, APGAR score, and NICU admission, patients who got low molecular weight heparin in addition to their normal treatment do better than those in the other group, which includes just those who received their regular regimen (control group).

Regarding APGAR score, there was statistically significant difference between the studied groups. After one minuet the mean APGAR score was 5.82±1.859 in group of patients who received low molecular weight heparin in addition to usual regimen. And 4.38±1.817 in cases received usual regimen only (p<0.001). While after five minuet the mean APGAR score was 6.68±1.362 in group of patients who received low molecular weight heparin in addition to usual regimen. And 5.04±1.702 in cases received usual regimen only (p<0.001).

Yueping et al. [16] observed that patients who began taking low molecular weight heparin at 6–8 weeks of pregnancy and continued to take it during the postpartum period had similar outcomes to ours. There were no thrombotic or hemorrhagic problems in the individuals.

CONCLUSION

From our study we concluded that low molecular weight heparin is effective in preventing development of severe preeclampsia in patients with mild preeclampsia on expectant management of this leading to less maternal, fetal and neonatal morbidity and mortality.

Conflict of interest : none

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