# A COMPARATIVE STUDY BETWEEN THE EFFICACY OF NIFEDIPINE AND HYDRALAZINE IN SEVER PREECLAMPSIA IN THE THIRD TRIMESTER OF PREGNANCY & COMPARISON THE PERINATAL OUTCOME IN SULAIMANI MATERNITY TEACHING HOSPITAL

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## ABSTRACT

### *Background*

Preeclampsia is an idiopathic disorder of pregnancy characterized by proteinuric hypertension; hydralazine is an arterial vasodilator antihypertensive drug. Nifedipine is a calcium channel blocker antihypertensive drug.

### *Objective*

To compare the effect of intravenous hydralazine and oral immediate release nifedipine capsule in patients with severe preeclampsia in their 3rd trimester of pregnancy and compare the early perinatal outcome.

### *Material and Methods*

A prospective cohort study set at Slemani Maternity Teaching Hospital, Sulaimani , Iraq, throughout period of January first 2015 to September first 2015. The study includes 50 patients diagnosed with sever preeclampsia (blood pressure ≥ 160/110 mmHg and > 1 gram proteinuria) in the third trimester of pregnancy, who admitted to Emergency Department of Sulaimania Maternity Teaching Hospital from January, first 2015 to September, first 2015. Patients had been divided into two groups, the first 25 patients had received hydralazine and the second 25 patients received nifedipine. The blood pressure and fetal heart rate recorded before and after the treatment, the target blood pressure: Systolic blood pressure < 160 mmHg and diastolic blood pressure < 110 mmHg.

### *Results*

Both drugs were ultimately effective in reaching the therapeutic goal because there were no failures requiring crossover in either study group. Patients received intravenous hydralazine achieved the therapeutic blood pressure more rapidly in (38.0±14.0) minutes (mean±SD) as compared with (51.3±23.9) minutes who received oral immediate release nifedipine. P=0.05. Both drugs had no effect on fetal heart rate but they had many maternal side effects especially with hydralazine which associated with more palpitation than nifedipine (12% versus 8%). In mode of delivery, 72% of women from hydralazine group and 52% of women from nifedipine group their pregnancies are terminated by caesarean section, While 36% of women from nifedipine group and 20% of women from hydralazine group were delivered vaginally.

### *Conclusion*

Both drugs are efficient in controlling the blood pressure in sever preeclampsia and no significant difference in perinatal outcome. Nifedipine needed longer period but less number of doses to reach the goal blood pressure. Because the nifedipine's oral bioavailability and less frequent side effects, it more preferable anti-hypertensive therapy in emergency cases compared to the hydralazine.

**Keywords:** *Nifedipine, Hydralazine, Preeclampsia, Mode of delivery and Neonatal outcome.*

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## INTRODUCTION

Preeclampsia is an idiopathic disorder of pregnancy characterized by proteinuric hypertension [1] . It is a multisystemic disorder usually associated with raised blood pressure and proteinuria after the 20th week of gestation. It is a part of spectrum of conditions known as the hypertensive disorders of pregnancy [2] .

### *Classification*

The International Society for the Study of Hypertensive in Pregnancy (ISSHP), uses the term 'gestational hypertension' to include all women with PIH whether proteinuric or not . Once proteinuria has developed, this is assumed to be preeclampsia [3]. Preeclampsia complicates 3-5% of all pregnancies [1]. Over 63000 women die worldwide each year in developing countries [4]. In the UK, pre-eclampsia is the second commonest cause of both direct maternal death and perinatal loss [5]. In developing nations, the incidence of the disease is reported to be 4-14% [6, 7]. Every year, over four million women develop the disorder all over the world [8].

### Risk factors

1-maternal primiparity [9, 10] age >35 years and <20 years, black race, family history of PE, obesity BMI> 35 Kg/$m^2$ and PE in previous pregnancy.

2-Thrombophilias and Autoimmune disorders, rheumatic disease and SLE [10].

3- Multiple pregnancy, molar gestation and assisted fertilization [10].

4- Pre-existing medical conditions diabetes mellitus, dyslipidemia, chronic hypertension, renal disease and vitamin D deficiency [11].

### *Etiology and pathophysiology*

Pre-eclampsia is called a "disease of theories" because genetic, immunologic, vascular, hormonal, nutritional and behavioral factors have all been proposed as the causes. Placental ischemia or hypoxia appears to be central to the development of the disease [12].

1-The immunological mechanism is known that from early pregnancy. Trophoblastic cell escape into the maternal circulation [13] .

2-Inadequate trophoblastic invasion: the spiral arterioles would have a higher resistance and results in decreased blood flow, and the preeclampsia is attempted to compensate for this [14].

3-Preeclampsia is thought to result from provoked activation and dysfunction of vascular endothelium [15]. Intact endothelium has anticoagulant properties, and endothelial cells blunt, the response of vascular smooth muscle to agonists by releasing nitric oxide [16]. The predominant pathophysiologic finding in preeclampsia and gestational hypertension is maternal vasospasm [17].

### *Diagnosis*

Mild high blood pressure (140-159 mmHg systolic or 90-159 mmHg diastolic measured on two occasions at least four hours apart). High blood pressure greater than or equal to 160 mmHg systolic or greater than or equal to 110 mmHg diastolic is a feature of severe preeclampsia [18]. Preeclampsia can develop before 34 weeks of gestation (early onset), at or after 34 weeks (late onset), during labor or postpartum with different etiologies for early and late onset disease [19, 20, 21].

### *Management*

The optimal management of a woman with preeclampsia depends on gestational age and severity of disease [22]. The only definitive treatment for hypertension in pregnancy is delivery of the fetus [23]. Many maternal and fetal deaths from preeclampsia are associated with substandard care and poor management, proper evaluation of preeclamptic pregnant women arrange adequate treatment at a proper time to ensure the wellbeing of the mother and fetus [24, 25].

### *Hydralazine*

Is a direct acting smooth muscle relaxant used to treat hypertension by acting as a vasodilator primarily, vasodilators act to decrease peripheral resistant [26]. Its mechanism of action by binding to and activating potassium channels on vascular smooth muscle. This prevents calcium-mediated activation and constriction of the smooth muscle, resulting in vasodilatation [27].The plasma half-life of hydralazine is 2 to 4 hours [28]. The most frequent side effects are: decreased uteroplacental perfusion, headache, tachycardia, palpitation and fluid retention [29]. Hydralazine interacts with NSAID; especially indomethacin which may be reduces the antihypertensive effects of hydralazine [30].

About the safety of hydralazine, no reports linking with congenital defects [31]. Neonatal thrombocytopenia and bleeding as intracranial hemorrhage secondary

to hydralazine have been reported in three infants [32]. Hydralazine readily crosses the placenta to the fetus [33].

### *Nifedipine*

It is a calcium channel blocker that used to treat high blood pressure. [34] Nifedipine has been used frequently as a tocolytic agent in premature uterine contractions [35]. About its safety in pregnancy the calcium channel blockers do not represent a major teratogenic risk. [36]. Nifedipine lowers the blood pressure without any apparent reduction in uteroplacental blood flow [37].

### *Perinatal Period*

The perinatal mortality refers to the number of stillbirths and deaths in the first week of life (early neonatal mortality) [38]. Early perinatal assessment had been done by many methods, the easiest one is Apgar Score System, and a normal Apgar score for the 5 minutes should be between 7 and 10 [39]. A low score at 1 minute is near-normal by 5 minutes. The Apgar score is not designed to predict the future health of the child [40].

### *Aim of the Study*

To compare between hydralazine and nifedipine in controlling sever hypertension in pregnancy, from 28 weeks gestational age till full term, identify any adverse effect of both medication on the mother and her baby (fetal and early neonatal) and comparing the effect of both drugs on the mode of delivery.

## PATIENTS AND METHODS

This study is comparative study which compare between effect of parentral hydralazine and oral immediate releasing nifedipine in lowering blood pressure in sever preeclamptic women in 3rd trimester of her pregnancy and to compare the perinatal outcome.

The study was done in Slemani Maternity Teaching Hospital from 1st January 2015 to the 1st September 2015 and the protocol was approved by committee of Obstetrics and Gynecology of the hospital.

The study enrolled 50 pregnant women with preeclampsia, their blood pressure > or equal to 160/110 mmHg with laboratory results shows > 1g proteinuria or two pluses (++) proteinuria who admitted to emergency room, divided into two groups: Group (A) treated with hydralazine and Group (B) treated with nifedipine.

The way of choosing the patient and treatment was done by taking the first 25 sever preeclamptic patients treated with intravenous hydralazine then the last 25 sever preeclamptic patient treated with oral nifedipine.

### *Inclusion criteria were:*

1. Pregnancy more than or equal to 28 weeks with viable fetus with confirmed sever preeclampsia (BP ≥160/110 mmHg and > 2+ proteinuria).

2. No contraindication for hydralazine and nifedipine.

3. Patients with singleton pregnancy.

4. Patients of all ages and parity.

### *Exclusion criteria include:*

1. Patients with cardiovascular disease.

2. Multiple pregnancies.

### *Taking blood pressure*

The mercury sphygmomanometer was used as method of blood pressure measurement. When the blood pressure was talking, the woman was be rested for 15 minutes and ideally sitting at a 45-degree angle or on left lateral position. The device cuff was of appropriate size. Success was defined as lowering the diastolic blood pressure to below 110 mmHg.

The physical examination was done by assessment of blood pressure, fundal height and uterine tenderness, epigastric or right upper quadrant tenderness.

Laboratory evaluation for all patients that included:

1. Quantitative assessment of urinary protein excretion with a dipstick.

2. Complete blood count and coagulation profile.

3. Renal function test.

4. Liver function test.

Gestational age determined by 1st trimester ultrasound. Fetal heart rate was measured by sonicaid.

### *Hydralazine administration: (group A)*

Two methods of administration of hydralazine injection used:-

1) Repeated intravenous injection: hydralazine vial 20 mg was diluted with 4ml of 0.9% sodium chloride solution (5 mg/ml). Bolus of 5 mg by slow intravenous

injection, checking the blood pressure after 15 min. if diastolic blood pressure is still higher than or equal 110mmHg then additional boluses doses 5 mg up to 3 doses until diastolic blood pressure lower than 110 mmHg. Once the diastolic blood pressure become lower than 110 mmHg the patients received:

2) Slow continuous infusion: hydralazine was prepared for intravenous continuous infusion by adding 20 mg of hydralazine to 200 ml of 0.9% sodium chloride. The rate of infusion was doubled at 30 minutes interval until a desired blood pressure was achieved up to 40 mg/hour.

### *Nifedipine administration: (Group B)*

Swallowing the capsule and the dose is 10 mg orally three times daily can be increased to 60 mg/day. Maternal outcome has measured by lowering of systolic blood pressure<160 mmHg and diastolic blood pressure <110 mmHg in scheduled dosage of allocated treatment.

### *Early perinatal Assessment*

Early perinatal assessment can be done by Apgar is a quick test performed on a baby at 1 and 5 minutes after birth [41].

### *Statistical analysis and data management*

The statistical Package for Social Science (SPSS, version 18) was used for data entry and analysis. Chi ($X^2$) square test of association was used to compare proportions of different factors among cases with same proportions among controls. Unpaired and paired student t test, are used to compare means of numerical variables among study groups. P value of < or equal 0.05 was regarded as statistically significant. Line graph used to present the data.

## RESULTS

The randomized fifty patients who diagnosed with PET were divided into two groups, one is Hydralazine group and other is nifedipine group. The groups were similar with respect to gestational age and mean systolic and mean diastolic blood pressure at time of enrollment. In our study we did not face a preeclamptic patient complicated by eclampsia or abruption placenta. Both drugs were ultimately effective in reaching the therapeutic goal because there were no failures requiring crossover in either study group. Table (1)

Patients received intravenous hydralazine achieved the goal therapeutic blood pressure more rapidly in (38.0±14.0) minutes (mean±SD) as compared with (51.3±23.9) minutes who received oral nifedipine (P=0.05). Table (2)

Table (3) shows the side effect of both drugs, in the study hdralazine was associated with more maternal palpitation than nifedipine (12% versus 8%). Just one patient from hydralazine group developed blurred vision while this side effect was not associated with nifedipine.

Table (4) shows the mean Apgar score in babies of patients received both drugs.

Table (5) shows the mode of delivery. 72% of women from hydralazine group and 52% of women from nifedipine group their pregnancies are terminated by caesarean section, While 36% of women from nifedipine group and 20% of women from hydralazine group were delivered vaginally. Other patients were discharged after controlling their blood pressure with normal Doppler study. Most of them had gestational age between 28-32 weeks. Five patients from hydralazine group their pregnancies are terminated by emergency caesarean section because of abnormal Doppler results after administration of the drug. Six patients were primigravida with preeclampsia, four patients the caesarean section was done because of failure of induction of labor. Two patients were had previous one scar in early labor with meconium stained liquor, the induction of labor was used for three patients.

In nifedipine group, four patients were delivered by caesarian section because of confirmed hellp syndrome, three patients due to failure of induction of labor, five patients were delivered by spontaneous vaginal delivery, while four patients were delivered by induction of labor.

**Table 1. The effect of both drugs on maternal blood pressure.**

| Drug group | | Mean | Std. Deviation | Difference in mean | P value |
|---|---|---|---|---|---|
| Hydralazine | SBP Before Rx | 171.6667 | 13.91683 | -28.5 | <0.05 |
| | SBP After Rx | 143.1667 | 18.40555 | | |
| | DBP Before Rx | 113 | 10.87547 | -26.6 | <0.05 |
| | DBP After Rx | 86.3333 | 9.37102 | | |
| Nifedipine | SBP before Rx | 169 | 10.9387 | -24.3 | <0.05 |
| | SBP After Rx | 144.6667 | 8.19307 | | |
| | DBP Before RX | 110.3333 | 3.19842 | -25.3 | <0.05 |
| | DBP After Rx | 85 | 6.82288 | | |

P value < 0.05 means statistically significant

**Table 2. The time of both drugs required to reach the goal blood pressure.**

| Group Statistics | Hydralazine | | Nifedipine | | P value |
|---|---|---|---|---|---|
| | Mean | Std. Deviation | Mean | Std. deviation | |
| Time in minutes | 38.0 | 14.2 | 51.3 | 23.9 | <0.05 S |

**Table 3. Side effects of both drugs.**

| Side effects | | Drugs | | Total of side effects |
|---|---|---|---|---|
| | | Hydralazine | Nifedipine | |
| Palipitation | No. | 3/25 | 2/25 | 5/50 |
| | Percent | 12% | 8% | 10% |
| Headache | No. | 2/25 | 4/25 | 6/50 |
| | Percent | 8% | 16% | 12% |
| Nausea and vomitting | No. | 1/25 | 1/25 | 2/50 |
| | Percent | 4% | 4% | 4% |
| Flushing | No. | 2/25 | 1/25 | 3/50 |
| | Percent | 8% | 4% | 6% |
| Blurred vision | No. | 1/25 | 0/25 | 1/50 |
| | Percent | 4% | 0% | 2% |
| Dizziness | No. | 1/25 | 1/25 | 2/50 |
| | Percent | 4% | 4% | 4% |

**Table 4. Apgar score as an indicator of early perinatal outcome in patients received both drugs.**

| Gestational Age | Drug group | N | Percentage | Apgar score of 5 minutes | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| 28 weeks-32 weeks | Hydralazine | 8 | 33% | 4.7 | 0.68 | >0.05 NS |
| | Nifedipine | 4 | 19% | 5.4 | 0.4 | |
| 32+weeks-36 weeks | Hydralazine | 9 | 37% | 6.4 | 0.54 | >0.05 NS |
| | Nifedipine | 10 | 40% | 7.1 | 0.64 | |
| 36+weeks-40 weeks | Hydralazine | 7 | 29% | 7.2 | 0.1 | >0.05 NS |
| | Nifedipine | 7 | 33% | 7.6 | 0.13 | |

**Table 5. Mode of delivery.**

| Characteristic | | Drug group | |
|---|---|---|---|
| | | Hydralazine | Nifedipine |
| CS | No. | 18 | 13 |
| | Percent | 72% | 52% |
| NVD | No. | 5 | 9 |
| | Percent | 20% | 36% |

## DISCUSSION

Even in developed countries, women still die from preeclampsia and eclampsia [2]. In this study both drugs were ultimately effective in reaching the therapeutic goal, which agree with Rezaei Z, Sharbaf FR,and their colleagues in 2011 which included fifty hypertensive pregnant women were enrolled in the study [42] and they found that nifedipine and hydralazine are safe and effective antihypertensive drugs, The good oral bioavailability and less frequent side effects of nifedipine made it more preferable in hypertension emergencies.

Our results disagree with Aali BS and Nejad SS.(2002) which was conducted on One hundred and twenty-six preeclamptic patients, they found that nifedipine is safe and more effective than hydralazine in controlling blood pressure in severe pre-eclampsia. It has the advantage of being cheaper and easily administered [43].

In our results, patients received intravenous hydralazine achieved the goal therapeutic blood pressure more rapidly in 38±14.0 minutes (mean±SD) as compared with 51.3±23.9 minutes in those received oral nifedipine (p=0.05). Only Mabi and colleagues (1993) found that the duration of action is varied in hydralazine group, with shortest duration occurring in those patients who required the highest dosage for blood pressure control [44], which disagree with our study.

In the results we found that nifedipine produced a smooth progressive fall in diastolic blood pressure to normal levels but with longer time than did hydralazine, which agree with LIU Qian-qian china and his colleagues to assess the efficacy, side effects and perinatal outcome of treated patients [45].

In the results there is no significant difference in fetal heart rate after treatment by both drugs, which

agree with Dr. L. A. Magee M.Sc.M.D and colleagues (2004) [46] but disagree with Patricia Smith Consultant (Obstetrics) and colleagues (2000) that found nifedipine was associated with more neonatal bradycardia than hydralazine [47].

In this study, hydralazine was associated with more maternal palpitation than nifedipine (12% versus 8%). Just one patient from hydralazine group developed blurred vision while this side effect was not associated with nifedipine.The results agree with Committee Opinions/Emergent Therapy for Acute-Onset, Severe Hypertension during Pregnancy and the Postpartum Period of ACOG in February 2015 [48].

### *Conclusion*

Both drugs are efficient in controlling the blood pressure in sever preeclampsia and no significant difference in perinatal outcome. Although Nifedipine needed longer period but same number of doses to reach the goal blood pressure. But because of its oral bioavailability and less frequent side effects, it looks more preferable anti-hypertensive therapy in hypertensive emergences of pregnancy compared to the Hydralazine.

### *Recommendation*

Oral immediate release nifedipine can be used to treat acute hypertension in pregnancy as alternative drug if hydralazine not present because it has the same efficacy, less side effect and does not affect the process of vaginal delivery, also we need another study to identify the post delivery complications and late neonatal outcome to see these drugs how can affect the mother and her baby in puerperal period.

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