

TO COMPARE THE INTRATHECAL EFFECTS OF MAGNESIUM SULPHATE AND CLONIDINE IN LOWER ABDOMINAL SURGERIES

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ABSTRACT

BACKGROUND

Amongst all regional techniques the subarachnoid block is the most convenient, early and effective method of anaesthesia for variety of surgical procedures and pain relief. A number of adjuvants such as opioids, sodium bicarbonate, vasoconstrictors, alpha-2 adrenoceptor agonists, cholinergic agonists etc. have been studied to prolong the effect of spinal anaesthesia. Use of opioids is very popular nowadays as it provides quicker onset and spread of anaesthesia and prolonged analgesia, but it is associated with side effects notably nausea, vomiting, pruritus, urinary retention and respiratory depression.

The present study was conducted to assess and compare the intrathecal effects of two non-opioid drugs, magnesium sulphate and clonidine in lower abdominal surgery.

MATERIALS AND METHODS

A hospital-based prospective randomised controlled study was conducted at a tertiary care centre. A total of 128 consecutive patients undergoing lower abdominal surgeries were taken up for the study after informed consent. The subjects were then randomly divided into either of the two groups (64 each): Group A - received 3 mL of 0.5% Hyperbaric Bupivacaine along with 0.2 mL magnesium sulphate (100 mg) and 0.3 mL of normal saline and Group B - received 3 mL of 0.5% Hyperbaric Bupivacaine with 0.5 mL (75 µg) of clonidine. The two groups were compared with respect to following parameters: Onset time and duration of sensory and motor block, duration of analgesia, haemodynamic effects and complications. Data was analysed with SPSS Ver. 21.0.

RESULTS

Onset of sensory block (2.34 vs. 2.53 secs) and motor block (2.77 vs. 3.58 secs; $p < 0.01$) was significantly faster in MgSO₄ group as compared to clonidine group. Post-induction, pulse rate, systolic and diastolic blood pressure was significantly lower in subjects of clonidine group as compared to MgSO₄ group. Total duration of sensory block (321.7 vs. 301.7 mins; $p < 0.01$) and motor block (223.4 vs. 204.5 mins; $p < 0.01$) was significantly more in clonidine group as compared to MgSO₄ group. Incidence of Bradycardia (18.8% vs. 0%) and hypotension (28.1% vs. 3.1%) was significantly more with clonidine as compared to Magnesium sulphate.

CONCLUSION

We thus conclude that co-administration of intrathecal magnesium with bupivacaine produces predictable rapid onset of surgical anaesthesia without any side-effects, and addition of clonidine to intrathecal bupivacaine produces prolonged duration of anaesthesia with sedation but leads to increased incidence of hypotension and bradycardia. The results of the present investigation suggest that magnesium may be a useful alternative as an adjuvant to intrathecal bupivacaine.

KEY WORDS

Bupivacaine, Clonidine, Magnesium Sulphate, Spinal Anaesthesia.

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BACKGROUND

In initial days of anaesthesia, it was common and only method to use general anaesthesia for all types of surgeries, whether it happened to be short or long, or of upper or of lower part of body. But it is a well-known fact that general anaesthesia has got its own disadvantages like physiological and pharmacological changes in body, use of multiple drugs and their interactions, need to produce full unconsciousness

even for short procedure and small part of body, longer hospital stay, postoperative drowsiness, nausea, vomiting etc. So, need of regional/ local technique arose. Amongst all regional techniques the subarachnoid block emerged as a convenient, early and effective method of anaesthesia for variety of surgical procedures and pain relief, especially for lower abdominal and lower limb surgeries.

The subarachnoid block has got inherent advantages like intense motor and sensory blockade, good relaxation, reliability, avoids side effects of multiple drugs used in general anaesthesia, no postoperative respiratory depression, nausea, vomiting, drowsiness etc. It also has good patient and surgeon's acceptability as well as safe enough for early discharge from the hospital. It can also be administered safely in many patients with those systemic diseases where general anaesthesia and endotracheal intubation can be hazardous like sensitive airway diseases, hepatic and renal diseases, endocrine disorders, old age, cardiac patients etc.^[1]

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First spinal anaesthesia was administered by Karl August Bier in 1898 at Royal Surgical Hospital of the University of Kiel, Germany. He performed a lumbar puncture and injected 3 cc of 0.5% cocaine solution into the subarachnoid space. Regional anaesthetic methods are commonly preferred in orthopaedic surgical procedures. This technique can be performed with the use of different local anaesthetics alone in different doses and by combining local anaesthetics with adjunct to obtain an adequate level of anaesthesia and analgesia with more stable haemodynamics.^[2]

Gordh was the first to use lignocaine for spinal anaesthesia in 1944. Special properties like potency, rapid onset of action, excellent power of diffusion, lack of tissue irritation, low toxicity, chemical stability after autoclaving, prolonged storage and good surface analgesia placed lignocaine ahead of other local analgesics. Because of lidocaine induced transient neurological symptoms and cauda equina syndrome (by use of higher 5% concentration), use of spinal lidocaine came under controversies. In 1957 Ekenstem synthesised Bupivacaine and reported that it had long duration of action with low toxicity compared with lignocaine. It is three to four times more potent and possessed longer duration of action than lignocaine.^[2]

A number of adjuvants such as Opioids (Morphine, Fentanyl, Nalbuphine, Buprenorphine), Sodium bicarbonate (NaHCO₃), vasoconstrictors (Epinephrine), alpha-2 adrenoceptor agonists (Clonidine, dexmedetomidine), cholinergic agonists, N-methyl-d-aspartate (NMDA) antagonists (Ketamine) and γ-aminobutyric acid (GABA) receptor agonists (Midazolam) have been studied to prolong the effect of Spinal anaesthesia.^[3] Use of opioids with bupivacaine is very popular nowadays as it provides quicker onset and spread of anaesthesia and prolonged analgesia, but it is associated with side effects notably nausea, vomiting, pruritus, urinary retention and respiratory depression. So there is a constant search about the drug which provides or prolongs the analgesia duration in postoperative period with minimal side effects.^[4,5]

Clonidine hydrochloride is an imidazole derivatives with alpha-2 adrenergic agonistic activity. The intrinsic analgesic effect of clonidine has been demonstrated with a large dose of clonidine alone given intrathecally or epidurally to control both intraoperative and postoperative pain. Epidural clonidine improves the quality of anaesthesia, reduces the doses requirement of the anaesthetic agent and provides a more stable cardiovascular course during anaesthesia with fewer side effects.^[6]

Magnesium is the fourth most plentiful cations in the body. It has antinociceptive effects in animal and human models of pain. It has been reported that intrathecal or epidural magnesium enhances opioid antinociceptive in an acute incisional model. These effects have prompted the investigation of magnesium as a postoperative analgesic.^[7]

This study was conducted to assess and compare the intrathecal effects of two non-opioid drugs, clonidine and magnesium with bupivacaine on quality of block.

MATERIALS AND METHODS

A hospital-based randomised controlled study was conducted at Department of Anaesthesia, Grant Medical College and Sir JJ Group of Hospitals, Byculla, Mumbai for a duration of one year. Consecutive type of non-probability sampling was used

for selection of study subjects. Patients with history of chronic disease like hypertension, diabetes mellitus, respiratory disease, epilepsy, cardiac disease, spinal disorders, chronic history of headache and backache, infection in the back and any absolute or relative contraindication to study drug were excluded.

The Sample Size was calculated using following Formulae-

$$n = (Z\alpha/2 + Z\beta)^2 * (SD^2) / d^2$$

n- Sample size

Zα/2 – Z value at 5% error (1.96)

Zβ – Z value at 20% (0.84)

SD- average standard deviation of the character = (SD1+SD2)/ 2

d - Clinically relevant effect (Taken as 1.0 minute)

Mean and SD - time to achieve T6 block in magnesium group (11.80 ± 3.21 minutes)

Mean and SD - Time to achieve T6 block in clonidine group (16.93 ± 3.43 minutes)

SD - 3.32

$$n = \frac{(1.96+0.84)^2 * (3.32^2)}{(1.0)^2}$$

n = 52 (approx.)

So minimum sample size required was 52 cases in each group, i.e. 104 cases. But we decided to take all the eligible cases coming to us during study period. Thus, a total of 128 consecutive eligible patients undergoing lower abdominal surgeries who came to our hospital during the study period were included in the study. These patients were randomly divided into two groups based on computer generated random numbers (64 each):

Group A

Received 3 mL of 0.5% Hyperbaric Bupivacaine along with 0.2 mL magnesium sulphate (100 mg) and 0.3 mL of normal saline.

Group B

Received 3 mL of 0.5% Hyperbaric Bupivacaine with 0.5 mL (75 µg) of clonidine.

After taking informed consent and confirming overnight fasting patient was taken to the operation table, connected to monitors and baseline vitals like BP, pulse rate and respiratory rate were recorded. After that an 18-gauge intravenous (IV) cannula was inserted at the forearm level, lactated Ringer's solution was administered as a bolus of 10 mL/kg before subarachnoid block to all patients.

Vitals just before lumbar puncture was noted. Spinal anaesthesia was performed at L3-L4 interspace (L4-L5 in case of failure) with the patient in sitting position by using a 23-gauge Quincke needle under strict aseptic conditions. Free flow of cerebrospinal fluid was verified before injection of the anaesthetic solution, which was administered over 30 seconds according to allocated group. The direction of the needle aperture was cranial during the injection. All patients were immediately placed in a supine position following the injection with a 15° head-down tilt to achieve level of block of

T8-T10. Monitoring was done using continuous electrocardiography (lead II and V), heart rate, non-invasive blood pressure and continuous pulse oximetry and all patients were given 4.0 L/ min of oxygen by venti-mask.

Vitals were checked immediately after SAB, 2 mins, 5 mins, 10 mins and every 5 mins till surgery. The level of sensory block was tested by pinprick bilaterally at mid-clavicular line, which was done every minute till the maximum sensory level was achieved and then after one hour at half an hour interval. Time of onset of motor block was assessed using Bromage scale. Side effects like Hypotension (SABP < 90 mmHg), Bradycardia (Pulse < 55/ min), Respiratory depression (Arterial oxygen saturation less than 90%), Pruritus and Nausea and Vomiting were noted.

The anaesthesiologist who performed the block and record the parameters was blind regarding the study to which the group belongs. The onset and duration of sensory block, highest level of sensory block, time to reach the highest dermatomal level of sensory block, motor block onset, time to complete recovery of motor block and duration of spinal anaesthesia was recorded.

The onset of sensory block was defined as time between injection of intrathecal anaesthetic agent and the absence of pain at T8 dermatome assessed by sterile pinprick at midclavicular line anteriorly every 5 mins for 30 mins after the injection, thereafter every 15 mins. The duration of sensory block was defined as the time of regression of two segments in the maximum block height, evaluated by pinprick. Onset of motor block was taken as the time taken to achieve Bromage grade 3 block from the time of subarachnoid injection.

Grading Used

1. For Sensory Blockade

- 0 - Sharp pain
- 1 - Touch sensation only
- 2 - Not even touch sensation

2. Motor Blockade: Modified Bromage score.

Score	Criteria
0	Full movement
1	Inability to raise extended leg, can bend knee
2	Inability to bend knee, can flex ankle
3	No movement

3. Pain: Postoperatively, the pain score was recorded by using Visual Analogue Pain Scale (VAS) between 0 and 10 (0= no pain, 10= worst pain).

4. Sedation: By using Sedation Score

- 1- Awake and alert
- 2- Drowsy, but responsive to command
- 3- Very drowsy, but responsive to pain
- 4- Unresponsive

Patients were allowed to receive rescue analgesics on demand. Intramuscular Diclofenac (1.5 mg/kg) was given as rescue analgesic. This constitutes the end point of study. Time from intrathecal injection to the first request of analgesics (i.e. duration of analgesia) was noted. Total analgesic dose in first 24 hours was recorded. Patients were kept under

observation for a total period of 24 hours to look for any side effects. The incidence of adverse effects such as nausea, vomiting, shivering, pruritis, respiratory depression, sedation and hypotension was recorded.

Statistical Analysis

Data were statistically described in terms of mean ($\pm$ SD), frequencies (Number of cases) and percentages when appropriate. Data were tested first for normal distribution by Kolmogorov-Smirnov test. Comparison of quantitative variables between the study groups was done using Student's t-test for independent samples if normally distributed. Mann-Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 21.

RESULTS

Mean age and anthropometric parameters were comparable between both groups (Table 1). Female predominance was seen in both study groups with 93% females to 7% males in the overall study. Both the groups were comparable with respect to ASA grade of the subjects with 89% patients were in ASA grade I, while remaining 11% were in grade II. Onset of sensory block (2.34 vs. 2.53 secs) and motor block (2.77 vs. 3.58 secs; $p < 0.01$) was significantly faster in MgSO₄ group (Group A) as compared to clonidine group (Group B). Time to reach maximum sensory block level was also lower in Group A subjects (6.38 vs. 8.14 sec; $p < 0.01$) (Table 2). After the induction, pulse rate, systolic and diastolic blood pressure was significantly lower in subjects of clonidine group as compared to MgSO₄ group, during most of the duration of surgery ($p < 0.05$) (Figure 1 - 3). Requirement of vasopressors during surgery was observed in 4.7% cases of MgSO₄ group as compared to 26.6% cases of clonidine group ($p < 0.01$), while requirement of Atropine during surgery was observed in 32.8% cases of clonidine as compared to none in MgSO₄ group ($p < 0.01$). Total duration of sensory block (321.7 vs. 301.7 mins; $p < 0.01$) and motor block (223.4 vs. 204.5 mins; $p < 0.01$) was significantly more in clonidine group as compared to MgSO₄ group. Also, time for rescue analgesia was significantly more in Clonidine group subjects (267.84 vs. 219.27 mins; $p < 0.01$) (Table 3). Sedation score was significantly higher in subjects of Clonidine group as compared to MgSO₄ group ($p < 0.01$) (Figure 4). Incidence of Bradycardia (18.8% vs. 0%) and hypotension (28.1% vs. 3.1%) was significantly more with clonidine as compared to Magnesium sulphate.

Variables	Group	N	Mean	SD	P-value
Age (yrs.)	A	64	43.19	10.40	0.423
	B	64	44.73	11.36	
Weight (kg)	A	64	59.75	5.27	0.363
	B	64	60.73	6.82	
Height (cm)	A	64	157.94	4.37	0.034
	B	64	156.42	3.56	

Table 1. Mean Age, Weight and Height Comparison

Variables	Group	N	Mean	SD	P-value
Onset of Sensory Block (mins)	A	64	2.34	0.60	< 0.05
	B	64	2.53	0.58	
Time for Peak Sensory Block (mins)	A	64	6.38	0.79	< 0.01
	B	64	8.14	0.77	
Time to reach Bromage B3 level	A	64	2.77	0.68	< 0.01
	B	64	3.58	0.81	
Max. Bromage Score	A	64	3.00	0.00	1.0
	B	64	3.00	0.00	

Table 2. Comparison of Mean Parameters regarding Onset of Anaesthesia

Variables	Group	N	Mean	SD	P-value
Time for Rescue Analgesia (mins)	A	64	219.27	22.66	< 0.01
	B	64	267.84	27.96	
Total duration of Sensory block (mins)	A	64	301.72	27.62	< 0.01
	B	64	321.72	8.32	
Total duration of Motor block (mins)	A	64	204.53	10.64	< 0.01
	B	64	223.36	14.39	
Duration of Surgery (mins)	A	64	57.01	7.21	0.096
	B	64	59.17	7.57	

Table 3. Comparison of Mean Parameters regarding recovery from Anaesthesia

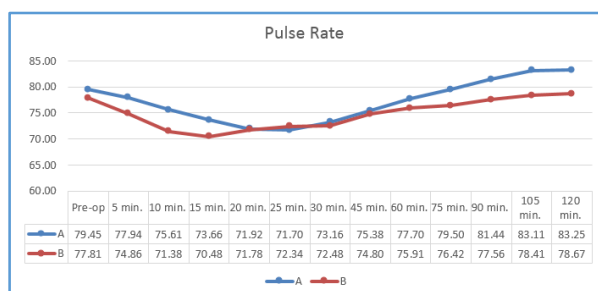


Figure 1. Distribution of Subjects as per Mean Pulse Rate Changes

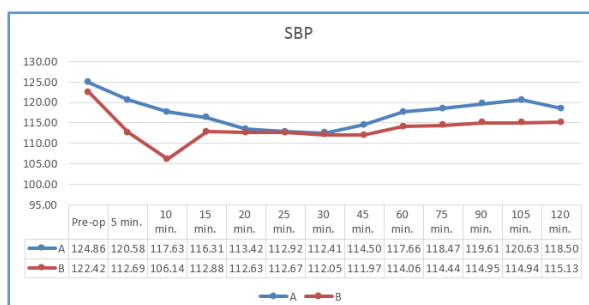


Figure 2. Distribution of Subjects as per Mean Systolic Blood Pressure Changes

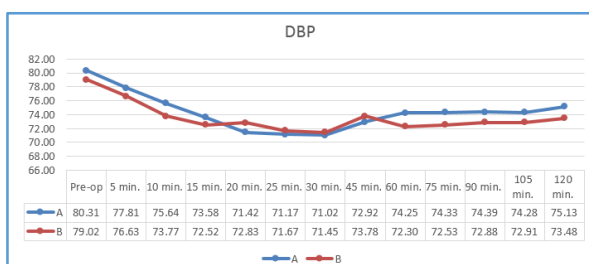


Figure 3. Distribution of Subjects as per Mean Diastolic Blood Pressure Changes

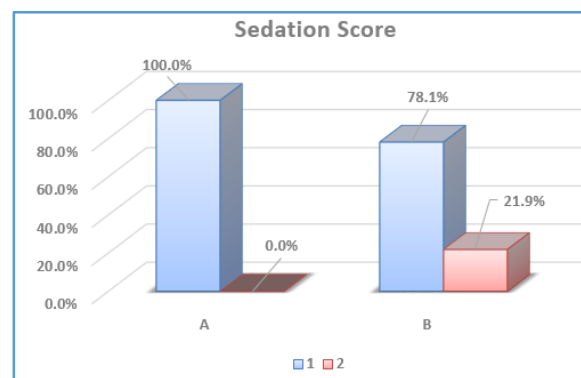


Figure 4. Distribution of Subjects based on Sedation Score

DISCUSSION

Postoperative pain should be effectively treated because it represents an important component of postoperative recovery. Effective treatment serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. The most common treatment practice is a polypharmacological approach. Noxious stimulation leads to the release of neurotransmitters, which bind to various subclasses of excitatory amino acid receptors including NMDA receptors. Activation of these receptors leads to calcium entry into the cell and initiates a series of central sensitisation such as wind-up and long-term potentiation in the spinal cord in the response of cells to prolonged stimuli^[8] NMDA receptor signalling may be important in determining the duration of acute pain.^[9]

Magnesium blocks calcium influx and non-competitively antagonises NMDA receptor channels.^[10] Non-competitive NMDA receptor antagonists can have an effect on pain when used alone.^[11] Co-administration of epidural magnesium for postoperative epidural analgesia provided a pronounced reduction in patient-controlled epidural fentanyl consumption without any side effects.^[11] Clonidine induces dose-dependent spinal cord antinociception, mainly through stimulation of α_2 -adrenoceptors in the dorsal horn, mimicking the activation of descending inhibitory pathways.^[12]

Most of these studies showed that systemic administration of magnesium is associated with smaller analgesic requirement and less discomfort in the postoperative period.^[13,14] In recent years, intrathecal administration of magnesium has been reported as an effective analgesic and as an adjunct to intrathecal lignocaine anaesthesia.^[15] It is possible that analgesic effect of magnesium occurred at the supraspinal level and might be related to its systemic absorption. Studies have shown that addition of intrathecal magnesium 50 mg to spinal anaesthesia prolongs the period of anaesthesia without additional side-effects.^[16,17]

Motor and sensory blockade effects of local anaesthetics are enhanced by clonidine. The effects of clonidine on the prolongation of nerve blockade are dose dependent.^[18]

In the present study we aimed to assess and compare the intrathecal effects of these two drugs, i.e. magnesium sulphate and clonidine in lower abdominal surgery. No study has yet compared the intrathecal effects of magnesium sulphate and clonidine in lower abdominal surgery. A study

by Ghatak T et al evaluated the effect of addition of magnesium or clonidine as adjuvant to epidural bupivacaine in lower abdominal and lower limb surgeries.^[19] While Choudhary A et al compared the onset and duration of analgesia with the epidural bupivacaine and its combination with either magnesium sulphate or clonidine to establish the ideal combination of drug with least side effects.^[20]

In the present study, onset of sensory block (2.34 vs. 2.53 secs) and motor block (2.77 vs. 3.58 secs; $p < 0.01$) was significantly faster in MgSO₄ group (Group A) as compared to clonidine group (Group B). While total duration of sensory block (321.7 vs. 301.7 mins; $p < 0.01$) and motor block (223.4 vs. 204.5 mins; $p < 0.01$) was significantly more in clonidine group as compared to MgSO₄ group. Also, time for rescue analgesia was significantly more in Clonidine group subjects (267.84 vs. 219.27 mins; $p < 0.01$).

In a study by Ghatak T et al,^[19] time to achieve T₆ block was least in epidural magnesium adjuvant group (11.80 ± 3.21 minutes) and highest (18.73 ± 2.79 minutes) in control group, whereas it was 16.93 ± 3.43 minutes in clonidine group of patients. The difference between the groups was statistically significant ($p < 0.01$). The time from epidural medication to two segment regression ranged from 123.00 ± 28.08 minutes in control group (Group A) to 145.33 ± 27.74 minutes in clonidine group (Group C) with an intermediate value (130.33 ± 33.94 minutes) in magnesium group (Group B) patients. The time from epidural medication to first epidural top-up was maximum (180.33 ± 29.97 minutes) in clonidine group followed by magnesium group (161.67 ± 30.10 minutes) and with a minimum (150.67 ± 35.80 minutes) in control group of patients ($p < 0.01$). These findings are in accordance with our observations that significantly faster onset of sensory block was seen in Magnesium group, while prolonged duration was associated with clonidine.

Choudhary A et al^[20] does not observe any difference regarding the onset time for sensory block. The time of onset of sensory analgesia is least with clonidine group (13.67 ± 2.54 minutes) followed by magnesium sulphate group (17.33 ± 2.86 minutes) and maximum in bupivacaine alone group (18.67 ± 2.54 minutes). The difference between the groups was statistically not significant ($p > 0.05$) between group 1 and 2 and significant ($p < 0.05$) between group 1 and 3 and 2 and 3. While the time of onset of motor block is least in clonidine group (20.31 ± 5.65 minutes) followed by magnesium group (28.2 ± 3.95 minutes) and maximum in bupivacaine group (33.21 ± 3.75 minutes). The difference among groups were highly significant ($p < 0.05$). However, as in our study, they also observed the mean duration of analgesia to be significantly prolonged in clonidine group (500 ± 22.74 minutes) followed by magnesium sulphate group (332 ± 24.83 minutes) and least in bupivacaine group (290 ± 28.77 minutes) ($p < 0.05$).

In the present study we observed that after induction mean pulse rate, systolic and diastolic blood pressure was significantly lower in subjects of clonidine group as compared to MgSO₄ group during most of the duration of surgery ($p < 0.05$). Incidence of Bradycardia (18.8% vs. 0%) and hypotension (28.1% vs. 3.1) were significantly more with Clonidine as compared to Magnesium sulphate.

After neuraxial or systemic administration, clonidine affects arterial blood pressure in a complex manner because

of opposing actions at multiple sites. The α_2 -adrenergic agonists reduce sympathetic drive and arterial blood pressure through effects at specific brainstem nuclei and sympathetic preganglionic neurons in the spinal cord. Eisenach et al^[21] showed that 160 µg clonidine decreases arterial blood pressure by 18% and reduces heart rate by 5 to 20%. In the study by Ghatak et al^[19] mean pulse rate, systolic and diastolic blood pressure was significantly lower in subjects of clonidine group, but any incidence of hypotension or bradycardia was easily managed by vasopressors and atropine. Incidence of Bradycardia (33.3% vs. 13.3%) and hypotension (73.3% vs. 63.35) were more with clonidine as compared to Magnesium sulphate. The increased incidence of hypotension and bradycardia in clonidine group as observed in the present study is in accordance with the studies of Rucci et al,^[22] Klimscha et al,^[23] Yuan-Shiou Huang et al^[24] and Michael J Paech et al.^[25]

In the present study, sedation was significantly associated with clonidine (21.9% vs. 0%; $p < 0.01$). Sedation is a side effect which is frequently associated with the use of clonidine in postoperative analgesia, often in conjunction with opioids.^[26] In a study by Ghatak et al,^[19] sedation was observed in seven patients (23.3%) in clonidine group (Group C) compared to none in magnesium group ($p < 0.01$). Various studies have shown that bolus dose of clonidine may cause significant sedation.^[19,20,24,26]

CONCLUSION

We thus conclude that co-administration of intrathecal magnesium with bupivacaine produces predictable rapid onset of surgical anaesthesia without any side-effects, and addition of clonidine to intrathecal bupivacaine produces prolonged duration of anaesthesia with sedation but leads to increased incidence of hypotension and bradycardia. The results of the present investigation suggest that magnesium may be a useful alternative as an adjuvant to intrathecal bupivacaine.

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