Original Article

A Comparative Study between Antihypertensive Drugs (Methyldopa, Labetalol, and Nifedipine) in Pre-Eclamptic Women: A Randomized Controlled Trial

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ABSTRACT

Objectives: The aim of the study was to compare efficacy, safety, and pregnancy outcome of antihypertensive drugs (methyldopa, labetalol, and nifedipine) used in management of preeclampsia (PE).

Methods: This randomized controlled trial study was carried out on 90 pregnant women with confirmed diagnosis of PE. The patients were divided into three equal groups: Group A: treated with alpha methyldopa 250 mg, group B: treated with labetalol 200 mg and group C: treated with nifedipine 10 mg.

Results: Pulsatility index (PI) of umbilical artery after treatment, resistive index (RI) of umbilical artery after treatment and PI of middle cerebral artery after treatment was significantly lower in groups B and C compared to group A. RI of middle cerebral artery was significantly higher in Group B and Group C than Group A (*P value* <0.001) while it was insignificantly different between Group B and Group C. There was no significant difference in mode of delivery, gestational age (GA (of the fetus at delivery, preterm delivery, postpartum hemorrhage, Hemolysis, elevated liver enzymes, and low platelet count (HELPP), placenta abruption syndrome, admission to neonatal intensive care unit (NICU), neonatal death at incubator and neonatal birth weight between the studied groups.

Conclusions: Labetalol and Nifedipine showed better efficacy and safety in management of PE as observed by stable blood pressure after treatment. Labetalol and Nifedipine were significantly better regarding Doppler indices (PI, RI) compared to Methyldopa.

Key Words: Biometry ultrasound, complications, doppler ultrasound, gestational age.

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INTRODUCTION

Pregnancy-induced hypertension (PIH) is estimated to affect about 0.34-11.5% of pregnancies globally, and approximately 11% of first pregnancies[1]. In Egypt, it was reported to affect 4.5% and 4.2% of pregnancies in two studies performed in Ain Shams and Zagazig University respectively[2,3].

PIH is classified into three categories: gestational hypertension, preeclampsia (PE), and eclampsia. Gestational hypertension is defined as the new onset of hypertension after 20 weeks of gestation. PE is known as a multi-organ disease process of unknown etiology, characterized by the development of hypertension and proteinuria after 20 weeks of gestation. Eclampsia is defined as the development of convulsions in preexisting PE[4]. For the mother, this includes a two- to four-fold increased risk of long-term hypertension, a doubling of the risk of cardiovascular mortality and major adverse cardiovascular events, and a 1.5-fold increased risk of stroke[5]. For the foetus, this includes antenatal risks of intra-uterine growth restriction (IUGR), preterm birth (most commonly iatrogenic), oligohydramnios, placental abruption, foetal distress, and foetal death in utero[6].

A combination of these factors results in decreased placental blood flow and oxygen supply and represses infiltrating cells after trophoblastic involvement[7]. Because of placental ischemia, the release of inflammatory cytokines, type-1 angiotensin II receptor autoantibodies, angiogenic and antiangiogenic factors, and syncytiotrophoblast-derived particles into the maternal circulation occur and precede the onset of symptomatic pregnancy hypertensive disorder[8]. The most prescribed drug for chronic hypertension during pregnancy is methyldopa. Methyldopa stimulates the central alpha-adrenergic receptors by a false neurotransmitter (α-methylnorepinephrine), which results

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in a decreased sympathetic outflow of norepinephrine to the heart, kidneys, and peripheral vasculature.

Nifedipine is a calcium channel blocker that has been used in pregnancy without any major issue. Long-acting nifedipine is preferred over short-acting nifedipine as the short-acting version of the medication can cause a significant drop in blood pressure, possibly leading to a reduction in uteroplacental perfusion[9,10].

The aim of the study was to compare efficacy, safety, and pregnancy outcome of antihypertensive drugs (methyldopa, labetalol, and nifedipine) used in management of PE.

PATIENTS AND METHODS

This randomized controlled trial study was carried out on 90 pregnant women aged from18 to 34 years old, body mass index (BMI) of less than 35 kg/m2, pregnant women with confirmed diagnosis of PE (new-onset hypertension [blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic], based on the International Society of the Study of Hypertension in Pregnancy criteria (2018)[11], a singleton living pregnancy and gestational age (GA) from 20 to 34 weeks]. The study was done from August 2022 to March 2023 after approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt. An informed written consent was obtained from the patients.

Exclusion criteria were the development of eclamptic fits during pregnancy, cardiovascular disease, endocrinal diseases (e.g., diabetes mellitus and thyroid dysfunction), hepatic or renal disease and immunological diseases e.g., systemic lupus erythromatosis.

Randomization and blindness

Based on the hospital records and according to the estimated annual rate of patients with pregnancy induced hypertension, the patients were divided randomly equally according to drug intake adjustment to three groups. Group A (Alpha methyldopa): treated with Aldomet ®, Algorithm S.A.L (250 mg) usual starting dosage of methyldopa is 250 mg two or three times a day in the first 48 hours, and the maintenance dose is 500 mg to 2 g in two to four doses. Group B (Labetalol): treated with Labipress ®, Al Debeiky Pharma (200 mg) starting oral dose 100 mg twice daily, and the dose was increased by 100 mg twice daily every 2-3 days based on the response of the blood pressure. Group C (Nifedipine): treated with epilat ®, EPICO (10 mg daily). An independent colleague prepared opaque sealed envelopes, containing either number I, II or number III, then conducted each patient to choose one of the opaque envelopes. After then, each patient was recruited to the suitable group according to the number in the envelope by the same colleague[12].

All patients were subjected to: history taking, clinical examination [mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP), mean HR, urinary dipstick proteinuria and blood pressure (BP) measurement Mean SBP and Mean DBP after treatment and time to reach the goal BP (SBP ≤140mmHg and/or DBP ≤90mmHg) (in days)], ultrasound (U/S) examination (doppler and biometry), measuring maternal outcomes [mode of delivery (Vaginal or Cesarean delivery), the incidence of postpartum hemorrhage, and the incidence of placenta abruption], measuring neonatal outcomes [birth weight (kg), gestational age)GA(of the fetus at delivery (days), preterm delivery, admission to neonatal ICU] and diagnosis of PE.

Ultrasound (U/S) examination

Standard fetal biometric parameters, Fetal weights were estimated using AC. It was performed on all patients while lying in a semi-recumbent position with slight lateral tilt with a small pillow under the right buttock. An ultrasound machine with Doppler unit and a convex linear transducer (3-5 MHZ) were used. Together with ultrasound scan, Doppler study was scheduled after medication, Systolic to Diastolic standard deviation (SD) of consecutive flow velocity waveforms were calculated. The angle between the ultrasonographic beam and direction of blood flow should be< 30 degree. The Doppler indices were calculated by the dedicated software supplied within the Doppler equipment.

Follow up

Patients were followed on a daily basis. Blood pressure was noted for different intervals of the pregnancy at every follow-up till controlling the blood pressure. The side effects of the drugs were analyzed. Maternal outcomes (such as placental abruption, parturition eclampsia) and fetal outcomes (such as perinatal mortality, low birth weight, intrauterine growth restriction, preterm labor) were assessed after the use of the drugs.

The primary outcome was control of blood pressure and prevention of complications of pre-eclampsia which include [Blood: Platelet count <100,000/microl (NICE<150000/microl), kidney: Serum creatinine >1.1 mg/dL (97.2 micromol/L) or doubling of the creatinine concentration in the absence of other renal disease, liver: transaminases at twice the upper limit of the normal concentrations, lung: Pulmonary edema and brain: Cerebral or visual symptoms]. The secondary outcomes were the effect of treatment on fetal weight and Doppler study, side effect of drug, maternal and Neonatal outcome.

Statistical analysis

Statistical analysis was done by SPSS v27 (IBM©,

Chicago, IL, USA). The Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analyzed by Kruskal-Walli's test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant[13].

RESULTS

There was no statistically significant difference in age, BMI, GA, gravidity, history and parity of PIH, mode of delivery, the average SBP, mean DBP, mean HR and urinary dipstick proteinuria between the studied groups. (Table1).

The average SBP, DBP and time to reach the goal was statistically significantly lower in group B and group C compared to group A, but there was no statistically significant difference in SBP, DBP and time to reach the goal after treatment between groups B and C. The number of patients who reached blood pressure goal (SBP ≤140 mmHg and/or DBP ≤90 mmHg) in group B and group C were statistically significantly higher compared to group A but there was no significant difference between group B and group C. (Table 2).

There was no significant difference in fetal weight, PI of umbilical artery RI of umbilical artery, PI of middle cerebral artery. RI of middle cerebral artery was statistically significant different among the studied groups (*P value* <0.001), RI of middle cerebral artery was statistically significantly higher in Group B and Group C than Group A (*P value* <0.001) while it was insignificantly different between Group B and Group C. The fetal weight was statistically significantly lower in group A than group B and higher in group A and group B compared to group C (*p <0.05*). PI of umbilical artery after treatment, RI of umbilical artery after treatment, PI of middle cerebral artery after treatment and RI of middle cerebral artery after treatment was statistically significantly lower in groups B and C compared to group A, but there was no statistically significant difference between groups B and C. (Table 3).

There was no statistically significant difference in mode of delivery, GA of the fetus at delivery, preterm delivery, postpartum hemorrhage, HELPP, placenta abruption syndrome, admission to neonate intensive care unit (NICU) and neonatal death at incubator between the studied groups. Neonatal birth weight was statistically insignificantly different among the three groups. (Table 4).

Table 1: Maternal and pregnancy characteristics, and clinical measurements at enrollment between the studied groups.

		Group A (n =30)	Group B (n =30)	Group C (n =30)	*P*
Age (years)		25.3 ± 3.04	26.2 ± 3.79	27.2 ± 4.02	0.145
BMI (kg/m^2)		27.83 ± 1.7	28.17 ± 2.12	27.87 ± 2.2	0.780
GA at enrollment (weeks)		34.83 ± 1.32	35.27 ± 1.01	35.37 ± 0.81	0.126
Gravidity		1 (1 - 2)	2 (1 - 2)	2 (1 - 2)	0.361
Previous history of PIH		3 (10%)	3 (10%)	1 (3%)	0.538
Parity		0 (0 - 1)	1 (0 - 1)	1 (0 - 1)	0.248
Mode of delivery in the last pregnancy	Vaginal delivery	10 (33.3%)	15 (50%)	12 (40%)	0.418
	Cesarean delivery	20 (66.7%)	15 (50%)	18 (60%)	
SBP at enrollment (m Hg)		156.17 ± 12.6	156.83 ± 9.51	159.33 ± 12.8	0.537
DBP at enrollment (mmHg)		107.67 ± 12	105 ± 12.03	110.5 ± 13.28	0.237
Mean HR (B/M)		96.1 ± 15.6	101.9 ± 19.23	98.5 ± 17.7	0.525
Urinary dipstick proteinuria	Nil	11 (37%)	7 (23%)	10 (33%)	0.884
	1+	7 (23%)	10 (33%)	9 (30%)	
	2+	10 (33%)	9 (30%)	8 (27%)	
	≥3+	2 (7%)	4 (13%)	3 (10%)	

Data are presented as mean± SD or frequency (%) or median (IQR). * Significant *p value* <0.05, BMI: Body mass index, GA: gestational age. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, B/M: Beat per Minute.

Table 2: Blood pressure measurement after treatment and goal reach in the studied groups

	(Group A (n =30	(Group B (n =30	(Group C (n =30	*P*
SBP after treatment (mmHg)	143.17 ± 13.8	133.33 ± 8.44	133.83 ± 11.19	0.003*
		P1: 0.01*, P2: 0.009*, P3: 1.000		
(DBP after treatment (mmHg	95.67 ± 11.2	95.67 ± 11.2	87.33 ± 13.24	*0.001
		P1: <0.001*, P2: 0.028*, P3: 0.946		
Reach blood pressure goal (N)	17 (56.7%)	26 (86.7%)	25 (83.3%)	0.039*
		P1: 0.009, P2: 0.024, P3: 0.718		
(Time to reach the goal (days	7.97 ± 1.43	4.2 ± 0.76	4.7 ± 1.29	*0.001>
		P1: <0.001*, P2: <0.001*, P3: 0.07		

Data are presented as mean± SD or frequency (%). * Significant *p value* <0.05, P1: Significance between group A and group B, P2: Significance between group A and group C, P3: Significance between group B and group C, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table 3: Ultrasound and doppler ultrasound at enrolment and after treatment in the studied groups

	(Group A (n =30	(Group B (n =30	(Group C (n =30	*P*
(Fetal weight(grams	287.38 ± 2350	235.6 ± 2436.67	190.46 ± 2460	0.338
PI of umbilical artery	0.06 ± 1.51	0.04 ± 1.49	0.05 ± 1.5	0.493
RI of umbilical artery	0.03 ± 0.76	0.02 ± 0.77	0.04 ± 0.75	0.098
PI of middle cerebral artery	0.14 ± 1.73	0.12 ± 1.75	0.1 ± 1.75	0.239
RI of middle cerebral artery	0.03 ± 0.77	0.04 ± 0.81	0.04 ± 0.82	*0.001>
		P1< 0.001*, P2<0.001*, P3: 0.318		
Fetal weight (grams)	320.22 ± 2956.67	220.87 ± 3153.33	239.95 ± 2803.33	<0.001*
		P1< 0.001, P2:0.04, P3: <0.001		
After treatment				
PI of umbilical artery	0.14 ± 1.1	0.04 ± 0.95	0.12 ± 0.98	<0.001*
		P1: <0.001*, P2: 0.002*, P3: 0.839		
RI of umbilical artery	0.09 ± 0.58	0.03 ± 0.47	0.02 ± 0.46	*0.001>
		P1: <0.001*, P2: <0.001*, P3: 0.317		
PI of middle cerebral artery	0.12 ± 0.75	0.03 ± 0.61	0.03 ± 0.6	*0.001>
		P1: <0.001*, P2: <0.001*, P3: 1.000		
RI of middle cerebral artery	0.05 ± 0.85	0.01 ± 0.9	0.02 ± 0.9	*0.001>
		P1: <0.001*, P2< 0.001*, P3: 0.930		

Data are presented as mean± SD or frequency (%). * Significant *p value* <0.05, P1: Significance between group A and group B, P2: Significance between group A and group C, P3: Significance between group B and group C, PI: Pulsatility index, RI: Resistance index.

Table 4: Maternal and neonatal outcomes in the studied groups

		Group A (n =30)	Group B (n =30)	Group C (n =30)	*P*
Maternal outcomes					
Mode of delivery	Vaginal delivery	7 (23%)	10 (33%)	9 (30%)	0.164
	Cesarean delivery	23 (77%)	20 (67%)	21 (70%)	
GA of the fetus at delivery (weeks)		37 (36.25 – 37)	37 (36 – 37)	37 (36 - 38)	0.917
Preterm delivery		6 (20%)	3 (10%)	5 (16.7%)	0.553
Postpartum Hemorrhage		3 (10%)	2 (6.7%)	2 (6.7%)	0.857
Placenta Abruption		0 (0%)	1 (3.3%)	1 (3.3%)	0.599
HELPP syndrome		2 (6.7%)	1 (3.3%)	1 (3.3%)	0.769
Neonatal outcomes					
Birth weight (kg)		2.89 ± 0.51	3.11 ± 0.35	2.92 ± 0.42	0.098
Admission to NICU		7 (23.3%)	2 (6.7%)	6 (20%)	0.186
		N=7	N=2	N=6	
Neonatal death at incubator		2 (29%)	1 (50%)	3 (50%)	0.699

Data are presented as mean± SD or frequency (%) or median (IQR). * Significant *p value* <0.05, HELPP: Hemolysis, Elevated Liver Enzymes, and Low Platelet Count, NICU: Neonatal intensive care unit, GA: Gestational age.

DISCUSSION

PE is a multisystem disorder of pregnancy which is a major cause of maternal and fetal morbidity and mortality worldwide. Pre-eclampsia often affects young and nulliparous women, whereas older women are at great risk of chronic hypertension with superimposed PE[14].

In the current study, after treatment the mean SBP and mean DBP were statistically significantly lower in group B and group C compared to group A but there was no statistically significant difference in SBP and DBP between groups B and C. In agreement with our results, El-sadek and Ahmed[15] showed that in labetalol group; 24% had SBP<150 mmHg, 76% had SBP >150 mmHg, DBP was <100 mmHg in 30%, and >100 mmHg in 70%, in α-Methyldopa group; 20 % had SBP<150 mmHg, 80% had SBP >150 mmHg, DBP was <100 mmHg in 26%, and >100 mmHg in 74%, there was nonsignificant difference between groups as regard BP before treatment. Our results agreed with Webster *et al*.[16] demonstrated that labetalol and nifedipine showed an effective controlling for diastolic and systolic blood pressure (labetalol 134/84 mm Hg versus nifedipine 134/85 mmHg).

According to our results, the number of patients who reached blood pressure goal (SBP ≤150mmHg and/or DBP ≤100mmHg) in group B and group C were statistically significantly higher compared to group A (p =0.009 and 0.024 respectively) but there was no statistically significant difference between group B and group C. Our findings agree with another study conducted by Babbar *et al*.[17] observed the mean BP after treatment with methyldopa and labetalol to be 146/94±13.4/7.5 mmHg and 133/84±14/11 mmHg respectively. In agreement with our results,, Velusamy[18] observed BP after treatment 132.70/89.50±14.40/9.41 with nifedipine and 132.46/87.95±14.08/9.19 with methyldopa.

In the present study, the time to reach the goal in group B and group C was statistically significantly lower compared to group A (p <0.001) but there was no statistically significant difference between group B and group C. In agreement with our results, El-sadek and Ahmed[15] reported that the time needed for BP controlling in labetalol group was significantly lower in comparison to α-Methyldopa group. This agreed to the study of Subhedar *et al*.[19] concluded that the mean period needed for BP controlling in methyldopa group was 42.22-h and in labetalol group it was 36.97-h. The variance among the studied groups was significant with labetalol display former controlling of BP in comparison to methyldopa.

In our study, fetal weight was statistically significantly higher in group A and group B compared to group C, but there was no statistically significant difference between groups A and B. In agreement with our results, El-sadek and Ahmed[15] reported that the median time from registration to labour was about one day, The occurrence of stillbirth, neonatal mortality, and neonatal morbidity didn't differ among groups. But the frequency of neonatal admissions to NICU was significantly high in babies of mothers allocated to nifedipine vs. labetalol (p=0·009) and methyldopa (p=0·004), predominantly owing to low or very low weights of birth. The mean periods of stay in ICU (lesser than vs at minimum 1-day) didn't vary among groups. As regards neonatal outcomes, a significant change was found among the study groups regarding GA, with non- statistically significant differences as regard mass of birth, Apgar at 1-min, and Apgar at 5-min. Our findings disagreed to Salama *et al*.[20] found that fetal weight was insignificantly different between Methyldopa and nifedipine groups. The different sample size may affect the results.

In our study, PI and RI of umbilical artery were statistically significantly lower in groups B and C compared to group A, but there was no statistically significant difference between groups B and C. RI of middle cerebral artery was statistically significant different among the studied groups (*P value* <0.001), RI of middle cerebral artery was statistically significantly higher in Group B and Group C than Group A (*P value* <0.001) while it was insignificantly different between Group B and Group C. Our findings agreed to Mohamed *et al*.[21] showed that the uterine artery RI did not show any significant change but there was a significant increase in Umbilical artery RI. In agreement with our results, Lima *et al*.[22] who conducted their prospective, observational, analytic cohort study on 47 pregnant women undergoing nifedipine tocolysis treatment, the middle cerebral artery RI was significantly reduced after 24 hours while in this study there was no significant change in Middle cerebral artery RI after seven days.

In the present study, there was no statistically significant difference in birth weight, GA at delivery, maternal outcomes (mode of delivery and preterm delivery) and complications (postpartum hemorrhage, placenta abruption, and HELPP syndrome) between the studied groups. In agreement with our results, Babbar *et al*.[17] noted that complications were more common with Nifedipine group as compared to Methyldopa and Labetalol group.

In our study, there was no statistically significant difference in admission to neonatal ICU or intrauterine death between the studied groups. In agreement with our results, Salama *et al*.[23] reported that there was no significant variation regarding the admission to neonatal ICU intrauterine fetal demise and neonatal death between the treatment groups.

Limitations of this study included that the study was conducted at a single center, which may limit the generalizability of the findings to other settings and

populations, did not assess long-term maternal or neonatal outcomes, focusing primarily on short-term outcomes and side effects, did not evaluate the impact of these antihypertensive agents on breastfeeding initiation and success, which could be important considerations in postpartum care.

CONCLUSIONS

Labetalol and Nifedipine showed better efficacy and safety in management of pre-eclampsia as observed by stable blood pressure after treatment, higher number of patients reached the goal with shorter time to reach the goal compared to Methyldopa. Labetalol and Nifedipine were significantly better regarding Doppler indices (PI, RI) compared to Methyldopa. Regarding safety, there was a significant reduction in birth weight in Nifedipine compared to Labetalol.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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