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Original Article

Pre-incisional epidural magnesium provides pre-emptive and postoperative analgesia in lower abdominal surgeries: a comparative study

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Abstract

Background: Magnesium sulphate has been used successfully as a non opioid analgesic adjuvant for postoperative pain management. This prospective controlled study was designed to evaluate the pre-emptive analgesic efficacy of adding magnesium to epidural analgesia in patients undergoing lower abdominal surgeries.

Methodology: In a randomized, double- blind study sixty patients undergoing lower abdominal surgery under general anesthesia were assigned to three groups. Pre-magnesium (Group PI), post-magnesium (Group PO) and control (Group C) group. Anesthetic technique was standardized. Patients in pre-magnesium group received bolus of magnesium 50 mg via epidural before induction of anaesthesia followed by boluses of 10 mg h^{-1} until end of surgery. Post-magnesium group patients received epidural saline during the same time periods plus bolus epidural magnesium 50 mg at the end of surgery. Patients in control group received epidural saline during all three periods. Patients in the magnesium groups received bolus epidural analgesia with Fentanyl 8mcg, Bupivacaine 0.1%, and Magnesium 8mg in a volume of 8 ml after operation, when patient complained of pain and VAS score was more than 4. Patients in the control group received epidural analgesia with Fentanyl 8 mcg and Bupivacaine 0.1% in a volume of 8ml. Blood Pressure, pulse rate, respiratory rate, time to the first request for analgesic, visual analogue scale at rest, 24 hour, opioids consumption and side effect profiles were studied for 24 hours postoperatively.

Results: The demographic parameters were comparable. Group PI had significantly lower VAS scores at all times 0,2,4,6,10,14,18 and 24 hours than those in the Group PO or Group C($P<0.05$). The groups were similar with respect to haemodynamic, respiratory variables and side effects.

Conclusion: Epidural Magnesium sulphate provided preemptive analgesia, and an analgesic-sparing effect that improved postoperative analgesia without increasing the incidence of side-effects.

Key words: analgesia; epidural; magnesium sulphate.

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Introduction

Pain is defined by the International Association for Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage".[1] Pain resulting from different tissue injuries may differ in its characteristics and mechanisms. Postoperative, incisional pain is a unique but common form of acute pain.[2] Effective postoperative pain management has a humanitarian role, but there are additional medical benefits for rapid recovery and discharge from hospital. The perioperative period is associated with a variety of pathophysiologic responses that may be initiated by nociceptive input. Transmission of nociceptive stimuli from the periphery to the Central Nervous System results in the neuroendocrine stress response. It results in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (e.g., cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II), and decreased secretion of anabolic hormones.[3] Uncontrolled postoperative pain may produce a range of acute and chronic effects.[4]

There are numerous experimental data that provide evidences that N-methyl-D-aspartate (NMDA) receptors play a significant role in neuronal plasticity and processes leading to central sensitization to pain.[5] NMDA antagonists have been shown efficacy in the reduction of acute postoperative pain and analgesic consumption.[6] Magnesium can be considered as a physiological blocker of NMDA receptors.[7] There are studies where magnesium has been administered by different routes such as intravenous, intrathecal or via epidural, that improved anaesthetic and analgesic quality.[8,9,10,11]The current randomized, double-blind, prospective study was designed to evaluate the analgesic efficacy of adding magnesium to an intermittent bolus epidural analgesia in patients undergoing lower abdominal surgeries.

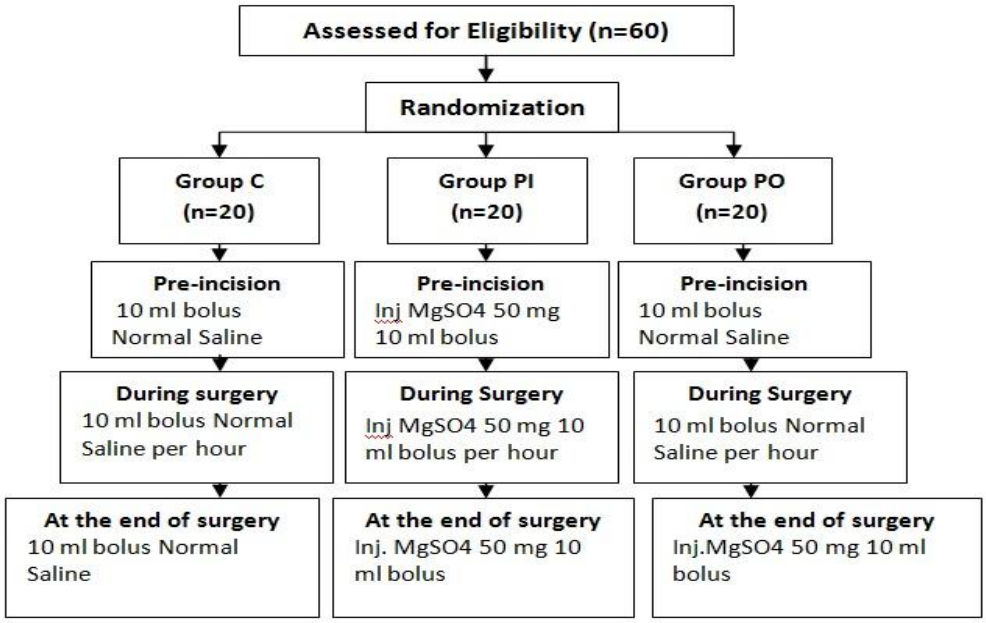
Methods

After obtaining approval from the Institutional Review Board and ethical committee of institute of medicine, we obtained informed written consent from 60 patients, ASA I and II, aged from 18 to 65 years. This was a randomized(Sealed envelope), double blinded prospective, placebo controlled experimental study involving three comparable populations of women undergoing lower abdominal surgeries, receiving pre-incisional, intra-operative and post-operative epidural magnesium sulphate. This study was done in Tribhuvan University Teaching Hospital, operation theatre, PACU and post operative ward from 10 May 2011 to 10 September 2011. Sixty patients were divided into three groups of twenty each. Exclusion criteria included ASA physical status - grade III or more, known history of hypersensitivity to any drug used, Patients who have contraindication to Regional Anaesthesia, history of chronic pain conditions, patients who have taken NSAID in last 24 hrs and patients with psychological disorder. The patients eligible for the study were evaluated pre-operatively, and randomly assigned to three study groups. In Group C, patients received only Bupivacaine and Fentanyl post operatively via epidural route. Patients in Group PI received magnesium sulphate pre-operatively, intraoperatively and continued post operatively with Bupivacaine and Fentanyl via epidural route. Patients in Group PO received magnesium sulphate with Bupivacaine and Fentanyl via epidural route post operatively only. Patients were instructed preoperatively during the pre-anaesthetic check up about the use of visual analogue scale (VAS) for the assessment of pain. They were instructed to point at the 10 cm long scale with 0 equaling no pain and 10 equaling worst possible pain. They were also counseled about sedation, dizziness, nausea and vomiting, and pruritus as possible post operative complication. The patients were fasted for 6 hours preoperatively. All patients were premedicated with Diazepam 0.2 mg/kg body weight orally the day and 2 hrs before surgery. In the preparation room, baseline vital parameters were recorded. Intravenous access was obtained. Before the induction of anaesthesia, an epidural catheter was placed at the L1-L2 intervertebral space under local anaesthesia with the use of loss of resistance technique, and correct positioning was confirmed by an injection of lidocaine 2% (3 ml) with epinephrine 1:200 000. The epidural was activated as shown in the consort flowchart in Figure 1.

General anaesthesia was induced with propofol 2 mg kg^{-1} intravenously(i.v) and fentanyl 2 mg kg^{-1} i.v. Vecuronium 0.1 mg kg^{-1} i.v. was given to facilitate tracheal intubation. Anaesthesia was maintained with oxygen and isoflurane 1–2%. Supplemental boluses of vecuronium 0.05 mg kg^{-1} i.v. were administered as required to maintain muscle relaxation during surgery. At the end of surgery, muscle relaxation was reversed by i.v. neostigmine 0.05 mg kg^{-1} and atropine 0.02 mg kg^{-1}. Intraoperative monitoring included ECG, systolic and diastolic blood pressure, mean arterial pressure (MAP), pulse oximetry and heart rate (HR) were recorded. Anesthesia assistants were instructed to prepare drugs for Epidural administration as per randomization. The time in the recovery room when patient

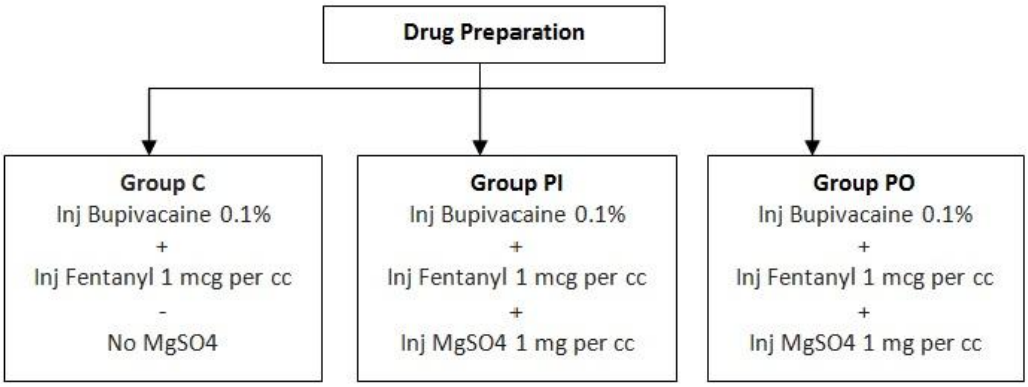
was received and first vitals were recorded was recorded as time 0. After completion of surgery epidural analgesia was prepared in a 50 cc syringe as following by anaesthesia assistant and sent to the post operative ward with the patient along with the sealed envelope.

Figure 1: Group Randomization



At the post operative ward, patients received epidural analgesia according to their group as mentioned in Figure 2.

Figure 2: Epidural Drug Preparation



Hypotension was treated with Inj. Mephentermine 6 mg i.v. for three times and co-administration of intravenous fluid bolus 10 ml per kg. Bradycardia was treated with 0.6 mg atropine i.v. every 3 to 5 minute to a total of 3 mg. Assessments of pain, nausea, vomiting and pruritus were performed at 0, 2, 4, 6, 10, 14, 18 and 24 h after arrival in the post anesthesia care unit or postoperative ward. As soon as patient complained of pain or VAS≥4, 8 ml volume was given via epidural catheter . The time when the epidural analgesia was given was noted by the nursing staff in the post operative ward. The interval from the end of surgery to the request of first dose of analgesic was recorded. If pain relief was unsatisfactory we waited for 15min, assessed VAS again and if it was ≥4, second bolus of 8 ml of the epidural dose was given. If even after two doses via epidural catheter did not provide pain relief, then the patient was excluded from the study and Inj Tramadol 50 mg i.v was given as rescue analgesia.

Patients with a severe nausea received Ondansetron 4 mg iv which was repeated every 15 min if not controlled. Patients with a severe pruritus received Ondansetron 8 mg iv in 100 ml NaCl 0.9% given over fifteen minutes. If no improvement was seen in 15 min, iv Naloxone 0.01 mg per kg was to be given and repeated every 5 min. Assessments of systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate were done 2 hourly for first 6 hours, then 4 hourly for the next 18 hours .The duration of study was till 24 hrs in the post operative period.

The statistical analysis of data was done by using SPSS software version 17. The following tests were used for data analysis Independent t test and chi square test. p value less than 0.05 was considered significant. Data are expressed as mean (SD) for quantitative measures.

RESULTS:

Of the 60 patients enrolled in this study, three were no exclusions. There were no significant differences among the three groups in the demographic profile with regards to age, weight and ASA PS (Table 3). The distribution of patients among the types of surgery performed and the duration of surgery were also comparable among the study population.

Table 1: Demographic Profile

Mean ± SD	**GROUP PI**	**GROUP PO**	**GROUP C**	**P value**
AGE (years)	38.05±11.80	38.30±10.37	39.05±10.40	>0.05
WEIGHT(kg)	55.75±7.99	56.95±9.21	56.25±7.89	>0.05
ASA PS I	15 (75)	18(90)	16(80)	>0.05
ASA PS II	5 (20)	2(10)	4(20)	>0.05
Duration of surgery	79.75±43	90.25±41.27	82.25±25.26	>0.05
Type of surgery				
Salpingoopherectomy	9(45%)	9(45%)	12(60%)	>0.05
TAH	11(55%)	11(55%)	8(40%)	>0.05

Baseline hemodynamic parameters like heart rate, MAP, SBP, DBP were also comparable among the study groups.

Table 2: Baseline Haemodynamic parameters

Mean ±SD	**Pulse(beats per minute)**	**SBP(mm of Hg)**	**DBP(mm of Hg)**	**MAP(mm of Hg)**
Group C	85.65±11.08	123.45±14.65	77.55±10.86	77.55±10.86
Group PI	83.10±10.53	122.20±12.67	75.15±9.033	90.83±9.41
Group PO	85.25±10.41	118.55±14.98	75.10±13.98	89.58±13.77

Patients in the Group PI had significantly lower VAS scores at all times 0, 2, 4, 6, 10 ,14, 18 and 24 hours than those in the Group PO or Group C ($P<0.05$). The minimum mean VAS score at rest in Group PI is 1.55±0.75 at 24 hr. The maximum mean VAS score at rest in group PI is 4.7±2.93 at 0 hour. Whereas, the maximum mean VAS score at rest in Group PO and Group C was 6.45±2.18 and 6.80±2.82 respectively at 0 hour. The mean VAS score was more than 4 only at 0 and 2 hours in group PI. The mean VAS scores at rest significantly lower in the Group PI compared with the Group PO or Group C.

Table 3: Postoperative Pain Scores in the three groups

Time(hr)	Group C (n=20)	Group PI (n=20)	GroupPO (n=20)
0	6.8±2.82	4.7±2.93	6.45±2.18
2	5.8±1.79	4.15±1.78	5.50±2.01
4	5.95±2.23	3.80±1.93	5.45±1.82
6	5.60± 1.42	3.25 ±1.65	5.35±2.00
10	5.40±1.69	3.65±1.98	5.70±2.34
14	5.15±1.69	2.7±1.41	4.80±1.64
18	5.8±1.88	1.8±1.00	5.15±2.00
24	3.90±1.37	1.55±0.75	3.75±1.61

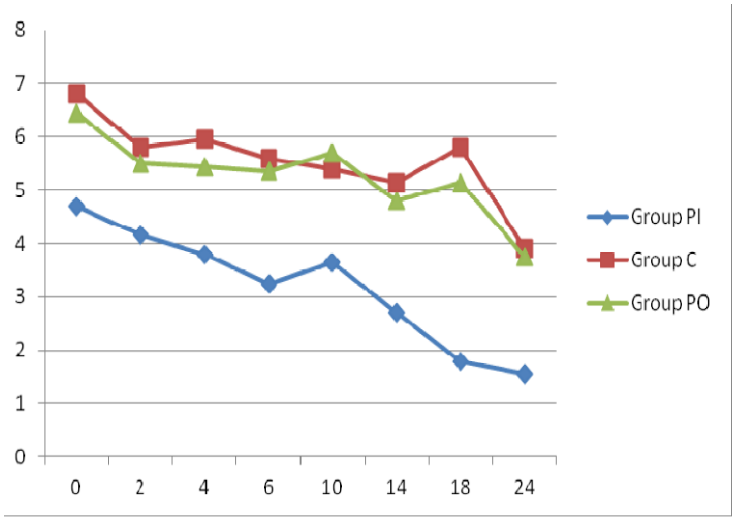


Figure 3: Comparison of Visual Analogue Score among Group PI, Group PO, Group C

The mean number of top up in the Group PI was 6.8 with SD of ± 1.28. In Group PO it was 8.35 with SD of ± 1.42 while it was 9.00 in the Group C with SD of 1.65. The minimum number of epidural top up in Group PI was 4 and maximum was 8. Whereas, the minimum number of epidural top up was 7 in group C and maximum were 12. There was significant difference in the number of postoperative epidural analgesic top up while comparing Group PI with Group PO, Group PI with Group C and Group PO with Group C. The mean duration of first bolus dose administered was 52.75 minutes in Group PI with standard deviation of ±21.61 minutes. While it was 34.25 minutes with standard deviation of ± 14.26 minutes in Group PO and 31.25 minutes with standard deviation of ±9.01 minutes in Group C. There was significant difference while comparing Group PI with Group PO, Group PI with Group C regarding the duration from the end of surgery to the first epidural bolus drug administered (P<0.05).

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depression in any case in 24 hours postoperatively. The incidence of nausea and vomiting was less in the Group PI patients compared to the Group PO and Group C patients but it was not statistically significant.

Discussion

The results of our study indicate that pre-emptive administration of epidural magnesium sulphate significantly reduces the incidence of pain after lower abdominal surgery. Patients who received epidural magnesium pre-incision, intraoperatively and postoperatively had significantly lower pain scores at 0, 2, 4, 6, 10, 14, 18 and 24 hour and had significantly decreased total drug requirements in the 24 hours study duration in comparison to the placebo group. The duration of analgesia was also significantly prolonged in the pre-incisional magnesium group. Patients in the Group PI had significantly low VAS scores at all times than those in the Group PO or Group C. The low VAS scores in magnesium group (Group PI and Group PO) may be due to anti-nociceptive effects and non competitive NMDA antagonist property of magnesium sulphate. Our results were comparable with a study published by S.Farouk[12] where he also reported low VAS scores up to three days with the use of continuous infusion of pre-incisional epidural magnesium which was continued intra-operatively and postoperatively. In this study, there were significantly lower VAS scores for the pre-magnesium group when compared with the post magnesium and control groups ($P<0.05$). The lower VAS scores in continuous infusion groups in this study as compared to our study could probably be explained by the fact that intermittent bolus doses were unable to maintain basal drug levels in the CSF as well as in the systemic circulation. In our study, the duration of first analgesic dose requirement after the end of surgery was significantly prolonged in Group PI when compared to Group PO and Group C. This also correlates with significantly lower VAS scores seen in Group PI in comparison to Group PO and Group C. Similar to our study, there was a study done by Hüban Dayiog et al.[13], where they investigated the effect of adding magnesium sulfate intrathecally in 60 patients undergoing knee arthroscopy, who were randomly allocated into two groups. There was significant difference between two groups in the time to first analgesic requirement ($P<0.05$). In our study, the duration of first analgesic dose requirement after the end of surgery was prolonged by 21 min in the magnesium group which is similar to a study done by Huban Dayiog et al.[13] In another study done by Buvanendra et al[14], who performed first prospective human study evaluating whether intrathecal magnesium could prolong spinal opioid analgesia, the median duration of analgesia in magnesium group was prolonged by 15 min. Thus, our study in addition to other studies shows that epidural magnesium prolongs the analgesic effect of opioid which also correlates with the lower VAS scores in the magnesium groups. In our study, the postoperative analgesic consumption in Group PI in terms of mean number of bolus was 6.80. Whereas in Group PO the mean number of bolus was 8.4, and in control group the mean number of bolus was 9. The total dosage of epidural analgesia consumed in 24 hours in our study was significantly less in Group PI when compared with Group PO and Group C. As seen in our study, the need for greater analgesic dose requirement in groups without magnesium has also been reported by Bilir and colleagues.[10] They studied the effect of magnesium given via epidural route on reduction of postoperative analgesic requirement in fifty patients.

The concept of pre-emptive analgesia was initially put forward by Crile[15] and then by Wall[16]. They suggested that the administration of opioids or local anaesthetics before surgery might reduce the C-fiber-induced injury barrage associated with incision and, thereby, the intensity of postoperative pain[17]. These concepts suggest that effective analgesia starts before incision and covers both the period of surgery and the postoperative period. The NMDA receptor antagonists like magnesium sulphate would appear to be potentially useful drug in this regard because of their effect in reducing central hypersensitivity and wind-up-like states in humans. In our study, the addition of magnesium 1 mg ml-1 in the multimodal analgesic mixture also produced an analgesic-sparing effect. It significantly reduced the analgesic mixture consumption in the pre- incisional magnesium group when compared with the post magnesium and the control groups. Our study thus showed that antinociceptive treatment with epidural magnesium which is a NMDA antagonist, started before noxious stimulation and extended into the postoperative period resulted in better pain control outcomes, and the effects were pre-emptive. In our study, the incidence of nausea and vomiting in Group PI was 6.67%, in Group PO was 10% and in Group C was 18.33%. In our study, assessing the level of postoperative complications like nausea and vomiting showed fewer incidence of lesser severity in magnesium group (Group PI and Group PO) in comparison to Group C, although they were statistically not significant. It also correlates with statistically significant, high VAS scores seen in Group C in comparison to Group PI and Group PO. There was only one incidence of pruritus in Group C which was treated with single dose Inj. Ondansetron 8 mg intravenously. In a study by S.Farouk[12], the incidence of nausea and

vomiting was 7% in all the three groups. Doses of epidural magnesium used in our study are within the range used in the previous studies.[10,12,14] Though our results regarding the incidence of nausea and vomiting were not statistically significant, it might have clinical implications. Hence we recommend larger studies to elicit statistically significant incidence of side effects. Lejuste[18] reported a case, where an intrathecal injection of 1000 mg of magnesium that produced a dense motor block followed by a complete resolution within 90 min and no neurological deficit at long-term follow-up. In our study, during observation none of our study cases showed any signs of neurological deficit. It could probably be justified by the low dose of magnesium that we have used in our study. In other studies[10,12,14] where dose of magnesium were similar to our study, no cases with any neurological deficit have been reported. Our study shows that magnesium can be used as an adjuvant to regional anaesthesia technique. The main aim of combining different analgesic drugs and techniques is to obtain synergistic or additive actions that allow a smaller dose of each agent to be used and, thereby, improve the safety profile. Our study has achieved that aim. Our study demonstrated that the pain intensity between the post-magnesium and the control groups was not statistically significant. This may suggest that epidural magnesium started after surgery neither prevents nor decreases establishment of central hypersensitivity, thus failing to decrease postoperative pain intensity for the post magnesium group compared with the control group. In animal research, it has been suggested that epidural block for a successful reversal of established hypersensitivity should be stronger in intensity and longer in duration than a preemptive effect. That is because the threshold of afferent input for re-initiation of central hypersensitivity is less than that for the initial central hypersensitivity.[19] Hence preoperative use of epidural magnesium for patients undergoing lower abdominal surgeries followed by epidural magnesium boluses during surgery with extension into the postoperative period provides pre-emptive effects on postoperative pain intensity and provides an analgesic-sparing effect without increasing the incidence of side-effects.

References

1 A sample list of frequently used terms. International Association for the Study of Pain Task Force on Taxonomy. In: Merskey NB, ed. Classification of Chronic Pain, 2nd ed. Seattle: IASP Press; 1994:209-214.
2 McMahon Stephen B, Koltzenburg Martin, editors. Wall and Melzack's textbook of pain. 5th ed. China. Churchill Livingstone. Elsevier. 2006.
3 Kehlet H: Modification of responses to surgery by neural blockade. In: Cousins MJ, Bridenbaugh PO, ed. Neural Blockade in Clinical Anesthesia and Management of pain, 3rd ed. Philadelphia: Lippincott-Raven; 1998; pg 119-122
4 Miller RD. Miller's anesthesia. Seventh edition. Philadelphia (PA): Churchill Livingstone; 2009.chapter 87: 586-587.
5Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebeskind JC, eds. Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues—Progress in Pain Research and Management. Vol. 1. Seattle: IASP Press, 1994; 173–87.
6 Fisher K, Coderre TJ, Hagen NA.Targeting the N-methyl-D-aspartate receptor for chronic pain management: pre-clinical animal studies, recent clinical experience and future research directions. J Pain Symptom Manage 2000;20:358-73.
7Fawcet WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. Br J Anaesth 1999;83:302-20.
8 Buvanendran A, Mc Carthy RJ, Kroin JS, Leong W, Perry P, Tuman KJ. Intrathecal magnesium prolongs fentanyl analgesia: a prospective, randomized, controlled trial. Anesth Analg 2002;95:661-7.
9Usmani H, Quadir A, Alam M, Rohtagi A, Ahmed G. Evaluation of perioperative Magnesium Sulphate infusion on postoperative pain and analgesic requirements in patients undergoing upper abdominal surgery. J Anesth Clin Pharmacology 2007;23:255-8.
10Bilir A, Gulec S, Erkan A, Ozcelik A. Epidural magnesium reduces postoperative analgesic requirement. Br J Anaesth 2007;98:519-23.
11 Arcioni R, Palmisani S, Tigano S. Combined intrathecal and epidural magnesium sulfate supplementation of spinal anesthesia to reduce postoperative analgesic requirements. Acta Anaesthesiol Scand 2007;51:482-9.
12 Farouk S. Pre-incisional epidural magnesium provides pre-emptive and preventive analgesia in patients undergoing abdominal hysterectomy. Br J Anaesth 2008;274:1-6.
13 Dayioglu H, Baykara ZN, Salbes A, Solak M, Toker K. Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee arthroscopy. J Anesth 2009;23:19-25.
14 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;95:661-7.
15 Crile GW. The kinetic theory of shock and its prevention through anociassociation. Lancet 1913;185:7-16.
16 Woolf CJ: Evidence for a central component of post injury pain hypersensitivity. Nature 1983;308:686-8.
17 Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebeskind JC, eds. Pharmacological Approaches to the Treatment of Chronic Pain: New Concepts and Critical Issues Progress in Pain Research and Management. Vol. 1. Seattle: IASP Press, 1994;173-87.
18 Lejuste MJLR. Inadvertent intrathecal administration of magnesium sulfate. S Afr Med J 1985;68:367-8.
19 Kissin I, Lee SS, Bradley EL Jr. Effect of prolonged nerve block on inflammatory hyper analgesia in rats: prevention of late hyper analgesia. A review. Anesthesiology 1998;88:24-32.