Original Article

A randomized clinical trial of intrathecal magnesium sulfate versus midazolam with epidural administration of 0.75% ropivacaine for patients with preeclampsia scheduled for elective cesarean section

Sophia Paleti, P Krishna Prasad[1], B Sowbhagya Lakshmi[1]

Department of Anaesthesiology, ACSR Govt.Medical College, Nellore, [1]Department of Anaesthesiology, Rangaraya Medical College, Kakinada, Andhra Pradesh, India

Abstract

Background and Aims: Magnesium sulfate and midazolam have been used as adjuvants to local anesthetics via intrathecal and epidural routes to augment the quality of block and prolong postoperative analgesia. This study compares addition of intrathecal magnesium sulfate versus intrathecal midazolam to epidurally administered isobaric ropivacaine as a part of combined spinal epidural technique in pre-eclamptic parturients undergoing elective cesarean section.

Material and Methods: After institutional ethics committee approval and written informed consent, 50 pre-eclamptic parturients were randomly allocated to one of the two groups of 25 each to either receive intrathecal magnesium sulfate (50 mg) or intrathecal midazolam (1 mg) in combination with epidural ropivacaine (0.75%; 14–16 ml). The onset and duration of sensory and motor blockade, duration of postoperative analgesia, postoperative visual analogue scores for pain, and perioperative side effects were noted. Data were analyzed statistically using Graphpad.com software.

Results: Onset times to sensory and motor blockade were faster in midazolam than in magnesium group ($P < 0.01$). Duration of sensory and motor blockade, and time to first request of analgesia were significantly longer in the magnesium group compared to the midazolam group ($P < 0.01$). The fetal outcomes according to APGAR scores were comparable in both the groups, the median APGAR score at 1 minute was 8 and at 5 minutes was 10 in both the groups.

Conclusion: Intrathecal magnesium with epidural ropivacaine significantly prolonged postoperative analgesia compared to intrathecal midazolam without any complications. Perioperative hemodynamics were comparable in both groups.

Keywords: Combined spinal epidural anesthesia, magnesium sulfate, midazolam hydrochloride, pre-eclampsia, pregnancy

Introduction

Regional anesthesia is the traditionally practiced technique in obstetric practice. It provides excellent intraoperative analgesia and can be extended to the postoperative period by adding adjuvants.[1]

Address for correspondence: Dr. P Krishna Prasad, Department of Anaesthesiology, Rangaraya Medical College, Kakinada - 533 001, Andhra Pradesh, India.
E-mail: drkp79@gmail.com

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_74_17

Preservative-free magnesium sulfate and preservative-free midazolam have been used in several obstetric clinical trials as adjuvants to local anesthetics via intrathecal and epidural routes and have proved to be efficacious in augmenting postoperative analgesia.[2,3] The rationale behind addition of intrathecal adjuvants to epidural local anesthetics is two-fold; first, they enhance the quality of analgesia by their localized action at the spinal level, and second, they prolong the time to first request of analgesia in the postoperative period.

How to cite this article: Paleti S, Prasad PK, Lakshmi BS. A randomized clinical trial of intrathecal magnesium sulfate versus midazolam with epidural administration of 0.75% ropivacaine for patients with preeclampsia scheduled for elective cesarean section. J Anaesthesiol Clin Pharmacol 2018;34:23-8.

Combined spinal epidural anesthesia (CSE) technique has gained popularity for parturients undergoing cesarean section to effectively prolong postoperative analgesia which promotes well-being and early bondage between the mother and the baby. Pre-eclamptic parturients are more prone to intraoperative hemodynamic fluctuations. Use of an adjuvant helps in maintaining hemodynamic stability while prolonging effective analgesia. Magnesium sulfate has been proven to intensify the quality of regional blockade by blocking N-Methyl D-Aspartate channels.[4,5] Among benzodiazepines, midazolam is a common agent used in CSE technique which produces profound intrathecal analgesia by reducing excitatory GABA-mediated neurotransmission.[6,7]

Isobaric ropivacaine (0.75%) produces effective epidural blockade in cesarean patients as proved in various clinical trials and its safer toxicity profile beneficial in obstetric patients. Hence in this study, the primary aim was to determine whether intrathecal magnesium or intrathecal midazolam along with epidural isobaric ropivacaine (0.75%) would prolong postoperative analgesia in pre-eclamptic parturients.

Material and Methods

This prospective double-blind, parallel design, interventional, randomized clinical trial was performed in a tertiary care hospital from January 2015 to December 2015. Participants were randomly assigned following simple randomization procedure using computer-generated random numbers to one of the two interventions by the researcher, a senior anesthesiologist not involved in the implementation of study. This study was registered at ClinicalTrial.gov with identification no.NCTO2619799. After institutional ethical committee approval and written informed consent, 50 pregnant women with mild pre-eclampsia posted for elective cesarean section were randomly allocated to group A (magnesium) or group B (midazolam).

Inclusion criteria were, parturients with mild pre-eclampsia, age18–28 years, weight 50–90kg, height150–170cm, belonging to ASA physical status II, posted for elective surgery. The following patients were excluded from the study: patients who refused to participate, HELLP syndrome prior magnesium therapy, history of any contraindications to regional anesthesia, thrombocytopenia (platelet count $<100000/mm^3$) cesarean for fetal distress, and history of allergy to study drugs.

Group A received 50 mg (0.1ml) of intrathecal preservative-free magnesium sulfate diluted to 1ml with normal saline and 14–16 ml of 0.75% epidural ropivacaine in CSE technique. Group B received 1 mg (0.2 ml) of intrathecal preservative-free midazolam diluted to 1 ml with normal saline and 14–16 ml of epidural 0.75% ropivacaine as a part of CSE technique. In both the groups, CSE technique was performed with 18-G epidural Tuohy needle and 27-G Whitacre tip spinal needle using a CSE set (B Braun, Germany) at L3–L4 or L2–L3 interspace using the midline approach in left lateral position.

An insulin syringe was used to measure drug volumes of less than 1 ml. The principal investigator loaded all the study drugs according to group allocation and provided them in sealed envelopes. The anesthesiologist who performed the CSE technique was a senior resident, unaware of the study drugs and group allocation.The allocation sequence was concealed from the senior resident who performed the technique by providing the study drugs just before the procedure in sequentially-numbered, opaque, and sealed envelopes. Intraoperative monitoring and data collection were done by another senior postgraduate who was also unaware of the study drugs. Hence, parturients, caregivers, and outcome assessors were blinded to interventions. All the parturients were given Inj. Pantaprazole 40 mg intravenous (IV) 1 h before surgery. No other premedication was administered. All parturients of both the groups were preloaded with 15 ml per kg of Ringer's lactate solution after securing an 18-G IV cannula.

Baseline hemodynamic parameters such as heart rate, noninvasive blood pressure (NIBP), pulse oximetry, respiratory rate, and temperature were recorded. All patients were shifted to the operating room in left lateral position. All the mentioned monitors were applied and 5 L/min of oxygen was administered to all the parturients with a Hudson face mask. The time of instituting CSE was noted in all the parturients. The following parameters were recorded in each group intraoperatively and postoperatively.

The primary outcome of this study was the time to first request for analgesia (duration of postoperative analgesia). The secondary outcomes of this study were sensory and motor characteristics, hemodynamic parameters and side effects. The sample size estimation was based on the time to first request analgesia. The onset and duration of sensory blockade was assessed with pinprick for every 2–3 min for the initial 20 min, and then every 30 min intervals until total regression of sensory blockade.

The onset and duration of motor blockade was assessed with Modified Bromage Score for every 2–3 min for the initial 30 min and then every 30 min intervals until complete regression of motor blockade. Hemodynamic parameters such

as pulse rate, systolic blood pressure, and diastolic blood pressure were monitored for every 2–3 min for the initial 30 min and later every 5 min throughout the surgery and until first 12 postoperative hours.

All parturients were observed for side effects such as bradycardia, hypotension, shivering, respiratory depression, nausea, vomiting and sedation throughout the intra-operative period and the first 12 postoperative hours.

APGAR scores of new born babies were also compared between the two groups at 1 min and 5 min after delivery.

Duration of sensory blockade was defined as the time from onset of sensory blockade to regression of sensory block to T_{12}. Duration of motor blockade was defined as the time from onset of motor blockade MB_3 to complete regression of motor block. Time to first request of analgesia was defined as the time interval from the time CSEA was administered till the parturient complained of pain (VAS >4) in the postoperative period (duration of postoperative analgesia). Postoperatively, pain was assessed using visual analog scale (VAS) score. Rescue analgesia was administered when VAS ≥4, with 1mg/kg of IV tramadol and 75 mg of IM diclofenac sodium as multimodal analgesia regimen. This study was completed after first 12 postoperative hours.

Based on a pilot study conducted in 10 patients, clinically significant difference in the mean time to first request of analgesia between groups was considered as 110 min. The mean time to first request analgesia in the pilot study was 395 ± 15 min in group A compared to 285 ± 22 minutes in group B. Using $\alpha = 0.05$ and power of the study being 80%, sample size was calculated to be approximately 24 in each group. The parturients in whom pilot study was performed were not included in the study.

All the data was tabulated and analyzed using the software Graph pad.com. Demographic data was analyzed using Student's *t*-test. Comparison of sensory and motor block characteristics between the groups were analyzed using Student's *t*-test. To test the normality of data distribution, the test used was Shapiro Wilk test, and the data was found to be normally distributed.Categorical data was analyzed using Chi-square test. Data was expressed as mean and standard deviation, absolute numbers, and median. $P < 0.05$ was considered significant.

Results

The flow of participants is represented in the CONSORT-flow diagram [Figure 1].The two groups were comparable with respect to age, weight, height, gestational age, ASA status, and duration of surgery [Table 1]. Characteristics of sensory and motor blockade are represented in Table 2.

Time to first request analgesia was significantly prolonged in Group A than Group B [Table 2].

The duration of sensory blockade was significantly prolonged in Group A [Table 2].

The duration of motor blockade was also prolonged in Group A than Group B [Table 2].

Onset time to sensory blockade T_6 was significantly earlier in Group B. Onset time to motor blockade MB_3 (Modified Bromage score 3) was also significantly earlier in Group B than group A [Table 2].

There were no significant differences in the mean arterial pressure in the two groups throughout the surgery [Figure 2]. Intraoperative mean heart rates were also comparable between the two groups [Figure 3].

Neonatal APGAR scores at 1 min and 5 min were comparable between the two groups. They were comparable [Table 3]. Patients of both the groups were assessed for side effects such as nausea, vomiting, shivering, sedation, pruritus and respiratory depression. The incidence of nausea, vomiting and shivering was comparable between the two groups [Table 4]. None of the patients in both the groups had sedation pruritis or respiratory depression. Urinary retention was not a problem because urinary catheter was left *insitu* for 24 hours.

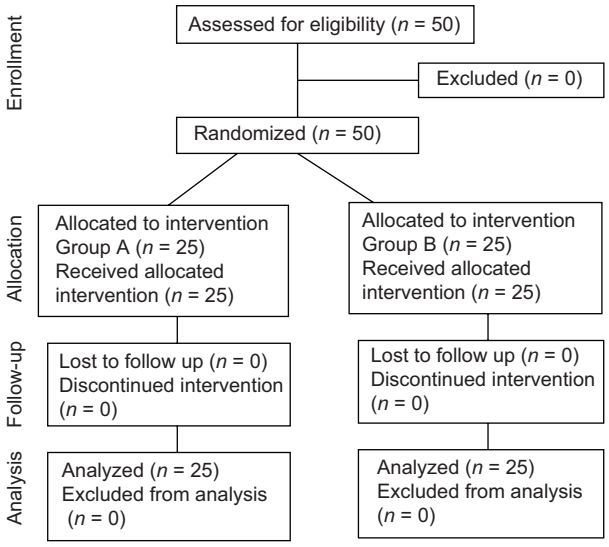

Figure 1: CONSORT diagram showing the flow of participants through each stage of the randomized trial

Discussion

CSE technique is effective for parturients undergoing lower segment cesarean section, especially parturients with heart disease complicating pregnancy, mild to severe pre-eclampsia, etc.[8] In this study, the advantage of CSE technique has been utilized in pre-eclamptic parturients where maintenance of stable hemodynamics in the intraoperative period is of utmost important for the mother as well as the fetus.

The present study demonstrates that addition of intrathecal magnesium sulfate to epidural ropivacaine isobaric 0.75% significantly prolonged postoperative analgesia when compared to intrathecal midazolam. The duration of sensory and motor blockade were significantly prolonged in magnesium group compared to midazolam group in this study. The hemodynamic and APGAR variables were comparable between the two groups.

The incidence of nausea, vomiting and were comparable between the two groups in this study. None of the parturients had side effects such as pruritus, respiratory depression and sedation.

Magnesium sulfate is a noncompetitive N-methyl-D-Aspartate (NMDA) receptor antagonist blocking ion channels in a voltage-dependent manner when used intrathecally.[9] Magnesium also reduces the activation of c-fibres by inhibiting the slow excitatory postsynaptic currents produced by NMDA receptors activation. NMDA receptor antagonists abolish calcium and sodium influx into cells leading to central sensitization and wind-up attributed to peripheral nociceptive stimulation.[10]

Table 1: Demographic data

Variable	Group A (*n*=25)	Group B (*n*=25)	*P*
Age (yrs)	23±2	26±3	0.5
Weight (kgs)	68±5	72±6	0.1
Height (cms)	156±3	158±6	0.09
Duration of surgery (min)	58±6	52±4	0.07

Data expressed as mean±SD and analyzed using Student's t test.

Midazolam provides spinal analgesia through GABA (gamma-amino butyric acid) receptors which are densely present in the lamina 2 of dorsal horn ganglia, a region which plays a prominent role in the processing of nociceptive and thermoceptive stimulation.[11] Midazolam also acts through spinal and opioid receptors activation.

Buvanendran *et al.* conducted the first RCT in humans using intrathecal magnesium with or without fentanyl combined with epidural fentanyl, bupivacaine, and adrenaline in obstetric patients for labor analgesia.[12] The epidural was instituted once the patient complained of pain. They concluded that intrathecal magnesium (50 mg) with fentanyl (25 μg) prolonged the duration of analgesia compared to fentanyl alone.

Boules *et al.* conducted a comparative study between the effects of intrathecal midazolam versus intrathecal midazolam plus magnesium sulfate in patients undergoing cesarean section, and concluded that addition of magnesium to intrathecal midazolam along with hyperbaric bupivacaine significantly prolonged the duration of postoperative analgesia without side effects.[13] The findings of the above study correlated with the observations of our study with respect to postoperative analgesia.

In the present study, the onset of sensory and motor blockade was earlier with midazolam compared to magnesium, similar to the observations in the study reported by Shashini *et al.*; where the authors compared the clinical effects of intrathecal midazolam 1mg versus intrathecal magnesium sulfate 50mg as adjunct to hyperbaric bupivacaine.[14] The difference is that, in our study ropivacaine was used in epidural route.

In a meta-analysis by Ismail *et al.*; intrathecal midazolam appears to improve perioperative analgesia and reduce nausea and vomiting during cesarean delivery.[15] Nishiyama *et al.*; conducted a histopathological study on spinal midazolam in cats and showed that intrathecal midazolam is free of adverse effects up to 2 mg.[16]

In this study, the rationale behind adding nonopioid intrathecal adjuvants alone with epidural local anesthetic was

Table 2: Characteristics of sensory and motor blockade

Variable	Group A (*n*=25)	Group B (*n*=25)	*P*
Onset of sensory blockade	9.9±1.4	7.9±0.9	0.002
Onset of motor blockade	12.5±1.6	7.7±3.2	0.002
Duration of sensory blockade	295±36	245±26.4	0.007
Duration of motor blockade	265±24.6	223±22.2	0.003
Time to first request analgesia	334±39	280±23.4	0.002

Student t-test. Data expressed as Mean+SD

to observe whether the opioid-sparing effects of magnesium or midazolam would result in prolongation of postoperative analgesia without side effects and whether they would prolong spinal analgesia by their localized action on the spinal nociceptive pathways, which may result in denser anti-nociception compared to epidural local anesthetic with adjuvants. Single-shot CSE technique was instituted in this study as per the protocol.

In a systematic review and meta-analysis by Morrison *et al.* the effects of intrathecal magnesium sulfate with or without lipophilic opioids in the presence or absence of local anesthetics were analyzed and it was concluded that the duration of spinal anesthesia may be increased by addition of intrathecal magnesium to lipophilic opioids with or without LA.[17]

Xaio *et al.* observed that addition of intrathecal magnesium to low-dose hyperbaric bupivacaine and sufentanil significantly prolonged the duration of analgesia compared to sufentanil and bupivacaine in severe pre-eclamptic patients.[18]

Dilesh *et al.* compared intrathecal dexmedetomidine versus fentanyl with epidural bupivacaine for labor analgesia and observed that intrathecal dexmedetomidine significantly prolonged the duration of labor analgesia compared to intrathecal fentanyl.[19] The methodology of the above study is similar to our study but differed in intrathecal adjuvants and epidural local anesthetic.

This trial is a systematically conducted randomized and double-blinded trial free of selection bias and analyzed using appropriate statistical tests and free of interpretation bias which are the main strengths of this trial.The main limitation of this study is the lack of a placebo group as one of the interventional arms.

This study adds to the present literature that the addition of intrathecal magnesium or midazolam to epidural local anesthetic prolongs postoperative analgesia with minimal opioid sparing side effects, but less prolongation of analgesia when compared to long acting opioids.

The major controversy of concern is regarding the neurotoxicity with intrathecal magnesium sulfate which has been evaluated in animal and human studies. The safety of intrathecal magnesium is evaluated in animal studies.In rats, a 1.26 mg intrathecal bolus of magnesium given on alternate days over a 30-day period produced transient motor and sensory block similar to lidocaine with no adverse clinical consequences.[20]

Several human studies used doses of intrathecal magnesium between 50 mg and 100 mg, which reported no deleterious effects.[20-22] The data on neuraxial administration of magnesium as an analgesic adjunct in the perioperative settings are promising.

There is considerable scope for future research with intrathecal magnesium in varied population groups and the dose range needed to be validated for routine clinical practice as magnesium provides opioid sparing analgesia.

Table 3: Apgar scores

Time (min)	Magnesium group *n*=25	Midazolam group *n*=25
1	8 (8-10)	8 (7-10)
5	10 (8-10)	10 (8-10)

Data expressed as Median and range

Table 4: Side effects

	Nausea	Vomiting	Shivering	*P*
Magnesium group (*n*=25)	1 (4%)	2 (8%)	2 (8%)	1.0
Midazolam group (*n*=25)	1 (4%)	3 (12%)	4 (16%)	

2×3 Fischer exact test. Data expressed as absolute Numbers and percentage

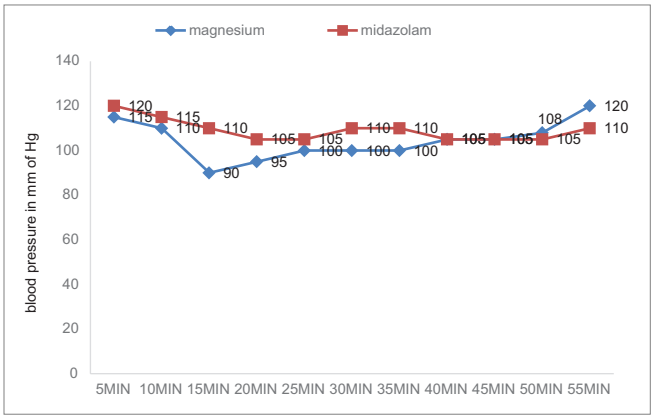

Figure 2: Intraoperative Mean systolic Blood Pressures

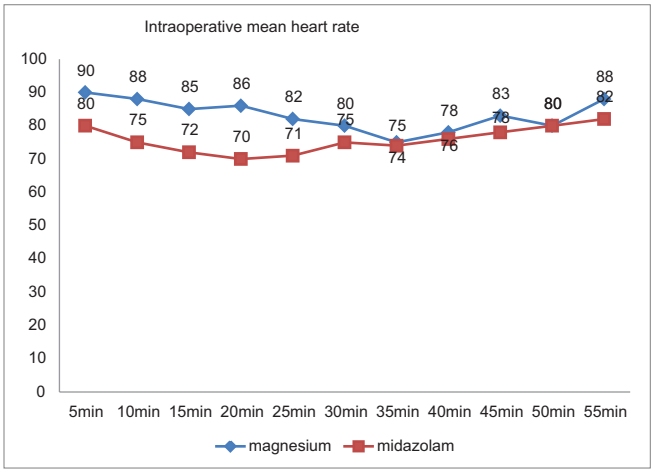

Figure 3: Intraoperative Mean Heart Rates

Conclusion

Intrathecal magnesium and midazolam produced effective neuraxial blockade with epidural 0.75% ropivacaine in pre-eclamptic parturients. Intrathecal magnesium with epidural ropivacaine significantly prolonged postoperative analgesia compared to intrathecal midazolam without any side effects.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Hood DD, Curry R. Spinal versus Epidural anaesthesia for caesarean section in severely preeclampsia patients. A retrospective survey. Anesthesiology 1999;90:1276-82.
2. Khalili G, Janghorbhani M, Sajedi P, Ahmedi G. Effects of adjunct intrathecal magnesium Sulphate to bupivacaine for spinal anaesthesia: A randomised, double-blind trial in patients undergoing lower extremity surgery. J Anesth 2011;25:892-7.
3. Bharathi N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to Bupivacaine improves the duration and quality of spinal anaesthesia. Acta Anaesthesiol Scand 2003;47:1101-5.
4. Yousef AA, Amr YM. The effect of adding magnesium sulphate to epidural bupivacaine and Fentanyl in elective caesarean section using combined spinal-epidural anaesthesia: A prospective double blind randomized study. Int J Obstet Anesth 2010;19:401-4.
5. Arciono R, Palmisani S, Tigano S, Santorsola C, Sauli V, Romano S, *et al*. Combined intrathecal and epidural magnesium sulphate supplementation of spinal anaesthesia to reduce post-operative analgesic requirements: A prospective, randomised, double-blind, controlled trial in patients undergoing major orthopedic surgery. Acta Anaesthesiol Scand 2007;51:482-9.
6. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal midazolam: A cohort study investigation safety. Anesth Analg 2004;98:1512-20.
7. Prochazka J. Intrathecal midazolam as an analgesic—10 years experience. Eur J Pain 2006; 10:202.
8. Collis RE, Davies DW, Aveling W.Randomised comparison of spinal-epidural and standard epidural analgesia in labour. Lancet 1995;345:1413-6.
9. Liu HT, Hollmann MW, Hoenemann CW, Liu WH, Durieux ME. Modulations of NMDA Receptor function by ketamine and Magnesium. Part II. Anesth Analg 2001;92:1173-81.
10. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293-9.
11. Edwards M, Serrao JM, Gent JP, Goodchild CS. On the mechanism by which midazolam Causes spinally mediated analgesia. Anesthesiology 1990;73:273-7.
12. Buvanendran A, McCarthy RJ, Kroin JS, Leong W, Perry P, Tuman KJ. Intrathecal magnesium prolongs fentanyl analgesia: A prospective, randomized, controlled trial. Anesth Analg 2002;95:661-6
13. Maged L, Boules, Joseph M, Botros.Comparative study between the effect of intrathecal Midazolam versus intrathecal Midazolam plus Magnesium sulphate on the efficacy and duration of analgesia in patients undergoing caesarean section. Ain-Shams J Anesthesiol 2015;8:70-5.
14. Shashini S, Nair AS, Gopal TVS. Clinical effects of intrathecal midazolam versus intrathecal magnesium sulphate as adjuncts to hyperbaric bupivacaine: A comparative study. Indian J Pain 2011;27:175-81.
15. Ho KM, Ismail H. Use of intrathecal midazolam to improve perioperative analgesia: A meta-analysis. Anaesth Intensive Care 2008;36:365-73.
16. Nishiyama T, Matsukawa T, Hanaoka K. Acute phase histopathological study of spinally administered midazolam in cats. Anesth Analg 1999;89:717-20.
17. Morrison AP, Hunter JM, Halpern SH, Banerjee A. Effect of intrathecal magnesium in the presence or absence of local anaesthetic with and without lipophilic opioids: A systematic review and meta-analysis. Br J Anaesth 2013;110:702-12.
18. Xiao F, Liu L, Zhang WP, Chang XY, Zhang YF. Original Article Effect of adding magnesium sulfate to intrathecal low-dose of bupivacaine for patients with severe pre-eclampsia undergoing cesarean delivery. Int J Clin Exp Med 2016;9:19749-56.
19. Dilesh PK, Eapen S, Kiran S, Chopra V. A Comparison of intrathecal dexmedetomidine verses intrathecal fentanyl with epidural bupivacaine for combined spinal epidural labour analgesia. J Obstet Anaesth Crit Care 2014;4:69-74.
20. Saeki H, Matsumoto M, Kaneko S, Tsuruta S, Cui YJ, Ohtake K, *et al*. Is intrathecal magnesium sulphate safe and protective against ischemic spinal cord injury in rabbits? Anesth Analg 2004;99:1805-12.
21. Malleswaren S, Panda N, Mathew P, Bagga R. A randomized study of magnesium sulphate as an adjuvant to intrathecal bupivacaine in patients with mild preeclampsia undergoing caesarean section. Int J Obstet Anesth 2010;9:161-6.
22. Unlugenc H, Ozalevli M, Gunduz M, Gunasti S, Urunsak IF, Gular T, *et al*. Comparison of intrathecal magnesium, fentanyl or placebo combined with bupivacaine 0.5% for parturients undergoing elective caesarean delivery. Acta Anaesthesiol Scand 2009;53:346-53.