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The Effect of Methyl Dopa, Nifedipine and Labetalol Treatment on Uterine, Umbilical and Fetal Middle Cerebral Artery Blood Flows in Cases Suffered from Pregnancy Induced Hypertension

Menna Allah Kamal Hassan[1*], Mohamed Mohsen Elnamory[1], Ayman Abd Elaziz Eldorf[1] and Hesham Mohamed Eltokhy[1]

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Treatment of severe maternal hypertension is strongly indicated for the prevention of maternal complications, such as cerebrovascular accidents and placental abruption, for avoiding extreme pre maturity. The selection criteria for the various antihypertensive drugs are somewhat unclear, and although vasodilator agents reducing peripheral vascular resistance (e.g., methyldopa, nifidipine and labetalol) have been accepted for general obstetric use. The aim of the study is to compare the effect of methyl dopa, nifedipine and labetalol treatment on the doppler indices of uterine, umbilical and fetal middle cerebral artery blood flows in cases suffered from pregnancy induced hypertension.

Methods: This prospective randomized comparative clinical trial study was carried out on 75 pregnant women suffered from pregnancy-induced hypertension. The patients were divided into three equal groups: Group I: received alpha methyldopa750 mg-2000 mg per day, Group II: received labetalol 100 mg twice per day and Group III: received nifedipine oral sustained tablets

**Corresponding author: E-mail: mennskama@gmail.com;*

20-120mg per day.
Results: Follow up of the patients was done with assessment of the outcome measures and statistical analysis was done and revealed that the use of alpha methyldopa, nifedipine and labatalol in pregnancy induced hypertension cases produce significant reduction of blood pressure ,prolong pregnancy duration, decrease the need for maternal admission to the ICU due to uncontrolled severe hypertension, decrease insignificantly the progression of mild preeclampsia to severe preeclampsia without producing negative effect on the mother or the fetus because these drugs did not impair the uteroplacental or middle cerebral blood flow documented by Doppler studies.
Conclusions: Use of methyl dopa, nifidipine and labetalol treatment in PIH cases make an improvement of uteroplacental and middle cerebral blood flow which indicated by maternal uterine, umbilical and fetal middle cerebral arteries doppler indices (resistive index, pulatility index and S/D ratio). Labetalol is ideal first line of treatment because it has potent and fast hypotensive effect without producing significant side effects on the mother or fetus.

Keywords: Methyl dopa; nifedipine; labetalol; uterine; umbilical; middle cerebral artery; pregnancy induced hypertension.

1. INTRODUCTION

Pregnancy induced hypertension is one of the most common cause of fetal and maternal morbidity and mortality it is one of the deadly triad with heamorrhage and infection world-wide. It calculates for a total of 7-10% of perinatal mortality in developed countries and 20% in developing countries (The perinatal mortality is 5% in mild pregnancy induced hypertension and 15 to 25% in severe pregnant induced hypertension) [1].

Treatment of severe maternal hypertension is still strongly indicated for the prevention of maternal complications, such as cerebrovascular accidents and placental abruption, for avoiding extreme pre maturity. The selection criteria for the various antihypertensive drugs are somewhat unclear, and although vasodilator agents reducing peripheral vascular resistance (e.g. methyldopa, nifidipine and labetalol) have been accepted for general obstetric use , there are still problems involved in calculating their benefits and potential hemodynamic hazards [2].

Oral labetalol is considered a first-line agent for non-severe hypertension in pregnancy and is in fact the only first line agent recommended by the British guidelines [3]. Long-acting nifedipine can be given orally at 10 mg to start, repeating after 30 minutes if required in this study clinically antihypertensive medications could have negative impact on uteroplacental blood flow by decreasing maternal peripheral blood pressure when there is existing raised uterine artery resistance The main pathologic feature of pregnancy induced hypertension is vasospasm, which leads to impairment of blood flow to various organs particularly the uterus .and placenta These placental blood flow abnormalities give rise to interference with fetal oxygenation and growth. It is now thought that uteroplacental ischaemia is responsible for pegnancy induced hypertension Abnormal umbilical artery Doppler velocimetry was found to be associated with more frequent growth retardation and fetal distress. The middle cerebral artery is the most studied cerebral artery because it is easy to sample; it provides information on the cerebral blood flow [3, 4].

The aim of the study is to compare the effect of methyl dopa, nifedipine and labetalol treatment on the doppler indices of uterine, umbilical and fetal middle cerebral artery blood flows in cases suffered from pregnancy induced hypertension.

2. PATIENTS AND METHODS

This is prospective randomized comparative clinical trial was carried out in Tanta University hospital at the department of Obstetrics and Gynecology from January 2020 to January 2021.

The study comprised 75 pregnant women suffered from pregnancy-induced hypertension.

Pregnancy induced hypertension was diagnosed if: Systolic blood pressure is 140 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher on two occasions at last 6 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure , pre – eclampsia if proteinuria: 0.3 g or more of protein

in a 24-hour urine collection (usually corresponds with 1+ or greater on a urine dipstick test) but:

Severe preeclampsia was diagnosed if: Systolic blood pressure is 160 mm Hg or higher or diastolic blood pressure 110 mm Hg or higher on two occasions at least six hours apart in a woman on bed rest. Other features are cerebral or visual disturbance s, pulmonary edema or cyanosis, epigastric or right upper quadrant pain, impaired liver function, thrombocytopenia.

2.1 Inclusion Criteria

- Pregnant woman aged 18 to 35 years old.
- Pregnancy induced hypertension defined as a resting blood pressure ≥ 150/100 mm hg on 2 occasions at least 6 h apart.
- Singleton pregnancy.
- Gestational age 24 to 35 weeks.

2.2 Exclusion Criteria

- Pre-Existing chronic Hypertension.
- Diabetes Mellitus.
- Chronic renal failure.
- Ischaemic cardiac disease.
- Patients received medical treatment for hypertension before inclusion to the study

The study population was assessed via the following: The patients were randomly allocated to groups using computer generated random number tables and opaque sealed envelopes containing the patients' group allocation. All patients were blinded to the allocation to avoid bias.

The patients were divided into three equal groups: Group I: Included 25pregnant women who received alpha methyldopa750 mg-2000 mg per day as antihypertensive (Aldomet 250 mg tab, Kahira pharm company, Cairo).

Group II: Included 25 pregnant women who received labetalol 100 mg twice per day as antihypertensive maximum dose 400 mg per day (Labipress100 mg tab, dBK pharma)

Group III: Included 25 pregnant women who received nifedipine oral sustained tablets 20-120mg per day as antihypertensive (Epilat Retard tab 20 mg, EIPICO).

The previous drugs were given to the patients if the blood pressure reached 150 mmHg systolic or 100 mmHg diastolic. The target is to keep the systolic blood pressure less than 140 mmHg and diastolic blood pressure (80 mmHg-90 mmHg) as recommended by the NICE guidelines (2010): "Hypertension in pregnancy: Diagnosis and management".

2.2.1 All patients in this study will be subjected to the following

I. History taking:
II. Clinical examination: General and obstetric examination.
III. Investigation: Routine antenatal investigations with specially serum uric acid and urine analysis.
IV. Ultrasound study:

- Measurement of fetal biometry.

Doppler US: Pulsatility and resistivity index, systolic / diastolic ratio of uterine, umbilical, and fetal middle cerebral arteries were measured before and after 2weeks of starting anti-hypertensive medication.

All cases were admitted to Tanta University hospital at the department of Obstetrics and Gynecology with performance of the following for all cases:

Daily assessment for clinical findings such as headache, visual disturbances, epigastric pain, and rapid weight gain.

- Daily maternal weight and intake and output assessment looking for signs of oliguria
- Frequent blood pressure readings typically every 4-8 hours.
- 24 hr. urine collection for protein.
- For mild preeclampsia, repeat lab tests twice weekly if stable values without progression; sooner if disease progression is questionable or if more significant disease is suspected.
- Daily fetal movement assessment.
- Ultrasound for fetal growth every 2 weeks.
- Weekly assessment of amniotic fluid (modified BPP).
- A course of dexamethasone given to women <34 weeks at risk of preterm labor.
- Indications of termination of termination of pregnancy:

2.3 Fetal Indications

- Fetal growth restriction.

- Non- reassuring fetal status.

2.4 Maternal Indications

- Development of severe preeclampsia

Termination of pregnancy was either by spontaneous vaginal delivery, induction of labor or cesarean section if indicated.

2.5 Outcome Measures

Maternal outcomes: Doppler velocimetry of the uterine arteries at presentation and after two weeks. Development of Severe preeclampsia Gestational age at delivery. Amniotic fluid index.

2.5.1 Fetal outcomes

Doppler velocimetry of the umbilical and middle cerebral arteries

- Intrauterine growth restriction.
- Preterm birth.
- Five-minute Apgar score.
- Respiratory distress syndrome.
- Admission to neonatal intensive care unit.

Sample size calculation: The power analysis and sample size was calculated using Epi-info software statistical package created by worldwide health organization and center for Disease Control and Prevention, Atlanta, Georgia, USA version2002. The criteria used for sample size calculation were as follows: 95% confidence limit, 80%power of the study and expected outcome in favorable treatment group 95% compared to least favorable treatment group is 60%. The sample size based on the previously mentioned criteria was found at N>23for each study group.

2.6 Statistical Analysis

Results were statistically analyzed by SPSS version 20(SPSS Inc., Chicago, IL, USA). Descriptive analysis was by percentage (%), mean and standard deviation. A one-way analysis of variance (ANOVA) a test was used to collectively indicate the presence of any significant difference between several groups for normally distributed quantitative variables. Post hoc test was used after one way ANOVA (F test) or Kruskal -Wallis test to show any significant difference between the individual groups. Paired t test was used to collectively indicate the presence of any significant difference between different time sequences for normally distributed quantitative variables. Chi-Squared ($\chi 2$) test was used to compare between two groups or more regarding one qualitative variable in 2x2 contingency table or complex table. P value≤ 0.05 was considered significant.

3. RESULTS

There were no statistically significant differences among the three studied groups in terms of all demographic characteristics (age, BMI, occupation and residency) ($p<0.05$). Table 1.

There were no statistically significant differences among the three study groups as regards parity, Number of Gestations and gestational age at presentation of study ($P>0.05$). It also demonstrates that, no statistically significant differences among the three study groups as regards presence of edema and proteinuria. Table 2.

There were no statistically significant differences among the three study groups as regards blood pressure measurements before and after treatment. Fig. 1.

There were highly statistically significant differences among within group comparison in terms of Resistance index (RI) measurements before and after treatment ($P<0.001$). Table 3.

There were highly statistically significant differences among within group comparison of Pulsatility index (PI) measurements of the studied groups before and after treatment with the exclusion of Methyl-dopa group in UM. Table 4.

There were highly statistically significant differences in terms of within group comparison of Systolic/diastolic (S/D) ratio measurements before and after treatment ($P<0.05$).Table 5.

There were highly statistically significant differences as regards time to control BP being decreased in Labetalol group followed by Methyl-dopa and lastly Nifedipine ($P<0.001$).Table 6.

Table 1. Demographic data of all participants

		Methyl-dopa group (n= 25)	Nifedipine group (n= 25)	Labetalol group (n= 25)	P	P1	P2	P3
Age (years)		24.88 ± 4.177	24.96 ± 3.155	26.84 ± 4.930	0.175	1	0.298	0.341
BMI (kg/m2)		30.12 ± 2.097	30.04 ± 2.034	30.39 ± 2.146	0.825	1	1	1
Occupation	Housewife	56.0% (14)	72.0% (18)	52.0% (13)	0.311	0.238	0.777	0.145
	Worker	44.0% (11)	28.0% (7)	48.0% (12)				
Residency	Urban	28.0% (7)	32.0% (8)	24.0% (6)	0.820	0.758	0.747	0.529
	Rural	72.0% (18)	68.0% (17)	76.0% (19)				

Table 2. Obstetric history and presence of edema and proteinuria of the studied groups

	Methyl-dopa group (n= 25)	Nifedipine group (n= 25)	Labetalol group (n= 25)	P	P1	P2	P3
Parity	0.96 ± 0.455	1.08 ± 0.759	1.0 ± 0.764	0.815	0.805	0.976	0.908
Number of Gestations	1.20 ± 0.408	1.44 ± 0.651	1.32 ± 0.476	0.273	0.241	0.696	0.695
Gestational age (weeks)	32.20 ± 1.414	31.40 ± 1.658	32.28 ± 1.339	0.073	0.178	1	0.116
Edema	64.0% (16)	76.0% (19)	68.0% (17)	0.645	0.355	0.765	0.529
Proteinuria	20.0% (5)	20.0% (5)	32.0% (8)	0.518	1.0	0.333	0.333

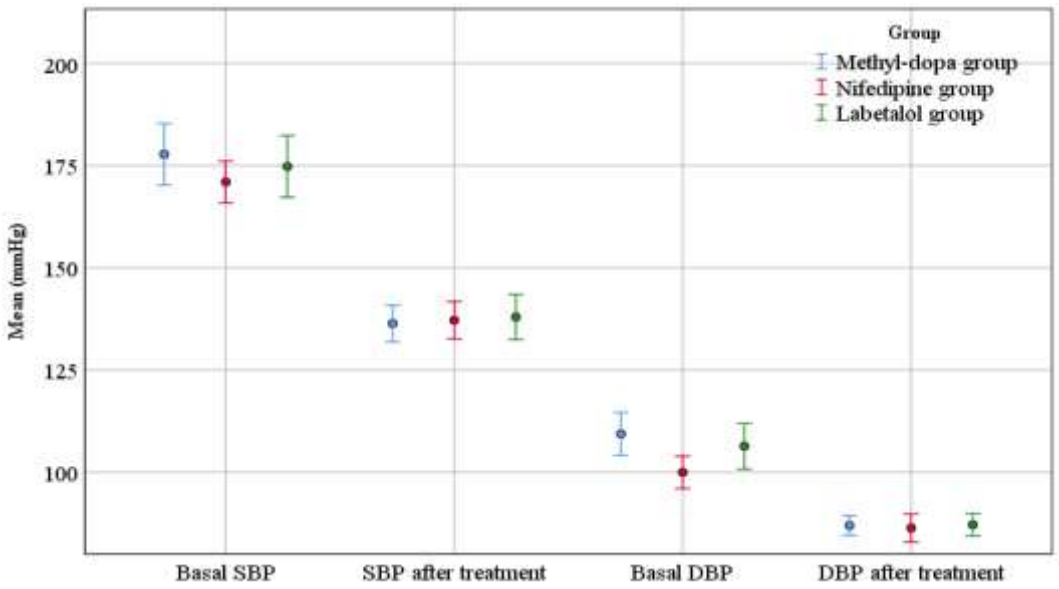

Fig. 1. Blood pressure measurements of the studied groups before and after treatment

Table 3. Within group comparison of Resistance index (RI) measurements of the studied groups before and after treatment

RI		Pre-treatment	Post-treatment	95% CI	P
Uterine artery	Methyl-dopa group	0.67 ± 0.080	0.57 ± 0.071	0.08, 0.13	< 0.001*
	Nifedipine group	0.70 ± 0.115	0.58 ± 0.089	0.10, 0.15	< 0.001*
	Labetalol group	0.66 ± 0.097	0.56 ± 0.094	0.08, 0.12	< 0.001*
Umbilical artery	Methyl-dopa group	0.67 ± 0.091	0.57 ± 0.076	0.06, 0.13	< 0.001*
	Nifedipine group	0.71 ± 0.138	0.58 ± 0.093	0.10, 0.17	< 0.001*
	Labetalol group	0.65 ± 0.107	0.55 ± 0.097	0.07, 0.12	< 0.001*
Middle cerebral artery	Methyl-dopa group	0.57 ± 0.051	0.70 ± 0.098	-0.09, -0.17	< 0.001*
	Nifedipine group	0.57 ± 0.074	0.73 ± 0.090	-0.12, -0.20	< 0.001*
	Labetalol group	0.57 ± 0.067	0.71 ± 0.113	-0.09, -0.18	< 0.001*

Table 4. Within group comparison of Pulsatility index (PI) measurements of the studied groups before and after treatment

PI		Basal	Post-treatment	95% CI	P
Uterine artery	Methyl-dopa group	1.22 ± 0.389	1.11 ± 0.316	0.06, 0.16	< 0.001*
	Nifedipine group	1.41 ± 0.375	1.24 ± 0.292	0.11, 0.24	< 0.001*
	Labetalol group	1.32 ± 0.360	1.15 ± 0.266	0.11, 0.23	< 0.001*
Umbilical artery	Methyl-dopa group	0.97 ± 0.311	0.94 ± 0.253	-0.01, 0.08	0.084
	Nifedipine group	1.13 ± 0.300	1.04 ± 0.234	0.04, 0.14	0.002*
	Labetalol group	1.06 ± 0.288	0.97 ± 0.213	0.04, 0.14	0.001*
Middle cerebral artery	Methyl-dopa group	1.35 ± 0.425	1.39 ± 0.396	-0.01, -0.08	0.022*
	Nifedipine group	1.50 ± 0.377	1.55 ± 0.365	-0.01, -0.08	0.015*
	Labetalol group	1.37 ± 0.331	1.43 ± 0.333	-0.02, -0.10	0.004*

Table (3) shows pregnancy outcome in the studied groups. There were no statistically significant differences among the three studied groups in terms of mode of delivery, APGAR, birth weight and NICU admission (P<0.05).Table 7.

4. DISCUSSION

Treatment of pregnancy-related hypertensive disorders, such as preeclampsia (PE), remains a challenging problem in obstetrics. Typically, aggressive antihypertensive drug treatment

options are avoided to prevent pharmacological-induced hypotension. Another major concern of administering antihypertensive drugs during pregnancy is possible adverse fetal outcome. In addition, management of hypertension during pregnancy in chronic hypertensive patients or in patients with prior kidney problems are carefully considered [5].

Our study revealed by comparing each group with the control group, there was significant reduction in average both after treatment systolic and diastolic blood pressure compared to systolic and diastolic blood pressure at presentation.

This is in agreement with (John et al., 2012) that revealed significant reduction in both systolic and diastolic blood pressure in preeclamptic patients receiving antihypertensive drugs especially among those receiving combination of alpha methyldopa and nifedipine [(119)]. This is also in agreement with (Subhedar et al., 2013) who compared effect of labetalol versus alpha methyldopa in 180 cases with mild preeclampsia. (Subhedar et al., 2013) found that labetalol produces more reduction and shorter time (36.97 hours) needed to control blood pressure than alpha methyldopa (42.22 hours) and this is in agreement with our study and also in agreement with (Dharwadkar et al., 2014) whose study done to assess the efficacy and safety of labetalol compared with methyldopa in the management of mild and moderate cases of pregnancy-induced hypertension (PIH). Their study included 40cases of mild preeclampsia and 40cases of gestational hypertension [6].

In our study found that alpha methyldopa, labetalol and nifedipine produce significant reduction of blood pressure in cases of pregnancy induced hypertension but labetalol produces more significant reduction in diastolic blood pressure compared to alpha methyldopa.

We studied the effect of drugs used in our study on Doppler to know if their hypotensive effect can affect the uteroplacental blood flow and compromise the fetus or not. Our study found that methyldopa, nifidipine and labetalol as anti-hypertensive drug make an improvement of maternal uterine artery, umbilical artery and middle cerebral artery indices by decrease S/D ratio, resistive index and pulsatility index of uterine artery and umbilical artery significantly and increase S/D ratio, resistive index and pulsatility index of fetal middle cerebral artery doppler.

Regarding BP before and after treatment, the current study demonstrated that, there were highly statistically significant decrease in SBP and DBP following the treatment in comparison with the pre-treatment measures (P<0.001) in three studied groups. In addition, blood pressure measurements before and after treatment demonstrated insignificant changes among the three studied groups.

In addition, there were highly statistically significant differences as regards time to control BP being decreased in Labetalol group followed by Methyl-dopa and lastly Nifedipine (P<0.001).

These results are in accordance with that of a study of Thakur et al. (2016) who conducted their study on M.Y. Hospital, for one year. Three groups each of 50 patients were given nifedipine, labetalol, and methyldopa. They demonstrated that, there was a significant fall of blood pressure among the three studied groups (P<0.05), while there were no significant differences among the three studied groups [6].

Table 5. Within group comparison of Systolic/diastolic (S/D) ratio measurements of the studied groups before and after treatment

S/D		Pre-treatment	Post-treatment	95% CI	P
Uterine artery	Methyl-dopa group	2.84 ± 0.601	2.52 ± 0.462	0.23, 0.41	< 0.001*
	Nifedipine group	3.17 ± 0.594	2.72 ± 0.475	0.35, 0.54	< 0.001*
	Labetalol group	2.97 ± 0.525	2.56 ± 0.396	0.31, 0.51	< 0.001*
Umbilical artery	Methyl-dopa group	2.47 ± 0.486	2.35 ± 0.363	0.03, 0.21	0.010*
	Nifedipine group	2.75 ± 0.514	2.51 ± 0.386	0.16, 0.34	< 0.001*
	Labetalol group	2.56 ± 0.418	2.37 ± 0.319	0.12, 0.27	< 0.001*
Middle cerebral artery	Methyl-dopa group	3.13 ± 0.646	3.01 ± 0.564	0.06, 0.18	< 0.001*
	Nifedipine group	3.42 ± 0.595	3.25 ± 0.598	0.11, 0.23	< 0.001*
	Labetalol group	3.22 ± 0.529	3.09 ± 0.518	0.07, 0.20	< 0.001*

Table 6. Time to control BP of the studied groups

	Methyl-dopa group (n= 25)	Nifedipine group (n= 25)	Labetalol group (n= 25)	P	P1	P2	P3
Time to control BP (hours)	62.88 ± 10.553	43.20 ± 7.348	33.36 ± 5.765	< 0.001*	< 0.001*	< 0.001*	< 0.001*

Table 7. Pregnancy outcome in the studied groups

		Methyl-dopa group (n= 25)	Nifedipine group (n= 25)	Labetalol group (n= 25)	P	P1	P2	P3
Mode of delivery	**CS**	24.0% (6)	16.0% (4)	20.0% (5)	0.779	0.480	0.733	0.713
	Vaginal	76.0% (19)	84.0% (21)	80.0% (20)				
APGAR		8.64 ± 1.469	8.64 ± 1.186	8.92 ± 0.997	0.652	1	1	1
Birth weight (gm)		3104 ± 205.1	3080 ± 170.7	3196 ± 185.9	0.077	0.903	0.263	0.097
NICU admission		24.0% (6)	12.0% (3)	12.0% (3)	0.567	0.371	0.371	1.0

In addition, another study Webster et al. (2017) demonstrated that, there was a significant fall of blood pressure following Labetalol and Nifedipine usage (P<0.05) [7].

Regarding time, to control blood pressure Dharwadkar et al. (2014) came in the same line to the current study as they conducted their study on eighty patients with PIH were randomly allocated to receive either labetalol (group A) or methyldopa (group B). They demonstrated that, labetalol has been very effective in control as well as earlier onset of action in PE patients in comparison with alpha methyl dopa [8].

In terms of resistance index (RI) measurements of maternal uterine, umbilical and fetal middle cerebral arteries of the studied groups before and after treatment, the current study revealed that, there were no statistically significant differences among the three studied groups (P>0.05). In addition, there were highly statistically significant differences among within group comparison in terms of Resistance index (RI) measurements before and after treatment.

Regarding Pulsatility index of the studied three arteries, the current study demonstrated that, there were no statistically significant differences among the three studied groups before and after treatment (P<0.05). In addition, there were highly statistically significant differences among within group comparison of Pulsatility index (PI) measurements of the studied groups before and after treatment with the exclusion of Methyl-dopa group in UM.

In the same line, Folic et al. (2012) conducted a prospective cohort study. Methyldopa effects were followed in 28 patients, and nifedipine effects in another 28 patients. There were also 28 healthy controls. The blood velocity waveform indices in uterine artery were significantly improved by nifedipine, but not by methyldopa [resistance index (F = 9.28, p = 0.000), pulsatility index (F = 11.37, p = 0.000), and S/D ratio (F = 9.07, p = 0.000)]) because the velocity indices values were at all times within the normal limits. However, neither methyldopa nor nifedipine affected the blood velocity waveform indices in umbilical artery, although in nifedipine group, the values of the indices were higher at all-time points. Neither methyldopa nor nifedipine affected the blood velocity waveform indices in fetal middle cerebral artery, although the values of the indices were lower at all-time points in nifedipine group [9].

In addition, Folic et al. (2012)demonstrated that, the values of the blood velocity waveform indices in uterine artery significantly decreased along the time points of follow-up in both control group [resistance index (F = 2.77, p = 0.045)], [pulsatility index (F = 4.11, p = 0.008)], and [S/D ratio (F = 2.91, p = 0.038)] and nifedipine group [resistance index (F = 5.76, p = 0.001)], [pulsatility index (F = 12.24, p = 0.000)], and [S/D ratio (F = 5.13, p = 0.002)], but not in methyldopa group [resistance index (F = 2.29, p = 0.083)], [pulsatility index (F = 6.42, p = 0.000)], and[S/D ratio (F = 2.12, p = 0.102)], where only pulsatility index dropped significantly [9].

Moreover, Folic et al. (2012) study revealed that, the values of the blood velocity waveform indices in umbilical artery significantly decreased along the time points of follow-up in both control group [resistance index (F = 3.29, p = 0.023)],[pulsatility index (F = 6.46, p = 0.000)], and [S/D ratio (F = 2.91, p = 0.038)] and nifedipine group [resistance index (F = 4.83, p = 0.003)], [pulsatility index (F = 8.51, p = 0.000)], and [S/D ratio (F = 7.03, p = 0.002)], but not in methyldopa group [resistance index (F = 1.02, p = 0.389)], [pulsatility index (F = 1.48, p = 0.224)], and [S/D ratio (F = 0.24, p = 0.872)] [9].

Furthermore, Folic et al. (2012) displayed that, the values of the blood velocity waveform indices in fetal middle cerebral artery significantly increased along the time points of follow-up in control group [resistance index (F = 5.03, p = 0.003)], [pulsatility index (F = 14.71, p = 0.000)], and [S/D ratio (F = 3.65, p = 0.015)], nifedipine group [resistance index (F = 4.82, p = 0.003)], [pulsatility index (F = 8.31, p = 0.000)], and [S/D ratio (F = 7.53, p = 0.001)], and in methyldopa group [resistance index (F = 5.99, p = 0.001)], [pulsatility index (F = 23.34, p = 0.000)], and [S/D ratio (F = 4.82, p = 0.003)] [9].

The current study demonstrated that, there were no statistically significant differences of Systolic/diastolic (S/D) ratio measurements of the studied arteries before and after treatment. In addition, there were highly statistically significant differences in terms of within group comparison of Systolic/diastolic (S/D) ratio measurements before and after treatment.

Regarding pregnancy outcome in the studied groups, the current study demonstrated that, there were no statistically significant differences among the three studied groups in terms of mode

of delivery, APGAR, birth weight and NICU admission.

On the contrary, Roberts et al. (2003) reported that, the gestational weight at delivery was significantly lower in nifedipine group, in comparison with both control ($p < 0.001$) and methyldopa group ($p = 0.008$). The difference was also significant among the study groups in body weight of the newborn at delivery ($F = 16.014$, $p = 0.000$): the body weight was significantly lower in nifedipine group, in comparison with both control ($p < 0.001$) and methyldopa group ($p = 0.025$) [10].

On the contrary, Folic et al. (2012) [11] reported that, the Apgar score was significantly different among the study groups ($F = 4.052$, $p = 0.010$): it was significantly lower in nifedipine group, but only in comparison with control group ($p = 0.048$).

Concerning treatment side effects in the studied groups, there were statistically significant differences among the three studied groups being increased in Methyl-dopa group ($P<0.05$).

In accordance, displayed that; labetalol has lesser side effects when compared to methyldopa. Labetalol is not associated with adverse fetal effects in the immediate and late neonatal period. The chances of spontaneous onset of labor were greater in the labetalol group when compared to methyldopa group. Though there was no difference in the groups with regard to obstetric intervention [12].

A study conducted by states *(*that adverse events observed were lower in the labetalol treated group compared to the methyldopa group [13]. In a study by patients receiving methyldopa complained of side-effects such as drowsiness (22.2%), headache (14.8%), nasal congestion (7.4%), postural hypotension (5.6%). 96 patients in labetalol group complained of dyspnoea, no other side-effects were noticed [14].

5. CONCLUSIONS

Use of oral anti-hypertensive drugs (methyl dopa, nifidipine and labetalol) in cases suffered from pregnancy induced hypertension have a significant benefit regarding reduction of blood pressure, prevention of cerebrovascular accidents, prolonging pregnancy duration, prevention or stop development severe preeclampsia and eclampsia cases. Oral anti-hypertensive treatment when blood pressure levels are ≥150/95 mmHg. Initiation of antihypertensive treatment at lower levels (≥140/90 mmHg) is suggested for women with a) gestational hypertension with or without proteinuria, b) pre-existing hypertension with the superimposition of gestational hypertension or c) hypertension with asymptomatic organ damage or symptoms at any time during pregnancy. Use of methyl dopa, nifidipine and labetalol treatment in PIH cases make an improvement of uteroplacental and middle cerebral blood flow which indicated by maternal uterine, umbilical and fetal middle cerebral arteries doppler indices (resistive index, pulatility index and S/D ratio).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Written consent was obtained from women enrolled in the study after explaining the method and the aim of the study.

ETHICAL APPROVAL

The study was approved by the ethical committee, Faculty of Medicine, Tanta University.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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