COMPARISON OF HYDRALAZINE AND NIFEDIPINE FOR SEVERE HYPERTENSION IN PREGNANCY

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ABSTRACT:

OBJECTIVE: To compare efficacy and safety of Hydralazine and Nifedipine in management of hypertension in pregnancy.
STUDY DESIGN: A Randomized control trial.
PLACE AND DURATION: Mother and Child Health Unit II, PIMS, Islamabad, from 1st January 2007 to 1st July 2007.
METHODOLOGY: Sixty patients of hypertension beyond 28 weeks of gestation were recruited for study after informed consent. The registered subjects were randomly allocated to Hydralazine group and Nifedipine group by using random number table. Blood pressure was checked in supine position on right arm before initiating treatment and thereafter checked at ½ hour, 1 hour, 1½ hour and 2 hours. Patients were observed for side effects of drugs.
RESULTS: The mean initial Blood pressure was 170/113 mmHg. Time for effective control of systolic BP was 1 hour in Nifedipine group and 1 ½ in Hydralazine group. Time taken for control of diastolic BP was same in both groups i.e. 1 hour. The mean prolongation of pregnancy was 4.5 days in Nifedipine group and 2 days in Hydralazine group with a significant difference of p value .02. Fewer doses were required in Nifedipine group. Hydralazine was more associated with palpitation (56%), flushing (56%), persistent Hypertension (HTN) (16.7%) and tachycardia > 110 bpm (20%). There was no significant difference in other variables measuring fetomaternal outcome except that Nifedipine caused headache in 73% patients after drug administration.
CONCLUSION: Nifedipine is more effective for control of Hypertension (HTN) in pregnancy.
KEY WORDS: Hypertension, Preeclampsia, Hydralazine, Nifedipine, Pregnancy.

INTRODUCTION

Hypertensive disorder of pregnancy constitutes the commonest but potential life threatening medical disorder diagnosed by obstetricians in clinical practice[1-3]. Reports into fetomaternal mortality have shown excess maternal and perinatal mortality associated with it[4-6]. Clinical course of Gestational hypertension is progressive with continuous deterioration that ultimately stop only by delivery. Early recognition and quick control of blood pressure is central to patient cure.[1] In the latest report from the Centre for Maternal and Child Enquiries (CMACE) in the UK, it was identified that failure to treat sustained severe hypertension is the most common cause of substandard care and death in women with pre-eclampsia[7].

Gestational hypertension is multifactorial condition secondary to abnormal placentation. The most common physical presentation is hypertension indicating systemic vasoconstriction secondary to widespread vascular endothelial dysfunction[1], other sign and symptoms are headache, visual disturbances and epigastric pain according to systemic involvement[1,8]. Patients of severe Preeclampsia may suffer from serious complications like convulsions, cerebrovascular accident and coagulopathy etc. [9] Worsening lab reports indicate severity of disease[10]. Still in recent years intracerebral haemorrhage contributes to 37% death, indicating suboptimal control of BP through poor monitoring and treatment[11]. A MAP of 140mmHg, that occurs at BP of 180/120mmHg is considered as a threshold for arterial damage, when it is crossed it result in loss of vascular auto-regulation with increased risk of cerebral haemorrhage [12].

Many emergency antihypertensive drugs are being used in different centres of world to control acute rise in B.P. Common agents are Hydralazine, Nifedipine and Labetalol[1,13].

Hydralazine is being used as an acute antihypertensive drug for > 40 years[14]. It is vasodilator mainly affect resistance vasculature (arterioles)[15,16]. Its side effects are headache, palpitation, flushing and vomiting and it is contraindicated with severe tachycardia, liver and heart failure.

Nifedipine is potent coronary and peripheral arterial vasodilator[15]. It is a calcium channel blocker. It is widely available and cheaper drug. It is given orally so its administration is easy[17,18]. Its sublingual route can cause fetal hypoxia but oral route gives good control of severe hypertension[19].Its concomitant use with magnesium sulphate (MgSO4) can result in neuromuscular weakness[20]. It can cause headache, tachycardia, flushing and constipation[21]

The 2010 UK National Institute for Health and Clinical Excellence (NICE), Hypertension in Pregnancy guideline recommended oral labetalol or Nifedipine for the treatment of severe hypertension in women during pregnancy or after birth.

Labetalol is adrenergic blocking agent. It has been extensively

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used in pregnancy and has favourable side effect profile however specific concerns have been raised about its association with neonatal bradycardia [22].

Multiple randomised controlled trials for the treatment of severe HTN are being conducted in different centres of world showing heterogeneous results of drugs in specific population of patients. In Cochrane database review no anti-hypertensive drug has been proven better than other[23]. The result of different trials has generated an uncertainty about the agent of first choice for severe hypertension[20].

We conducted this study to compare efficacy and safety of Hydralazine and Nifedipine in management of hypertension in pregnancy. There is paucity of prospective studies on the subject in our country therefore, to know the effectiveness and fetomaternal safety profile of Hydralazine in our setup, we decided to compare it with Nifedipine that is cheap, freely available and commonly used antihypertensive agent.

METHODOLOGY

This Randomized control trial was conducted in, Mother and Child Health Unit II, PIMS Islamabad over a period of six months from 1st January 2007 to 1st July 2007. Non probability convenience sampling was employed to select 60 patients of severe hypertension in pregnancy. These patients were divided in two groups comprising of 30 members in group A and B respectively. Pregnant patients admitted with BP > 160/110 mmHg beyond 28 weeks of gestation were recruited for study in high dependency area of labour ward. Informed consent was taken after explaining the procedure, pros and cons of study. Patients who had history of heart failure, coronary heart disease, renal disease, and severe tachycardia were excluded.

The patients were randomly allocated to Hydralazine Group-B and Nifedipine Group-A. Detailed history about headache, vomiting, visual complaints and epigastric pain was taken along with examination. Fetal cardiotocography was done. Among investigations urine R/E, complete blood picture, SGOT, PT (Prothrombin time), APTT (activated partial thromboplastin time), Uric acid and serum creatinine were sent according to need and severity of patient. Blood pressure was checked in supine position on right arm with standard mercury sphygmomanometer before initiating treatment and thereafter it was checked at ½ hour, 1 hour, 1½ hour and 2 hours

Tablet Nifedipine 10 mg per oral was given to Group A, with a sip of water. It was repeated after half an hour if diastolic blood pressure was still > 100 mmHg and followed by 20 mg tablet Nifedipine 12 hourly for 24 hours.

Injection Hydralazine 5 mg was given over 10 minutes to Group B and was repeated after half an hour until diastolic B.P was 90-100 mmHg. Patients were put on 20-40 mg tablet hydralazine in divided doses for 24 hours.

Patients were observed for side effects after giving drug. Fetal cardiotocography was done after an hour of giving drug and repeated if needed. Patients were followed till delivery to see prolongation of pregnancy. Efficacy was taken as early drop in systolic BP of 20 mmHg and early drop in diastolic B.P to 90-100 mmHg. Time taken for effective control of B.P (½ hour -2 hour) was seen. Maternal outcome measures considered for safety after drug administration were hypotension, placental abruption, $mgso_4$ given, palpitation, flushing, epigastric pain, tachycardia >110 bpm, vomiting and persistent hypertension. Data was entered on pre designed proforma. Induction of labour and delivery of fetus was done as per obstetric indications. Neonatal assessment was done by looking at Apgar score at one minute for fetal outcome.

Descriptive statistics were calculated. Mean ± S.D was calculated for all quantitative variables like maternal age, gestational age, presenting B.P and pulse. Frequency and percentages were presented for gravidity, hypotension, abruption, need of caesarean section due to fetal distress, need of $MgSO_4$, headache, vomiting palpitation, flushing, epigastric pain, non-reassuring CTG and for persistent HTN. Independent sample t-test was used to compare efficacy of both drugs at different time periods and to compare prolongation of pregnancy with both drugs. Chi-square test was used to compare presenting complaints, parity and complications between both groups. P value of ≤ .05 was considered statistically significant.

RESULTS

A total of sixty patients with hypertension were enrolled in this study. The demographic features of both groups were similar. Mean age was 27.2 years in both groups with minimum age of 18 years and maximum age was 36 years**.** Mean gestational age was 36.2 weeks in Hydralazine group and in 36. 6 weeks in Nifedipine group. Relation to parity shows that maximum numbers of patient (Total 35, 58.3%) were primigravidas in both groups (P value .432). This signifies that disease with its associated morbidity is more common in first pregnancy. Mean presenting BP was 169/113mmhg in hydralazine group and 171/113 mmHg in nifedipine group. (Table -I).

Effective control of systolic BP was achieved earlier in nifedipine arm of study. After ½ hour of administration of drug systolic BP was reduced in both groups but not to required level. But one hour after administration of drug, mean drop in systolic B.P was more in nifedipine group (25mmHg) that is significantly different from hydralazine group (p value .04), that was unable to drop systolic B.P by 20 mmHg. Even after 1 ½, nifedipine brought more drop in systolic B.P with a mean of 28.8 mmHg while in hydralazine group mean drop in systolic B.P was 25.6 mmHg. Thus data analysis shows that mean time taken for effective control of systolic B.P was 1 ½ hour in hydralazine group and 1 hour in nifedipine group. (Table - II).

With regard to diastolic B.P, both drugs were unable to control diastolic B.P ½ an hour after drug administration. But after 1 hour, diastolic B.P was controlled in both groups with no significant difference of p value (0.273). Mean value of diastolic B.P for hydralazine was 97mmHg and for nifedipine it was 95 mmHg. Thus both drugs required same time span for bringing diastolic B.P to 90-100 mmHg. This signifies that efficacy of hydralazine and nifedipine for controlling diastolic B.P is same. (Table - III).

Data analysis indicates significantly fewer drug administrations

in nifedipine arm of study. In nifedipine group two doses (each of 10 mg) were sufficient in 50 % patients to control BP while in hydralazine group only 20 % patients received 2 doses (each 5 mg) for B.P control**.** (Table - IV)

Nifedipine helped to prolong pregnancy by mean of 4.5 days with significant difference (p value .02) from hydralazine group where mean prolongation of pregnancy was 2 days**.** Regarding side effects, hydralazine was associated with more maternal palpitations (56%), flushing (56%) and maternal tachycardia > i.e. 110 bpm in (20%) patients when compared to Nifedipine with significant p value of .000 and .04 respectively. Nifedipine was associated with headache after administration of drug in (73%) patients with significant difference from Hydralazine group, p value 0.018, as in hydralazine group only (43%) patients had headache after course of drug completion. Regarding other variables like hypotension, placental abruption, need for Lower segment cesarean section (LSCS) for fetal distress and need for magnesium sulphate there was no significant difference found in p values. As per fetal concerns no significant difference was noticed in the variables measuring fetal outcome that were Apgar score <7 and non-reassuring CTG (p value 0.60 and 0.598 respectively). (Table - V).

Hydralazine was different from nifedipine in an impact on persistent HTN. Nifedipine was associated with a trend towards lower rate of persistent hypertension (6.7%) while in Hydralazine group 16.7% patients had their diastolic BP persistently higher above 100 mmHg and 3.3% patients have diastolic BP of 105 mmHg after complete course of drug administration. (Figure-1).

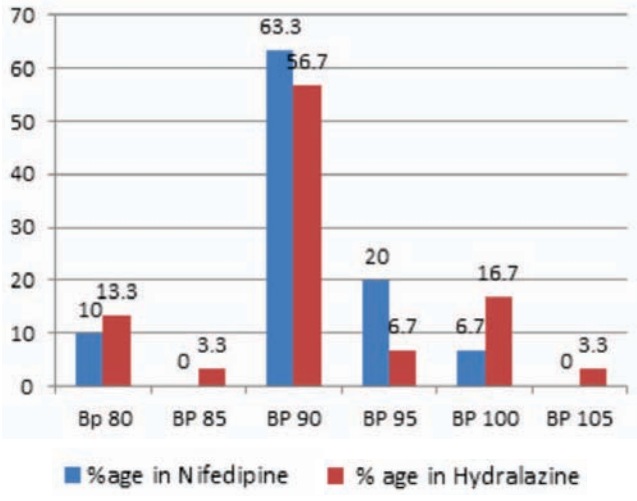

FIG - 1: % AGE OF PATIENTS IN BOTH GROUPS 100 mmHg) IN EACH GROUP, (N=30)

TABLE-I: DEMOGRAPHIC DATA OF STUDY PATIENTS (N=60)

Variables	Nifedipine n= 30	Hydralazine n=30
Age (years)) ± S.D	27.7 ± 4.2	27 ± 4.2
Gestational age (weeks ± S.D)	35.6 ± 3.1	36.2 ± 2.6
Systolic BP at presentation	171±13.9	169±13.67
Diastolic BP at presentation	113±5.7	113±9.4
Primigravida	16(53%)	19(63%)
multigravida	14	11

Parity of patients (Primigravida 35) P – value = .432

TABLE-II: CONTROL OF SYSTOLIC BLOOD PRESSURE AFTER INTERVENTION IN BOTH GROUP (EFFICACY) (N=60)

TIME	Mean drop in systolic blood pressure mmHg ± S.D Nifedipine group n = 30	Mean drop in systolic blood pressure mmHg ± S.D Hydralazine group n =30	P value
After 1/2 hour	16.8 ± 7.7	13.6 ±10.9	.199
After 1 hour	25.5 ± 12.0	19.1 ± 11.6	.043*
After I ½ hour	28.8 ± 10.5	25.6 ± 10.9	.259
After 2 hour	34.6 ±12.7	32.1 ± 10.2	.40

* P – value significant at 5% level of significance

TABLE-III: CONTROL OF DIASTOLIC BP AFTER INTERVENTION IN BOTH GROUP (EFFICACY) (N=60)

Diastolic blood pressure mmHg ±S.D	Nifedipine group n =30	Hydralazine group n =30	P value
After1/2 hour	101 ± 6.4	101.3 ± 6.0	.837
After 1 hour	95 ± 5.3	97 ± 5.19	.273
After 1 ½ hour	91 ± 3.1	93 ± 6.0	.115

TABLE-IV: DOSES OF HYDRALAZINE AND NIFEDIPINE REQUIRED, IN EACH GROUP (N=30)

Name of Drug	No. of doses	No. of patients	Percentage %
Nifedipine	1	8	26.7
	2	15	50.0
	3	5	16.7
	4	2	6.7
Hydralazine	1	6	20.0
	2	6	20.0
	3	9	30.0
	4	9	30.0

TABLE-V: FETOMATERNAL OUTCOMES FOR SAFETY AND PROLONGATION OF PREGNANCY (N = 60)

Variables	Nifedipine group n=30	Hydralazine group n= 30	P value
Hypotension	4 (13.3%)	5 (16.7%)	.718
Headache after drug administration	22 (73.3%)	13 (43.3%)	.018*
Palpitation	2 (6.7%)	17 (56.7%)	.00*
Flushing	2 (6.7%)	17 (56.7%)	.00*
Tachycardia >110 bpm	1 (3.3%)	6 (20%)	.044*
Vomiting after drug administration	3 (10%)	2 (6.7%)	.640
Epigastric pain after drug administration	2 (6.7%)	1 (3.3%)	.554
Persistent HTN	2 (6.7%)	6 (20%)	
Placental abruption	1 (3.3%)	2 (6.7%)	.554
LSCS	4 (13.3%)	4 (13.3%)	1
MgSO4 given	9 (30%)	10 (33.3%)	.781
Non reassuring CTG	11 (36.7%)	13 (43.3%)	.598
Apgar score	12 (40%)	14 (46.7%)	.602
Prolongation of pregnancy in days	4.5	2.1	.020

* P - value significant at 5% level of significance.

DISCUSSION

Gestational HTN is disease of primigravidas[24], as seen in our study; most patients were primigravidas (58.3%). This is in consistence with the study of Brosens I[25]. In our study the eeffective control of BP was achieved in both groups but systolic BP was controlled more rapidly by nifedipine than hydralazine and with fewer doses required. This is in accordance with the study by Aali BS in Iran in 2002[17]. Oral nifedipine was also found to lower blood pressure more quickly in a RCT in 2013 by shekhars[26].In a prospective study by Begum et al hydralazine bolus injection took mean time of 65.23+/-23.38 minutes to drop diastolic BP to 90-95 mmHg[27]. In our study hydralazine took 60 minutes to drop diastolic BP to 90mmHg and 90 minutes for dropping systolic BP by 20 mmHg.

The BP lowering effect of hydralazine is unpredictable for timing and magnitude, sometimes patient even does not respond to hydralazine with resultant persistent HTN as seen in an RCT by Cham C[20]. This corresponds to results of our study where 20% patients had their BP persistently above 100 mmHg despite 4 doses of hydralazine. In our study nifedipine was associated with lower rate of persistent severe hypertension as compared with hydralazine as same as it is seen in Cochrane Database Syst Rev. 2013, that women who were allocated calcium channel blockers were less likely to have persistent high blood pressure compared to those allocated hydralazine[28].

Hydralazine and nifedipine both drugs may cause hypotension during treatment course. As seen in randomized trials by Magee et al, hydralazine in continuous infusion is associated with more episodes of hypotension.[29] In our study 16.7% patient had hypotension in hydralazine group. R Clfkova does not recommend hydralazine as a first therapy of choice because of its association with multiple side effects[30]. A Meta analysis by Magee LA supports the use of antihypertensive drugs other than hydralazine for management of severe HTN[20]. In a study by Maharaj B, hydralazine was associated with significant rise in heart rate[31]. Gracia et al also noticed that palpitation and tachycardia are more frequently associated with hydralazine[32]. The results of our study for these variables correspond well to the findings of these studies. Thus our study shows that Nifedipine is safe and efficacious for controlling severe hypertension this is in accordance with meta-analysis done by Shekhar S [13]Moretti et al has not reported any side effects associated with nifedipine[33]. On the contrary, in our study nifedipine was associated with headache in 73.3% patients.

Fenakel K et al compared nifedipine and hydralazine and found that both drugs result in prolongation of pregnancy, but in their study difference between both drugs was not statistically significant[34]. This is in accordance to our study where both drugs also resulted in prolongation of pregnancy but our results are however at variance to this study in the respect that in our study the difference in prolongation of pregnancy was significant (P value .02) in the favour of nifedipine which resulted in more prolongation of pregnancy with a mean of 4.5 days when

compared to hydralazine group.

Based on RCTs in pregnancy and postpartum, T Firoz, LA Magee found that Nifedipine is a reasonable agent for control of severe hypertension with high success rates when compared with parenteral Hydralazine or labetalol [7] this is in accordance with our study. In some studies its concomitant use with magnesium sulphate is associated with more neuromuscular weakness and respiratory arrest[1, 23]. Use of nifedipine can also result in postpartum haemorrhage. These observations were not made in our study.

The results of our study show that Hydralazine is less efficient than nifedipine in control of systolic B.P and it results in persistent hypertension in some patients. It was associated with multiple maternal side effects like palpitation, flushing and tachycardia. While Nifedipine seems to be a good and rapid agent for control of hypertension along it was associated with fewer side effects and it also helped in prolongation of pregnancy more than hydralazine. Considering these facts, Nifedipine can be considered a safe, efficacious and easily administrable drug in patients of hypertension in pregnancy.

CONCLUSION

Nifedipine is more effective for control of hypertension in pregnancy.

Contribution of Author:

Jaweria Faisal: Literature review, planned study, conducted research and wrote article.
Zeba Munzar: Literature review and Introduction writing.
Tooba Riaz: Abstract writing and statistics.
Nusrat Junjua: Literature review and Discussion writing.

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