Magnesium Sulphate Versus Labetalol for Control of Blood Pressure in Severe Preeclamptic Parturients Undergoing Cesarean Section Under Epidural Anesthesia

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Abstract

Introduction: Preeclampsia is a syndrome characterized by hypertension and proteinuria. It affects 2-7% of healthy nulliparous women. Magnesium sulphate is the drug of choice for seizure prophylaxis and also it has cardioprotective effect with minimal side effects.

Objective: To Compare between the effects of magnesium sulphate and labetalol on hemodynamics stability in severe preeclamptic patients as well as neonatal outcome.

Patients and Methods: 60 patients with severe preeclampsia were enrolled in the study. They were randomly allocated into two groups. The first group received magnesium sulphate while the other group received labetalol. Blood pressure and heart rate were followed-up intraoperative and 24 hours postoperative.

Results: Labetalol group had statistically significant lower blood pressure and heart rate measurements throughout the operation and during postoperative period.

Conclusion: Use of Labetalol resulted in more controllable blood pressure levels and heart rates compared to magnesium therapy. Its use was not associated with seizures or poor neonatal outcome.

Key Words: Severe preeclamptic parturients – Cesarean section – Epidural anesthesia – Magnesium sulphate versus labetalol.

Introduction

PREECLAMPSIA is a syndrome characterized by hypertension and proteinuria, and a common fetal feature is intrauterine growth restriction [1]. It affects 2-7% of healthy nulliparous women and is a major cause of maternal and fetal morbidity and mortality [2]. It is further sub classified into late-onset and early onset, mild and severe, and into a maternal and fetal syndrome [1]. Its causes are multifactorial, and the disease is characterized by endothelial and platelet dysfunction with intense vasoconstriction, leaky capillaries, and intravascular volume contraction culminating in multiorgan hypoperfusion with the potential for significant end-organ damage [3].

The cornerstone of management of preeclampsia remains seizure prophylaxis, fluid and antihypertensive therapy, expeditious delivery and critical care management. Magnesium sulphate is the drug of choice for seizure prophylaxis in severe preeclampsia. Although its reported catastrophes are rare, it has several side effects [4].

Rapid infusion of magnesium may lead to flushing, bradycardia, cardiac arrhythmia or even cardiac arrest has been reported. Frequent serum magnesium level monitoring is also needed during its infusion to decrease risk of hypermagnesaemia and toxicity. Toxicity leads to renal impairment, loss of deep tendon reflex, hypotension, arrhythmias, respiratory depression and coma [5].

Magnesium ions suppress calcium influx in cardiac myocytes, exerting cardioprotective effect and decreasing cell injury induced by ischemia and reperfusion [6]. While labetalol is predominantly a nonselective β-blocker with some selective a-blocking effects. It decreases maternal systemic vascular resistance, slows the heart rate and reduces the incidence of ventricular arrhythmias. Labetalol may be used for seizure prophylaxis in patients with preeclampsia [7].

The American college of obstetrician and gynecologists guidelines confirms that regional anesthesia
may be used safely in severely preeclamptic patients without coagulopathy [1]. In these cases the insertion of a spinal or epidural catheter may precede the onset of labour or patient’s request for labour analgesia. Regional anesthesia may decrease the swings in blood pressure exacerbated by pain response in severe preeclampsia. Judicious volume expansion is typically recommended before regional anesthesia using 5-10ml/Kg of crystalloid or colloid [3].

Patients and Methods

The study was done prospectively in the Obstetrics and Gynecology Department of Cairo University Hospitals on 60 severe preeclamptic parturient undergoing cesarean section from 2009-2013.

Sample size measurement:

Power analysis was performed using unpaired $t$-test for independent samples on troponin level because it was the main outcome variable in the present study. A pilot study was done before starting this study because there are no available data in literature for mean and standard deviation of troponin level after receiving labetalol in management of patients with severe preeclampsia. The results of the pilot study showed a mean troponin level of 0.09 in five patients who received magnesium with standard deviation 0.03, the mean troponin level in patients who received labetalol was 0.06 with standard deviation 0.03. Taking power 0.9 and alpha error 0.05, a minimum sample size of 23 patients was calculated for each group. A total number of 30 patients in each group were included to compensate for possible dropouts.

Inclusion criteria:

Severe preeclamptic patient submitted for cesarean section with singleton baby and gestational age >32 weeks. Severe preeclampsia is considered if systolic blood pressure on admission exceeds 160mmHg and/or diastolic blood pressure exceeds 110mmHg, obtained on at least two separate occasions and proteinuria on urine dipstick 3+ or more.

Exclusion criteria:

- Age >40 years.
- Multiple gestations.
- History of cardiac diseases including: Chronic hypertension, patients receiving coronary vasodilators, $\beta$-blockers or calcium channel blockers.
- History of left ventricular impairment (EF <0.5 or acute pulmonary oedema).
- Hepatic (elevated liver enzymes more than two folds), pulmonary, vascular, renal or endocrinical diseases.
- Coagulopathy or patients on anticoagulants or antiplatelet.
- Renal impairment (serum creatinine >1.5mg/L) or oliguria (<400ml/day).
- Imminent eclampsia (severe headache, visual disturbance, epigastric pain, hyperreflexia, dizziness and fainting, or vomiting).
- HELLP syndrome.
- Abruptio placenta, placenta previa, or fetal distress according to CTG scores.

Preoperative assessment and evaluation:

Patients were admitted for careful history taking, clinical examination and investigations that included: complete blood picture, liver and kidney functions tests, coagulation profile (PC, PT, INR, and PTT), 24 hour urine albumin, ECG and echocardiography.

Preoperative preparation:

A written informed consent was obtained. Patients were randomly allocated into 2 equal groups each containing 30 patients using computer generated numbers and concealed using sequentially numbered, sealed opaque envelope technique.

Group I: Magnesium sulphate group (M):

All patients in this group received 4gm of IV magnesium sulphate diluted in 100ml of 0.9% normal saline over 30 minutes followed by an infusion of 1g/hr (up to 24 hours postoperatively) till reaching target blood pressure (systolic 140-150mmHg, or diastolic 90-100mmHg). While patients in the other group received the same infusion rate of 0.9% saline.

Group II: Labetalol group (L):

Labetalol was given 20mg IV bolus, followed by 40mg IV if not effective within 10 minutes: then 80mg IV every 10min. till reaching target blood pressure (systolic 140-150mmHg, or diastolic 90-100mmHg) to maximum total dose 220mg/ 24 hours.

The target systolic blood pressure was 140-150 mmHg or diastolic blood pressure of 90-100 mmHg. If this was not reached by any of the tested medications, hydralazine 2.5mg/20min. was given.

All patients were managed as follows:

On admission to OR 2 IV lines were inserted, and then magnesium sulphate or labetalol were given. Volume expansion using 300-500ml hydroxyethyl starch, followed by a balanced crystalloid solution administered at 2ml/Kg/h. The target systolic blood pressure 140-150mmHg or diastolic
blood pressure 90-100mmHg. If this was not reached by any of the tested medications, hydralazine 2.5mg/20min. was given.

Anesthetic technique: (Epidural anesthesia):
All patients received a standardized epidural anesthesia to attain a T4 sensory level block with catheter inserted at level of L3-L4 inter vertebral space.

Monitoring:
- Routine monitoring (five leads ECG, invasive and non-invasive arterial blood pressure, pulse oximetry).
- Total dose of antihypertensive drugs: Hydralazine and labetalol.
- Fetal heart rate monitoring.
- Neonatal heart rate and 1 and 5 minutes APGAR score.
- Seizure.

Post operative management:
The patients were admitted in ICU for the first 24 hours postoperative. The antihypertensive drugs were continued. ECG, blood pressure, CVP and urine output were monitored closely. Post-operative analgesia by continuous epidural infusion of 0.125% bupivacaine with fentanyl 2ºg/ml at rate 8-10ml/hr.

Statistical analysis:
Data are presented as median and range, mean SD or percentage, as appropriate. Comparison between two groups is done using unpaired t-test and repeated measures with two-way ANOVA as post-hoc procedure for comparisons against baseline values to further investigate any statistically significant findings. Indices are analyzed using Chi-square test or Fisher’s exact where appropriate. Values less than 0.05 are considered significant. All statistical data analysis is performed using SPSS version 11.5 (SPSS, Chicago, IL).

Results
The demographic distribution of the patients in the two groups showed no statistically significant difference as regards age (group I 28±3yrs, group II 26±4yrs), weight (group I 85±5.8Kgs, group II 88±4.1Kgs) and gestational age (both groups 37±1.3 weeks).

No statistically significant difference was found between the two groups as regard hemoglobin concentration, platelet count, creatinine, serum albumin, liver enzymes.

There were no significant changes in the baseline or serial (6, 12, 18, 24 hours) post-operative ECGs of any patients in the two groups.

As regarding the Mean arterial blood pressure, the labetalol group showed statistically significant decrease in blood pressure throughout the operation and continued during the first postoperative hour (Fig. 1). There was no statistically significant difference between the two groups during postoperative period.

![Mean arterial blood pressure measurements in both groups.](image)

On comparing the mean blood pressure within the magnesium group, all readings were significantly lower than the admission measurement (Table 1).

<table>
<thead>
<tr>
<th>Table (1): Group M, analysis of different mean blood pressure measurements (mmHg) versus baseline measurement.</th>
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<tr>
<td><strong>Group M (mmHg)</strong></td>
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<tr>
<td>Admission</td>
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<tr>
<td>Induction of anesthesia</td>
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<tr>
<td>Mean Intraoperative</td>
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<tr>
<td>Skin closure</td>
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<td>24h postoperative</td>
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</table>

Data are presented as mean±standard deviation (SD).
* : Statistically significant between group difference (p<0.05).

Also, comparison between the mean blood pressure within the labetalol group showed that all readings were significantly lower than the admission measurement (Table 2).
**Discussion**

Magnesium sulphate is the drug of choice for seizure prophylaxis in severe pre eclampsia. Magnesium is a natural calcium antagonist. It acts on most types of calcium channels in vascular smooth muscle cells exerting substantial arterial blood pressure-lowering properties. This will result in reduction of peripheral and cerebral vascular resistance. Apparently, vasodilation is mediated by blocking calcium influx and competitive inhibition of calcium binding. The vasodilatory potential of magnesium occurs in large arteries such as the aorta, in smaller resistance vessels as the mesenteric arteries and in the cerebral arteries. Vasodilatation of cerebral arteries could account for its anticonvulsant action [8,9].

Magnesium appears to trigger the release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, which is synthesized by the endothelium of vessels. In pre-eclampsia, acute magnesium sulphate administration improved endothelial function and a rapid fall in systemic vascular resistance followed. Subsequently, blood pressure decreased transiently and cardiac index increased [8].

However, during magnesium infusion, the patient should be monitored closely to detect early signs of toxicity. Also, frequent serum magnesium level should be obtained.

Labetalol is predominantly a nonselective β-blocker with some selective α-blocking effects. It decreases maternal systemic vascular resistance, slows the heart rate and reduces the incidence of ventricular arrhythmias. It causes reduction in myocardial oxygen consumption. There is no change in afterload observed after treatment with Labetalol [7].

Parturient receiving labetalol in this study had lower heart rate compared to those in magnesium group. This is due to its β blocking effect. Also, the magnesium group patients received hydralazine as an antihypertensive which causes reflex tachycardia.

Labetalol group had statistically significant lower blood pressure measurements throughout the operation and during postoperative period. There was no statistical significant difference between the two groups regarding fetal and neonatal heart rates.

Studies by McCoy et al., [10], and Garden et al., [11], found that Labetalol was associated with

<table>
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<th>Table (2): Group L, analysis of different mean blood pressure measurements (mmHg) versus baseline measurement.</th>
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<tr>
<td><strong>Group L</strong></td>
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<tr>
<td>Admission</td>
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<td>Induction of anesthesia</td>
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<td>24h postoperative</td>
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</tbody>
</table>

Data are presented as mean ± standard deviation (SD).

* : Statistically significant between group difference (p≤0.05).

**Baseline Heart rate (HR) recordings were comparable. While in the other readings, labetalol group showed statistically significant lower heart rates (Table 3).**

<table>
<thead>
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<th>Table (3): Heart rate (beats/min) measurements in both groups.</th>
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<tr>
<td><strong>Group M</strong></td>
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<tr>
<td>Preoperative</td>
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<tr>
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<td>6hr post operative</td>
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**Dose of antihypertensive:** In the labetalol group, the dose of labetalol needed to control blood pressure ranged from 60-220mg/24hr. None of the patients required hydralazine.

In magnesium group, the dose of hydralazine needed to control blood pressure ranged from 20mg to 100mg.

**Fetal heart rate:** There was no statistically significant difference in fetal heart rate between the two groups.

**Neonatal outcome:** There was no statistically significant difference in neonatal outcome as regard the weight and heart rate between the two groups. The Apgar score in both groups in the first minute ranged from 9 to 10. While the 5 minute Apgar score in both groups, ranged from 9 to 10.

**Seizures:** The patients in the two groups did not suffer from any attack of seizure either intraoperative or the first post operative day.
a trend toward more severe maternal hypotension and more neonatal bradycardia.

Magee et al., published a Meta-analysis of randomized controlled trials of short acting anti-hypertensives for severe hypertension in pregnancy. Hydralazine was associated with a trend towards less persistent severe hypertension, more maternal hypotension, maternal side effects and with less neonatal bradycardia than Labetalol [12].

Another recent study by Tabasi et al., done on 190 severe preeclamptic patients compared the use of hydralazine versus labetalol. Blood pressure controls, as well as the maternal and neonatal outcomes were compared between two groups. It concluded that there was no statistical significant difference in maternal and neonatal outcomes in both groups [13].

The major side effects associated with labetalol therapy are tiredness, dizziness, headaches, gastrointestinal symptoms, “tingly” scalp sensations and postural hypotension [14]. However, patients in our study receiving labetalol did not report any of these side effects.

Conclusion:

Use of Labetalol resulted in lower blood pressure levels as well as lower heart rates compared to magnesium therapy. Its use was not associated with seizures or poor neonatal outcome.

References