HYDRALAZINE VERSUS GLYCERYL TRINITRATE IN SEVERE PRE-ECLAMPSIA AND ECLAMPSIA, A COMPARATIVE STUDY

Shahida Iftikhar[1], Nuzhat Rasheed[1], Muhammad Anwar[2], Shamsa Humayun[3]

ABSTRACT

Background: Hypertension during pregnancy is a common medical condition worldwide, occurring in 12-22% of all pregnancies. In the developed world, the incidence of hypertension and the severity of its complications is reduced markedly, because of the effective and widespread antenatal care services. However, hypertension still remains one of leading cause of maternal morbidity and mortality in developing coutnries.. **Objectives:** To compare the efficacy and safety profile of hydralazine with glyceryl trinitrate (GTN) in women with severe pre-eclampsia and eclampsia. **Patients and Method:** This quasi experimental study was conducted in Department of Obstetrics & Gynecology, Sir, Ganga Ram Hospital Lahore, over a period of six months, from July 2006 to January 2007. A total of 100 patients were included in this study. 50 patients were given hydralazine and 50 patients received Nitroglycerine. **Results:** In groups A and B, mean age was 26.8 ± 5.6and 25.4 ± 4.8, respectively. In both groups, the systolic and diastolic blood pressures of patients were not significantly different from each other. Mean time needed to achieve effective blood pressure control in group A (hydralazine) was 31.0 ± 13.9 minutes and in group B (GTN) was 23.± 20.3 minutes. Time interval between effective blood pressure control and new hypertensive crisis was significantly prolonged in group A (96.1 ± 27.2 Vs 73.8 ± 18.1, P< 0.05) **Conclusion:** GTN takes less time for effective control of blood pressure than hydralazine and safety profile is comparable with hydralazine.

Keywords: Eclampsia, Severe pre- eclampsia, GTN, Hydralazine

INTRODUCTION

Hypertensive disorders occur in 6-8% of all pregnancies and are the 2nd leading cause of maternal death and contribute to significant neonatal morbidity and mortality.[1] Hypertension in pregnancy is defined as one diastolic blood pressure (B.P) reading of at least 110mmHg or two consecutive diastolic blood pressure readings of atleast 90mmHg, not <4 hours apart after 20 weeks of pregnancy.[2]

The incidence of pregnancy induced hypertension (PIH) varies with age, parity, geographic distribution and socioeconomic status. The risk factors for pregnancy induced hypertension are age under 20 and over 35 years, first pregnancy, previous history of severe pregnancy induced hypertension, family history of pre-eclampsia, short stature, migraine, chronic renal disease and diabetes.[3,4]

The hypertensive disorders of pregnancy affect more than 10% of antenatal population of the U.K.[5] Each year it complicates 80,000 pregnancies in the United Kingdom and account for 12-24% of antenatal admissions. The incidence of hypertensive disorders is slightly lower i.e. 6-7% in the USA as compared to 10-12% of pregnancies in Pakistani population.[6] In a review of different medical disorders affecting pregnancy it was seen that the prevalence of pregnancy induced hypertension was 19.92% in Pakistan.[7]

The main cause of death in pre-eclampsia and eclampsia was attributed to cerebrovascular complications, primarily cerebrovascular haemorrhage. Renal and hepatic failure are also frequently listed as the cause of death. Disseminated Intravascular Coagulation (DIC) is another important cause seen in 15% of hypertensive deaths.[8]

The fetal complications include IUGR, intrauterine fetal hypoxia and acidosis, premature birth and death.[9] Ninety percent of patients presenting with proteinuria before 34 weeks of gestation delivered infants weighing less than 25th percentile.[10] Perinatal mortality increases rapidly once proteinuria is established. IUD (intrauterine death) comprised 8.5% of all these perinatal deaths.[11]

Severe hypertension i.e diastolic blood pressure of 110mmHg or more in pre-eclampsia and eclampsia can be dangerous and maternal death probably occurs due to cerebral haemorrhage secondary to hypertension.[12,13] Severe hypertension can also lead to cardiac failure and pulmonary edema.

In our hospital, a large number of patients come to the casualty department with the diagnosis of pregnancy induced hypertension, pre-eclampsia and eclampsia. Most of them have already developed complications.

An important part of any management protocol is administration of antihypertensive agents where hypertension is severe i.e. blood pressure

1. Department of Gynaecology, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan.
2. Department of Community Medicine, Sheikh Zayed Medical College,Rahim Yar Khan.
3. Department of Gayne & Obs, Sir Ganga Ram Hospital, Lahore

Correspondence: Dr. Nuzhat Rasheed
Assistant Professor of Gynaecology, SZMC, RYK

≥160/110mmHg.[14] The ideal drug for this purpose should act quickly, without causing fetal or maternal side effects. Hydralazine has been used as a standard treatment for this purpose.[15,16] Hydralazine where given in the form of boluses is safe and effective but there are problems with hydralazine use. It can cause a precipitous reduction in blood pressure thus adversely affecting the mother as well as uteroplacental flow.[17,18] It may also lead to maternal tachycardia and fluid retention and must be administered parentrally. Other antihypertensive drugs like labetalol and nifedipine are being used for antihypertensive therapy. Labetalol is not available in Pakistan. Infusion of glyceryl trinitrate can be used and causes no significant adverse effects to the mother and fetus.[19] Hydralazine an arteriolar dilator which decreases after load. Nitroglycerin, in low doses, is mainly a venodilator and decreases preload but in high doses it is both an arteriolar and venodilator.

As most of the emergency antihypertensive drugs like hydralazine are not easily available, remains out of stock and most of the time are not available in Pakistan, alternative drug GTN (which is used most commonly in Ischaemic Heart Diseases (IHD)) may be used. So the objective of present study was to compare the efficacy and safety profile of hydralazine with glyceryl trinitrate (GTN) in women with severe pre-eclampsia and eclampsia.

PATIENTS AND METHODS

This study was conducted in Department of Obs/Gynae, Sir Ganga Ram Hospital, Lahore over a period of six months from July 2006 to Jan 2007. A total of one hundred patients were included, 50 patients were given hydralazine (Group A) and 50 patients received nitroglycerine (Group B). For the purpose of blinding it was ensured that patient were not knowing the type of the drug given to them. An informed verbal consent was taken from each study subject. For the diagnosis of severe pre-eclampsia one or more of the following should be present:.

1. Blood pressure reading of ≥ 160 mmHg systolic or ≥ 110mmHg diastolic with the patient at rest.
2. Proteinuria level of at least 5gms in 24 hours urine collection.
3. Cerebral or visual disturbances, scotoma or blurred vision.
4. Pulmonary oedema or cyanosis.
5. Epigastric or upper quadrant pain caused by stretching of glisson's capsule.
6. Impaired LFT's (liver function test) of unknown etiology.
7. Thrombocytopenia
8. IUGR(Intrauterine growth retardation) or oligohydroamniose with abnormal umbilical artery doppler reading.

Eclampsia is described as "The occurrence of convulsions in women whose condition also meet the criteria for pre- eclampsia and the co- incidental neurological disease such as epilepsy does not cause the convulsion.

Inclusion Criteria

All patients with severe pre eclampsia and eclampsia having gestational age > 20 weeks uptil weeks (from last menstrual period or from the last ultrasonography available.

Exclusion criteria

Ischemic heart disease
Rheumatic valve disease
Hypersensitivity to drug during the study

Data collected on every patients included age, gestational age, parity, pre eclampsia or eclampsia, pulse rate, systolic blood pressure, diastolic blood pressure, time needed to achieve blood pressure control in minutes and mean urinary out patients. The data analysis was done on SPSS Version 16.

RESULTS

A total of 100 patients were divided into two groups. Fifty patients received hydralazine (Group A) and 50 patients glyceryl trinitrate (Group B). It was found that 16 patients (32%) in group-A and 22 patients (44%) in group-B were between 18-23 years of age 21 patients (42%) in group-A and 16 patients (32%) in group-B between 24-29 years. The age group between 30-34 years had 4 patients (8.0%) in group-A and 8 patients (16%) in group-B. There were 9 patients (18%) in group-A and 4 patients (8%) in group-B who were 35-40 years of age. In group-A and group-B mean age was 26.8±5.6 and 25.4±4.8, respectively. There were no statistically significant difference between two groups. (Table I)

Sixteen patients (32%) in group-A and 14 patients (28%) in group-B were had gestational age between

26-30 weeks. 12 patients (24%) in group-A and 17 patients (34%) in group-B had gestational age between 31-34 weeks. 15 patients (30%) in group-A and 17 patients (34%) in group-B (P > 0.05) had gestational age between 35-38 weeks and between 39-40 weeks of gestation, 7 patients (14%) in group-A and 2 patients (4%) in group-B (Table-I).

Parity distribution revealed that 28 patients (56%) in group-A and 26 patients (52%) in group-B were primigravidae while 22 patients (44%) in group-A and 24 patients in group-B were multigravidae (Figure I).

Distribution of cases by diagnosis revealed that 42 patients (84%) in group-A and 44 patients (88%) in group-B were diagnosed as pre-eclampsia cases while 8 patients (16%) in group-A and 6 patients (12%) in group-B were eclamptic (P>0.5) (Figure I).

In two groups, the systolic blood pressure and diastolic blood pressures of patients were not significantly different from each other. P value was observed 0.98 and 0.73, respectively. Mean time needed to achieve effective blood pressure control in group-A (hydralazine) was 31.0±13.9 minutes and in group-B (GTN) was 23.1±20.3 minutes (Table II).

It means GTN takes less time for blood pressure control i.e. statistically significant (P= 0.02) (Table II). Time interval between effective blood pressure control and new hypertensive crisis was significantly prolonged in group-A (96.1±27.2vs 73.8±18.1) p values 0.04 was observed (Table-II).

Mean urinary output was more in group-B as compared to group-A (918.0±527.0 vs 802.0±360.0 mls). Results were statistically insignificant (p=0.19) (Table-II).

After initial stabilization, new hypertensive crisis occurred in 13 patients (26.0%) in hydralazine group and 9 patients (18.0%) in GTN group. There was no statistically significant difference between two groups (Table III).

Regarding side effects of safety profile new maternal headache occurred in 21 patients (42.0%) in group-A and 30 patients (60.0%) in group-B. There was no statistically significant difference between the two groups (P=0.07) (Table-III). Maternal tachycardia occurred in both groups with almost equal frequencies. Nausea and vomiting were observed in 16 patients (32.0%) in group-A and in 24 patients (48.0%) in group-B. Results were statistically insignificant (P= 0.10) (Table-III). Sudden fall of blood pressured occurred in 2 patients (4%) in group-A and in 9 patients (18%) in group-B. There was statistically significant difference between the two groups (P= 0.02) (Table-III).

Comparing both groups regarding fetal outcome, Apgar score at 5 minutes in 5 babies (17%) in group-A and 3 babies (11%) in group-B was less than 6 (Table IV) (P = 0.88).

Table I: Distribution of cases by Maternal age and Gestational age

Age (Year)	Group-A (Hydralazine) n=50	Group-B (Glyceryl Trinitrate) n=50	Gestational age (weeks)	Group-A (Hydralazine) n=50	Group-B (Glyceryl Trinitrate) n=50
	No. (%)	No. (%)		No. (%)	No. (%)
18-23	16 (32)	22 (44)	26-30	16 (32)	14 (28)
24-29	21 (42)	16 (32)	31-34	12 (24)	17 (34)
30-34	04 (08)	08 (16)	35-38	15 (30)	17 (34)
35-40	09 (18.)	04 (08)	39-40	07 (14)	02 (04)
Mean ± SD	**26.8±5.6 years**	**25.4±4.8 years**	**Mean ± SD**	**33.5±4.0weeks**	**31.1±3.4weeks**
P value	**0.17**		**P value**	**0.56**	

Figure I: Distribution of cases by Parity and Diagnosis

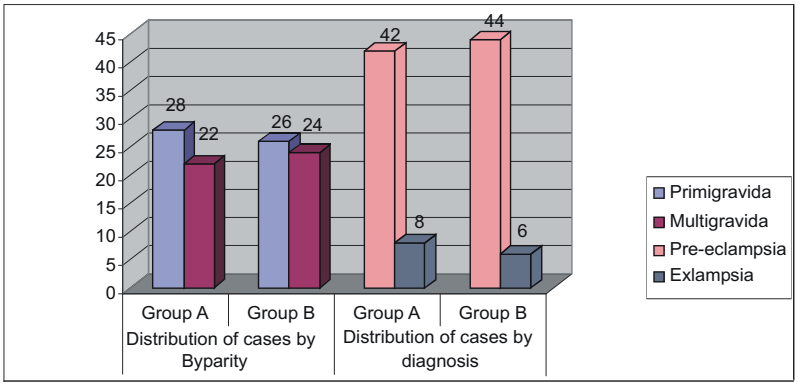

Table II: Distribution of cases byefficacy of drug

Variables	Group-A (Hydralazine) Mean±SD	Group-B (Glyceryl Trinitrate) Mean±SD	P value
Systolic blood pressure before drug administered	166.1+16.0 (mmHg)	166.2+22.8 (mmHg)	0.98**
Diastolic blood pressure before drug administered	116.4+8.2 (mmHg)	117.0+9.0 (mmHg)	0.73**
Time needed to achieve effective B.P control (min)	31.0+13.9 (min)	23.1+20.3 (min)	0.02**
Time interval between effective B.P control and new hypertensive crisis (min)	96.1+27.2 (min)	73.8+18.1 (min)	0.04*
Mean urinary output (mls) in 24 hrs	802.0+360.3 (mls/24 hrs)	918.8+527.0 (mls/24 hrs)	0.19**

Table No III: Comparison of complications observed in Group A (Hydraliazine) and Group B (Glyceryl trinitrate)

	New hypertensive crisis		Maternal headache		Nausea/ vomiting		Sudden fall of blood pressure	
	Group-A No.(%)	Group-B No.(%)	Group-A No.(%)	Group-B No.(%)	Group-A No.(%)	Group-B No.(%)	Group-A No.(%)	Group-B No.(%)
Yes	13 (26.0)	09 (18.0)	21 (42)	30 (60)	16 (32)	24 (48)	02 (04)	09 (18)
No	37 (74.0)	41 (82.0)	29 (58)	20 (40)	34 (68)	26 (52)	48 (96)	41 (82)
Total	**50 (100)**	**50 (100)**	**50 (100)**	**50 (100)**	**50 (100)**	**50 (100)**	**50 (100)**	**50 (100)**
	P value = 0.33		**P value = 0.07**		**P value = 0.10**		**P value = 0.02**	

Table IV: Distribution of cases by Apgar score

Apgar Score	Group-A (Hydralazine) n=29		Group-B (Glyceryl Trinitrate) n=27	
	No.	%	No.	%
At 1 minute				
< 6	08	27.6	06	22.2
6-10	21	72.4	21	77.8
Mean ± SD	**5.7±2.5**		**6.6±1.5**	
P value	**0.09**			
At 5 minute				
< 6	05	17.3	03	11.1
6-10	24	82.7	24	88.9
Mean + SD	**7.1±3.8**		**8.6±1.9**	
P value	**0.07**			

DISCUSSION

Worldwide reports about maternal mortality have consistently shown the high maternal mortality associated with the hypertensive disorders of pregnancy, particularly the severe hypertension of pre-eclampsia.[19] In the most recent triennium in the UK series maternal mortality from hypertension diseases was most commonly attributed to intracerebeal haemorrhage.[19] There is general consensus that maternal risk is decreased by antihypertensive treatment that acutely lowers very high blood pressure. Recognition of this specific risk has meant that control of acutely raised blood pressure has become central for women with severe hypertension, particularly that of pre-eclampsia.

Hydralazine has been used for control of blood pressure in severe pre-eclampsia and eclampsia. The other two short acting drugs like labetalol and oral or sublingual nifedipine has also been used more commonly for control of blood pressure.

A meta-analysis of randomized controlled trials of short acting anti-hypertensive for severe hypertension in pregnancy was published in BMJ 2003.[20] In this meta-analysis 21 trials were included, eight compared hydralazine with labetalol. Hydralazine was associated with less persistent hypertension than labetalol but more severe hypertension than with nifedipine. Hydralazine was associated with more maternal hypertension, more caesarean section, more placental abruption, more maternal oliguria, more adverse effect on FHR, and more low Apgar scores. Hydralazine was associated with more maternal side effects and with less neonatal bradycardia (risk difference 0.24).[20] So they concluded that hydralazine should not be used as 1st line treatment for severe hypertension in pregnancy, but trials were not powered enough to make clinical recommendations.

In this study when hydralazine was compared with GTN, effective control of blood pressure was achieved more earlier with GTN than with hydralazine. Side effects of both drugs were almost similar.

A study was conducted in 1996 Aligarh Muslim University, India, comparing sublingual nifedipine and topical nitroglycerine in peripartum period in severe pre-eclampsia. Results showed that nitroglycerine was more effective in treating hypertension, which is comparable to present study.[21]

A randomized clinical trial comparing hydralazine and other drugs like labetalol in severe hypertension of pregnancy was published in September 2006 in European Journal of Obstetrics and Gynaecology. It was conducted on 200 women, with severe hypertension of pregnancy. Women were randomized to receive hydralazine (5mg boluses) or labetalol. The main outcome measures were, successfully lowering blood pressure and maternal hypotension. No significant difference was observed between two drugs. Regarding the use of hydralazine results are comparable with present study.[22]

The results of present study are comparable with the study conducted at Department of Obstetrics & Gynaecology, Cumhuriyet University, School of Medicine, Turkey, on the effect of GTN on hypertension of severe pre-eclampsia, eclampsia and HELLP syndrome. It was retrospective study, carried out on small sample of 55 women. They studied the efficacy of GTN for blood pressure control and side effects (headache, mode of delivery and perinatal outcomes). The results showed that, GTN infusion causes significant reduction in blood pressure in pre-eclampsia, eclampsia and HELLP syndrome. GTN infusion was associated with headache and flushing.[19]

This study suggested that infusion of GTN can be used as an alternative agent to well-known drugs and cause no significant adverse effect to mother and fetus. Aali and Nejad conducted a comparative study between nifedipine and hydralazine as a 1st line agent to control blood pressure in severe pre-eclampsia. It was a single blind randomized clinical trial. Results are comparable with present study regarding the use of hydralazine.[23] The use of oral nifedipine is easy in conscious patients; GTN is especially helpful in patients with mental status changes during and after an eclamptic attack, while beginning an anti-hypertensive agent for the 1st time. According to our experience, GTN can be accepted as more effective anti-hypertensive agent with an earlier effect than hydralazine, and side effect profile is comparable with hydralazine.

CONCLUSION

On the basis of results comparing hydralazine with glyceryl trinitrate (GTN), glyceryl trinitrate (GTN) takes less time for effective control of blood pressure than hydralazine. Safety profile is comparable with hydralazine.

REFERENCES

1. Thomas T, Jophy R, Mhaskar A, Misquith D. Are we increasing serious maternal morbidity by postponing termination of pregnancy in severe preeclampsia/ eclampsia? Obstet Gynaecol. 2005;25:347-51.
2. Higgins JR, Walshe JJ, Halligan A, O'Brien E, Conroy R, Darling MR. Can 24-hour ambulatory blood pressure measurement predict the development of hypertension in primigravidae? Br J Obstet Gynaecol. 1997; 104: 356-62.
3. Manga MH, Tayyab M, Hussain Z, Anjum S. Coagulation abnormalities in pre-eclampsia. A study of 40 subjects. Annals KEMC. 2000; 6: 409-11.
4. Walfisch A, Hallak M. hypertension in pregnancy. In: James DK, Steer PJ, Weiner CP, Gonik B, editors. High risk pregnancy. Management option. 3rd ed. Philadelphia: W.B. Saunders, 2006: 640-788.
5. Gupta M, Shennan AH, Halligan A, Taylor DJ, de Swiet M. Accuracy of oscillomatric blood pressure monitoring in pregnancy and pre-eclampsia. Br J Obstet Gynaecol. 1997;104:350-5.
6. Pervene K, Baig M. Influence of blood pressure changes with and without proteinuria outcome of pregnancy. The Professional 2000;7:62-5.
7. Rana S, Asif K, Saeed S, Majid T, Yusuf W. Standard of Obstetric care. Audit in obstetrics. Pak J Obstet Gynaecol. 1997; 12: 1-35.
8. Mackay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. Obstet Gynecol. 2001;97: 533-8.
9. Saudan P, Brown MA, Buddle ML, Jones M. Does gestational hypertension become pre-eclampsia? Br J Obstet Bynaecol. 1998: 105: 117-84.
10. Douglas KA, Redman CW. Eclampsia in the United Kingdom. BMJ. 1994 26;309: 1395-400.
11. Deny IJ, Wiekinsa LS, Shiuta RT, Beeug DG Confliction views on the measurement of blood pressure in pregnancy. BJOG 1991; 98: 241-3.
12. Cunningham RG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC, Hankins GDL, et al. William's Obstetrics. 20th edition. London: Prentice Hall International. 1997: 393-375.
13. Nicoloso E, d'Ercole C, Cassel N, Azoulay P, Cravello L, Boublie L, et al. Serious forms of arterial pregnancy-related hypertension Rev Fr Gynecol Obstet. 1994; 89: 476-88.
14. Belfort MA, Anthony J, Buccimazza A, Davey DA. Hemodynamic changes associated with intravenous infusion of the calcium antagonist vreapamil in the treatment of severe gestational proteinuric hypertension. Obstet Gynecol. 1990; 75: 970-4.
15. Barton JR, Hiett AK, Conover WB. The use of nifedipine during the postpartum period in patients with severe preeclampsia. Am J Obstet Gynecol. 1990; 162: 788-92.
16. Begum MR, Quadir E, Begum A, Akhtar S, Rahman K. Management of hypertensive emergencies of pregnancy by hydralazime bolus injection vs continuous drip- - a comparative study. Medscape Womens Health. 2002; 7: 1.
17. Vink GJ, Moodley J, Philpott RH. Effect of dihydralazime on the fetus in the treatment of maternal hypertension. Obstet Gynecol. 1980; 55:519-22.
18. Naden RP, Redman CW. Antihypertensive drugs in pregnancy. Clin Perinatol. 1985;12:521-38.
19. Cetin A, Yurtcu N, Guvenal T, Imir AG, Duran B, Cetin M. The effect of glyceryl tirnitrate on hypertension in women with severe preeclampsia, HELLP syndrome, and eclampsia. Hypertens Pregnancy. 2004; 23:37-46.
20. Dadelszen P. Hydralazime for treatment of severe hypertension in pregnancy: meta-analysis. BMJ. 2003: 327:955-7.
21. Begum R, Iqbal F, Main M. Tewai K, Siddiqui MMH. A comparative study of sublingual nifedipine and topical nitroglycerine during the peripartum period in patients with severe pre-eclampsia. J Obstet Gynaecol India 1996;46: 196-9.
22. Paulino V, Gracia DC, Martin L, Esteban P, Jaun C, Vega M. Severe hypertension in pregnancy; hydralazine of labetalol: a randomized clinical trial. Euro J Obstet Gynecol Reprod Med. 2006; 128: 157-82.
23. Aali BS, Nejad SS.. Nifedipine or hydralazine as a first-line agent to control hypertension in severe preeclampsia. Acta Obstet Gynecol Scand. 2002; 81:25-30.