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METHYLDOPA VERSUS NO DRUG TREATMENT IN THE MANAGEMENT OF MILD PRE-ECLAMPSIA
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METHYLDOPA VERSUS NO DRUG TREATMENT IN THE MANAGEMENT OF MILD PRE-ECLAMPSIA

E.M. ELHASSAN, O.A. MIRGHANI, A.B. HABOUR and I. ADAM

ABSTRACT

Objectives: **To evaluate the efficacy of methyldopa in the treatment of mild pre-eclampsia, to prevent its progress and to investigate its effect on the pregnancy outcomes.**
Designs: **Randomised clinical trial.**
Setting: **Wad Medani Hospital in the central Sudan.**
Subjects: **Seventy primigravidae with single, alive baby of 28-36 weeks gestational age suffering from true mild pre-eclampsia were enrolled. The patients were randomised in two groups, treatment group who received methyldopa 750- 4000 mg/day (n=34) and a control group who received no treatment (n=36). All the (treatment and control) patients were drug followed as in-patients till the delivery, seen with their babies on the days 7, 42 after the delivery.**
Main outcomes measures: **The outcomes examined were, rise of the diastolic blood pressure to 110 mm Hg or more, occurrence of imminent eclampsia or the eclampsia, if the maturity could be achieved, occurrence of intrauterine growth retardation, abruptio placentae, mode of delivery, birth weight, placental weight, perinatal death, Apgar score and referral of the babies to the pediatrician.**
Results: **Three out of 34 (8.8%) of the treatment group had a rise in the diastolic blood pressure of 110 mm Hg, 18/36(50%) of the control had a rise in the diastolic blood pressure of 110 mmHg ($p < 0.05$). Three out of thirty four (8.8%) of the treatment group developed imminent eclampsia, while 10/36 (27.8) of the control group developed imminent eclampsia ($p<0.05$). The maturity was achieved in 82.3% and 88.8% of the treatment and the control, respectively ($p > 0.05$). There were ten (14.2%) perinatal deaths, four of them in the treatment group, while six in the control ($p > 0.05$). There was no difference regarding birth weight, occurrence of intrauterine growth retardation, placental weight, mode of delivery, Apgar score, referral of the babies to the paediatrician. No patient developed eclampsia or abruptio placenta; there was no maternal death in both groups.**
Conclusion: **Methyldopa can prevent the progress of the mild pre-eclampsia to severe pre-eclampsia, without affecting the maturity, birthweight or the neonatal outcomes.**

INTRODUCTION

High blood pressure complicates almost 10% of all pregnancies(1) and pre-eclampsia complicates about seven per cent of pregnancies(2). It is a major cause of maternal mortality worldwide(3). Pre-eclampsia may lead to eclampsia, prematurity, intrauterine growth retardation, perinatal morbidity and mortality(4,5). Pre-eclampsia is an important health problem everywhere, dangerous for both the mother and the foetus, unpredictable in its onset or progress and incurable except by termination of pregnancy(5). Pre-eclampsia may endanger the life of the mother by uncontrolled high blood pressure, or by cerebral haemorrhage, which is a prominent feature in a woman dying of pre-eclampsia(6).

Management of pre-eclampsia has a considerable disagreement about it. Aggressive management with immediate delivery leads to high neonatal morbidity and mortality resulting from prematurity(7). In severe hypertension, there is no role of the expectant management and antihypertensive drugs should be employed even without foetal benefit, but in mild hypertension the value of the treatment is much less certain(8). In order to be of value, not only should hypotensive agents be able to lower the blood pressure, but also they must prevent the maternal complications and to improve foetal outcomes(9).

Methyldopa is the commonly used drug for the treatment of hypertension in pregnancy, because of its safety and it has no negative effect on the utroplacental heamodynamics(10). Despite its familiarity and safety, it has little effects in improving birthweight, placental weight and maternal or perinatal outcomes(11,12). These studies had been carried in hypertension during pregnancy. Few studies - if any were carried to test the efficacy of methyldopa in mild pre-eclampsia. This was the objective of this study.

MATERIALS AND METHODS

The study was randomised controlled clinical trial, patients were primigravidae with mild pre-eclampsia. Mild pre-eclampsia is defined as diastolic blood pressure of 90-109 mmHg in two readings six hours apart by the same investigator and their urine showing 2+ or more of albumin by dip stick. Patients carrying single, viable baby of 28-36 weeks gestation. The gestational age was calculated from the last menstrual period and confirmed by the ultrasound in the first or second trimester. Written informative consent was obtained from the patients and their husbands. Patients were randomly allocated in the treatment group (n=34) who received methyldopa 750 mg initially and increased gradually to 4gm maximum and the control (n=36) that received no treatment but admitted to the hospital (this is the policy of obstetricians in the hospital to ensure the patients' compliance to the bed rest), observed and investigated and followed like the treatment group. Detailed questionnaire including demographic data, clinical and obstetrical history was filled. All the patients were asked about their complaints specifically any symptoms suggestive of imminent eclampsia, that is, persistent headache, epigastric or right upper quadrant pain, vomiting and visual disturbance. In all patients blood pressure was measured by mercury sphygmomanometer while the patient in the right lateral tilt position using the right arm; the first and fourth sounds of Korttokoff were used to determine the systolic and diastolic blood pressure respectively. The full physical and obstetrical examinations were completed. All the patients were admitted to the hospital at least till the delivery, which had been planned to be at the thirty seventh weeks. After the vaginal delivery (Caesarean section deliveries were discharged on the eighth day) patients were discharged to be seen with their babies on the sixth week, provided that their diastolic blood pressure was below 90 mm Hg.

The maternal investigations included: repeated platelet count, serial measurement of uric acid, serum creatinine, liver function tests and serial ultrasound to detect intrauterine growth retardation (largest fluid pocket < 2 cm in vertical dimension). The objective of the treatment in patients receiving methyldopa was to keep the diastolic blood pressure below 90 mm Hg. To achieve the desired blood pressure, methyldopa was started at 750 mg/ day and increased as needed to maximum of 4gm/ day by divided doses.

Maternal indications for the delivery were uncontrolled severe hypertension inspite of maximal doses of methyldopa (in the control cases once their diastolic blood pressure reach 110 mmHg they would be given methyldopa), new onset of the above symptoms, which suggest imminent eclampsia, vaginal bleeding, rupture of the membranes, preterm labour, or attainment of 37 weeks. Caesarean section was performed for obstetrical reason only.

In both groups when the diastolic blood pressure reached 110 mm Hg (severe pre-eclampsia), the patient received the management adopted in Wad Medani hospital for severe pre-eclampsia which include methydopa. The hospital policy is to terminate pregnancy in cases of imminent eclampsia regardless of their gestational age.

Outcome variables include adequacy of the blood pressure control, incidence of abruptio placenta, incidence of imminent eclampsia or eclampsia, incidence of preterm delivery, incidence of foetal growth retardation, mode of delivery, birthweight and placental weight, Apgar score. Referral of the babies to the paediatrician, proportion of infants admitted to the special- care neonatal units, perinatal death and the maternal death.

Data were recorded as mean and standard deviation. Statistical analysis used the Student's t- test, $\chi 2$, and Fisher's exact test when applicable. P value of <0.05 was considered significant.

RESULTS

Of the seventy primigravidae enrolled for the study, thirty four received methyldopa (MSD) starting 750mg/day and increased as needed according to the diastolic blood pressure control, but the maximum dose was 4000mg. 36 out of 70 received no treatment but were closely observed in the hospital.

Table 1 shows different clinical and biochemical variables in the two groups, the treatment and the control. There was no significant difference between the two groups, and all these values were in the normal ranges. Six patients who enrolled in the study showed feature of intrauterine growth retardation by the ultrasound, three of them in the control and three in the treatment group. During the follow up one patient in the treatment group developed the features of intrauterine growth retardation. The mean stay in the hospital was not significantly different between the two groups (p = 0.72).

Table 1

Compares the mean (S.D.) different variables in the treatment group and controls at the time of admission

Variable	Treatment group (n=34)	Control (n-=36)	P value of t-test
Age in years	22.3 (5.2)	21.1 (5.4)	0.76
Height in cm	158.9 (6.2)	159.5 (6)	0.861
Weight in kg	65.83 (4.62)	67.16 (6.5)	0.88
Systolic blood pressure mmHg	147.4 (8.6)	144.7 (6.5)	1.43
Diastolic blood pressure mmHg	102.4 (2.5)	101.4 (2.3)	1.67
Gestational age in weeks	34.8 (2.3)	35.1 (2.4)	0.71
Haemoglobin gm/dl	9.10 (1.13)	9.4 (1.4)	0.16
Urea in mg/dl	20.2 (3.6)	20.9 (3.4)	0.84
Serum creatinine md/dl	0.5 (0.23)	0.6 (0.20)	0.15
Serum albumin g/dl	3.1 (0.6)	3.0 (0.5)	0.19
Uric acid mg/dl	4.5 (1.6)	4.8 (1.4)	0.53
Platelet count 10^3/mm	201.9 (34)	215.5 (38.1)	0.4
Alkaline phosphatase K.AU	8.5 (2.8)	9.5 (2.6)	0.17

Table 2

Compares different maternal variables in the treatment groups and the control as mean (S.D) or number (%) as appropriate.

Variable	Treatment (n=34)	Control (n=36)	Significance
Imminent eclampsia	3 (8.8)	10 (27.7)	0.016
Diastolic blood > 110 mmHg ie severe pre-eclampsia	3 (8.8)	18 (50)	0.00017
Systolic blood pressure at the start of labour	131.8 (7.5)	137.5 (6.8)	0.83
Diastolic blood pressure at the start of labour	91.8 (6.03)	89.6 (4.6)	0.24
Gestational age at delivery	37.5 (1.1)	37.7 (0.8)	0.84
Days of stay in the hospital	24.7 (7.7)	21.2 (11.2)	0.72
Vaginal delivery	20 (58.8)	22 (61.1)	0.10
Cesarean section	14 (41.2)	14 (38.8)	0.20
Systolic blood pressure 6 weeks after delivery	120.4 (5.8)	120.3 (6.4)	0.63
Diastolic blood pressure 6 weeks after delivery	79.4 (5.1)	77.03 (7.9)	0.072

Table 2 compared the maternal outcomes in the two groups. Three of the 34(8.85%) patients in the treatment group, developed symptoms of imminent eclampsia, while ten of the 36(27.7%) in control developed the symptoms suggestive of imminent eclampsia, the difference was highly significant (p = 0.016). Three out of the 34(8.85%) in the treatment group had their diastolic blood shoot to 110 mmHg and remained so, while 18 out of 36 (50%) of the control had their blood pressure reached this level. The difference was highly significant (p = 0.00017).

Eleven patients of the control group whose diastolic blood pressure reached 110 mmHg (severe pre-eclampsia) at 35.8 weeks gestational age, had been followed for the mean of 9.7 days, received methydopa for this high blood pressure to achieve the maturity. There were no significant differences in the mean systolic and diastolic blood pressure in the two groups at the start of labour (Table 2).

Table 3

Neonatal outcomes as mean (S.D.) or number (%) as appropriate.

Variable	Treatment group n=34	Control group n=36	Significance
Baby birth weight (kg)	2.7 (0.3)	2.6 (0.3)	0.8
Apgar score 1 more than 7	33 (97)	34 (94.4)	0.82
Apgar score 5 more than 7	31 (91.2)	34 (94.4)	0.82
Placental weight (gm)	423.7 (59)	429.2 (56.9)	0.77
Referral of the baby	11 (32.3)	7 (19.4)	0.21
Perinatal death	4 (11.7)	6 (16.6)	0.37

Table 3 shows different neonatal outcome. There were no significant difference in the mean birthweight, mean placental weight, Apgar score, and mean gestational age at the time of delivery and perinatal or early neonatal death. Non of the patients developed abruptio placenta, eclampsia and there was no maternal death in either group. There were ten perinatal deaths, four of them in the treatment and six in the control group (no significant difference was found). The cause of death in these 10 varied as, three were due to imminent eclampsia induced prematurely, three out of ten deaths was attributed to intrauterine growth retardation, two out of ten died because of asphyxia, one death on the fourth day was due to jaundice and the tenth death was due to prematurity. No difference in the mean maternal systolic and diastolic blood pressure in the two groups in the postpartum period.

DISCUSSION

This study was carried out to show the effect of methyldopa in mild pre-eclampsia in Sudanese patients in their third trimester. For medical and ethical reasons, inspite of the bias it may bring, it was not a blind study, the control patients need to be known to the investigator in order to give them the treatment in case of severe pre-eclampsia. Three patients in the treatment group developed severe pre-eclampsia, while ten patients in the control group developed imminent eclampsia, the difference was significant ($P < 0.05$), also their blood pressure was to some extent controlled in comparison to the group who received no treatment. The character of methyldopa in controlling the blood pressure in pre-eclampsia was found in another study by Wide-Swensson et al (10).

The study showed no significant differences in maternal complications or perinatal outcomes. Thus the mean birth weight, placental weight, Apgar scores, perinatal deaths were not different between the two groups, and no patient developed eclampsia or abruptio placenta. In addition the two groups had no difference in the gestational age at the time of the delivery.

The reduction of the maternal blood pressure, without any maternal or foetal affection was shared by the new (antihypertensive) drugs, for example, recently magnesium reduces the blood pressure effectively-in comparison to methyldopa without any difference in the maternal or neonatal outcomes(13). Although, our study was for pre-eclampsia, we also compared our findings with others in which methyldopa was used in hypertension in pregnancy. The findings of lowering maternal blood pressure without maternal or foetal benefits in our study, goes with the findings of Sibai and colleagues where the blood was controlled better in the patients who received methyldopa or labetlol in comparison to the group who were given no treatment, but this reduction was not associated with any difference in the maternal or perinatal outcomes(11).

There were no significant differences in the mean gestational age at the delivery or the birth weight in the two groups. In the two studies the gestational age at the time of the delivery was higher in the group treated with methyldopa (14,15). In one of them there was concomitant increase in the birth weight in the treatment group(14), while the other failed to demonstrate this increment(15).

Although in our study there were no direct foetal benefits, but there were significantly less patients in the treatment group than in the control who developed severe pre-eclampsia (8.8% versus 27.8%, $p > 0.05$). This was clinically important to prevent the progress of mild to severe pre-eclampsia. In this study the maternal and foetal monitoring were started on admission and performed frequently thereafter. We believe that this intensive monitoring was responsible for reduction of maternal complications, and absence of maternal deaths. Because of this monitoring the patients complaints typical of severe pre-eclampsia were detected and treated appropriately. So methyldopa in this study prevented the progress of mild pre-eclampsia to severe pre-eclampsia, without prolonging the pregnancy or increasing birthweight.

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Letter to the Editor-in-Chief

Dear Sir

RE: EXPERIENCE OF ROAD TRAFFIC ACCIDENT VICTIMS AT THE NAIROBI HOSPITAL, SAIDI AND KAHORO

We were extremely interested to read the evaluation of the pre-hospital and initial care of the injured from road traffic accidents at the Nairobi Hospital

It is unfortunate that this experience is the same as we have found throughout the Continent at many well known teaching hospitals as well as mission hospitals.

In part to try and address this recognised and now quantified problem, we were fortunate through the auspices of the Leverhalme Trust to set up a one day trauma management course based on the internationally accepted to those resources available in most district and mission hospitals in Africa. With the help of the Mine Hospitals and the University Teaching Hospital in Lusaka these courses were commerced in 1996 and indeed enough instructors are now available to run these courses within Zambia.

The course comprises a complete set of lecture notes, scenarios and slides which allow the running of the course for anyone who is either ATLS postitive or has undertaken the ZTMC (Zambia Trauma Management Course itself.

As has been said already many stalwarts of African orthopaedics and surgery it is essential that we find our own solution relevant to our facilities and staffing rather than purely import Western World guidelines, which cannot be achieved with current financial and equipment restraints.

We would be happy to send out the course material to any interested teachers or departments in the form of a CDROM containing all slides and data. Ironically we found that this was the best means to propagate the information rather than the more extensive slide and manual version.

Yours sincerely,

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