VOLUME - 10, ISSUE - 02, FEBRUARY - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Anesthesiology

A COMPARATIVE STUDY OF EPIDURAL BUPIVACAINE WITH CLONIDINE AND EPIDURAL BUPIVACAINE WITH MAGNESIUM SULPHATE FOR PERIOPERATIVE ANALGESIA IN PATIENTS UNDERGOING LOWER LIMB SURGERY

Swarup Pandit — Specialist Anaesthesiologist, WBHS, West Bengal, India.

Tapobrata Mitra — Associate professor, Anaesthesiology, Murshidabad Medical college & Hospital, Berhampore, West Bengal, India

Baisakhi Laha — Associate Professor, Anaesthesiology, IPGME&R, Kol 20,West Bengal India.

Paramita Pandit* — Assistant professor, Department of Anaesthesiology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India.
*Corresponding author

ABSTRACT

Background: Epidural anaesthesia is a safe and inexpensive technique with advantage of providing surgical anaesthesia and prolonged postoperative analgesia. Use of adjuvant drugs with local anaesthetics increases its potency and decreases its dose requirement. **Aims and Objectives:** The aim of the study was to compare the perioperative analgesia effect of adjuvant clonidine with adjuvant magnesium sulphate when used in epidural anaesthesia with bupivacaine hydrochloride. **Materials and Methods:** A randomized, double blind, controlled study was conducted for 12 months in a tertiary care hospital of India. A total (n=60) patient aged 20-60 years, weight 50-75 kgs of either sex with ASA I and ASA II waiting for lower limb surgery were randomly allocated into two equal groups. Group BC (n=30) received epidural bupivacaine (0.5%) with clonidine (75 mcg) and Group BM (n=30) received epidural bupivacaine (0.5%) with magnesium sulphate (50 mg). Similar anaesthesia technique was performed for both the groups. Onset of anaesthesia, duration of anaesthesia and analgesia, haemodynamic and respiratory parameters were recorded at various time interval. **Result:** Onset of anaesthesia was faster and statistically significant ($p<0.0001$) in Group BM but duration of anaesthesia and analgesia were longer and statistically significant ($p<0.0001$) in Group BC. There was comparable demographic, haemodynamic and respiratory parameters in both the groups. **Conclusion:** Epidural bupivacaine with clonidine produces prolonged analgesia in comparison to epidural bupivacaine with magnesium sulphate.

KEYWORDS : Epidural anaesthesia; Clonidine; Magnesium sulphate; perioperative analgesia

INTRODUCTION

Epidural anaesthesia is a safe and popular technique for surgical anaesthesia as well as for post-operative analgesia. It has been shown to blunt the stress response to surgery, decrease intraoperative blood loss, reduce the incidence of postoperative thromboembolic events and decrease morbidity and mortality in high risk surgical patients.[1] It can be used to extend analgesia into postoperative period, where their use has been shown to provide better analgesia than can be achieved with parenteral opioids.[2]It has become a common practice to use polypharmacy approach for treatment of intra and post-operative pain, because no drug has yet been identified that specifically inhibits nociception without associated side effects.[3]

Bupivacaine hydrochloride is one of the most widely used amide local anaesthetic drug. It blocks the inward flow of sodium ions and thus preventing the generation of action potential by preventing molecular membrane reconfiguration from the inactive (time bound) to resting (sodium impermeable) and subsequently to the active (sodium permeable) state. Bupivacaine is long-acting, approximately 3-7 times more potent than lignocaine or mepivacaine and 8 times more potent than procaine. When used in 0.5% and 0.75% concentration, it provides adequate surgical anaesthesia while analgesia can be obtained with concentrations as low as 0.125% to 0.25%.[4]

Clonidine has been used as an adjuvant in regional anaesthesia in various settings.[5,6] It is an alpha-2 adrenergic agonist that produces analgesia via a non-opioid mechanism. When injected epidurally it easily penetrates blood brain barrier to reach the hypothalamus due to high lipid solubility. It stimulates inhibitory alpha2 adrenoceptors to reduce central neural transmission in the spinal neurons. The receptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites. Inhibition of substance-P release is believed to involve in the analgesic effect. Sedation after epidural administration of clonidine likely reflects systemic absorption and vascular redistribution to higher centers. It is also helpful in sparing local anaesthetic doses, which consequently reduces the incidence of side effects associated with larger doses of these anaesthetics.[7,8] The combination of epidural Clonidine has been used as an adjuvant in regional anaesthesia in various settings.[5,6]

After sodium, potassium and calcium, magnesium is the most abundant cation in our body. It has antinociceptive effects in animal and human models of pain.[9] Noxious stimulus produces an influx of calcium ion through both voltage sensitive calcium channels that facilitates presynaptic release of neurotransmitters and post synaptic N-methyl D-aspartate calcium channels which triggers the sequence of events leading to cellular hyper excitability.[10] Studies in animal models of persistent pain in which central sensitization is present support this theory.[11] Magnesium is a relatively harmless molecule, non-expensive may provide perioperative analgesia on the biological basis for its potential antinociceptive effect.[12] These effects are primarily based on physiological calcium antagonism, that is voltage-dependent regulation of calcium influx into the cell, and noncompetitive antagonism of N-methylD-aspartate (NMDA)receptors.[3] The use of magnesium as an adjuvant in the context of perioperative analgesia is novel.

There is no ideal drug or combination of drugs for perioperative epidural analgesia. Keeping these lacunae in mind, this study was conducted to compare epidural plain bupivacaine with clonidine and plain bupivacaine with magnesium sulphate in patients undergoing elective lower

limb surgery in respect of onset and duration of sensory analgesia and anaesthesia, onset and duration of motor block, incidence of side effects.

MATERIALS AND METHODS

A randomized, parallel group, double-blind, controlled study was conducted on (n=60) patients of both sexes aged 20-60 years and weight within 50-75 kgs with ASA grade I and grade II in a tertiary care hospital of India for a time of 12 months (April 2012 to March 2013). After getting approval from Institutional Ethical Committee, patients waiting for elective lower limb surgery were selected and written informed consent were obtained from them before including them in the study. Patients with local infection in the lumbar region, known hypersensitivity to amide local anaesthetic, bleeding diathesis, spinal deformity, diabetes mellitus, known neurological, cardiac, renal, metabolic and psychological disorder, present history of analgesic use for chronic pain syndrome were excluded. Randomization done by using online software into Group BC (n=30) and Group BM (n=30). Group BC patients with height >160 cm received total volume of 20 ml (19 ml of plain 0.5% bupivacaine + clonidine 1ml containing 75 mcg) and those with height <160 cm received a total volume of 15ml (14ml of 0.5% bupivacaine + clonidine 1 ml containing 75 mcg) through the epidural route. On the other hand, Group BM patients with height >160 cm received a total volume of 20ml (19 ml of 0.5% bupivacaine + magnesium sulphate 1ml containing 50 mg) and those with height <160 cm received a total volume of 15 ml (14 ml of 0.5% bupivacaine + magnesium sulphate 1ml containing 50mg) through the epidural route. Both patients and anaesthetist were not aware about group allocation. Data assessment after statistical analysis was done by another independent anaesthetist.

All patients received Tab Diazepam 10 mg orally night before surgery. Injection Metoclopramide 10 mg and injection Ranitidine 50mg were given intramuscularly 1 to 2 hours before operation. After arrival to operation theatre, 18G cannulation were done, routine monitoring was started and baseline values noted. All were preloaded with 15ml-20ml/kg of Ringer's Lactate solution over 15 minutes before administering epidural block.

Injection bupivacaine hydrochloride (0.5%) vial, injection clonidine (150mcg/ml) ampule, injection Magnesium Sulphate preservative free (50mg/ml) ampule, injection lignocaine hydrochloride 2% with adrenaline vial were kept ready before epidural administration. Drugs of the same pharmaceutical brand were used in all patients. The drugs were prepared by an anaesthesiologist who was not involved in the study.

The patients were kept in sitting position and overlying skin was prepared with spirit-povidone iodine-sprit, followed by antiseptic draping. After proper identification of space, 2ml of injection lignocaine 2% with adrenaline was used to infiltrate the skin and subcutaneous tissue at L_{2-3} or L_{3-4} interspace. For epidural anaesthesia 18G Tuohy needle was used. Epidural space was identified by loss of resistance to air technique. After negative aspiration test for blood and CSF, a test dose was administered with 3 ml of inj. Lignocaine hydrochloride 2% with adrenaline and monitoring was done to note any haemodynamic changes indicative of intravascular injection. After ensuring proper epidural placement of the needle tip, the study drug was slowly injected in small increments with repeated aspiration test as per protocol. After placement of study drug, epidural needle was removed; the puncture site was sealed with antiseptic dressing. Monitoring of vital signs was continued throughout the procedure. The patients were made supine. No other analgesic was given to the patients intraoperatively. The patients were administered O_2, 3 L/min through face mask. The surgery was allowed after desired block height and analgesia of epidural injection. The following parameters were noted:

Onset of Sensory Block: Assessed by pin prick method at every 3 minutes interval. Time duration was assessed from local anaesthetic solution injection to epidural space to start of loss of pain sensation to pin prick.

Duration of Sensory Block: Assessed every 15 minutes postoperatively by pin prick method. Time duration was assessed from onset of sensory block to regression of dermatome of two segments.

Height of Block: Assessed by pin prick method over dermatomal segments.

Onset of Motor Block: Assessed every 3 minutes by modified Bromage scale (0 - no paralysis, 1-inability to raise extended leg, 2-inability to flex knee, 3-Inability to flex ankle and first toe). Time duration was assessed from the time of injection of local anaesthetic solution to achieve motor scale 2 or more.

Duration of Motor Block: Assessed by modified Bromage scale every 15 minutes post operatively. Time duration was assessed from onset of motor block to regaining of full motor power and joint movement.

Duration of Analgesia: Assessed every 15 minutes postoperatively by 10 cm Visual Analogue Scale (VAS=0 - no pain, 10 - worst possible pain). Time duration (minute) was assessed from onset of sensory block to first request for rescue analgesic or VAS score 4 or more. Rescue analgesic injection Diclofenac sodium 1.5mg/kg was given intramuscularly.

Haemodynamic parameters (Heart rate, Systolic BP, Diastolic BP), Respiratory rate were noted at 0, 15, 30, 60, 75, 90, 120, and at 240 mins from administration of epidural anaesthesia. Side effects like nausea, vomiting, hypotension, shivering, headache, etc were noted.

STATISTICAL EVALUATION

Sample size calculation was done by taking duration of analgesia as primary outcome variable of interest. It was estimated that n = 26 (recruitment target achieved, n = 30 in each group) will be required per group to detect 60 minutes difference in this parameter with 80% power and 5% probability of Type I error. This calculation assumed a standard deviation of 75 minutes in duration of analgesia. For statistical analysis, raw data entered into a MS Excel spread sheet and analysed by SPSS 12 (statistical software version 12). Unpaired student's t– test was used to compare normally distributed numerical variables. All analysis were two-tailed and p value <0.05 was taken to be statistically significant.

RESULTS

In this study 60 patients were allocated for statistical analysis. Demographic data and duration of surgery were not statistically different in the two groups (Table 1). There was significant difference (p value <0.05) in respect to onset of sensory and motor block, duration of sensory and motor block, duration of analgesia among the study groups (Table 2, Table 3). The patients in magnesium sulphate group showed faster onset of sensory and motor block but the patients in clonidine group showed longer duration of sensory and motor block and longer duration of analgesia.

Haemodynamic parameters (HR, SBP, DBP) were comparable in both groups (Table 4, Table 5, Table 6). There was decreasing trend in heart rate, systolic blood pressure, diastolic blood pressure in both the groups initially and this fall were within normal range. No case of hypotension (reduction of blood pressure>20% of base line) was found.

However, hypovolemia was not allowed during perioperative period with infusion of Ringer's Lactate solution (as hypovolemia is not tolerated in patients with sympathetic block). The fall in blood pressure, often accompanied by reduction in heart rate, is usual after epidural block. The gradual fall of blood pressure in epidural block may be due to slow spread of block and there is more time for auto compensation to occur.

There was no significant difference in respiratory rate in the two groups (Table 7). Height of block was comparable in two groups (Table 8).

The incidence of side effects was not significant in any of the groups (Table 9).

Table 1: Demographic characteristics of the patients and surgery time in both the groups

Variables	Group BC (n=30)	Group BM (n=30)	P value
Age(years)	34.26±11.63	34.20±11.35	0.982
Gender Male Female	 14 16	 16 14	
Weight(kg)	58.43±8.58	57.10±9.16	0.563
Height(cm)	151.70±7.45	151.96±8.193	0.895
Duration of surgery(minute)	96.83±17.93	96.66±19.71	0.972

Data expressed in mean ± SD

Table 2: Onset of sensory block and motor block in both the groups

Parameter	Group BC (n=30)	Group BM (n=30)	P value
Onset of sensory block(minute)	15.57±2.27	12.93±1.14	<0.0001
Onset of motor block(minute)	22.30±2.24	18.16±1.96	<0.0001

Data expressed in mean ± SD

Table 3: Duration of sensory and motor block and duration of analgesia in both the groups

Parameter	Group BC (n=30)	Group BM (n=30)	P value
Duration of sensory block(minute)	133.27±4.17	127.77±4.84	<0.0001
Duration of motor block(minute)	171.62±6.29	154.70±6.44	<0.0001
Duration of analgesia (minute)	205.40±10.60	192.80±8.69	<0.0001

Data expressed in mean ± SD

Table 4: Comparison of heart rate (HR) in both the groups

TIME	GROUP BC (MEAN±SD)	GROUP BM (MEAN±SD)	SIGNIFICANCE (p VALUE)
0 Min	81.33 ± 5.88	80.00 ± 7.08	0.43
15 Mins	81.46 ± 5.65	80.13 ± 6.76	0.41
30 Mins	74.86 ± 4.62	73.33 ± 5.19	0.37
60 Mins	68.67 ± 3.79	68.80 ± 4.41	0.90
75 Mins	71.00 ± 5.47	71.33 ± 4.14	0.79
90 Mins	72.86 ± 4.71	73.26 ± 5.90	0.77
120 Mins	70.60 ± 4.36	69.73 ± 5.95	0.52
240 Mins	73.93 ± 4.77	74.86 ± 4.86	0.45

Table 5: Comparison of systolic blood pressure (SBP) in both the groups

TIME	GROUP BC (MEAN±SD)	GROUP BM (MEAN±SD)	SIGNIFICANCE (p VALUE)
0 Min	124.33 ± 7.33	124.80 ± 6.94	0.80
15 Mins	125.16 ± 6.60	124.73 ± 8.32	0.82
30 Mins	109.33 ± 6.11	108.86 ± 5.93	0.76
60 Mins	106.33 ± 5.77	107.33 ± 6.17	0.79
75 Mins	112.40 ± 6.41	113.06 ± 5.81	0.67
90 Mins	115.53 ± 4.56	116.20 ± 5.97	0.62
120 Mins	122.86 ± 6.42	121.40 ± 7.48	0.41
240 Mins	121.53 ± 4.09	122.67 ± 3.57	0.25

Table 6: Comparison of diastolic blood pressure (DBP) in both the groups

TIME	GROUP BC (MEAN±SD)	GROUP BM (MEAN±SD)	SIGNIFICANCE (p VALUE)
0 Min	77.60 ± 5.83	77.20 ± 6.04	0.79
15 Mins	73.93± 6.76	74.80 ± 6.69	0.61
30 Mins	66.20 ± 4.76	65.66 ± 5.06	0.67
60 Mins	66.06 ± 5.10	66.06 ± 4.53	1.00
75 Mins	70.06 ± 3.91	70.40 ± 4.08	0.74
90 Mins	73.20 ± 4.22	72.93 ± 4.32	0.80
120 Mins	73.73 ± 4.63	74.26 ± 5.65	0.69
240 Mins	76.80 ± 5.21	77.13 ± 5.08	0.80

Table 7: Comparison of respiratory rate (RR) in both the groups

TIME	GROUP BC (MEAN±SD)	GROUP BM (MEAN±SD)	SIGNIFICANCE (p VALUE)
0 Min	16.33 ± 2.17	16.66 ± 2.12	0.54
15 Mins	16.53 ± 2.51	16.66 ± 1.98	0.82
30 Mins	16.80 ± 1.86	16.40 ± 2.74	0.51
60 Mins	16.93 ± 1.87	16.66 ± 1.91	0.58
75 Mins	17.33 ± 1.91	17.06 ± 1.87	0.58
90 Mins	17.13 ± 2.01	17.40 ± 1.75	0.58
120 Mins	17.20 ± 1.93	16.93 ± 1.94	0.59
240 Mins	16.86 ± 1.94	16.46 ± 1.87	0.41

Table 8: Comparison of block height between two groups:

CATEGORY	UPTO T6	UPTO T7	UPTO T8
GROUP BC	8	16	6
GROUP BM	8	16	6
TOTAL	16	32	12

P value = 1.00

Table 9: Comparison of incidence of side effects between two groups:

SIDE EFFECTS	GROUP BC	GROUP BM	SIGNIFICANCE (p value)
Nausea and vomiting	4 (13.33%)	7(23.33%)	0.506
Shivering	2(6.67%)	3(10.00%)	1.000
Sedation	2(6.67%)	1(3.33%)	1.000
Headache	2(6.67%)	1(3.33%)	1.000

DISCUSSION

Epidural anaesthesia with local anaesthetics has the advantages of optimal perioperative conditions including

analgesia with better postoperative outcome and lesser incidence of complications. Many local anaesthetics have been used as for epidural anaesthesia, but bupivacaine is the most commonly used agent. Adequate postoperative analgesia could be achieved without profound inhibition of motor fibers with less concentration of bupivacaine due to its differential blockade property.

Previously many drugs have been added as an adjuvant with local anaesthetics. Clonidine and magnesium sulphate were used as adjuvant in this study. Use of magnesium sulphate as adjuvant is relatively new.

Clonidine, an alpha agonist, augments the action of local anaesthetics in regional blockades by interrupting the neural transmission of painful stimuli in Ad and C fibers as well as augments the blockade of local anaesthetic agents by increasing the conductance of K+ ions in the nerve fibers. It also exerts a vasoconstricting effect on smooth muscle, which results in a decreased absorption of the local anaesthetic drug and eventually prolongs the duration of analgesia.[20]

Till now very few studied magnesium as an adjuvant. Magnesium is relatively harmless molecule, not expensive and its potential antinociceptive effect is promising.[12] Intravenous MgSO4 prolongs analgesia and lesser discomfort in post-operative period.[13,14] Intrathecal MgSO4 also prolongs post-operative analgesia. Mechanism of intrathecal MgSO4 is postulated to be supraspinal. However, KO et al with 50mg/kg IV failed to demonstrate an increase in the CSF MgSO4 level and they did not find any significant increase in the post-operative analgesia.[19] In this perspective 50mg of epidural MgSO4 is too small dose that should have any supraspinal effect after crossing the duramater. The primary mechanism of action of MgSO4 being antagonism of NMDA receptors, it can be postulated that quicker onset and prolonged analgesia of MgS04 with bupivacaine may be due to their direct effects on the nerve roots in the epidural space alone.

In this study 60 patients with similar demographic characteristics and similar type and duration of surgery were divided in two groups. Group BC (n=30) received epidural 0.5% bupivacaine hydrochloride with 75 mcg clonidine and Group BM (n=30) received epidural 0.5% bupivacaine hydrochloride with 50 mg magnesium sulphate.

Benhamou D, Thorin D, Brichant JF et al studied the analgesic efficacy and side effects of a spinal block with hyperbaric bupivacaine with clonidine (75mcg) and fentanyl (12.5 mcg) and they found improvement of intraoperative analgesia by adding clonidine to bupivacaine, but side effects were not increased with a small dose of intrathecal clonidine.[15] Angelo RD, Evans E, Dean LA et al observed that 50 mcg spinal clonidine administered with 7.5 mcg spinal sufentanil and 2.5 mg spinal bupivacaine as labour analgesia using combined spinal-epidural technique, significantly prolonged the analgesia but the side effects like motor block, sedation, hypotension were not increased.[16] In our study we found increased duration of sensory, motor block and increased duration of analgesia with clonidine, but no significant hypotension, sedation and other side effects.

Buvanendran et.al showed intrathecal magnesium (50mg) prolongs fentanyl (25mcg) analgesia. There was no associated increase in adverse effects in the group that received intrathecal magnesium. In our study we found good analgesic effect of magnesium sulphate group and no significant adverse effects.[18] Ghatak et.al evaluated effect of magnesium sulphate vs. clonidine as an adjunct to epidural bupivacaine in lower abdominal and lower limb surgeries. One group received 50 mg magnesium with bupivacaine intrathecally and another group received 150 mcg clonidine with bupivacaine intrathecally. They found onset of anaesthesia was faster in magnesium group and prolongation of anaesthesia, sedation was higher with clonidine group.[17] In this study we found the same regarding onset and duration of anaesthesia. There was no significant respiratory rate and haemodynamic changes in both groups. Few minor side effects like nausea, vomiting, headache and shivering were found in our study groups but they were statistically not significant.

CONCLUSION

Single dose epidural bupivacaine hydrochloride (0.5%) with 50 mg magnesium sulphate produces rapid onset sensory and motor block. On the other hand, duration of sensory and motor block and duration of analgesia prolongs with single dose epidural bupivacaine hydrochloride (0.5%) with 75 mcg clonidine. Epidural anaesthesia and use of lower doses of magnesium sulphate and clonidine is good to maintain respiratory rate, haemodynamic parameters. It is reasonable to study with large sample size and different doses of clonidine and magnesium sulphate for lower abdominal or lower limb surgery.

REFERENCES

1. Yeager M, Glass D, Neff R, Brinck Johnsen T. Epidural anaesthesia and analgesia in high-risk surgical patients. Anaesthesiology 1987; 66:729
2. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr Wu CL. Efficacy of postoperative epidural analgesia; A meta-analysis. J Am Med Assoc 2003; 290:2455
3. Sirvinskas E, Laurinaitis R. Use of magnesium sulphate in anaesthesiology. Medicine 2002; 38:147-50
4. Lee A. Fleisher, Roger A. Johns,John J savaree, Jeanine P. Wiener Kronish:Miller's Anaesthesia 6;1675
5. Hayashi Y, Maze M. Alpha2 adreno-receptor agonists and anaesthesia. Br J Anaesth 1993; 71:108
6. Eisenach JC, De Kock M, Kilmscha W.2 Adrenergic agonists for regional anaesthesia: A clinical review of clonidine. Anaesthesiology 1996; 85:655-674
7. Sia AT. Optimal dose of intrathecal clonidine added to sufentanyl plus bupivacaine for labour analgesia. Can J Anaesth 2000; 47:875-880
8. Benhamopu D, Thorin D, Brichant JF, Dilland P, Milon D, Schneider M. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during caesarean section. Anaesth Analg 1998; 87:609-613
9. Begon S,Pickering G, Dubray C. Magnesium increases morphine effect in different experimental models of pain. Anaesthesiology 2002; 96:627-632.
10. Zarauza R, Fernandez A N, and Iribarren M J et al. A comparative study with oral nifedipine, intravenous nimodipine and magnesium sulphate in postoperative analgesia. Anesth Analg.2000; 91: 938 –943.
11. Coderre T J, Katz J, Vaccarino A L, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain. 1993; 52:259–285.
12. Lysakowsi C, Dumont L, Czarnetzki C, Trame MR. Magnesium as an adjuvant to postoperative analgesia:A systematic review of randomized trial. Anaes Anal 2007; 104:1532
13. Tramer MR, Scheneider J, Marti RA, Kaplan R. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996; 84: 340
14. Koinig H, Wallner T, Marhofer P, Andel H, Ho¨rauf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. Anesth Analg 1998; 87:206–210
15. Benhamou D, Thorin D, Brichant JF, Dailland P, Schneider M. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anaesth Analg 1998; 87:609-613
16. Angelo RD, Evans E, Dean L A, Gaver R, Eisenach JC. Spinal clonidine prolongs labour analgesia from spinal sufentanyl and bupivacaine. Anaesth Analg 1999;88:573-576
17. Ghatak T, Chandra G, Malik A, Singh D, Bhatia VK. Evaluation of magnesium sulphate vs. clonidine as adjunct to epidural bupivacaine. Indian J Anaesth 2010; 54: 308-313
18. 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
19. Ko SH, Lim HR, Kim DC, Han YJ, Choe H, Song HS. Magnesium sulphate does not reduce postoperative analgesic requirements. Anesthesiology 2001; 95: 640
20. Mizobe T, Maze M. Alpha2 adrenergic agonists and anaesthesia. Int Anaesthesiology Clin. 1995; 33:81-102