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Methyldopa versus nifedipine or no medication for treatment of chronic hypertension during pregnancy: A multicenter randomized clinical trial

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ABSTRACT

Objective: To assess the maternal and fetal outcome in women with mild to moderate chronic hypertension on antihypertensive drug (methyldopa or nifedipine) therapy compared to no medication.
Methods: This multicenter randomized clinical trial was conducted at Menoufia University hospital, Shibin El-kom Teaching hospital and 11 Central hospitals at Menoufia governorate, Egypt.490 pregnant women with mild to moderate chronic hypertension were randomized into three groups; methyldopa group (n = 166), nifedipine group (n = 160) and control or no medication group (n = 164) who were followed from the beginning of pregnancy till the end of puerperium to record maternal and fetal outcome.
Results: Mothers in the control (no medication) group were more prone for the development of severe hypertension, preeclampsia, renal impairment, ECG changes, placental abruption and repeated hospital admissions ($p < 0.001$) when compared to mothers in both treatment groups (methyldopa and nifedipine). Neonates in the control (no medication) group were more prone for prematurity and admission to neonatal ICU ($p < 0.001$).
Conclusion: Antihypertensive drug therapy is advisable in mild to moderate chronic hypertension during pregnancy to decrease maternal and fetal morbidity. When considering which agents to use for treatment, oral methyldopa and nifedipine are valid options.

1. Introduction

Chronic hypertension affects about 1–5% of women during the reproductive years in different populations. Women with chronic hypertension are at significant risk for maternal morbidity and mortality, in terms of development of severe hypertension with its squeal; yet it remains unclear whether antihypertensive treatment during pregnancy lowers these risks or not [1–3].

Lowering the blood pressure by antihypertensive drugs in women with mild to moderate chronic hypertension has no significant effect on the risk of small for gestational age (SGA) and preeclampsia as recently reported [4] while another recent study concluded an increased risk of severe maternal hypertension (adjusted odds ratio, 1.8) when blood pressure was not tightly controlled during pregnancy [5].

A recent four-year observational study at our institution revealed increased maternal and fetal morbidity following discontinuation of antihypertensive drugs in mild to moderate chronic hypertension in terms of the development of severe hypertension, renal impairment, ECG changes, placental abruption, repeated hospital admissions for blood pressure control, preterm delivery and neonatal ICU admission [6].

The aim of this study was to assess the maternal and fetal outcome in women with mild to moderate chronic hypertension on antihypertensive drug (methyldopa or nifedipine) therapy compared to no medication.

2. Materials and methods

This multicenter randomized clinical trial was conducted at the departments of Obstetrics and Gynecology at Menoufia University hospital, Shibin El-kom Teaching hospital and 11 Central hospitals at Menoufia governorate, Egypt in collaboration with the Community Medicine and Public Health, Cardiology and Pediatrics departments at the respective hospitals during the period between the beginning of

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August 2017 and the end of August 2018 which is the last day of follow up of the last recruited participant.

The study protocol was formally reviewed and approved at Menoufia faculty of Medicine with Ethical clearance letter number 426H/2017 in 17 July 2017 with similar approval obtained from the Ministry of Health (MOH letter number 1436). All study participants signed an informed consent form after thorough explanation of the study objectives.

Pregnant women diagnosed with mild to moderate chronic hypertension without medication and without features of end organ affection as renal or hepatic impairment, fundal changes; with systolic blood pressure of 140–159 mmHg or diastolic blood pressure of 90–109 mmHg, at the beginning of pregnancy (between 6 and 10 weeks) were included in the study after thorough history taking, clinical examination, laboratory investigations included complete blood count, kidney and liver function tests, fundus examination, ECG and Obstetric Ultrasound.

Women with multiple pregnancies, proteinuria at less than 20 weeks' gestation, having other associated medical disorders as diabetes mellitus, bronchial asthma & epilepsy as well as pregnancies complicated by fetal malformations; were excluded from the study.

Based on the result of previous study [6] with 40% difference between treatment and non-treatment groups of mild to moderate chronic hypertension regarding the development of severe hypertension, 145 patients were needed in every single group for the study to have 90% power to detect 10% difference between the three groups ($p = 0.05$, two-sided) with inclusion of extra 15% patients to compensate for possible drop out cases. Fig. 1 revealed the flow diagram.

Randomization was performed using computer-generated simple random tables with patients randomly allocated into three groups in the ratio of 1:1:1 as follows:

Group 1 (Methyldopa group): included 166 patients who received methyl dopa tablets 1–2 gm per day in divided doses for blood pressure control. (Aldomet, 250 mg tablet Kahira Pharma. & chem. ind. co. Egypt).

Group 2 (Nifedipine group): included 160 patients who received Nifedipine tablets 20–40 mg per day in divided doses for blood pressure control. (Epilat retard 20 mg tablets, EIPICO pharmaceuticals, Egypt).

Group 3 (no medication group): included 164 patients who received placebo tablets (vitamin-C tablets). (Cevarol tablet 500 mg, Memphis pharmaceuticals, Egypt).

Patients in the three groups received low dose aspirin from the 12th week through 36th weeks of pregnancy (Aspirin 81 mg, European Egyptian Pharm.ind. Egypt) to decrease the risk of development of preeclampsia.

Serial blood pressure (BP) measurements were taken during the antenatal care visits which were assigned regularly every 2–4 weeks based on previous BP readings. The dosage was adjusted according to BP readings with management of adverse effects if raised by the participants. Patients who developed severe hypertension were managed by the addition of another antihypertensive agent if they already received the maximal dosage of the particular antihypertensive drug.

Randomization was accomplished using cards. 504 sequentially numbered, opaque, sealed envelopes were used, containing 168 cards

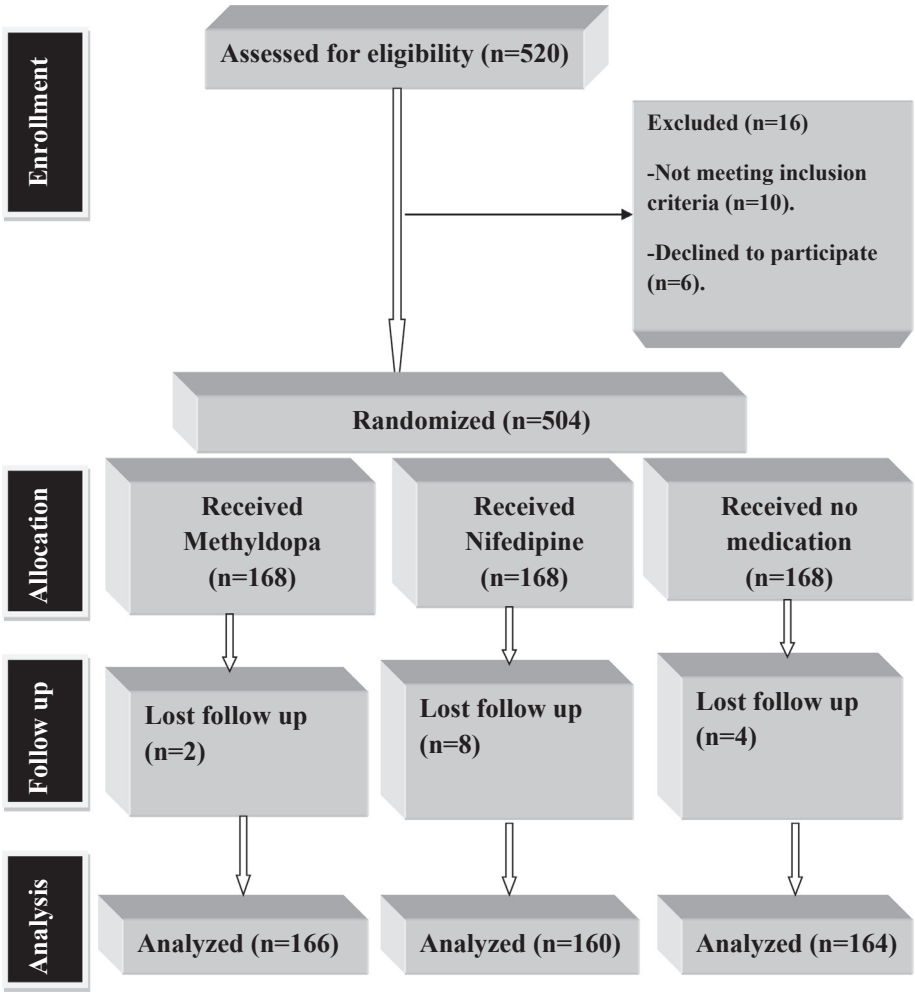

Fig. 1. The CONSORT Flow Diagram.

Table 1
Maternal characteristics.

	Methyldopa group (n = 166)	Nifedipine group (n = 160)	Control group (n = 164)	Chi square test	P-value
Age (years):				0.34	> 0.05
20–30	80 (48.2%)	72 (45%)	76 (46.3%)		
31–40	86 (51.8%)	88 (55%)	88 (53.7%)		
Parity:				0.26	> 0.05
P1-2	70 (42.2%)	64 (40%)	66 (40.2%)		
≥P3	96 (57.8%)	96 (60%)	98 (59.8%)		
Body mass index (Kg/m^2):				0.22	> 0.05
18–25	80 (48.2%)	76 (47.5%)	78 (47.6%)		
25.1–29.9	56 (33.7%)	52 (32.5%)	54 (32.9%)		
≥30	30 (18.1%)	32 (20%)	32 (19.5%)		
SBP at enrollment (mmHg)	150.52 ± 5.97	151.11 ± 5.21	151.2 ± 5.36	0.31*	> 0.05
DBP at enrollment (mmHg)	98.3 ± 4.23	98.51 ± 4.11	98.22 ± 4.36	0.34*	> 0.05
Gestational age at enrollment (Weeks)	8.22 ± 1.68	8.12 ± 1.77	8.24 ± 1.45	0.28*	> 0.05
Duration of hypertension (years)	3.43 ± 1.81	3.92 ± 1.32	3.62 ± 1.74	0.864*	> 0.05
Past history of adverse obstetric outcome†	52 (31.3%)	48 (30%)	58 (35.4%)	1.16	> 0.05

* Student *t*-test, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, † Adverse outcome included preeclampsia, small for gestational age, placental abruption and perinatal mortality.

Table 2
Maternal outcome.

	Methyldopa group (n = 166)	Nifedipine group (n = 160)	Control group (n = 164)	Chi square test	P-value	OR at 95% CI
Severe hypertension	38 (22.9%)	36(22.5%)	88 (53.6%)	47.26	< 0.001	0.26 (0.16–0.41)† 0.25 (0.15–0.41)* 1.02(0.61–1.72)‡
Preeclampsia (PE)	44 (26.5%)	46 (28.7%)	80 (48.8%)	22.79	< 0.001	0.37(0.23–0.59)† 0.41(0.26–0.66)* 0.89(0.55–1.45)‡
Renal impairment	32 (19.3%)	34 (21.3%)	88 (53.6%)	56.67	< 0.001	0.21 (0.13–0.34)† 0.23 (0.14–0.38)* 0.88 (0.52–1.52)‡
Hepatic impairment	36 (21.7%)	38 (23.8%)	48 (29.3%)	2.70	> 0.05	–
ECG changes	36 (21.7%)	40 (25%)	92 (56.1%)	52.45	< 0.001	0.22 (0.13–0.35)† 0.26 (0.16–0.42)* 0.83 (0.50–1.39)‡
Placental abruption	10 (6.02%)	12 (7.5%)	38 (23.2%)	27.55	< 0.001	0.21 (0.10–0.44)† 0.27 (0.13–0.54)* 0.79 (0.33–1.88)‡
Hospital admissions	32 (19.3%)	34 (21.3%)	72 (43.9%)	30.34	< 0.001	0.31 (0.19–0.50)† 0.34 (0.21–0.56)* 0.88 (0.52–1.52) ‡
Venous thromboembolism	4 (2.4%)	4 (2.5%)	6 (3.7%)	0.57	> 0.05	–
Cesarean Delivery	52 (31.3%)	48 (30%)	58 (35.4%)	1.16	> 0.05	–
Maternal mortality	0	0	0	–	–	–

OR at 95% CI = Odd's ratio at 95% Confidence interval, † OR between Methyldopa and Control group, * OR between Nifedipine and Control group, ‡ OR between Methyldopa and Nifedipine group.

labelled as 'methyldopa', 168 cards labeled as 'nifedipine' and 168 cards as 'vitamin-C'. All of the envelopes were mixed together and placed in a box. The envelops were further divided into two equal parts to be kept at the Pharmacy of Menoufia University hospital while the other was kept at the main Insurance Pharmacy of the MOH. When the Obstetrician at the antenatal care clinic in the included hospitals prescribed an antihypertensive drug, the pharmacist in charge selected a random envelope from the box. The three drugs are rounded, white tablets of nearly the same size; accordingly, the three drugs were indistinguishable to the participants.

Follow up of participants via regular ANC visits till delivery and throughout the puerperium to record the obstetric outcome.

2.1. Outcome measures

Maternal outcome: development of severe hypertension (systolic blood pressure ≥160 mmHg and/or diatolic blood pressure ≥110 mmHg) at ANC visits or if they sought the Emergency department, superimposed preeclampsia (a new onset proteinuria with 0.3 g of protein or more in a 24-h urine specimen after 20 weeks' gestation), eclampsia (generalized convulsions), renal impairment (elevated serum creatinine > 1.1 mg/dl), liver impairment (elevated liver enzymes twice the normal values), ECG changes (left ventricular heave and/or strain pattern), placental abruption based on clinical presentation and confirmed by ultrasound, mode of delivery, hospital admissions for blood pressure control twice or more during pregnancy, venous thromboembolism (VTE) and maternal mortality. Indications of delivery were based primarily upon clinical presentation and gestational age e.g. patients who developed severe preeclampsia or eclampsia at any gestational age were managed by termination of pregnancy according to our hospital policy, patients who developed severe FGR …etc

Fetal-neonatal outcome: small for gestational age (SGA) defined as a birth weight < 10th percentile, birth weight, 5 min Apgar score, preterm labour (delivery < 37 weeks), gestational age at delivery, intrauterine fetal demise (IUFD), admission to neonatal intensive care unit (NICU) and neonatal death (defined as death during the first four weeks after delivery).

Table 3
Fetal and neonatal outcome.

	Methyldopa group (n = 166)	Nifedipine group (n = 160)	Control group (n = 164)	Chi square test	P-value	OR at 95% CI
Small for gestational age	38 (22.9%)	40 (25%)	32 (19.5%)	1.43	> 0.05	–
Intrauterine fetal demise	4 (2.4%)	4 (2.5%)	6 (3.7%)	0.57	> 0.05	–
Prematurity	30 (18.1%)	42 (26.3%)	50 (30.5%)	7.03	0.029	0.50 (0.30–0.84)†
						0.81 (0.50–1.32)*
						0.62 (0.36–1.05)‡
Gestational age at delivery (Weeks)	35.6 ± 2.62	35.42 ± 2.44	35.56 ± 2.5	0.89	> 0.05#	–
Birth weight (Kg)	2.24 ± 0.62	2.26 ± 0.66	2.25 ± 0.6	0.56	> 0.05#	–
Apgar score < 7 at 5 min	10(6.02%)	12 (7.5%)	38 (23.2%)	27.55	< 0.001	0.21 (0.10–0.44)†
						0.27 (0.13–0.54)*
						0.79 (0.33–1.88)‡
Prematurity	30 (18.1%)	42 (26.3%)	50 (30.5%)	7.03	0.029	0.50 (0.30–0.84)†
						0.81 (0.50–1.32)*
						0.62 (0.36–1.05)‡
Admission to NICU	22 (13.3%)	26 (16.3%)	48 (29.3%)	15.12	< 0.001	0.37 (0.21–0.65)†
						0.47 (0.27–0.80)*
						0.79 (0.43–1.46)‡
Neonatal mortality	6 (3.6%)	8 (5%)	12 (7.3%)	2.30	> 0.05	–

Student *t*-test, OR at 95% CI = Odd's ratio at 95% Confidence interval, † OR between Methyldopa and Control group, * OR between Nifedipine and Control group, ‡ OR between Methyldopa and Nifedipine group.

2.2. Statistical analysis

The data collected were tabulated & analyzed by SPSS (Statistical Package for the Social Science software, Chicago, IL, USA) version 22 and the analysis of the results was per protocol analysis. Chi square and Fischer's exact tests as appropriate. P-value less than 0.05 considered statistically significant and less than 0.001 was highly significant.

3. Results

There was no significant difference between the three groups regarding maternal demographic data in terms of age, parity and body mass index, systolic and diastolic blood pressure at enrollment, gestational age at enrollment, duration of chronic hypertension and past history of adverse obstetric outcome ($p > 0.05$) as depicted in Table 1.

Mothers in the control (no medication) group were more prone for the development of severe hypertension, preeclampsia, renal impairment, ECG changes, placental abruption and repeated hospital admissions ($p < 0.001$) when compared to mothers in both treatment groups (methyldopa and nifedipine). There was no significant difference between the three groups regarding the development of hepatic impairment, venous thromboembolism and cesarean delivery ($p > 0.05$) as revealed in Table 2.

Neonates in the control (no medication) group were more prone for prematurity, low Apgar score < 7 at 5 min and admission to neonatal ICU ($p < 0.001$) with no differences in the rates of small for gestational age, birth weight, gestational age at delivery, intrauterine fetal demise and neonatal death ($p > 0.05$) when compared to their counterparts in the treatment groups as shown in Table 3.

4. Discussion

The present study confirmed the beneficial use of antihypertensive drugs in patients with mild to moderate chronic hypertension with significant reduction in the rates of severe hypertension, preeclampsia, renal impairment, ECG changes, placental abruption and repeated hospital admissions as well as prematurity and admission to neonatal ICU.

Although a recent systematic review and *meta*-analysis suggested that lowering the blood pressure by antihypertensive drugs in women with mild to moderate chronic hypertension has no significant effect on the risk of small for gestational age (SGA) and preeclampsia [4]. Other trials refuted this conclusion [7,8].

Thirty three patients with mild to moderate chronic hypertension were allocated to receive calcium channel blockers plus low-dosage aspirin and vitamin C throughout pregnancy. None of them developed severe preeclampsia or eclampsia [7].

A recent prospective study of 586 women with pre-pregnancy chronic hypertension, in the absence of renal or liver disease who were divided into three groups; group 1 (n = 199), blood pressure (BP) < 140/90 mm Hg without antihypertensive medication; group 2 (n = 220), BP < 140/90 mm Hg with antihypertensive medication; and group 3 (n = 167), systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg, despite antihypertensive medication; was designated to control the blood pressure with antihypertensive drugs; There was a significant increase from group 1 to group 3 in the incidence of severe hypertension (10.6%, 22.2%, and 52.1%), preterm preeclampsia with onset at < 37 weeks of gestation (7.0%, 15.9%, and 20.4%), and small for gestational age (13.1%, 17.7%, and 21.1%)in patients with delayed initiation of drug therapy during the first trimester [8].

Methyldopa was associated with better obstetric outcome when used to control blood pressure during pregnancy particularly in women with pre-existing hypertension [9].

Calcium channel blockers inhibit the L-type calcium channels in the cardiac and vascular smooth muscle cells, which exerts negative inotropic effects on the heart and causes vasodilation, leading to decreased systemic vascular resistance [10].

Nifedipine was found to be comparable to intravenous hydralazine, oral and intravenous labetalol for treatment of severe hypertensive emergencies during pregnancy as well as to control blood pressure in chronic hypertension [11–15].

The increased morbidity related to hypertensive disorders of pregnancy is presumed to be associated with the development of severe hypertension which could be brought down by decreasing its incidence via antihypertensive drug therapy.

A recent retrospective cohort study of 2252 women with acute severe intrapartum hypertension and 93,650 women without severe hypertension delivering between July 2012 and August 2014 at 15 hospitals in United States; revealed a significantly higher risk of severe maternal morbidity in women with acute severe intrapartum hypertension with oral nifedipine being the most effective first-line medication followed by intravenous labetalol and intravenous hydralazine [16].

The perinatal mortality rate was not significantly different among the treatment and control groups which could be attributed to the use of low dose aspirin in all participants.

Previous systematic review confirmed that aspirin reduces the risk of perinatal mortality and preeclampsia in women with historical risk

factors [17], especially when initiated before 17th week gestation in another recent trial [18].

The use of either methyldopa or nifedipine in the current study was not associated with grave maternal or fetal adverse effects and both drugs were well-tolerated and did not require specific intervention or mandate drug stoppage for mild complaints as headache or palpitations.

The study design in addition to focusing on particular maternal and fetal adverse events constitutes the main strength of the current study.

Inability to report life-threatening maternal complications as pulmonary edema and stroke secondary to their rarity may be one of the study limitations.

5. Conclusion

Antihypertensive drug therapy is advisable in mild to moderate chronic hypertension during pregnancy to decrease maternal and fetal morbidity. When considering which agents to use for treatment, oral methyldopa and nifedipine are valid options.

Declaration of Competing Interest

We certify that no actual or potential conflicts of interest in relation to this article exist.

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