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**ORIGINAL ARTICLE**

# Randomized Controlled Trial of Labetalol Versus Hydralazine, for Severe Hypertension in Obstetric Patients, at Tertiary Care Hospital of Karachi

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## ABSTRACT

**Background:** Blood pressure ≥160/110 mm Hg, is indication for urgent drug therapy in obstetric women, to prevent complications and deaths. There is limited data for comparison of Labetalol to Hydralazine in emergent treatment of severe pregnancy related hypertension.

**Methods**: Randomized controlled trial, analyzed 184 women with severe hypertension at ≥28 weeks of pregnancy or within 72 hours after delivery, from October 2012 to September 2014. Ninety-two patients in each group received intravenous Labetalol or Hydralazine boluses, repeated every 10 or 20 minutes respectively (maximum 5 boluses). Outcome measures comprised blood pressure reduction <160/110 mm Hg, mean arterial pressure, severe persistent hypertension, number of boluses, maternal hypotension, tachycardia, adverse effect on fetal heart, still birth and neonatal bradycardia. Data was collected on a semi - structured proforma and analyzed through SPSS version 20. Numeric outcome measures were compared by Mann Whitney U test or independent sample t test according to normality distribution. Qualitative measures were compared by Chi square or Fisher's exact test. Level of significance was <0.05

**Results:** There was no significant difference in reduction of systolic, diastolic blood pressure and severe persistent hypertension, between Labetalol and Hydralazine (p>0.05). Tachycardia, palpitation, headache, were significantly higher (p <0.05) in Hydralazine group. Adverse effects on fetal heart were not statistically significant. Numbers of boluses were significantly lower in labetalol group.

**Conclusion:** Labetalol is equal to hydralazine in reducing severe pregnancy related hypertension. Maternal side effect profile of Labetalol is better, and it achieves blood pressure control with reduced boluses.

**Keywords:** Pregnancy-induced hypertension, Hypertensive crisis, Labetalol, Hydralazine, Pregnancy, Preeclampsia, Antihypertensive agent.

## INTRODUCTION

Hypertensive disorders of pregnancy(H.D.P) are among the leading causes of maternal deaths, following hemorrhage and infection throughout the world.[1] Every year 63,000 women die of hypertensive disorders in pregnancy and 95% of these deaths occur in low income countries.[1,2] H.D.P include gestational hypertension, preeclampsia and chronic hypertension and chronic hypertension with superimposed preeclampsia. [3,4] Severe hypertension is defined as systolic blood pressure (SBP) ≥160mmHg and /or diastolic blood pressure (DBP) ≥110mmHg and requires emergency treatment to prevent stroke, death and other adverse maternal and fetal outcomes. [4,5,6] Intravenous (IV) drugs are feasible and fast route for control of severe hypertension in pregnancy. Labetalol and Hydralazine are among intravenous antihypertensive agents recommended for hypertensive obstetric patients. Hydralazine has long been much familiar in obstetric practice; it is a direct arterial vasodilator but causes reflex tachycardia, headache, hypotension. [7,8] Labetalol is a combined alpha and beta blocker so it avoids tachycardia.[3,9] Latest Cochrane systematic review of treatment for severe hypertension in pregnancy included only 4 trials (274 women) for comparison of these two drugs; and only 2 trials reported severe persistent hypertension.[10] It suggested further large trials to compare detailed outcomes. Comparison of these drugs in terms of efficacy, safety and fetomaternal outcome is limited and their relative effectiveness in the treatment of severe hypertension in pregnant and postpartum women, has not been adequately studied. Our trial adds significant information about efficacy and numerous outcomes following intravenous treatment with these drugs in our women with hypertensive disorders of pregnancy.

## METHODS

In this prospective, randomized controlled trial registered in clinical trials.gov (NCT 0002050529), 184 patients, with severe hypertension defined as SBP ≥160 & / DBP ≥110 mm Hg were enrolled at tertiary care hospital of Karachi. The study was approved by the institutional review board of the Dow University of health Sciences Karachi. We calculated sample size assuming the prevalence of severe persistent hypertension of 0.5% with hydralazine and 10% with labetalol, and maternal hypotension as 1.4% with labetalol and 11.76% with hydralazine[7], the sample size required to detect a difference with a power of 80%, was 87 for each group.

Pregnant women ≥28 weeks of gestation or within 72 hours after delivery were enrolled from October 2012 to September 2014. Informed written consent was obtained from the patient or husband. Patients admitted through emergency or outpatient department with severe hypertension were recruited. Patients with asthma, cardiac failure, heart block, pacing device in place or cardiac arrhythmia were excluded. Patients were randomly allocated in 1:1 ratio, by sealed envelope method, to receive IV Bolus injection of Labetalol (Group A) and Hydralazine (Group B). Measures like height, weight, and BMI were taken and a detailed clinical history was recorded on the preformed proforma. Demographic data included age, residence, gestational age, parity and mode of delivery. The baseline values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded with mercury sphygmomanometer and treatment was initiated with the allocated drug. For I.V labetalol (Inj 50mg/10 ml ampoule), an initial dose of 20mg bolus was administered intravenously over 2 minutes, and boluses of 40 mg, 80 mg, 80 mg repeated at 10 minutes intervals, , if required till SBP became <160 and DBP <110 mmHg or maximum cumulative dose of 300mg (total 5 bolus doses). In Hydralazine group B, (inj 20mg/ml) bolus of 5 mg (slow intravenously over 2 minute) If SBP had not reduced to <160 mmHg and DBP <110 mmHg, further boluses of 5 mg were repeated every 20 min till SBP and DBP were reduced <160 and 110 mm Hg respectively or maximum 5 boluses i.e. 25 mg cumulative dose was reached. Blood pressure measurements were recorded every 10 and 20 minutes interval throughout treatment. Fetal cardiotocography (CTG) was done in pregnant participants, on admission and after 2 hours of treatment initiation. Failure to reduce SBP<160 & DBP<110 mm Hg with maximum 5 consecutive bolues was labelled as severe persistent hypertension, and patient was switched to alternate treatment regimen (A to B and vice versa). Primary outcome measures were, lowering of SBP<160 mmHg and DBP <110 mmHg(efficacy), severe persistent hypertension, number of boluses used.

Secondary outcome measures were headache, maternal hypotension, tachycardia, adverse effect on fetal heart as per operational definition, still birth and neonatal bradycardia were noted for further analysis. Data was entered and analyzed through analytical software, SPSS version 20. Numeric outcome measures were compared by Mann Whitney U test and independent sample t test according to their normality distribution. Qualitative measures were compared by Chi square or Fisher's exact test. Level of significance was ≤0.05.

**Operational Definitions:** Maternal hypotension : Systolic BP <110mmHg or diastolic BP <70 mmHg.

Neonatal bradycardia: Heart rate <100 beats/minute.

Adverse effect on fetal heart rate (FHR) was defined as cardiotocograph (C.T.G) tracing category; suspicious or pathological C.T.G [11,12], 2 hour after starting treatment, with a normal tracing on admission.

**Data Collection & statistical analysis:** A semi-structured proforma was used to collect data on patient's demographic, baseline information, outcome measures, Data was entered and analyzed through SPSS version 20. Numeric outcome measures were compared by Mann Whitney U test and independent sample t test according to their normality distribution. Qualitative measures were compared by Chi square or Fisher's exact test. Level of significance was ≤0.05.

## RESULTS

Table 1 shows maternal demographic features (age, parity, height, weight, BMI), gestational age, systolic, diastolic and mean arterial pressure on enrolment. It shows no significant difference between all demographic characteristics, and blood pressure confirming that both groups were similar at randomization. Analysis was done for 184 cases, i.e. 92 in each group, except for gestational age as 7 patients in group A and 8 patients in group B were postpartum. Mean age of patients in group A (Labetalol) was 25.89±5.20 year and group B (Hydralazine) was 26.95±6.09 years and they were not statistically significant (p=0.293). Mean parity in group A (Labetalol) was 1.51±1.94 and in group B (Hydralazine) was 1.609±2.36 Primigravidae were 53.3% in group A and 45.7% in group B. Mean systolic blood pressure (SBP) on treatment allocation was 174.66±20.11 mm Hg in A and 176.34±20.66 mmHg in B group. Mean Diastolic blood pressure (DBP) was 115.41±11.70 mm Hg in A and 117.10±12.26 mmHg in B group. Mean arterial pressure (MAP) of group A and group B were 133.43±11.41 mmHg and 135.75±13.18 mmHg respectively. Both groups were similar with regard to age, parity, income groups and ethnicity.After treatment with each drug there was no significant difference between groups in SBP,DBP,and M.A.P p>0.05. Seven women(7.6%) in Labetalol and 4(4.3%) women in Hydralazine group had severe persistent hypertension, who responded to alternate drug.

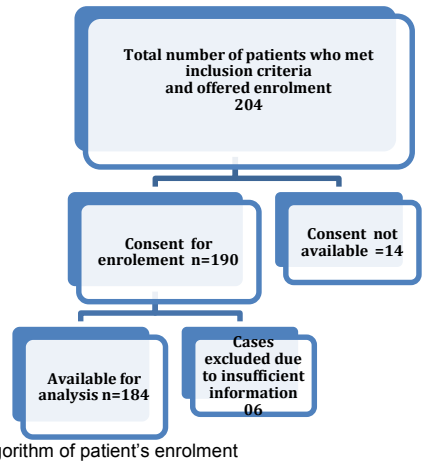


Figure 1: algorithm of patient's enrolment

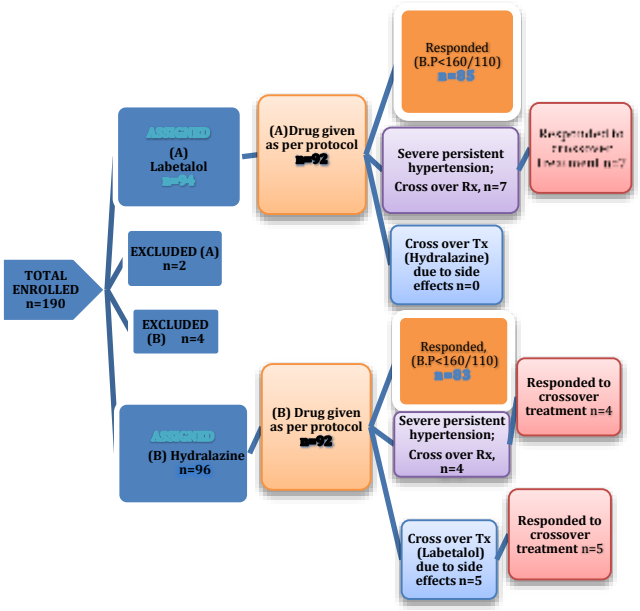


Figure 2: Scheme of Treatment Allocation And Response

Table 1: Maternal demographic features, systolic, diastolic and mean blood pressure on treatment allocation.

| Maternal Variables | | Median | Mean±SD (95 % CI) | P value |
|---|---|---|---|---|
| Maternal Age (Years) | A. Labetalol | 25 | 25.891±5.20 (24.81-26.97) | 0.293 |
| | B. Hydralazine | 26 | 26.96±6.08 (25.70-28.22) | |
| Parity | A. Labetalol | 1 | 1.511±1.94 (1.10-1.91) Median 1 | 0.601 |
| | B. Hydralazine | 0 | 1.609±2.36 (1.11-2.09) | |
| ●Gestational age(weeks) | A. Labetalol | 36.70 | 35.99±2.89 (35.37-36.61) | 0.333 |
| | B. Hydralazine | 36.00 | 35.32±3.611 (34.56-36.08) | |
| Weight(Kg) | A. Labetalol | 65.00 | 64.96±8.46 (63.21-66.72) | 0.389* |
| | B. Hydralazine | 65.00 | 66.07±8.94 (64.22-67.92) | |
| Height (cm) | A. Labetalol | 155.00 | 155.58±3.80) (154.72-156.45) | 0.888 |
| | B. Hydralazine | 155.00 | 154.17±14.15 (151.06-157.28) | |
| Body mass index ($kg/m^2$) | A. Labetalol | 26.83 | 26.94±3.06 (26.31-27.58) | 0.401* |
| | B. Hydralazine | 27.40 | 27.34±3.27 (26.66-28.02) | |
| Systolic Blood pressure (mm of Hg) | A. Labetalol | 170.00 | 174.66±20.94 (170.33-179.00) | 0.377 |
| | B. Hydralazine | 170.00 | 176.34±20.66 (172.06-180.62) | |
| Diastolic Blood pressure (mm of Hg) | A. Labetalol | 110.00 | 115.41±11.70 (112.99-117.74) | 0.225 |
| | B, Hydralazine | 117.00 | 117.10±12.26 (114.56-119.64) | |
| Mean Arterial pressure (mm of Hg) | A. Labetalol | 130.00 | 135.16±13.08 (132.45-137.87) | 0.232 |
| | B. Hydralazine | 133.00 | 136.99±13.47 (134.20-139.78) | |

Analyzed on 92 cases in each group p value calculated by Mann Whitney U test. Pregnant in group A, Labetalol n=85, group B, Hydralazine n=84, postpartum n=7 in group A and n=8 in group p value calculated by independent sample t test.

Table 2: Comparison Of Primary Outcome Measures (Numeric Variables) Between Two Treatments

| Outcome Variables | GROUP A LABETALOL n=92 Mean ±SD (C.I) | GROUP B HYDRALAZINE n=92 Mean ±SD (C.I) | P value |
|---|---|---|---|
| Systolic Blood pressure after allocated treatment | 145.35±11.20 (143.11-147.75) | 145.94±12.00 (143.45-148.43) | 0.502 |
| Diastolic Blood pressure after allocated treatment | 95.36±8.87 (93.53-97.20) | 95.43±9.53 (93.46-97.40) | 0.443 |
| Mean arterial pressure after allocated treatment | 112.05±8.88 (110.22-113.90) | 112.27±9.61 (110.28-114.26) | 0.446 |
| Mean drop in Systolic blood pressure with drug Rx | 29.22±19.57 (25.17-33.28) | 30.39±18.79 (26.49-34.28) | 0.467 |
| Mean drop in diastolic blood pressure with drug Rx | 20.04±12.69 (17.41-22.67) | 21.88±12.87 (19.21-24.54) | 0.309 |
| Mean drop in mean arterial pressure (MAP) with drug Rx | 23.10±13.15 (20.38-25.82) | 24.71±12.61 (22.10-27.32) | 0.231 |
| Mean no. of boluses | 2.01±1.18 (1.77-2.26) | 2.43±1.08 (2.21-2.66) | 0.002 |
| Time taken (minutes)to lower B.P below threshold; <160/110 | 20.45±21.39 (20.02-28.88) | 49.78±23.57 (44.89-54.66) | <0.001* |
| Dose(mg) of allocated Rx | 78.80±84.34 (61.34-96.27) | 12.12±5.30 (11.02-13.22) | <0.001* |
| APGAR at 1minute | 5.78±2.52 (5.22-6.35_ | 5.36±2.82 (4.71-6.00) | 0.551 |
| APGAR at 5 minutes | 7.21±2.97 (6.54-7.87) | 6.74±3.35 (5.97-7.50) | 0.747 |

Analysis based on intention to treat, as it includes all 92 cases in each group
p value calculated by Mann Whitney U test. *significant at <1%

Table 3: Comparison of Qualitative, Primary and Secondary Outcome Measures Between Two Treatments.

| Qualitative outcome measures | GROUP A LABETALOL n=92 (%) | GROUP B HYDRALAZINE n=92 ( % ) | P value |
|---|---|---|---|
| Primary outcome measures: | | | |
| Reduction in SBP<160, DBP<110 mm Hg | 85 (92.39) | 83 (90.21) | 0.601 |
| Severe Persistent hypertension | 7 (7.60) | 4 (4.34) | 0.351 |
| No. of doses: | | | |
| Single Bolus | 40 (43.5) | 16 (17.4) | <0.001* |
| 2-3 | 39 (42.4) | 58 (63.1) | 0.005* |
| 4-5 | 13 (14.1) | 18 (19.5) | 0.325 |
| Secondary outcome measures: | | | |
| Need for cross over treatment | 07 (7.60) | 9 (9.78) | 0.104 |
| Maternal Hypotension | 01 (1.1) | 7 (7.60) | 0.064● |
| Maternal tachycardia | 0 | 8 (8.69) | 0.007●* |
| ♥Headache | 2 ♥ (2.46) | 10 ♥ (12.82) | 0.030* |
| ♥♥Palpitation | 0 | 6 ♥♥ (7.22 ) | 0.014●* |
| Nausea vomiting | 3 (3.26) | 5 (5.43) | 0.720● |
| ♥♥Dizziness | 2 ♥♥ (2.59) | 5 ♥♥ (6.02) | 0.445 |
| Bronchospasm | 0 | 0 | |
| Maternal bradycardia | 0 | 0 | |
| *Adverse effect on fetal heart | 2 (2.9) | 5 (7.14) | 0.450 |
| **Stillbirth | 10 (7.60) | 13 (14.13) | 0.353 |
| Neonatal bradycardia | 1 (1.49) | 0 | 0.519● |
| ♥Placental abruption | 1 (1.17) | 0 | 1.000● |
| ♣Oliguria | 1 ♣ (1.14) | 1 ♣♣(1.16) | 1.000 |
| Cesarean for uncontrolled blood pressure | 0 | 0 | |
| ◄APGAR < 7 at 1 minute | 17 (25.37) | 20 (32.25) | 0.238 |
| ◄APGAR < 7 at 5 minutes | 5 (7.46) | 5 (8.06) | 0.507 |
| Neonatal intensive care unit(NICU)admission | 11 (11.95) | 14 (15.21) | 0.515 |

p value calculated by Fisher's exact test. *** p** value significant.

**Adverse effect on fetal heart:** % calculated out of n=68 in group A, n=70 in group B, as 15 in group A (i.e. 9 with suspicious and 6 with pathological fetal heart trace(CTG), and 16 in group B (i.e. 10 with suspicious and 6 with pathological fetal heart trace(CTG)presented .

♥For Headache{n(A)=81,(B)=78},♥♥ palpitation and Dizziness {n(A)=77,(B)=83},♣oliguria{n(A)=87, (B)=86}, ♥Abruptio placentae{n(A)=84(B)=82};for all these, % calculated out of mentioned{n} number of cases, since those already presenting with these outcomes before starting treatment were not included.

**Stillbirth: Includes intrauterine death on admission; 04 in group A, 3 in group B. Four (4) in labetalol group and 8 in hydralazine group had grade 3 meconium on admission.

◄ APGAR % calculated out live born babies{n(A)=77,(B)=83},

## DISCUSSION

Recent evidence suggest that SBP ≥160 mm may cause stroke and mandates treatment.[6,13,14,15]Centre for maternal and child enquries (CMACE) in its 2006-2008 report's top 10 recommendations included managing systolic hypertension[15].In severe hypertension, MAP should be reduced by 20%-25% in the first few hours [5,16] Cerebral hemorrhage, cardiovascular complications and deaths occur in pregnant women even if systolic blood pressure is below 160-170 mm[15,16]. Clinical recommendations and guidelines agree that pregnant/obstetric women with severe hypertension should have their SBP and DBP controlled to <160 and <110 mm of Hg respectively [5,6,16,17], The Cochrane review of antihypertensive drugs in pregnancy found few trials comparing Labetalol to Hydralazine, underlining the need for bigger trials with more outcome measures.[10,13] There is only one Panamian trial with 261 women, compared parenteral labetalol to hydralazine.[18] In our study, younger age and primiparity were predominant in both groups. As expected for severe hypertension majority of patients were diagnosed as eclampsia or preeclmapsia. Eclampsia was diagnosed in 35.32% of study population, 45.7% (n=42) in group A and 25% (n=23) in group B. Preeclampsia was the next frequent; 23.91% (n=22) group A versus 44.56% (n=41) in group B This is explained by young ag marriage in our society and higher proportion of primigravidae. In study from Nigeria by Noumber et al, Primigravidae were present in over 50% of total 126 participant pregnant women.[19]

Majority of women weighed <70 kg. Group A included 85 and B included 84 pregnant women. Majority of women delivered; Group A 77, (83.6%), Group B n=75, (81.5%). Majority had gestation >=34 weeks who delivered; 87.34% (n=69) in group A, and, 71.23%, (n=52) in group B. Ten in group A and 21 in group B were <34 weeks pregnant. In agreement to our findings, Vigil-Vigil De Gracia et al, in both their clinical trials of 200 pregnant women and 82 postpartum mothers, also did not find difference in lowering blood pressure and severe persistent hypertension. [20,21] Purvi from India in their study also found similar efficacy- and no difference in severe persistent hypertension, but more response with single bolus of labetalol.[22] However, a recently published RCT from Mardan used single bolus, reported significantly more drop of MAP with IV labetalol; 30.05 ± 5.32 mmHg versus Group B (hydralazine), 22.19 ± 8.27 mm Hg.[23]In our study severe persistent hypertension though greater in Labetalol group(7 vs 4 cases), but was not statistically significant. In the largest clinical trial (261 women) by Delgado, Hydralazine though caused more severe persistent hypertension 4.6% ; than labetalol but this effect was also not significant[18].

In our study, time to achieve desired effect was lower with Labetalol as explained by response with single bolus dose in 43.5% versus 17.4 % and number of boluses were significantly less compared to Hydralazine. However, Noumber et al from their RCT in Nigerian women found equal proportion of women who responded to single versus multiple boluses.[19]

Maternal hypotension, nausea, vomiting, oliguria, and adverse fetal cardiac effects observed as suspicious or

pathological CTG, were statistically insignificant in our results. However, Labetalol had substantially lower maternal tachycardia, palpitation and headache($p<0.05$). Noumber in their study also found significantly increased headache in Hydralazine group. [19]However, Indian study on treatment groups of 76 patients each did not find difference in these adverse effects [22]. Magee et al in meta analysis of 21 clinical studies, found more headache, palpitations, and tachycardia with Hydralazine[7]. Adverse effects on fetal heart are not significantly different, but lesser with Labetalol; 2.9% % Vs 7.14%. APGAR scores were also not significantly different. Purvi et al from India similarly report no significant difference[22]. Only one baby had neonatal bradycardia after treatment was from group A (Labetalol) was macrosomic and had hypoglycemia, so Labetalol per se, doesn't seems to be the cause of bradycardia.

Only two Panamanian clinical trials, comparing these two medicines with large sample sizes of 200 and 261 have been published in indexed medical journals [18,20].

**Study Strength:** Our research with sample of 184 is externally valid since most outcomes have narrow confidence intervals. We comprehensively studied numerous outcomes. We performed alternate therapy to test response to severe persistent hypertension.

**Limitations:** The present study was limited regarding adverse effect on fetal heart, as analysis of adverse effect on fetal heart, (secondary outcome) was done for 138 cases, since 31 cases were excluded from analysis as those cases presented with suspicious or abnormal CTG on admission. Our study also included postpartum patients and some pregnancies <37 weeks were kept on expectant management for which neonatal outcomes were not available.

## CONCLUSION

Our trial shows comparable efficacy of Labetalol equal to Hydralazine in managing severe hypertensive urgencies and emergencies in obstetric women. Maternal adverse effect profile of Labetalol is better, since tachycardia, palpitation and headache are significantly more with Hydralazine. Adverse effects on fetal heart are not significantly different, though lesser with Labetalol. Both drugs are useful alternative for patients not responding to one drug or who develop adverse effects. Labetalol is an effective and safe antihypertensive choice in pregnant women. Therefore, at preterm gestations while awaiting fetal maturity continued therapy with its oral preparation having wide therapeutic dosage range, makes it feasible and convenient choice.

**Abbreviations: A.C.O. G:** American College of Obstetricians and gynecologists; **C.H. K:** Civil Hospital Karachi; `SBP: Systolic blood pressure; **DBP:** Diastolic blood pressure: **H.D. P:** Hypertensive disorders of Pregnancy; **HTN:** Hypertension; **MAP:** Mean arterial pressure; **NICE:** National institute of clinical excellence; **WHO:** World Health Organization; **Rx:** Treatment; **SBP:** Systolic blood pressure

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