Impact of adding midazolam to bupivacaine 0.5% in regional spinal anesthesia on maternal middle cerebral artery velocimetry in parturients with severe preclampsia

mina maher Raouf (drmina2015@gmail.com)
High education ElMinia

Hany Kamal mikhail
Elminua

mohammad ahmed amin
Elminia

samar mahamad magdy
ElMinia

Research article

Keywords: Severe preclampsia, transcranial doppler, midazolam and spinal anesthesia

DOI: https://doi.org/10.21203/rs.3.rs-29084/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Severe preclampsia is a challenging issue facing both intensivist and anesthetic team carrying both maternal and fetal morbidity and mortality. Termination of pregnancy after blood pressure control is the golden key in management. Cerebral complications due to diffuse cerebral vasospasm are most common and serious. Intrathecal midazolam with its gamma amino butyric action may antidote glutamate mediated sympathetic surge and decreasing cerebral vasospasm. Temporal view transcranial doppler imaging maternal middle cerebral artery is used to examine Blood flow indices namely pulsatility index and resistive index. One hundred Ladies with severe preclampsia scheduled for urgent caeserian section were recruited in 2 groups, both received 10mg bupivacaine 0.5%, Midazolam group received 1mg midazolam and the other group received 0.2ml sterile saline 0.9% NaCl. All vascular indices were significantly better in midazolam group, less ICU stay.

Background

Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm occurring after 20 weeks of pregnancy and can present as late as 4-6 weeks postpartum [1]. The incidence of preeclampsia in the United States is estimated to range from 2% to 6% in healthy, nulliparous women [2]. In developing nations, the incidence of the disease is reported to be 4-18% [3], with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries [4].

Risk factors for preeclampsia include primigravida, diabetes mellitus, kidney disease, chronic hypertension, previous personal or family history of pre-eclampsia, maternal age more than 35 years, obesity, antiphospholipid antibody syndrome and multiple gestations [5].

Pre-eclampsia can be diagnosed through Systolic blood pressure \( \geq 140 \text{ mm Hg} \) or diastolic \( \geq 90 \text{ mm Hg} \) on two separate readings taken at least four to six hours apart after twenty weeks [6]. In a woman with essential hypertension beginning before twenty weeks gestational age, the diagnostic criteria include an increase in systolic blood pressure (SBP) by \( \geq 30 \text{mmHg} \) or an increase in diastolic blood pressure (DBP) \( \geq 15 \text{ mmHg} \), also Proteinuria \( \geq 3 \text{ grams (300mg)} \) is considered a diagnostic tool [7].

The rationale for the administration of intrathecal midazolam focuses on the awareness that it is an agonist at the benzodiazepine binding site, a subunit of the pentameric gamma-aminobutyric acid (\( GABA-A \)) receptor. The agonist occupancy of the benzodiazepine binding site enhances the activity of GABA at the GABA-A receptor [8].

Transcranial Doppler ultrasonography (TCD) is considered the sole noninvasive real-time neuroimaging modality for the evaluation of characteristics of blood flow in basal intracerebral vessels. TCD adds physiologic information to structural imaging. Additionally, TCD has been rapidly evolving from a simple, noninvasive diagnostic tool to an imaging modality with a broad spectrum of clinical applications [9].
**Primary objective:**

1- Does intrathecal midazolam can dampen vascular indices of maternal middle cerebral artery in ladies with severe preclampsia.

**Secondary objectives**

1- Incidence of mortality and morbidity

2- Cerebrovascular complications (Intracranial hemorrage ....)

**Methods**

This prospective randomized double-blind study was approved by the local ethics committee of the Faculty of Medicine, ElMinia University, and registered at clinical trials under the number of (NCT04283110). It was adhered to the Declaration of Helsinki and involved 100 ladies recruited into two groups, 50 lady each. Both groups received subarachnoid block with 10 mg bupivacaine 0.5% plus 1mg of midazolam in midazolam group or 0.2 ml sterile saline 0.9% NaCl as a placebo for equi-volume injection. Exclusion criteria included refusal for regional anesthesia or any condition prohibit subarachnoid block as coagulopathy.

An informed consent has been obtained from all participants who were randomly and equally allocated into two groups through web-based randomizer ([https://www.randomizer.org/](https://www.randomizer.org/)). Double blind fashion was executed (neither the observer nor the parturients was aware of study design).

Diagnosis of severe preclampsia was held by senior obstetric resident of charge at the emergency room (ER). Two cardinal criteria must be checked, noninvasive blood pressure (NIBP) ≥ 140/90 mmHg (two readings 5 minutes apart), albuminuria >+++ by boiling method. Presentation by imminent symptoms as headache, blurring of vision and nausea, HELLP syndrome (hemolysis of RBCs, elevated liver enzymes and low platelets) (hemolysis of RBC evidenced by elevated indirect bilirubin and lactate dehydrogenase > 600 IU, platelet count < 100,000, if two of the above mentioned criteria were found, diagnosis of severe preeclampsia was declared. Pelvic ultrasound was done to confirm fetal state to exclude any fetal compromise and clarify complications.

Immediately after diagnosis, admission to obstetric Intensive care unit, Two wide bore cannulae (20 gauge, ultramed, Belguim) were inserted, one for drugs and the other for emergency. Full monitoring tools were applied (NIBP, Electrocardiography, pulse oximetry and urinary foley catheter (16 gauge) was inserted after vaginal sterilization with Povidone iodine (7.5%). Investigations were performed: complete blood picture, liver functions, renal functions (serum urea and serum creatinine). Loading dose of Magnesium Sulphate (MgSO\textsubscript{4}) (1gm/10ml amp) 4gm on 200 ml Ringer lactate over 20 min followed by a maintenance infusion of 1 to 2 g/h by controlled infusion pump. Our target was to control MAP between 90-100mmHg over 45 minutes, during MgO4 infusion, Meticulous monitoring for signs of MgSO4 toxicity.
(respiratory rate <16 cycles per min, loss of knee jerk reflex, urine output less than 0.5 ml/kg/h). Any sign
of the above mentioned criteria mandated immediate stop infusion of MgSO4 at once and serum
Magnesium was checked. If MAP was ≥110mmHg despite of MgSO4 infusion, Nitroglycerin (Nitronal,
50mg /50ml,Sunny pharmaceutical) in an incremental dose starting with 1 mic/kg/h , upper maximum
dose was 10 mic/kg. Our goal was to control of MAP gently to 80-100mmHg. Before C.S, another pelvic
U/S was performed to evaluate fetal state. Brain imaging (brain CT and MCA trans-cranial Doppler
performed and the results were documented. Throughout this management, All resuscitative measures
(endotracheal tube, Atropine and Adrenaline) were ready for any emergency beside continuous
cardiocotography (CTG) to detect any pathological fetal deceleration. Transcranial Doppler probe
(Toshiba apio500 with convex probe 2-5mhz) rested on the temporal window (just above the zygomatic
arch between eye &ear). Ladies were positioned in a semi-recumbent position with a 15-degree left lateral
tilt.

A transcranial Doppler probe with a 10 mm sample volume was used to insonate the M1 (first 2 cm of
the middle cerebral artery) portion of the middle cerebral artery by means of the transtemporal approach
then the mean flow velocity, pulsatility index and resistance index values were recorded.

**Data collection** included haemodynamic data, urine output, serum urea and creatinine, dose and duration
of nitroglycerine, pulsatality index, resistive index, mean flow velocity and incidence of complications.

**Statistical analysis**: We have determined a significant difference in the values of pulsatality index and
resistive index by using the power of 80% and a significance level of 5%, and accordingly sample size
was determined to be 50 participants in each group. Collected data were firstly assessed by Kolmogorov-
Smirnov for the normality, and were presented as a number, percentage, mean ± SD or median (range).
Chi-square test and Fisher Exact test were used to compare qualitative variables. Continuous variables
were compared with t-test (Parametric data) or Mann-Whitney U test (Non-parametric data). A two-tailed p
< 0.05 was considered statistically significant. P-value considered statistically significant when P < 0.05.
Data entry and data analysis were done using SPSS version 19 (Statistical Package for Social Science.

**Results**

**Parameters assessed**: 

Table 1 shows the demographic data (age) of the parturients. The 100 participants were equally
randomized between the two groups as shown in the CONSORT flow-chart (Fig.1), and they were
comparable regarding their demographic details with insignificant differences in between.

Table 2 showed Changes in systolic blood pressure (SBP) in studied groups:

Regarding changes in SBP, there was a statistically significant difference between the two groups
immediately after induction, 5 min, 10 min after induction, after delivery of placenta, 20 min, 30 min of
operation and all values during first 24 h postoperatively. Intragroup comparison showed significant
statistical difference between pre induction values and all intra and postoperative values in both groups. Decline in SBP was steady and gentle in (M) group while it was sharp in (C) group. Rebound systolic hypertension was more evident in (C) group rather than (M) group.

Table 3 shows Changes in diastolic blood pressure (mmHg) in studied groups: Regarding changes in DBP among the studied groups pre, intra and post operatively were statistically significant difference between the two groups, 5 min, 10 min after induction, after delivery of placenta, one h, four hs, six hs, 12 hs, 18 hs and 24 h postoperatively.

Intragroup comparison showed significant statistically difference between pre induction values and all intra and postoperative values in both groups.

DBP decreased gently in (M) group but it showed sharp decrease in the (C) group with noticeable rebound hypertension occurred postoperatively.

Table 4 of nitroglycerine dose, Post operatively, 24 cases in (C) group mandated use of nitroglycerine to control postoperative rise in blood pressure with mean±SD 3024±1855.1 mic/kg and total duration 754 hs (32 days nearly) while in (M) group, statistically less number of cases (7) and less incremental dose (mean±SD 2013±1210.4 mic) and short duration (174 hours, about 8 days). There was a significant difference between the studied groups regarding (Number of cases, total dose & total duration of nitroglycerine infusion with (p value = 0.004))

Table (5) shows mean serum creatinine among studied groups. With no statistically significant difference between studied groups as regard serum creatinine.

Table 6 shows fetal APFAR score. There is no significant difference among studied groups regarding APGAR score.

A: activity, P: pulse, G: grimace, A: appearance, R: respiration.

Table 7 represents complications among studied groups:

Table 8 represents pulsatality index among studied groups, There was a significant difference between studied groups at 6 h and 24 h postoperatively with (p value <0.001, <0.001) for the Rt side and (0.003 and, 0.004) for the Lt side.

There was also a significant difference between the PI values among (M) group at 6h and 24 h compared with basal value on both sides.
Table 9 of MFV among studied groups, There was no significant difference in between or inside studied groups by comparing the MFV.

Table 10, By comparing the RI values among studied groups, There was a statistical significant difference between baseline values and values at 6 and 24 hours postpartum on both sides.

Discussion

Preeclampsia is a challenging obstetric emergency facing both anesthetists and intensivists. Preeclampsia confers high incidence of maternal and fetal morbidity. During the period of the current study, the incidence of severe preeclampsia in our hospital was 15.4% (352 preeclamptic ladies out of 2282 presented in the ER for emergency termination of pregnancy). Severe preeclampsia is the most common cause of urgent C.S and admission to obstetric ICU in our center

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 (Joris et al., 2018).

Transcranial doppler is the only noninvasive real-time neuroimaging modality for the evaluation of characteristics of blood flow in intracranial 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 (Tsivgoulis et al., 2009).

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 (D) that are not affected by the acetylcholine, so free from effect of MgSO₄ on these receptors (Purkayastha and Sorond, 2012). This clarifies any change in the values of resistive indices is exclusively explained by intrathecal midazolam effect.

Control (C) Group showed a noticeable decline in both systolic and diastolic blood pressure either after subarachnoid block or after placental delivery while postoperatively, there was a rebound systolic and diastolic hypertension in the same group. Consequently, more number of cases (24) were in need to higher incremental doses of nitroglycerine (mean ±SD (3024±1855.01mic/kg)) and lasting for longer duration (32 days). In (M) group, we noticed that decline was steady and gentle in both systolic and diastolic blood pressure after subarachnoid block and placental delivery with minimal rebound hypertension postoperatively, less number of ladies (7) were in need of incremental doses of nitroglycerine (mean±SD2013±1210.4) with less duration (8 days explained by the fact that midazolam has a bupivacaine -sparing effect and thus causes gradual sympathectomy. Pharmacokinetics of midazolam points to its preferential diffusion to lamina II in posterior horn cell in grey matter of spinal cord away
from the lateral horn cells hosting sympathetic nuclei thus preserve sympathetic tone to some extent (Shadangi et al, 2011)

In agreement of our study, Sanwa et al, 2013 studied the bupivacaine sparing effect of intrathecal midazolam in sub-arachnoid block for cesarean section and discovered that the hypotensive episodes was greater in control group while all Midazolam groups (1mg, 1.5mg and 2 mg) showed steep values of SBP and DBP( less episodes of hypotension).

Neuronal complications of severe preeclampsia (eclampsia, PRESS and intracranial hemorrhage) are the most common cause of maternal and fetal morbidity and mortality. Incidence of neuronal complications was higher in (C) group, 40 cases) while only 9 cases in (M) group.

Intracranial haemorrhage was in focus in one lady in (C) group. She experienced both systolic and diastolic hypertension, early nitroglycerin infusion started immediately after ICU admission for 24 hours postpartum. The lady developed 2 attacks of eclamptic fits during this period. Mechanical ventilation was initiated immediately after first fit to protect airway and prevention of aspiration pneumonia. Brain CT revealed massive lt parieto-occipital hematoma.

Acute kidney injury in sever preeclampsia is the second cause for maternal and fetal morbidity and mortality. Diffuse release of vasospastic materials (endothelin, serotonin, noradrenaline and abruptio placenta) are the main stay for both direct and indirect renal injury.

Urine output, serum urea and serum creatinine were higher in (C) group, while in (M) group it showed less amount of urine output with lower serum urea and creatinine. This can be explained as there were 2 cases in (C) group with acute kidney injury managed by forced diuresis. (M) group showed significant lower incidence than (C) group. For renal impairment at (C) group; one case (2%) had acute renal injury with subsequent elevation in the renal function responded to fluid challenge and forced diuresis. Also there was a case of acute renal failure was refractory to fluid challenge and frusemide infusion, was elicited for hemodialysis.

In agreement with our study, Goplani et al, 2008 reported a study between January 2004 and May 2006, 772 patients with ARF were admitted at the Institute Of Kidney Diseases and Research Centre and Institute Of Transplantation Sciences. A total of 92 patients with ARF were pregnant. Of these, 22 patients had the evidence of renal disease prior to pregnancy and were excluded; hence, 70 patients with pregnancy-related ARF were studied.

Pregnant women who were healthy previously and had developed ARF were diagnosed in oliguria (Urine output <400 ml/d) and for mounting azotemia (Serum creatinine >2mg%). The incidence of ARF due to
pregnancy related hypertension was 10%. A majority of the patients (97.14%) underwent hemodialysis, while one died without dialysis; further, one patient underwent peritoneal dialysis due to hypotension and died later. Peritoneal dialysis was initially performed in 8 patients (11.42%) due to initial hypotension, 7 patients among which improved and received hemodialysis later.

Impaction of sever preeclampsia on liver is evident. Increased hepatic vascular bed resistance, We noticed that serum ALT post operatively 24 h was significant in control group than in M group. ALT is more sensitive in cases of acute liver injury. This finding can be explained by more number of HELLP syndrome parturient preoperatively in control group. For liver impairment, in (C) group one case experienced acute fulminant hepatitis 24 h postpartum. This case was included in HELLP syndrome criteria (elevated ALT, AST more than 5 folds, Platelets<100000) secondary to vasospasm of the hepatic vascular bed. Patient responded to medical management (liver support, Vit k) patient was referred to tropical department with no mortality.

Regarding non cardiogenic pulmonary edema, two cases at (C) group were detected after 12 h postpartum, managed with forced diuresis(frusimide 0.2-2 mg/kg/h). Two patient were mechanical ventilated after failure of force diuresis (RR 35 c/m, PH < 7.1 and Spo2< 90%). Both patients could not be weaned from mechanical ventilation, both parturient were mechanically ventilated for 3 days. At (M) group one case with non cardiogenic pulmonary edema managed with mechanical ventilation and successfully weaned after 24 h.In the all above mentioned cases echo cardiograph was done revealed normal LT ventricular systolic function.

Mortality rate was higher in (C) group than (M) group. Three cases were enrolled in mortality, 2 parturients with non cardiogenic pulmonary edema and on case with ICH.No mortality was detected in (M) group.

In a study carried out with Ghulmiyyah et al, 2012 mortality and morbidity related to preeclampsia were as the following: death 0-15, aspiration pneumonia 2-10, pulmonary edema 3-12, abruptio placentae 7-10, disseminated coagulopathy 7-20, acute renal failure 5-10, cardiopulmonary arrest 2-10, liver failure 1-10 where lower values were in developed countries and higher values were in developing countries.

Transcranial Doppler was very helpful in detection and prediction of incidence of eclampsia as there were a noticeable elevation in MCA resistive indices in (C) group rather than (M) group. Cerebral vasospasm as a component of the pathophysiology in eclamptic women has been consistently described with transcranial Doppler ultrasound. This is illustrated by elevated middle cerebral blood flow velocities and high resistive and pulsatility indices in patients with preeclampsia. Doppler indices in MCA has been shown to be significantly higher in preeclamptic women in control group as compared with that in preeclamptic women in midazolam group. Many of the agents used have potent vascular effects and may
have caused cerebral vasodilatation. Reduction in the MCA pulsatility index after intrathecal midazolam therapy suggests that vasospasm in MCA is alleviated.

Regarding PI and RI they were of great value in both correlation and prediction of neuronal complications (PRESS, eclampsia). Intrathecal midazolam has dampened the PI value post partum 6 h and 24h, this can be attributed to antidoting of GABA mimetic action of intrathecal midazolam against excitatory glutamate. Strong correlation with ischemic infarction and post partum eclampsia was conclusive specifically in PI and RI as they expressed the total vascular resistance of MCA to blood flow.

We reported high predictive value of PI (>1.3) with incidence of eclampsia reached to >80%. PI changed more than RI with relief of excitatory glutamate and aspartate. PI was more sensitive than RI in both prediction and correlation of neuronal complications.

Risk stratification based on serial management by TCD indices concluded that patients with PI (1-1.3) at risk of PRESS, PI (1.3-1.8) at risk of eclampsia and PI (1.8-2.5) at risk of ICH.

In controversy with us, Riskin et al, 2002 studied 166 women in the second trimester of pregnancy to measure peak, end-diastolic, and mean velocities in the middle cerebral arteries. Middlecerebral arteries pulsatility and resistive indices were lower in the women with preeclampsia who were initially normotensive compared with the pregnant women who were normotensive (0.83 and 0.54 vs 0.73 and 0.50, respectively; \( P < .05 \)). This can be explained by early use of oral antihypertensive drugs (alphamethyldopa) which mediate cerebral vascular vasodilatation.

Preeclamptic patients in both groupshave been evaluated with transcranial Doppler ultrasound in the immediate and extended postpartum periods. Williams et al, 2015 investigated 46 preeclamptic women in the antepartum period and again at 24 and 48 hours postpartum. They determined that these patients had elevated systolic, diastolic, and mean velocities in the MCA 24 hours postpartum compared with those in the antenatal period. They also demonstrated a further increase in all velocities at 48 hours postpartum. The same investigators also found that preeclamptic women, compared with normotensive women, had elevated cerebral blood flow velocities in the antepartum period and at 24 and 48 hours postpartum. These data suggest that the cerebral vasculature of preeclamptic women is in a vasoconstricted state before delivery as well as in the immediate postpartum period (i.e., up to 48 hours after delivery) compared with normotensive women.

TCD velocimetry indices were very helpful in prediction and detection of incidence of complications, when regression analysis was done for PI basal, PI 6 hit showed that the most powerful index that can predict complications was PI (\( R^2 = 0.405 \)). This means that two indices included can predict 81% of cases with complications which is highly significant value.

Bivariate correlation revealed significant positive moderate association between PI BASAL, PI 6hr, and presence of complications (\( r = 0.526, 0.574, p <0.001 \)).
Conclusion

Intrathecal midazolam was beneficial in decreasing cerebral vasospasm and cerebral complication in parturients with severe preclampsia.

Limitations To Our Study

There were some limitations to the present study:

1. The difficult transport of patients was the cause of relatively few number of TCD readings of the maternal MCA, for fear of complications.
2. Invasive blood pressure wasn't available in our ICU, so we relied on NIBP on our work that was more sensitive to TCD.
3. Exclusion of end organ failure patients from the study.

Abbreviations

DBP .... Diastolic blood pressure.
CT ...... Computerized tomography
CTG ...... Cardiotocography
NIBP ... non invasive blood pressure
MAP ... Mean arterial blood pressure
MFV ...... Mean flow velocity
SBP .... Systolic blood pressure.
PI ..... Pulsatality index
RI..... Resistive index

Declarations

Acknowledgements

We are gratful to dr Gehad fathi, assistant lecturer of anesthesia who helped us in data collection. The authors dive thanks to Departement of obstetric and gynecology for their effort and help in lady transfer and fetal monitoring.

Funding
None.

Author information

Affiliations

- Departement of anesthesia and ICU. Faculty of medicine, ElMinia university. ElMinia. Egypt
- Departement of radiodiagnosis. Faculty of medicine, ElMinia university. ElMinia. Egypt

Contributions

Dr Mina M. Raouf had full access to all the data in the study, and take the responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Hany K. Mikhail designed the study protocol and generated random allocation sequence.

Dr Samar M. Magdy managed the literature searches, clinical cases and wrote the first draft of manuscript

Dr. Mohammad A. Aminn: pre and postpartum transcranial Doppler via temporal bone.

Corresponding author

Correspondence to Mina Maher Raouf.

Ethics declarations

Ethics approval and consent to participate

The current research is adherent to declaration of Helsinki over ethical committee record 293.9/2019. Written consent was taken from lady herself or next of kinn, Consent is in arabic and including agreement for cesarian section and another one for research participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

We declare that we have no funding source.

Author information
All authors contributed equally to this work.

References

1. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. Journal of pregnancy. 2012;2012.
2. Vatten LJ, Skjaerven R. Is pre-eclampsia more than one disease?. BJOG: An International Journal of Obstetrics & Gynaecology. 2004 Apr;111(4):298-302.
3. Ngoc NT, Merialdi M, Abdel-Aleem H, Carroli G, Purwar M, Zavaleta N, Campódonico L, Ali MM, Hofmeyr GJ, Mathai M, Lincetto O. Causes of stillbirths and early neonatal deaths: data from 7993 pregnancies in six developing countries. Bulletin of the World Health Organization. 2006;84:699-705.
4. Arulkumaran N, Lightstone L. Severe pre-eclampsia and hypertensive crises. Best Practice & Research Clinical Obstetrics & Gynaecology. 2013 Dec 1;27(6):877-84.
5. Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, Hildebrand AM, Reese PP, Storsley L, Gill JS, Segev DL. Gestational hypertension and preeclampsia in living kidney donors. New England Journal of Medicine. 2015 Jan 8;372(2):124-33.
6. Hauser S, Longo DL, Jameson JL, Kasper DL, Loscalzo J, editors. Harrison's principles of internal medicine. McGraw-Hill Companies, Incorporated; 2012.55–61.
7. Brigo F, Nardone R, Tezzon F, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review with meta-analysis. Epilepsy & Behavior. 2015 Aug 1;49:325-36.
8. Bohlhalter S, Weinmann O, Mohler H, Fritschy JM. Laminar compartmentalization of GABAA-receptor subtypes in the spinal cord: an immunohistochemical study. Journal of Neuroscience. 1996 Jan 1;16(1):283-97.
9. Williams K, Galerneau F. Maternal transcranial Doppler in pre-eclampsia and eclampsia. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2003 May;21(5):507-13.
10. Tsivgoulis G, Alexandrov AV, Sloan MA. Advances in transcranial Doppler ultrasonography. Current neurology and neuroscience reports. 2009 Jan 1;9(1):46-54.

Tables

Table 1: Age in the 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
Table (2): Systolic blood pressure (mmHg) among studied groups:

| Time                  | Midazolam group (N=50) | Control group (N=50) | P-value |
|-----------------------|------------------------|-----------------------|---------|
| Basal (preoperative)  | 160.6±13.3#            | 164.07±17.4#          | 0.264   |
| Before induction      | 148.6±7.0#             | 150.7±10.7#           | 0.230   |
| After induction       | 134.4±8.1#             | 129.4±14.05#          | 0.032*  |
| 5 minutes             | 124.4±11.6#            | 116.07±20#            | 0.012*  |
| 10 minutes            | 120.9±10.9#            | 111.7±18.7#           | 0.004*  |
| After delivery of placenta | 116.2±10.4#         | 107.4±15.9#           | 0.002*  |
| 10 minutes            | 118.0±9.03#            | 116.4±16.9#           | 0.574   |
| 20 minutes            | 120.0±8.08#            | 125.09±15.6#          | 0.043*  |
| 30 minutes            | 120.6±7.9#             | 127.4±16.1#           | 0.008*  |
| 10 minutes Postoperatively | 127.8±12.0#         | 135.8±15.6#           | 0.004*  |
| 30 minutes Postoperatively | 130.6±12.5#         | 138.03±14.6#          | 0.007*  |
| One hour Postoperatively | 129.4±12.5#         | 138.8±13.6#           | <0.001* |
| Four hours Postoperatively | 133.0±12.4#         | 144.9±14.8#           | <0.001* |
| Six hours Postoperatively | 134.4±14.02#        | 148.4±14.7#           | <0.001* |
| Twelve hours Postoperatively | 129.1±27.4#        | 148.8±14.7#           | <0.001* |
| Eighteen hours Postoperatively | 134.6±15.5#       | 145.8±14.8#           | <0.001* |
| Twenty-four hours Postoperatively | 131.8±15.3#       | 146.2±16.1#           | <0.001* |
**Analysis of quantitative data by independent sample t-test**

*: significant difference between two studied groups at <0.05

### Table (3): Diastolic blood pressure among studied groups:

|                          | Midazolam group N=50       | Control group N=50       | P-value     |
|--------------------------|-----------------------------|--------------------------|-------------|
| **Basal (preoperative)** | Mean ±SD                    | Mean ±SD                  | 0.535       |
|                          | 97.4±5.9#                   | 98.2±7.4#                 |             |
| Before induction         | 93.8±5.6#                   | 92.9±7.01#                | 0.501       |
| After induction          | 85.4±8.3                    | 83.3±9.3#                 | 0.244       |
| 5 minutes                | 84.2±11.9#                  | 74.5±16.4#                | 0.001*      |
| 10 minutes               | 78.6±10.1#                  | 70.5±13.7#                | 0.001*      |
| After delivery of placenta | 76.4±10.05#                 | 68.2±11.08#               | <0.001*     |
| 10 minutes               | 77.6±8.9#                   | 73.9±11.5#                | 0.076       |
| 20 minutes               | 79.2±8.04#                  | 81.1±9.7#                 | 0.269       |
| 30 minutes               | 79.2±8.2#                   | 81.7±9.3#                 | 0.147       |
| 10 minutes Postoperative | 84±7.5#                     | 85.4±10.2#                | 0.409       |
| 30 minutes Postoperative | 84±7.8#                     | 85.8±8.7#                 | 0.258       |
| One hour Postoperative   | 84.2±8.8#                   | 89.02±8.06#               | 0.005*      |
| Four hours Postoperative | 85.6±8.6#                   | 91.5±8.5#                 | 0.001*      |
| Six hours Postoperative  | 88.3±9.3#                   | 92.1±9.2#                 | 0.044*      |
| Twelve hours Postoperative | 87.1±8.5#                | 93.7±11.9#                | 0.002*      |
| Eighteen hours Postoperative | 85.8±8.8#               | 91.9±7.2#                 | <0.001*     |
| Twenty-four hours        | 86±10.1#                    | 91.3±7.7#                 | 0.003*      |
| Postoperative            |                             |                          |             |
*: significant difference between two studied groups at <0.05
# significant difference inside the same group

**Table 4** dose of nitroglycerine intra and postoperative.

| ml/min | Midazolam group N=50 | Control group N=50 | P-value |
|--------|-----------------------|--------------------|---------|
|        | Mean ±SD              | Mean ±SD           |         |
| Intraoperative | 198±93               | 160±104            | 0.643   |
| Postoperative  | 2764±1007            | 3283±1503          | 0.047*  |

Analysis of quantitative data by independent sample t-test

**Table 5** representing serum urea pre and postoperative.

| Mmol/L       | Midazolam group N=50 | Control group N=50 | P-value |
|--------------|-----------------------|--------------------|---------|
|              | Mean ±SD              | Mean ±SD           |         |
| Basal (preoperative) | 26.1±8.8              | 30.8±18.6          | 0.077   |
| Twenty-four hours Postoperative | 23.9±8.9              | 30.6±15.4          | 0.009*  |
| Forty-eight hours Postoperative  | 26.2±7.7              | 31.03±17.05        | 0.070   |

**Table 6** representing serum creatinine pre and postoperative.
| Mg/dl                  | Midazolam group N=50 | Control group N=50 | P-value |
|-----------------------|-----------------------|---------------------|---------|
| Basal (preoperative)  | 0.82±0.18             | 0.85±0.29           | 0.617   |
| Twenty-four hours Postoperative | 0.84±0.17             | 0.89±0.42           | 0.456   |
| Forty-eight hours Postoperative | 0.82±0.17             | 0.97±0.60           | 0.089   |

**Table 7** representing fetal APGAR score.

|                  | Midazolam group N=50 | Control group N=50 | P-value |
|------------------|-----------------------|---------------------|---------|
| Mean ±SD         | 8±0                   | 8±0                 | 1.000   |

**Table 8** representing complications.
|                          | Midazolam group N=50 | Control group N=50 | P-value |
|--------------------------|-----------------------|---------------------|---------|
| **Eclampsia**            |                       |                     |         |
| Yes                      | 9(18%)                | 17(34%)             | 0.005*  |
| 1 seizure                | 2(4%)                 | 3(6%)               |         |
| 2 seizures               | 4(8%)                 | 12(24%)             |         |
| 3 seizures               | 3(6%)                 | 2(4%)               |         |
| **PRESS**                |                       |                     |         |
| Yes                      | 8(16%)                | 22(44%)             | 0.004*  |
| **Intracranial hemorrhage** |                     |                     |         |
| Yes                      | 0(0%)                 | 1(2%)               | 0.315   |
| **Acute renal failure**  |                       |                     |         |
| Yes                      | 0(0%)                 | 1(2%)               | 0.315   |
| **Acute renal injury**   |                       |                     |         |
| Yes                      | 0(0%)                 | 1(2%)               | 0.315   |
| **Liver cell Failure**   | YES                   |                     |         |
|                         | 0(0%)                 | 1(2%)               | 0.315   |
| **Pulmonary edema**      |                       |                     |         |
| Yes                      | 1(2%)                 | 2(4%)               | 0.559   |
| **Need for intubation**  |                       |                     |         |
| Yes                      | 1(2%)                 | 3(6%)               | 0.309   |
| **Weaning**              |                       |                     |         |
| Yes                      | 1(2%)                 | 0(0%)               | 0.317   |
| **Mortality**            |                       |                     |         |
| Yes                      | 0(0%)                 | 3(6%)               | 0.080   |
Table 9 representing Pulsatality index.

|          | Midazolam group | Control group | P-value |
|----------|-----------------|---------------|---------|
|          | N=50            | N=50          |         |
| Mean     | Mean            | ±SD           | ±SD     |
| RT       | Basal           | 1.17±0.56     | 1.36±0.64| 0.121   |
|          | Six hours       | 0.90±0.60     | 1.39±0.73| <0.001* |
|          | Twenty-four     | 0.77±0.46     | 1.29±0.67| <0.001* |
|          | hours           | #             | #       |
| LT       | Basal           | 1.80±2.6      | 1.23±0.67| 0.147   |
|          | Six hours       | 0.83±0.56     | 1.23±0.74| 0.003*  |
|          | Twenty-four     | 0.79±0.47     | 1.12±0.63| 0.004*  |
|          | hours           | #             | #       |

Table 10 representing mean flow velocity.

|          | Midazolam group | Control group | P-value |
|----------|-----------------|---------------|---------|
|          | N=50            | N=50          |         |
| Mean     | Mean            | ±SD           | ±SD     |
| RT       | Basal           | 65.5±17.8     | 61.9±25.3| 0.411   |
|          | Six hours       | 64.7±20.8     | 61.6±23.5| 0.476   |
|          | Twenty-four     | 65.8±18.7     | 62.7±20.1| 0.430   |
|          | hours           |               |         |
| LT       | Basal           | 61.8±19.9     | 65.7±20.2| 0.326   |
|          | Six hours       | 66.3±21.4     | 62.8±19.5| 0.395   |
|          | Twenty-four     | 64.4±22.2     | 61.4±20.5| 0.482   |
|          | hours           |               |         |

Table 11 shows resistive index
|        |          |          |          |          |
|--------|----------|----------|----------|----------|
|        | Midazolam group N=50 | Control group N=50 |          |          |
|        | Mean ±SD | Mean ±SD | P-value  |          |
| RT     |          |          |          |          |
| Basal  | 0.69±0.30 | 0.79±0.34 | 0.127    |          |
| Six hours | 0.56±0.26 | 0.81±0.33 | <0.001*  |          |
| Twenty-four hours | 0.51±0.19 | 0.74±0.30 | <0.001*  |          |
| LT     |          |          |          |          |
| Basal  | 0.76±0.23 | 0.67±0.23 | 0.057    |          |
| Six hours | 0.50±0.21 | 0.69±0.27 | <0.001*  |          |
| Twenty-four hours | 0.49±0.24 | 0.68±0.35 | 0.003*   |          |

Figures
Figure 1

CONSORT flow chart.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010checklist.doc
- CT.docx