"COMPARISON OF EFFICACY OF ORAL NEFIDIPINE VS. INTRAVENOUS HYDRALAZINE IN SEVERE PREECLAMPTIC PATIENTS"

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ABSTRACT

BACKGROUND: To compare the efficacy of oral Nifedipine vs. intravenous hydralazine in severe preeclamptic patients at Obstetrics and Gynecology department, Khyber Teaching Hospital, Peshawar

METHODS: This study was conducted in the in the Department of obstetrics & gynecology, Khyber Teaching Hospital Peshawar from 09th May 2015 to 9th November,2015. Through a randomized controlled trial Study Design, a total of 254 patients presenting with severe pre-eclampsia were randomly allocated in group of two, the group A patients were exposed to nifedipine while patients in group B were subjected to IV hydralazine. Total sample size was 254 (127 in each group) patients calculated from fall of BP in hydralazine and nifedipine group 6.7 and 16.7% respectively. Moreover, it was a Randomized controlled trial in which consecutive technique of sampling was used.

RESULTS: A total of 254 women presenting with severe preeclampsia were included in our analysis. The group A patient mean age was 27.63 + 5.72 years while in B group was 27.51 + 5.7 years. These patients allocation was done in two groups each having 127 patients. In our study, we either received patients with multiparty (parity 1-5) or grand multiparty (parity greater than 5). We had 92.9% multiparous in A group and 91.3% multiparous in B group.
On applying the operational definition of efficacy, we observed that 40.2% A group pateients (Nefidipine Group) and 26.8% B group patients (Hydralazine Group) were found to have lowered BP to suffice its definition. Statistically significant difference (p =0.025)was observed by applying chi square test.

CONCLUSION: Our data confirmed that Oral Nifedipine is highly effective than intravenous hydralazine in the treatment of severe pre-eclampsia. Our study proved that the mean systolic blood pressure after oral nifedipine was lower than intravenous hydralazine for effective blood pressure control in hypertensive disorders of pregnancy. Since our study didn't focus on the adverse effects of these two drugs, we recommend more randomized controlled trials taking into account the safety of these drugs in addition to their efficacy so that future recommendations may be posted for the routine use of best efficacious and safe drug.

KEY WORDS: Preeclampsia, nifedipine, hydralazine, hypertensive disorders of pregnancy

INTRODUCTION

Increased maternal and fetal mortality and morbidity is correlated with hypertension in pregnancy. Hypertensive disorders have made complication in almost 8 % of total spregnancies.1 Mother and fetus are highly affected due to complication of unrestrained high blood pressure during pregnancy and they affect multiple organ system. Maternal problems of preeclampsia comprise of HELLP syndrome, DIC, acute renal failure, pulmonary edema, liver hemorrhage, stroke, placental abruption and seizure activity. To prevent the progression of the condition the early detection of the pregnancy-induced hypertension and preeclampsia play a vital role. But however the hypertensive disorders have slightly different level of stages among several organizations during pregnancy. In lowering of maternal blood pressure the efficacy of hydralazine was found to be less as compared to nifidipine.2 Additional evaluation is required to find out other sign and symptoms that may show hypertensive disorders during pregnancy. Other sign and symptoms that may be related to blood pressure increase include epigastric pain, sudden swelling of feet, face and hands, persistent severe headache, vomiting, and changes in vision. Decrease in platelets, increased liver enzymes and high level of creatinine may be caused by preeclampsia. 3

Since 1950 hydralazine is used for the medication of hypertension and it is considered to be one of the first oral antihypertensive agent. It is basically pthalazine derivative with a hydrazine moiety at the position 1 of the ring. Other antihypertensive agents like beta blockers and diuretics has also been used in combination with hydralazine. Pharmacological effects of hydralazine like reflex tachycardia and fluid retention are the main reasons behind their use in combination with others antihypertensive agents. 4

In treatment of hypertensive problems during pregnancy, different agents like labetalol, methyldopa, hydralazine, nefedipine, and nicardipine may have a role but it is difficult for practitioner to determine that which agent will be used in first line. No guidelines are available for the

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first line treatment and the practice varies depending upon the stage of gestation, severity of the disease, region and fetal and maternal status.5According to a study in 2013 by Saira et al, in which two patients (6.7%) of hydralazine group and five patient (16.7%) of nefedipine group (p=0.22) were observed to have sudden fall of blood pressure. 6According to another study in 2011, Oral nifedipine was required with less frequent doses compared to intravenous hydralazine. No episodes of hypotension were there after hydralazine and one after nefedipine.7

While there are many antihypertensive agents, To solve the problem that whether antihypertension treatment in mild-to-moderate hypertension in pregnancy is beneficial than risk for mother and fetus, to establish the BP levels for the beginning of treatment and to specify drugs, large randomized controlled study is needed to be done. This study will help us in establishing which drug is better and efficacious in controlling hypertension in preeclamptic patients.

MATERIALS AND METHODS

This study was done at Obstetrics and Gynecology department, Khyber Teaching Hospital, Peshawar. Study duration was 6 months. (from 09th May 2015 to 9th November,2015.). Through a Randomized controlled study design, Consecutive (non probability sampling) 254 patients were included in the study that were divided further into two groups. (127 patients in each group.)

All pregnant patients with systolic blood pressure of more than 160 mm of Hg and a diastolic blood pressure of more than 110 mm of Hg on two occasions four hours apart after 20 weeks of gestation with proteinuria in reproductive age group i.e. 18-45 yrs. of age were included in the study. However, women presented with Chronic hypertension, Heart diseases including IHD or History of intolerance/hypersensitive to nefidipine/hydralazine were excluded in order to reduce confounders and bias in my study results.

The hospital research and ethical board approved our study before conduction. All women meeting the inclusion criteria and presenting to the department with hypertension of pregnancy requiring medical intervention was invited to participate in the study and was admitted for further management. The study purpose was explained to all women and signed a written consent. All women were given the suggested dose of hydralazine and nefidipine as per ACOG guidelines, under supervision of an expert obstetrician fellow of CPSP. Patient was randomized in to two group one group is nefidipine and other is hydralazine's group. Maternal monitoring will include a record of pulse rate, respiratory rate, blood pressure and urine output every 3 hours till the target BP is reached and thereafter for 24 hours. Fetal monitoring was done using fetal heart rate [FHR]. If there is no resurgence, BP was recorded hourly till delivery and 8th hourly for 24 hours' post-partum.

In the event of non-reassuring fetal or maternal status, cross over therapy was initiated or expelled delivery instituted according to the treating clinician in accordance to the protocol followed in our institute.

All above mentioned information was recorded and proforma was designed.. In order to control the bias in the study strict criteria for exclusion was followed.

The data was entered and analyzed using SPSS version 10.0. Categorical variable like efficacy was described in terms of frequencies and percentages. Quantitative variables like age, parity, gravidity. On arrival Blood Pressure and urine albumin was described as mean standard deviation. All results were presented in tables and diagrams.

Chi square test was applied to compare the efficacy of both drugs keeping p-value 0.05 as significant. Efficacy was stratified among age parity and BP on arrival. Post stratification chi square test was applied taking p value 0.05 as significant.

RESULTS

The study comprised a total of 254 pregnant women diagnosed with severe preeclampsia according to operational definitions. Lottery method was used for the random allocation of the patient into groups. Group A patient were subjected to nifedipine and to hydralazine B group patient were subjected.

The mean age of patients in group A was 27.63 + 5.72 years while in group B it was 27.51 + 5.7 years. We also divided the age into four different categories i.e. up to 25.00 years. 25.01 to 30.00 years, 30.01 to 35.00 years and 35.01 year & above.

In our study, we either received patients with multiparty (parity 1-5) or grand multiparty (parity greater than 5). We had 92.9% multiparous in group A and 91.3% multiparous in group B.

The mean systolic blood pressure on arrival was 186.29 + 11.55mmHg in group A and while it was 188.28 + 21.05mmHg in group B. Statistical insignificant difference (p=0.353) was observed by applying independent sample T test. The mean diastolic blood pressure on arrival was 117.18 + 4.26mmHg in group A and while it was 118.25 + 3.89mmHg in group B. A p value of 0.009 was observed after applying independent sample T test which is statistically insignificant.

We also took 24-hour urinary albumin excretion among all women and expressed it in terms of either 3+ or 4+ according to laboratory reports. In our study, 67.7% of women were having 3+ urinary albumin in group A while it was 63% in group B. No statistically significant difference was observed by using chi square test (p=0.429) (Table 1)

TABLE NO: 1: 24 HOUR URINARY ALBUMIN EXCRETION IN BOTH GROUPS (n=127 in each group)

24 hour urinary protein * Group of Patient Cross tabulation

			Group of Patient		Total
			Nifedipine Group	Hydralazine Group	
24 hour urinary protein	3 +	Count	86	80	166
		% within Group of Patient	67.7 %	63.0 %	65.4%
	4 +	Count	41	47	88
		% within Group of Patient	32.3 %	37.0 %	34.6%
Total		Count	127	127	254
		% within Group of Patient	100.0 %	100.0%	100.0%

P Value: 0.429

All the patients were subjected to the dose and duration of drug according to international guidelines and as per allocation of their groups. All patients were carefully followed up to determine the follow up systolic blood pressure and to measure efficacy of the drug.
We applied paired T test to determine the significance of drop in systolic blood pressure from baseline to follow up in the individual groups. In group A, the mean follow up systolic blood pressure was 161.88 + 15.27mmHg. The difference between baseline and follow up systolic BP with a p value of 0.000 was significant statistically after paired T test was applied.
In group B, the mean follow up systolic blood pressure was 167.4 + 17.23mmHg. The difference between baseline and follow up systolic BP was significant statistically (p=0.000) after paired T test was applied.
ON follow up, the mean systolic BP in group A was 161.88 + 15.27mmHg while in group B it was 167.4 + 17.23mmHg. A statistically significant difference (p=0.007) was observed after student T test was applied. (Table 2)

TABLE NO: 2:
COMPARISON OF MEAN FOLLOW UP SYSTOLIC BLOOD PRESSURE IN BOTH GROUPS (n=127 in each group)

Group Statistics

	Group of Patient	N	Mean	Std. Deviation	Std. Error Mean
BP on Follow up	Nifedipine Group	127	161.8898	15.27433	1.35538
	Hydralazine Group	127	167.4016	17.23841	1.52966

P Value: 0.007

On applying the operational definition of efficacy, we observed that 40.2% patients in group A and 26.8% patients in group B were found to have lowered BP to suffice its definition. On applying Chi square test, statistically significant difference (p=0.025) was observed. (Table 3). We stratified the efficacy in either groups with regards to age categories, parity and categories for BP on presentation.

TABLE NO: 3: COMPARITIVE EFFICACY BETWEEN BOTH GROUPS (n=127 in each group)

Group of Patient * Efficacy Cross tabulation

			Efficacy		Total
			Yes	No	
Group of Patient	Nifedipine Group	Count	51	76	127
		% within Group of Patient	40.2%	59.8%	100.0%
	Hydralazine Group	Count	34	93	127
		% within Group of Patient	26.8%	73.2%	100.0%
Total		Count	85	169	254
		% within Group of Patient	33.5%	66.5%	100.0%

P Value: 0.024

DISCUSSION

The leading cause of the maternal and fetal mortality and mortality is hypertensive conditions that constitute about 12-22% of all pregnancies. In some cases it has association with proteinuria which is a multisystem problem and is also called preeclampsia which cause severe concerns if not diagnosed and managed timely. In order to save mothers and babies and to decrease the adverse outcomes from this multi-organ disease, the vital requirements including improved community health education, obstetrical facilities and parental care are needed

Protocol determined management are required for the cases of hyper-tension of greater than 160/110 mm of Hg and also required for hypertension with other complications like epigastric pain, visual disturbance and headache.

Development of hypertension, proteinuria or both characterize the pre-eclampsia in women after 20 week of pregnancy with a previous history of normal BP. 3-5% of the first pregnancies and 1% of the subsequent pregnancies are complicated by Pre-eclampsia.8 eclampsia that is characterized by generalized tonic-clonic convulsions that develop with hypertension induced or aggravated by pregnancy in some women..9

In developed countries 1 out of 2000 pregnancies is complicated by eclampsia while in case of developing countries this complication varies between 1 out of 100 to 1 out of 1700 pregnancies.10 Many other predisposing factors are also there for eclampsia / pre-eclampsia. More commonly it is found in primigravida that are under 20 or over the age of 30 years.9

The challenging use of antihypertensive agent in case of pre-eclampsia is the reduction of blood pressure for the safety of mothers and no compromise on the uteroplacental perfusion at the same time. The ideal antihypertensive agent used in severe hypertension treatment should be potent, acting rapidly and should have no side effects for fetus and mother. 11

In case of acute management of severe hypotension in pregnancy the most widely antihypertensive agent is intravenous hydralazine which is a drug of first choice. It is advantageous because of having no adverse effects on circulation of fetus and also it can be used orally, IV / IM12. In one of the study done at UK teaching hospital by S. Paterson – Brown, hydralazine IV bolus was received by 70 women, the reduction in the arterial pressure was 12mmHg after 1st bolus dose and it was controlled in 89% by bolus injection13.

This study was designed for comparatively efficacy of Hydralazine and Nifedipine used in women with severe pre-eclampsia. It was also preferred to compare parental effects in terms of reduction in systolic blood pressure to a value below 160mmHg.

In acute emergencies hydralazine can be safely used as a first line of treatment. 254 patients (127 in each group) were chosen for this study and found that most of them were multipara and fewer were grand multipara. Comparatively similar results were observed in a study done by Brown on 825 women with pre-eclampsia. 14

For the evaluation of critical determination of the effect of hydralazine, women with severe pre-eclampsia were included. There was effective reduction in both systolic and diastolic blood pressure by the administration of IV bolus doses according to the blood pressure. In pregnancy nifedipine is mostly used as a calcium channel blocker. As there is limited availability of safety data hence their recommendation is only done if these are not effective. Desirable efficacy of hydralazine was found in eclampsia and pre-eclampsia patient in emergency department at Maroondah Hospital Australia by Lew and Klonis. Initial agent of choice in Australia is intravenous .15

The study of Aali and Nejad16 also indicated better efficacy for nifedipine than hydralazine, because of fewer doses, more rapid effect and greater mean urinary output for nifedipine treated group. Similar to our findings, the study of Fenakel et al.17 showed greater efficacy of nifedipine than hydralazine to achieve

desired blood pressure in severe pre-eclampsia according to greater proportion of patients effectively controlled for blood pressure, furthermore they showed less fetal distress and less average of days spent in neonatal intensive care unit (NICU) for nifedipine17. Also similar to our findings, the study of Kwawukume and Ghosh18 has revealed better efficacy for nifedipine in controlling blood pressure in severe pre-eclampsia than hydralazine because of greater proportion of effectively controlled patients.

Dimitrios et al. also showed no adverse fetal side effects after administration of nifedipine for obstetric indication19. The same has been experienced in the study of Vermillion et al. when they compared oral nifedipine with intravenous labetalol20. But no hypotension was developed for pre-eclamptic pregnant patients receiving sublingual nifedipine in another study16. Hypertensive crisis was detected for pre-eclamptic pregnant patients receiving nifedipine in our study as in both above mentioned studies, but in different proportion of patients. There was a higher association of the hydralazine with more severe hypotension than nifedipine in a study done by Magee et al which was a meta-analysis of randomized controlled trials, in which they compare hydralazine with other short acting antihypertensive agents. Association of the hydralazine was more towards maternal side effects while less bradycardia was observed in neonates. According to the conclusion of the study clinical practice cannot be guided with these results and powerful trial are needed for this purpose.21 In another study done by Sven M et al, women with pregnancy induced hypertension were administered with nifedipine sublingually and they observed that in case of laryngoscopy and intubation Nifedipine is effective in attenuating the hypertensive response but not in case of tachycardia response in patients that are scheduled for caesarean section under general anesthesia22.

The maximum number of the patients in our study were less than 25 years of age according to the age distribution. After 45 years there is a sharp increase in the incidence but after 55 years it remains more or less static. Similar comparable results were observed in another study done on age distribution.23 In our current study 50% of the preeclamptic women were < 25 years of age. In our study it was observed that maternal age is highly associated with pre-eclampsia frequency. It was observed more commonly below the age of 20 years and their frequency become less between 31-40 years. Our these results were comparable to the done by Chen CY and Shaheen B et al24,25.

Nifedipine is more preferable than other antihypertensive agents in case of hypertension emergency of pregnancy if pharmacokinetic properties of nifedipine are considered like rapid onset, long duration of action, good oral bioavailability More investigations are necessary to demonstrate urinary output, hypertensive crisis and less adverse effects as definite advantage for either medicine.

CONCLUSION

Oral nefidipine is observed to highly effective than intravenous hydralazine in the treatment of severe pre-eclampsia. Our study proved that the mean systolic blood pressure after oral nifedipine was lower than intravenous hydralazine for effective blood pressure control in hypertensive disorders of pregnancy. Since our study didn't focus on the adverse effects of these two drugs, we recommend more randomized controlled trials taking into account the safety of these drugs in addition to their efficacy so that future

recommendations may be posted for the routine use of best efficacious and safe drug.

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