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To study the changes in fetal hemodynamics with intravenous labetalol or nifedipine in acute severe hypertension

Shalini Gainder[a,*,1], Monika Thakur[a,*,1], S.C. Saha[a], Mahesh Prakash[b]

[a] Department of Obstetrics & Gynaecology, PGIMER Chandigarh, India
[b] Department of Radiodiagnosis, PGIMER Chandigarh, India

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ABSTRACT

Objective: To compare the efficacy of intravenous labetalol or oral nifedipine in treatment of acute maternal hypertension and study the fetal hemodynamic changes using color Doppler ultrasound that follows treatment.
Study design: Thirty women with severe preeclampsia having acute hypertension (more than or equal to 160/105 mmHg) were randomized in 2 groups to receive intravenous labetalol or oral nifedipine until blood pressure was lowered to less than or equal to 140/90 mmHg. Doppler vascular indices namely pulsatility index, resistance index, S/D ratio of umbilical (UA) and middle cerebral artery (MCA) were measured baseline at the time of acute severe hypertension and repeated after control of blood pressure, to assess the changes in fetal hemodynamics if any with labetalol or nifedipine.
Results: Both nifedipine and labetalol were found to be effective when used for rapid control of blood pressure. Mean age of women in both groups and mean gestational age was statistically comparable. No change in fetal heart rate before and after treatment was observed in both groups. Doppler vascular indices of UA and MCA showed no significant changes as compared to baseline values in both groups.
Conclusion: The use of labetalol and nifedipine were not related to any significant changes in fetal Doppler, which is reassuring about the safety of these drugs when treating acute severe hypertension in pregnancy. Choice between these two drugs should be based on cost, availability respective contraindications, and clinician's experience.

1. Introduction

The hypertensive disorders of pregnancy (HDPs) complicate about 3–10% of pregnancies [1–3]. They are one of the major contributors to maternal and fetal mortality and morbidity globally, with approximately 30,000 maternal and 500,000 perinatal deaths attributed to the HDPs annually [2,4]. Hypertensive disorders of pregnancy are also associated with impaired uteroplacental circulation and consequent intrauterine growth restriction [5].

Antihypertensive agents are used to prevent and treat severe hypertension. Among all the antihypertensive drugs available labetalol and nifedipine are the two most commonly drugs employed to treat acute severe hypertension in pregnancy. The objective of treating severe hypertension is to avoid vascular damage (encephalopathy and hemorrhage) and congestive heart failure due to blood pressure elevation without causing excessive reduction in blood pressure that would critically affect uteroplacental perfusion [6,7]. It is predicted that maternal hypertension may have impact on the fetal circulation and with effect of antihypertensive drug which cause relaxation of blood vessels, some change in utero-placental flow and fetal vascularity may be expected.

By using Doppler velocimetry the effect of pharmacologic agents on maternal, fetal, and placental circulations can be observed. Till now studies have compared labetalol and hydralzine in terms of its effect on uteroplacental circulation. But no study has yet compared the effect of labetalol and nifedipine on uteroplacental circulation which are the most common drugs used in acute severe hypertension in pregnancy. In this study, we analysed variables of the fetal arterial doppler with labetalol or nifedipine in acute hypertensive emergencies, before and after control of hypertension.

2. Methods

This Randomized control study was conducted at the Post Graduate

* Corresponding authors.
E-mail addresses: sgainder@gmail.com (S. Gainder), thakurmonika126@gmail.com (M. Thakur).
[1] These two authors take full responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Institute of Medical Education and Research, Chandigarh from July 2012 to November 2013 after approval from institute's ethics committee. Informed written consent was obtained from all patients.

2.1. Subjects

Thirty pregnant women with singleton pregnancy having acute severe hypertension with gestational age between 26 and 40 weeks were enrolled in this study. Acute severe hypertension was defined according to the guidelines of the National High Blood Pressure Education Program (NHBPEP) as sustained high blood pressure ≥ 160 mm Hg systolic, ≥105 mm Hg diastolic or both. [8] Women with eclampsia, multiple gestation or abruptio placentae were excluded. Women with other comorbidities including chronic hypertension, long standing diabetes mellitus, chronic kidney disease or aortic coarctation were also excluded. The patients was then randomly allocated into either labetalol or nifedipine group according to the table of random numbers.

2.2. Vitals monitoring

The woman made to seated comfortably with her legs resting on a flat surface. The maternal blood pressure was evaluated by using a standard mercury sphygmomanometer in the nondominant arm. Maternal heart rate and systolic, diastolic and mean arterial pressure was recorded before and after the administration of labetalol or nifedipine.

2.3. Treatment of acute severe hypertension

Labetalol or nifedipine was used according to the American Congress of Obstetricians and Gynecologists (ACOG) guidelines (2002) [9]: Nifedipine: A 10 mg tablet per orally will be administered every 15–30 min until blood pressure is lowered to equal or below than 140/90 mm Hg. A maximum of 3 doses will be given. Labetalol: A 20-mg intravenous bolus dose will be administered followed by 40 mg if not effective within 10 min; then, 80 mg every 10 min until blood pressure is lower than 140/90 mmHg or maximum a total dose of 220 mg is given.

2.4. FHR tracing

A fetal heart tracing before administration of drug and after control of blood pressure was recorded on Huntleigh Healthcare BD4000XS. Any change in the baseline heart rate pattern was also compared.

2.5. Ultrasonography

After patient was recruited, an ultrasonography and color Doppler study was conducted to measure fetoplacental circulation. Before the Ultrasound examination, the pregnant women made to rest for 10 min with their back supported in a 45 degree position to prevent compression of the inferior vena cava. Baseline doppler study was performed immediately before the treatment, repeated after BP of < 140/90 is achieved. In order to minimize the bias observer was blinded to the group allocation of the patient. Doppler US was performed on Phillips Electronics IU22, using a 2–5 MHz broadband probe.

For evaluation by Doppler US, a low filter (100 Hz) was used to prevent loss of the diastolic flow component and the insonation angle was always kept less than 60 degree to avoid artifacts in the spectral Doppler. Doppler analysis of the fetal umbilical artery and middle cerebral arteries was performed during periods of fetal rest in the presence of a fetal heart rate of 120–160 bpm. For the acquisition of the tracing of the umbilical artery, the artery was identified with color Doppler of a free loop and the 3 mm samples was positioned in such a way as to permit evaluation of both the artery and vein, with the Doppler spectrum being evaluated until five similar consecutive waves were obtained by free loop color Doppler. For the identification of the fetal middle cerebral artery, an axial section of the fetal head was obtained at the level of the thalamus and of the cavum septum pellucidum. The transducer was then moved up to the willis polygon and the pulsation of the two middle cerebral arteries was observed. The dial was calibrated for a sample volume of 1 mm and was placed on the middle cerebral artery as close as possible to the skull cap, before its bifurcation.

Standard Doppler indices of vascular resistance were obtained from at least three similar consecutive waveforms. On the basis of the systolic (S), average (A), and diastolic (D) flow velocity, following were computed:

Pulsatility Index (PI) (S-D)/A
Resistance index (RI) (S-D)/S
Systolic/Diastolic ratio (S/D) (S/D)

However, the various indices and ratio were computed automatically by the ultrasound machine and no manual calculations were performed in present study. Measurements were made in the following vessels: umbilical artery and middle cerebral artery. During the study, care was taken to apply minimal pressure to the maternal abdomen with the transducer, as fetal head compression is associated with alterations of intracranial arterial waveforms.

2.6. Statistical analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). All quantitative variables e.g. S/D ratio, RI, PI was estimated using measures of central location mean, median and measures of dispersion standard deviation and standard error. Normality of data was checked by measures of skewness and Kolmogorov Smirnov tests of normality. In between group comparisons for normally distributed data means was compared using student's *t*-test unpaired and for skewed data distribution of two groups comparison was made by Mann Whitney test respectively. Whereas, within group comparisons student *t*-test paired and Wilcoxon signed rank test was applied for normal and skewed data respectively. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi square or Fisher's exact test whichever was applicable. The observed changes in these parameters {(value observed during acute severe hypertension) – (value observed after labetalol or nifedipine)} were compared between the groups by using the unpaired *t*-test. All statistical tests were two-sided and was performed at a significance level of $p \leq 0.05$.

3. Results

The women recruited to the labetalol and nifedipine groups had a

Table 1
Comparison of age and gestational age between pregnant women randomized to receive either labetalol or nifedipine.

Characteristics	Labetalol group (n = 15) Mean ± standard deviation	Nifedipine group (n = 15) Mean ± standard deviation	p-Value
Age (in years)	26.13 ± 3.815	25.47 ± 3.583	0.62
Gestational Age (in weeks)	$35^{4/7} \pm 2^{4/7}$	$34^{4/7} \pm 3$	0.32

Table 2
Comparison of blood pressure and Doppler parameters from fetal umbilical and Middle cerebral arteries observed during acute severe hypertension (pre) with values observed after labetalol (post).

Labetalol	Pre (Mean ± standard deviation)	Post (Mean ± standard deviation)	P Value
Mean Systolic Blood Pressure (mm of Hg)	166 ± 15.02	129.33 ± 8.83	< 0.001
Mean Diastolic Blood Pressure (mm of Hg)	118.67 ± 6.3	88.4 ± 5.08	< 0.001
Umbilical artery PI	1.52 ± 0.87	1.42 + 0.704	0.329
Umbilical artery RI	0.68 + 0.083	0.71 ± 0.28	0.623
Umbilical artery S/D	2.68 ± 0.66	2.62 ± 0.68	0.080
Middle Cerebral Artery PI	1.79 ± 1.28	1.77 ± 0.957	0.918
Middle Cerebral Artery RI	0.706 ± 0.083	0.762 ± 0.154	0.145
Middle Cerebral Artery S/D	3.46 + 1.00	3.50 ± 1.07	0.790

p values were obtained by using paired *t*-test.
PI = pulsatility index; RI = resistance index.

Table 3
Comparison of blood pressure and Doppler parameters from fetal umbilical and Middle cerebral arteries observed during acute severe hypertension (pre) with values observed after nifedipine (post).

Nifedipine	Pre (Mean ± standard deviation)	Post (Mean ± standard deviation)	P Value
Mean Systolic Blood Pressure (mm of Hg)	162.66 ± 11.62	129.47 ± 5.78	< 0.001
Mean Diastolic Blood Pressure (mm of Hg)	113.73 ± 6.13	89.2 ± 2.59	< 0.001
Umbilical artery PI	1.33 ± 0.61	1.52 + 0.76	0.065
Umbilical artery RI	0.65 ± 0.114	0.71 ± 0.96	0.145
Umbilical artery S/D	2.73 ± 0.716	2.92 ± 0.624	0.192
Middle Cerebral Artery PI	1.28 ± 0.678	1.40 ± 0.59	0.119
Middle Cerebral Artery RI	0.77 ± 0.472	0.80 ± 0.34	0.442
Middle Cerebral Artery S/D	3.56 ± 2.70	3.50 ± 2.21	0.340

p values were obtained by using paired *t*-test.
PI = pulsatility index; RI = resistance index.

comparable demographic profile. The mean maternal age was 26.13 years in the labetalol group and 25.47 years in the nifedipine group. The mean gestational age at the diagnosis was $35^{4/7}$ weeks in labetalol group and $34^{3/7}$ weeks in nifedipine group [Table 1]. When comparing blood pressure and Doppler parameters values observed during acute severe hypertension and after treatment with labetalol or nifedipine until blood pressure lower than 140/90 mm Hg we observed a significant reduction in systolic and diastolic blood pressure in both labetalol group [Table 2] as well as in nifedipine group [Table 3]. There was no maternal hypotension during the trial period in either group. When evaluating umbilical artery Doppler parameters, increase in RI was observed, while a decrease in both PI and S/D was observed in those who received labetalol however the difference was not statistically significant [Table 2].

When comparing maternal and fetal heart rate before and after treatment no significant differences were observed in both labetalol (maternal heart rate: 88.53 ± 9.05 bpm vs. 86.53 ± 8.36 bpm, p = 0.055; fetal heart rate: 132.13 ± 6.94 bpm vs. 131.47 ± 7.07 bpm, p = 0.096; pre- vs. post treatment values, respectively) and nifedipine groups (maternal heart rate: 82.27 ± 8.27 bpm vs. 83.20 + 7.39 bpm, p = 0.05; fetal heart rate: 128 + 7.74 bpm vs. 126.80 + 6.48 bpm, p = 0.26; pre- vs. post treatment values, respectively). When comparing changes in the evaluated parameters between pregnant women who received labetalol or nifedipine, no significant difference was observed in umbilical artery indices [Table 4]. On intergroup comparison percentage change in middle cerebral artery of both groups were calculated and all PI (p value = 0.927), RI (p value = 0.790) and S/D (p value = 0.191) were found to be statistically not significant [Table 4].

Table 4
Percentage change in Doppler parameters of fetal umbilical and middle cerebral arteries observed during treatment of acute severe hypertension after antihypertensive: intergroup comparison.

	Labetalol (percentage change)	Nifedipine (percentage change)	P value
Umbilical artery PI	2.73	−19.9	0.052
Umbilical artery RI	−4.6	−11.8	0.546
Umbilical artery S/D	1.26	−10.9	0.111
Middle Cerebral Artery PI	−12.02	−13.03	0.927
Middle Cerebral Artery RI	−8.37	−20.38	0.790
Middle Cerebral Artery S/D	−1.06	−12.7	0.191

− sign indicates improvement data expressed as percentage.
p values were obtained by using paired *t*-test.
PI = pulsatility index; RI = resistance index.

4. Discussion

Hypertension is one of the most common medical disorders of pregnancy. Antihypertensive agents used to prevent and treat severe hypertension prolong the pregnancy and thereby increases the gestational age and viability of fetus. Acute severe hypertension is associated with generalized arteriolar vasoconstriction with reduced uteroplacental flow

and consequent deficit of oxygen supply in the areas of maternal fetal exchange, submitting the fetus to hypoxia [10] Thus, it is thought that administration of antihypertensives may improve uteroplacental flow, due to reduction of uterine vascular resistance and due to relieve in the vasoconstriction. Whereas inversely sudden lowering of blood pressure may cause a reverse effect, reducing uteroplacental flow and worsening the intrauterine conditions. Uteroplacental blood flow is often decreased in hypertensive pregnancy and so it is important to avoid using drugs which might reduce it still further.

Various drugs have been used for acute blood pressure control during hypertensive emergencies in pregnancy. Hydralazine had been the drug of choice for a long time; however a meta-analysis of clinical

trials reported worrisome maternal and fetal side effects with its use. This decline of hydralazine has led to the emergence of labetalol or nifedipine for control of blood pressure in hypertensive emergency during pregnancy. Till now studies have compared labetalol and hydralazine in terms of its effect on uteroplacental circulation. No study in the past has yet compared the effect of labetalol and nifedipine on uteroplacental circulation. The present study will further add support to recent guidelines and expert opinion that oral nifedipine and intravenous labetalol are suitable first line antihypertensives in hypertensive emergencies during pregnancy.

In present study there were no significant differences observed in the maternal and fetal heart rate before and after treatment with labetalol (maternal heart rate 88.53 ± 9.054 bpm vs. 86.53 ± 8.365 bpm p = 0.055; fetal heart rate 132.13 ± 6.947 bpm vs. 131.47 ± 7.070 bpm, p = 0.096; pre- vs. post treatment values, respectively). Similarly Shekhar et al [11] also reported decline in maternal heart rate to be not significant and no change in the fetal heart rate was found in both labetalol and nifedipine group. Concerning Doppler evaluation in our study no statistical significant reduction in either of umbilical artery and middle cerebral artery was observed as compared to baseline after administration of intravenous labetalol which is in accordance with previous studies. No study in past has compared the changes in fetal hemodynamics with nifedipine and labetalol. Although studies have compared labetalol and hydralazine in terms of its effect on uteroplacental circulation. Baggio et al [12] evaluated 16 pregnant women with gestational age between 20 and 32 weeks in acute severe hypertension which were randomly allocated to receive either hydralazine and labetalol. Despite the observed increase in resistance index of uterine arteries associated with hydralazine, the use of hydralazine and labetalol was not related to any significant changes in fetal Doppler as seen in our study. Similar study was conducted by Harper et al [13] who randomly allocated 30 hypertensive pregnant women to 10 mg of intravenous hydralazine or 100 mg of labetalol and he also had comparable results showing that maternal blood pressure decreased significantly after both drugs. PI of umbilical artery decreased after hydralazine and increased after labetalol. They attributed the decrease in PI after hydralazine due to vasodilation, and the increase in PI after labetalol to vasoconstriction in the fetoplacental circulation, suggesting that fetal beta-blockade may occur after treatment with labetalol. However, no statistical significant changes in either of indices were observed in our study which indicates that both oral nifedipine and intravenous labetalol regimens are effective as well as safe when used in severe hypertension in pregnancy.

5. Conclusion

In conclusion, we observed that both drugs were highly effective in reducing blood pressure of pregnant women with acute severe hypertension. Both the drugs were not related to any significant changes in fetal doppler and this information is reassuring about the safety of these drugs in the treatment of acute severe hypertension in pregnancy. Therefore the choice between these two drugs should be based in other criteria such as respective contraindications, costs, availability and clinician's experience.

6. Contribution of authors

SG was involved in the conception and design of the study. SCS & MP helped in acquisition of data. MT and SG analyzed the data, reviewed the literature and wrote the manuscript. SCS gave conceptual advice. All the authors read and approved the final manuscript.

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References

[1] L.A. Magee, A. Pels, M. Helewa, et al., The hypertensive disorders of pregnancy (29.3), Best Practice Res. Clin. Obstetr. Gynaecol. 29 (5) (2015) 643–657.
[2] P. von Dadelszen, L.A. Magee, Pre-eclampsia: an update, Curr. Hypertens Rep. 16 (8) (2014) 1–14.
[3] L.A. Magee, A. Pels, M. Helewa, E. Rey, P. von Dadelszen, Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy, Pregnan, Hyperten. Int. J. Women's Cardiovasc. Health 4 (2) (2014) 105–145.
[4] P. von Dadelszen, L.A. Magee, Preventing deaths due to the hypertensive disorders of pregnancy, Best Practice Res. Clin. Obstetr. Gynaecol. 36 (2016) 83–102.
[5] J. Miller, S. Turan, A.A. Baschat, Fetal growth restriction, Semin. Perinatol. 32 (2008) 274–280.
[6] A.C. Bolte, H.P. van Geijn, G.A. Dekker, Management and monitoring of severe preeclampsia, Eur. J. Obstet Gynecol. Reprod. Biol. 96 (2001) 8–20.
[7] P. Vigil-De Gracia, M. Lasso, E. Ruiz, J.C. Vega-Malek, F.T. de Mena, J.C. Lopez, Severe hypertension in pregnancy: Hydralazine or labetalol. A randomized clinical trial, Eur. J. Obstet Gynecol. Reprod. Biol. 128 (2006) 157–162.
[8] Report of the National High Blood Pressure Education Program, Working group report on high blood pressure in pregnancy, Am. J. Obstet Gynecol. 183 (2000) S1–S22.
[9] ACOG Committee on Practice Bulleteins-Obstetrics, Diagnosis and management of preecampsia and eclampsia, Obstet Gynecol. 99 (2002) 159–167.
[10] K.P. Williams, S. Wilson, Antepartum middle mean cerebral blood flow velocity correlation with maternal hemodynamics, Hypertens Pregnancy 18 (1999) 273–278.
[11] S. Shekhar, C. Sharma, S. Thakur, S. Verma, Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy, Obstet Gynecol. 122 (5) (2013) 1057–1063.
[12] M.R. Baggio, W.P. Martins, A.C. Calderon, A.T. Berezowski, A.C. Marcolin, G. Duarte, et al., Changes in Fetal and Maternal Doppler parameters in acute severe hypertension Treament with Hydralazine or Labetalol, Ultrasound Med. Biol. 37 (2011) 53–58.
[13] A. Harper, G.A. Murnaghan, Maternal and fetal haemodyanmics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalaol, Br. J. Obstet Gynaecol. 98 (1991) 453–459.