Research Article

Effect of Adding Midazolam to Bupivacaine 0.5% in Spinal Anesthesia on Middle Cerebral Artery Blood Flow in Patients with Pre-eclampsia

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Abstract
Introduction: Preeclampsia is a clinical syndrome defined as the new onset of hypertension and proteinuria during the second half of pregnancy. **Aim of the work: The main target of the current research is**: to exploit the GABA mimetic and potentiating effect of intrathecal midazolam to ameliorate the glutamate mediated preecmlapsia induced neuronal excitotoxicity and cerebro-vasculer vasospasm assessed by blood flow vascular indices (pulsitility index, resistive index and mean flow velocity) in maternal MCA in case of sever preeclampsia. **Patients and methods:** The current study was planned to be double blind placebo controlled single center randomized prospective study in which 100 parturient ASA IIe with severe preeclampsia were recruited into 2 groups 50 ladies in each group scheduled for emergency C.S after obtaining approval of the local ethics committee of Faculty of Medicine, El-Minia University and informed written consent from parturients husband or next of kin. Study was carried out from December 2017 to August 2018. **Results:** This prospective randomized double blind study included 100 parturient allocated in 2 groups, 50 cases in each. All studied groups received lumbar subarachnoid block by bupivacaine 0.5%12.5 mg + 1 mg midazolam in (M) group or 0.2 cm sterile saline 0.9% Nacl in (C) group. **Recommendations: We recommend:** Future studies on midazolam impact over maternal MCA resistive indices should examine different. 1- Using intrathecal midazolam in the dose of 1 mg in cases of severe preeclampsia as an adjuvant to bupivacaine 0.5% in the dose of 12.5 mg. 2- Increasing frequency of TCD readings to be at the base, 6h, 12h, 18h & 24hs to be more accurate. 3- Using TCD antenatal in the future studies to early pick up ladies that may develop preeclampsia.
Keywords: Midazolam, Bupivacaine

Introduction
Preeclampsia is a clinical syndrome defined as the new onset of hypertension and proteinuria during the second half of pregnancy. It affect 3% to 5% of pregnancies and is a leading cause of maternal and fetal mortality and morbidity especially in developing countries[(1)].

Pre-eclampsia has a complex pathophysiology, the primary cause being abnormal placentation. Defective invasion of the spiral arteries by cytotrophoblast cells is observed during pre-eclampsia. Recent studies have shown that cytotrophoblast invasion of the uterus is actually a unique differentiation pathway in which the fetal cells adopt certain attributes of the maternal endothelium they normally replace. In pre-eclampsia, this differentiation process goes away[(2)].

The abnormalities may be related to the nitric oxide pathway, which contributes substantially to the control of vascular tone. Moreover, inhibition of maternal synthesis of nitric oxide prevents embryo implantation. Increased uterine arterial resistance induces higher sensitivity to vasoconstriction and thus chronic placental ischemia and oxidative stress. This chronic placental ischemia causes fetal complications, including intrauterine growth retardation and intrauterine death. In parallel, oxidative stress induces release into the maternal circulation of substances such as free radicals, oxidized lipids, cytokines, and serum soluble vascular endo-thelial growth factor. These abnormalities are responsible for endothelial dysfunction with vascular hyperpermeability, thrombophilia, and hypertension, so as to compensate for the decreased flow in the uterine arteries due to

peripheral vasoconstriction. In severe pre-eclampsia, elevated cerebral perfusion pressure is counterbalanced by increases in cerebro-vascular resistance and cerebral blood flow is unaffected[3].

In eclampsia a significant fall in cerebral vascular resistance occurs which, in the presence of increases in cerebral perfusion pressure, leads to hyperperfusion. Cerebral vascular changes to date have not been sensitive enough to predict the development of pre-eclampsia or eclampsia[4]

Accommodation to normal pregnancy includes a decrease in both systolic and diastolic BP as a result of a decrease in systemic vascular resistance primarily secondary to vasodilation. Relaxin up regulates nitric oxide synthase (NOS), the enzyme that generates NO from arginine, via the endothelial endothelin B receptor. In preeclampsia, derangement of endothelial-derived vasoactive factors is thought to result in the predominance of substances that are vasoconstrictors (endothelin, thromboxane A2) over vasodilators (NO, prostacyclin). Hypertension, defined as repeat BP measurements ≥140/90 mmHg, results from abnormal vasoconstriction[5].

Midazolam is an IV anesthetic drug exerts its effect by occupying benzodiazepine receptor that modulates γ-amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain. Benzodiazepine receptors are found in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, inferior colliculus, brain stem, and spinal cord[6].

Aim of the work

The main target of the current research is: to exploit the GABA mimetic and potentiating effect of intrathecal midazolam to ameliorate the glutamate mediated preecmlapsia induced neuronal excitotoxicity and cerebro-vasculer vasospasm assessed by blood flow vascular indices (pulsitility index ,resistive index and mean flow velocity) in maternal MCA in case of sever preeclampsia.

Patients & Methods

The current study was planned to be double blind placebo controlled single center randomized prospective study in which 100 parturient ASA IIe with severe preeclampsia were recruited into 2 groups 50 ladies in each group scheduled for emergency C.S after obtaining approval of the local ethics committee of Faculty of Medicine, El-Minia University and informed written consent from parturients husband or next of kin. Study was carried out from December 2017 to August 2018.

Exclusion criteria:

1. Any condition with fetal compromise as intra uterine growth retardation or intra uterine fetal death (IUGR, IUFD)
2. Any condition prohibit spinal anesthesia (coagulopathy, patient refusal, Psychiatric disorders)
3. End organ failure as chronic renal failure.

Patients groups and study design:

On enrollment into the study, the ladies were allocated into 2 groups of 50 patients each by using a computer generated tables and the randomization sequence was concealed by closed envelop assignment held by a staff not in duty with data collection. Double blind fashion was carried out (neither the observer nor parturients was aware of the study design nor randomization assignment)

Group (C) (control group):

Received 12.5 mg (2.5cm) bupivacaine (0.5%) (Marcine, Astrazenca) +0.2 cm sterile saline (0.9%).

Group (M) (midazolam group):

Received 12.5mg (2.5cm) bupivacaine (0.5%) (Marcine, Astrazeneca) +1mg (0.2cm) midazolam (5 mg, Dormicum, Roche).

Both groups received the same volume of injectate given intratheclly under complete sterile conditions.

Results

This prospective randomized double blind study included 100 parturient allocated in 2 groups, 50 cases in each. All studied groups received lumbar subarachnoid block by bupivacaine 0.5% 12.5mg + 1mg midazolam in (M) group or 0.2 cm sterile saline 0.9% Nacl in (C) group.

Study design:

- **Group (C) (control group)**:

Received 12.5mg bupivacaine (0.5%) (Marcine, Astrazeneca) + 0.2cm saline (0.9%).

- **Group (M) (midazolam group)**:

Received 12.5mg bupivacain (0.5%) (Marcine, Astrazeneca) +1mg midazolam (Dormicum, Roche).

Parameters assessed :

1- age: (data expressed as mean ±SD):

Table (1): age distribution among studied groups:

Age in years	Midazolam group N=50	Control group N=50	P-value
Mean ± SD	32.1±5.5	30.5±6.9	0.066

SD: standard deviation
Analysis of quantitative data by independent sample t-test
The two studied groups were comparable as regard the age.

Discussion

Preeclampsia is a challenging issue facing obstetricians, anesthetists and intensivists due its profound prevalence carrying high incidence of morbidity and mortality for both maternal and fetal side**.**

During the period of the current study (from December 2017 to August 2018), the incidence of preeclampsia in our hospital was 15.4% (352 preeclamptic ladies out of 2282 presented in the ER for emergency termination of pregnancy). This implicates that preeclampsia is the most common cause of emergency C.S and admission to obstetric ICU.

The middle cerebral artery is the largest branch of the internal carotid artery carrying 75% of total CBF supplies a portion of the frontal lobe and the lateral surface of the temporal and parietal lobes. Minor changes in blood flow velocity in MCA correlates well with global CBF[(7)]**.**

TCD is the only noninvasive real-time neuroimaging modality for the evaluation of characteristics of blood flow in intracerebral vessels that adds physiologic information to structural imaging. TCD can provide information about vascular stenosis and occlusion, the hemodynamic status of the cerebral circulation, and real-time monitoring of vascular indices. TCD is useful for detecting increased intracranial pressure[(8)].

In the current study, TCD assess the proximal portion of the MCA through temporal window, this examined segment contains two types of receptors; Serotonin (5HT) and Dopamine receptors that are not affected by the acetylcholine, so free from effect of $MgSO_4$ on these receptors[(9)]**.** This clarifies any change in the values of resistive indices is exclusively explained by intrathecal midazolam effect.

Our study was enrolled on double blind placebo controlled single center prospective randomized study from December 2017 to August 2018. This study included one hundred parturients,

American society of Anesthiologist (ASA) physical status IIe with severe preeclampsia scheduled for emergency caesarian section. The parturient were allocated into 2 groups of 50 patients each.

Recommendations

We recommend:

1. Future studies on midazolam impact over maternal MCA resistive indices should examine different.
2. Using intrathecal midazolam in the dose of 1 mg in cases of severe preeclampsia as an adjuvant to bupivacaine 0.5% in the dose of 12.5 mg.
3. Increasing frequency of TCD readings to be at the base, 6h, 12h, 18h & 24hs to be more accurate
4. Using TCD antenatal in the future studies to early pick up ladies that may develop preeclampsia.

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