Effect of Nifedipine on Uterine and Middle Cerebral Artery Doppler in Pre-Eclampsia Patients

Original Article

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ABSTRACT

Background: Preeclampsia AKA PE was defined based on NICE guidelines as new hypertension presenting after 20 weeks with significant proteinuria. Severe pre-eclampsia is pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or hematological impairment. Nifedipine is used for control of blood pressure in cases with preeclampsia aiming to prevent rise of blood pressure during expectant management of these cases.

Objective: To evaluate changes in uterine artery and middle cerebral artery Doppler indices before and a week after Nifedipine administration for control of blood pressure in PE patients.

Design: Prospective observational study over six months that started to recruit patients from Mansoura university hospitals antenatal care clinics from May, 2019 to December, 2019.

Methods: Doppler on uterine and middle cerebral artery was done before and a week after administration of Nifedipine. Dose of nifedipine: starting dose 10 mg orally twice daily increased after 48hs according to response. Maximum safe dose is 60 mg per day in dividing doses 8 hours apart. Drug stopped immediately if severe side effects like sudden hypotension where IV fluids and corticosteroid to support blood pressure will be commenced immediately. If no respons after maximum dose of medication conservative management was abandoned and delivery took place.

Main Outcome Measure: Changes in uterine and middle cerebral artery Doppler indices before and after Nifedipine administration. Use of these changes to evaluate decisions for conservative management in preeclampsia patients.

Conclusion: Nifedipine is a valid option to treat hypertensive patients, however more extended studies on fetal effects are required.

Key Words: Nifedipine, preeclampsia, umbilical artery doppler.

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INTRODUCTION

Pre-eclampsia (PE) is a well know spectrum of signs rather symptoms in human pregnancies. It has been studied over the years and estimated to have rate of prevalence of 5-8%. It is basically a new onset of high blood pressure in pregnancy that mostly diagnosed after 20 weeks of pregnancy. PE by definition is the rise in systolic and diastolic blood pressure ≥140/90 mmHg on two occasions at least 4 hours apart, and an evidence of proteinuria. However, the absence of proteinuria doesn't exclude PE as new-onset hypertension in pregnancy that coincide with any of the following biochemical changes: reduced platelet count<100,000/µl, deranged renal function (raised > 1.1 mg/dl or doubled serum creatinine concentration with no evidence of past history of renal pathology, compromised liver function (elevated liver transaminases to twice normal concentrations), pulmonary edema, or cerebral or visual problems[1]. Maternal mortality is the scariest consequence of PE, resulting in about 50 000–60 000 deaths per annum worldwide[1]. Besides, the increased risk of the mother and her child to develop cardiac/ vascular/thromboembolic complications and impaired glucose tolerance later in life[2].

In the vein of pathogenesis of PE, a wide platform of factors, genetic and environmental has been investigated that resulted in communal outcome which is the definite treatment of the wide spectrum syndrome is to terminate the pregnancy[3]. In recent studies, PE has two subtypes based on the onset of diagnosis. Generally, It is divided into early- and late-onset PE[4]. The most common type of PE is the late onset (> 80%) of pre-eclampsia cases.

Pre-eclampsia is known of its significant maternal and fetal morbidity/mortality. Abnormal placentation and defective vascular response are the major concerns in pregnancies complicated by PE that result in placental hypoxia and ischemia. Thus, these placental changes can be measure by doppler ultrasound[5].

Currently, Calcium-channel blockers (nifedipine, diltiazem and verapamil) have been used safely in pregnancy

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and especially in diabetic patients due to its protective effect on kidneys. There was no proven teratogenic effect of tits use in PE to control blood pressure[6]. Furthermore, nifedipine is widely used in obstetrics mainly preterm as tocolytic agent and hypertensive disorders to control blood pressure. It does not appear to have any deleterious effects on the uterine or umbilical blood flow[7]. however, the use in preeclampsia where the impaired placental blood flow is a major concern was not investigated in a large scale so there is an utterly need to explore positive/negative or even neutral effect of Nifedipine on these vulnerable feto-placental circulations[8].

PATIENTS

A prospective cohort study at department of Obstetrics and gynecology Mansoura university hospital from May to December, 2019. 20 Cases enrolled in the study were preeclampsia patients, singleton pregnancy between 20 and 37weeks of gestation. Only cases with moderate and severe hypertension (150/100 to 159/109 mmHg and 160/110 mmHg or higher respectively) were enrolled in the study.

Informed consent was obtained from all patients prior to inclusion in the study. The study was approved by the local ethics committee IRB with the code number R/16.10.63.

Exclusion criteria were: unstable patient requiring emergency pregnancy termination, fetal indication for termination as fetal distress, history of chronic hypertension or any chronic disease (liver, heart or renal disorders), multiple pregnancy or preeclampsia > 37ws gestation.

After enrollment in the study each patient received nifedipine, 10 mg orally every 8 hours and doses were adjusted according to normalization of blood pressure (systolic blood pressure less than 150 mmHg and diastolic blood pressure between 80 – 100 mmHg). Maternal monitoring included blood pressure measurement at least four times daily, biochemical studies based on the severity of preeclampsia.

DOPPLER STUDY

Examinations were performed prior to therapy and 7 Days after the initial dose. Cases who delivered before repetition of Doppler study were excluded. In order to minimize the observer-related variations, all Doppler studies were performed by the same practitioner. All patients were positioned in a left recumbent to prevent maternal hypotension. All records were taken during a period of fetal rest, as previously described (no uterine contractions and fetal movements)[7] The average examination duration was 25–35 min.

Uterine and middle cerebral artery blood flow velocity waveforms were obtained using a an EcoDoppler Ansaldo AU-560, with a 3.5 MHz. The systo- diastolic (S/D) ratio, the resistive index and the pulsatility index (PI) Umbilical artery velocimetric waves: The Doppler sampling was done very close to the placenta insertion, as this enabled visualization of the degree of trophoblastization, the implant and the placenta condition. In order to achieve the most reliable measurement, the sampling was carried out at the midportion of the umbilical cord. The records sustained by the fetal descending aorta were carried out along its length between the thorax and the abdomen, Middle cerebral artery velocimetric waves: The cross-section used for the measurement of the biparietal diameter was found and, with an upward movement of the probe, the scissure of Silvius was identified where the artery begins. In brief, MCA-PI values were obtained at the point at which the artery passes by the sphenoid wing close to the circle of Willis. Doppler flow velocimetry of the Uterine arteries was performed according to the usual technique on both left and right side. After the intersection between the uterine artery and the iliac vessel was obtained on ultrasound screen, its ascendant branch was selected.

RESULTS

Descriptive data

The sample included (20 cases) had attended their antenatal appointments as mean± SD of 3±2. The mean age for patients recruited in this study was 25 ± 4 years, the gestational age was 34± 2weeks, their BMI (body mass index) was 29± 3 and the estimated fetal weight (EFW) was 1950 ± 520 grams. There was no indication for magnesium sulfate or steroids injections in the studied cohort.

Analytical data

The results showed that there was significant improvement in blood pressure parameters after treatment with Nifedipine ($p < 0.001$). Moreover, there was no significant change in Umbilical artery systolic/ diastolic ratio. However, the umbilical artery pulsatility index and resistive index were significantly increased from 1.25±0.38 and 0.72±0.07 to 1.48±0.34 and 0.87±0.10 respectively (p *value* < 0.001). The middle cerebral indices systolic / diastolic ratio and pulsatility index were significantly reduced from 5.16±1.50 and 1.81± 0.31 to 3.56±0.75 and 1.31±0.19 respectively ($p< 0.0001$). Similarly, there was a significant reduction in uterine artery pulsatility index after treatment with nifedipine from 1.18 ± 0.26 to 0.91±0.15 on the left side and from 1.15 ± 0.22 to 0.85+± 0.05 on the right side ($p< 0.001$). In addition, middle cerebral artery and uterine artery resistive indices did not show remarkable change after seven days of nifedipine treatment for high blood pressure (Table 1).

Table 1: Comparison of doppler indices before and after treatment

	Groups				*P*
	Before treatment		After treatment		
	Mean	±SD	Mean	±SD	
SBP	156.50	7.34	136.50	4.49	<0.001
DBP	102.45	5.99	83.85	5.01	<0.001
MBP	120.47	4.94	101.40	3.62	<0.001
UA/SD	3.49	0.70	3.73	0.86	0.009
UA/PI	1.25	0.38	1.48	0.34	<0.001
UA/RI	0.72	0.07	0.87	0.10	<0.001
MCA/SD	5.16	1.50	3.56	0.75	<0.001
MCA/PI	1.81	0.31	1.13	0.19	<0.001
MCA/RI	0.72	0.18	0.66	0.06	0.2
RT Uter.A.RI	0.90	0.18	0.84	0.04	0.2
RT Uter.A.PI	1.15	0.22	0.85	0.12	<0.001
LT Uter.A.RI	0.89	0.19	0.85	0.05	0.2
LT Uter.A.PI	1.18	0.26	0.91	0.15	<0.001

SBP: systolic blood pressure, DBP; Diastolic blood pressure, MBP; mean blood pressure, UA/SD; umbilical artery systole-diastolic, UA/PI; umbilical artery pulsatility index, UA/RI; umbilical artery resistive index, MCA/SD; middle cerebral artery systolic diastolic, MCA/PI; middle cerebral artery pulsatility index, MCA/RI; middle cerebral artery resistive index, RT Uter.A.RI; right uterine artery resistive index, RT Uter.A.PI; right uterine artery pulsatility index, LT Uter.A.RI; left uterine artery resistive index, LT Uter.A.PI; left uterine artery pulsatility index

DISCUSSION

Timely diagnosis and management of PE are paramount to prevent maternal and fetal consequences of this unique condition. The progression of PE is unpredictable. The main cure is delivery, however in case of prematurity weighing risks and benefits of early delivery and fetal risks versus controlling blood pressure to minimize maternal risks and appropriate delivery interval is the key. The choice of antihypertensive has been investigated and NICE recommends labetalol as first line and Nifedipine as second line. Nifedipine is well known as a tocolytic agent in preterm labour. In the current study, the effect of Nifedipine on maternal and fetal doppler indices was investigated [9,10].

The studies that are available in literature to evaluate the doppler effect of Nifedipine in PE patients are scarce. However, a thorough review of databases MEDLINE/ PUBMED and Cochrane registry was done to find only three studies[11,12,13].

Herein study the doppler studies; uterine, umbilical, middle cerebral arteries were performed before and a week after treatment of Nifedipine for high blood pressure control in patient diagnosed with PE. Short term effect up to 48 hours was studied by previous studies. Lima etal[14] reported no significant change in umbilical and uterine artery resistive indices after 24 hours of oral Nifedipine as a tocolytic. In the current study, we agree with Lima etal that uterine artery resistive index did not show any significant change but there was a significant increase in Umbilical artery resistive index RI. According to Lima etal results, 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.

Another two studies[14,15], showed a significant reduction of PI in both middle cerebral and uterine arteries and no change in umbilical artery PI. In correlation with the present study, both middle cerebral and uterine arteries PI were reduced significantly while the umbilical artery PI was significantly increased after seven days of nifedipine to control blood pressure.

There are discrepancies in the data available as a result of small number studies, small sample of population studied and non-persistent study methodology that highlight the need for multicenter randomized control trial on national and international level.

Recent study[16] in 2021, pointed the detrimental effect of Nifedipine on hypoxic fetus. From a clinical perspective, Nifedipine is a widely used medication in hypertensive patients where restricted fetal growth is not uncommon. The current study, there was no abnormal doppler indices or any evidence of reduced growth However it was proved in the recent experimental study that hypoxic fetus is vulnerable to right side heart failure.

The limitations in this study are mainly the lack of control group, the nifedipine posology and small number of patients included in the study. From ethical point of view, it is not applicable not to give treatment for high blood pressure in pregnancy but the alternative is to compare different antihypertensives on the doppler indices; maternal and fetal. Future aspiration is to include more sample population and divide patients in groups according to the used dose of nifedipine and different antihypertensive.

CONCLUSION

Nifedipine is a potent antihypertensive agent that could potentially increase umbilical artery doppler indices and reduce middle cerebral and uterine artery indices. The outcome in this study was not clinically significant. We suggest further large-scale study to overcome the limitations.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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