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Magnesium sulfate vs clonidine as an adjunct to epidural bupivacaine: A randomized controlled study

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ABSTRACT

There are limited studies conducted to examine the effect of magnesium sulphate administered as an adjunct to epidural bupivacaine. An attempt is made in the present research to compare onset of sensory block and motor block, time required for two segment regression, and incidence of post-operative complications between magnesium sulphate and clonidine co-administered epidurally as an adjunct to bupivacaine for lower abdominal and lower limb surgeries. In all ninety patients scheduled for lower abdominal and lower limb surgeries under epidural block of bupivacaine were randomized into two groups. Magnesium sulfate was administered to 45 patients (Group A) whereas clonidine was given to 45 patients (Group B). Mean onset of sensory block, mean onset of motor block, mean time required for two segment regression, mean time required for first analgesia and incidence of post-operative complications were recorded. Quantitative variables were compared using unpaired student's "t" test whereas qualitative variables were compared using Chi-square test. Time of onset of sensory block and motor block, time required for two segment regression, time for post-operative analgesia and incidence of untoward side effects were significantly higher in clonidine group as compared to magnesium sulfate group. Clonidine produced prolonged duration of anesthesia with sedation. Magnesium sulfate is better than clonidine as an adjuvant to bupivacaine in epidural anesthesia.

INTRODUCTION

Various drugs can be used as an adjuvant to epidural anesthesia like dexmedetomidine, clonidine, fentanyl, and magnesium sulfate. These drugs increase the duration of analgesia and reduce the adverse effects associated when a single drug is given in high doses. In addition to their dose sparing effects, epidural adjuvants are administered to reduce the dose, produce neural block rapidly, improve the quality and increase the duration of neural blockade.[1] Magnesium has antinociceptive effects and it will be useful to study the role of addition of magnesium to provide analgesia posr-operatively. Magnesium is also a relatively harmless molecule and is cheap. [2] Clonidine is centrally acting partial α2 adrenergic agonist. It produces antinociception by stimulating postsynaptic α_2 adrenergic receptors in the dorsal horn of spinal cord.[3] There are limited studies conducted to examine the effect of magnesium sulphate administered epidurally as an adjunct to epidural bupivacaine. Previous study had compared 50 mg of magnesium sulfate and 150 µg clonidine. There is need to compare clonidine with different dosage of magnesium sulfate. [4] An attempt is made in the present research to compare onset of sensory block and motor block, time required for two segment regression, and incidence of post-operative complications between magnesium sulphate and clonidine co-administered epidurally as an adjunct to bupivacaine for lower abdominal and lower limb surgeries.

MATERIALS AND METHODS

This prospective observational study was conducted between April 2016 and September 2017. The scientific advisory committee and institutional ethics committee of the hospital approved our study. Written informed consent was taken from all the patients before the study. Patients between 18 and 55 years posted for lower abdominal and lower limb surgeries under epidural anesthesia belonging to American Society of Anesthesiologist (ASA) grade I and II were included. Exclusion criteria were pregnant or lactating women, patients who had HB1Ac>8%, patients with Body mass index (BMI) > 25 kg/m^2,

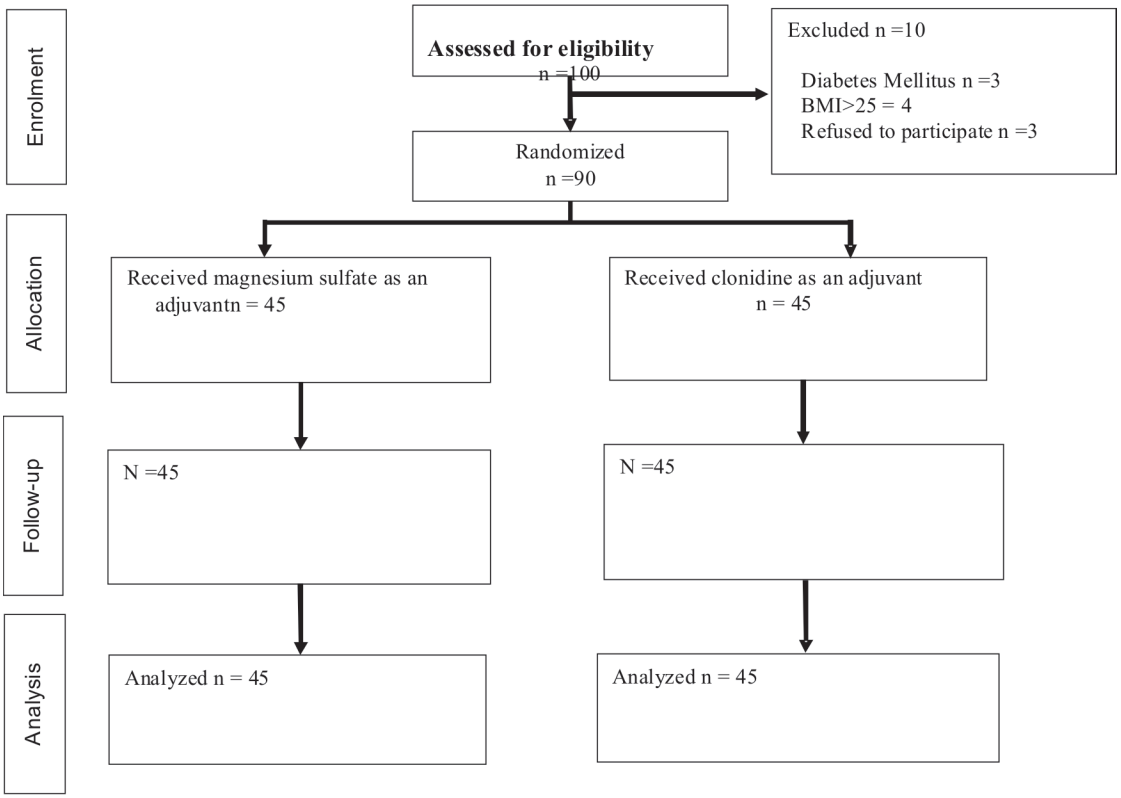

Fig 1 : CONSORT flow diagram

patients using regular analgesic medication for chronic pain, and patients with spinal cord disease.

Out of 100 patients assessed for eligibility, 10 were excluded. In all 90 patients were randomized using computer generated randomization code. [Fig.1] This manuscript adheres to the applicable CONSORT guidelines. We used sealed envelope for randomization with block size four. Forty five patients received magnesium sulfate (Group A) whereas and 45 patients received clonidine (Group B) as an adjuvant. This was done under the supervision of a senior a nesthesiologist. Researcher and patients were blind as to their group assignment.

Pre-anesthesia checkup was done one day prior to surgery. Patients were evaluated for systemic diseases if any. Laboratory investigations such as prothrombin time, platelet count, renal function tests, liver function tests, and 12- lead ECG were taken. Details of the procedure were explained to the patients. The patients were educated about the visual analogue scale (VAS) score.

An intravenous (IV) access with 18G cannula was secured. One liter of ringer lactate was infused as preload. Patient was kept in sitting position. Epidural space was identified at L3-L4 level. Local skin infiltration with 2 mg of 2%lidocaine was given. In the midline, an 18 gauge Tuohy needle was introduced. Needle was advanced slowly till loss of resistance was felt. After entering into an epidural space, single shot epidural injection was administered. Isobaric bupivacaine 0.5% (20mL) with 75 mg magnesium sulfate (diluted in 5 mL 0.9% normal saline) was administered to Group A patients, whereas isobaric bupivacaine 0.5% (20mL) with 150 µg clonidine (diluted in 5 mL 0.9% normal saline) was administered to Group B patients. After injecting the desired concentration and dose, patients were placed in supine position with a pillow under their shoulder.

In the operation theatre, adequate IV access was confirmed. Standard monitors were attached. Noninvasive blood pressure, pulse-oximeter, and ECG were monitored. After injection, vital parameters were recorded at every five minute interval till 30 m. Hypotension was defined as systolic blood pressure <90 mm of Hg. Tachycardia and bradycardia were defined as heart rate (HR)>100/minutes or HR <60/minutes respectively.

Onset of sensory block was assessed bilaterally by using pin prick technique (target sensory level block was T6 dermatome) with 25 G disposable needle. The time required to achieve T6 dermatome level from the time of epidural injection was defined as the time for onset of sensory block.

Motor block was assessed by using modified bromage motor scale as follows:

0: no motor block.

1: inability to raise extended legs.

2: inability to flex knees.

3: inability to flex ankle joint.

The time required to achieve Grade 3 motor block from the time of injection was defined as the time of onset of motor block.

Sedation was assessed by a four point sedation score

0 = awake and alert.

1 = mildly sedated, easily aroused,

2 = moderately sedated, aroused by shaking.

3= deeply sedated, difficult to be aroused by physical stimulation.

Time for two segment sensory regression (T6 to T8) was assessed after sensory blockade height reached maximum T6 level. Sensory block was then assessed every 15 minutes till it got regressed to T8 level. This time was noted. Occurrence of any adverse effects such hypotension, bradycardia, nausea, vomiting, and shivering was recorded. Mean time for first post-operative analgesic requirement was assessed. Pain was assessed with VAS score post-operatively. If VAS score was ≥ 4, injection paracetamol 1 gm was given IV. This time was noted as first post-operative analgesic requirement. On the basis of a previously published study, [5] a sample size of 45 patients in each group was calculated by a formula [6] with 80 % power and 5 % probability of Type I error to reject null hypothesis.

STATISTICAL ANALYSIS

The data were entered in MS Excel. Statistical analysis was done by using Statistical Package for Social Sciences (SPSS ver 21.0, IBM Corporation, USA) for MS Windows. The data on categorical variables is shown as n(% of cases) and the data on continuous variables is presented as mean ± standard deviation (SD). Comparison of categorical and continuous variables was done using Chi-square test/ Fisher's exact and unpaired students 't' test respectively. P-values less than 0.05 were considered statistically significant.

RESULTS

Out of 100 patients assessed for eligibility, 10 were excluded because of diabetes mellitus (3), BMI > 25 (4), refused to participate (3). Ninety patients were randomly allotted [Fig.1]. In all, data of 90 patients (45 patients in each group) were analyzed.

Mean age, sex distribution, mean BMI, and ASA physical status were comparable in Group A and Group B [Table 1]. Mean onset of sensory block, mean onset of motor block, mean time required for two segment regression, and incidence of post-operative complications was significantly higher in Group B compared to Group A [Table2]. Time for post-operative analgesia and incidence of sedation was significantly higher in clonidine group. Mean heart rate, mean systolic blood pressure, and mean diastolic blood pressure post-operatively at 10 m, 15 m, 20 m, 25 m and 30 m post-operatively was significantly higher in Group A compared to Group B [Fig. 2].

Table 1 : Baseline characteristics

Demographic characteristic	Group A (N = 45)	Group B (N = 45)	p value
Mean age in years (SD)	37.8 (± 10.7)	37.2 (± 10.4)	0.800
Gender, no (%)			
Male	26 (57.8)	25 (55.6)	
Female	19 (42.2)	20 (44.4)	0.832
Mean BMI inkg/m^2 (SD)	22.4 (± 1.7)	22.4 (± 1.5)	0.964
ASA Grade (%)			
I	23(51.1)	25(55.6)	
II	22(48.9)	20(44.4)	0.673

ASA- American Society of Anesthesiologist
BMI- Body mass index
SD- Standard deviation

Table 2 : Comparison of outcome variables

Outcome variables	Group A (N = 45)	Group B (N = 45)	p value
Mean onset of sensory block in minutes (SD)	14.7 (± 1.8)	21.2 (± 1.4)	0.001
Mean onset of motor block in minutes (SD)	20.3 (± 1.4)	25.5 (± 1.0)	0.001
Mean time required for two segment regression in minutes (SD)	166.4 (± 7.8)	188.8 (± 5.3)	0.001
Mean time for first post-op analgesia in minutes (SD)	382.9 (± 36.8)	457.6 (± 19.2)	0.001
Incidence of untoward side effects (%)			
Nil			
Shivering	38 (84.4)	18 (40.0)	0.001
Sedation	4 (8.9)	7 (15.6)	
Nausea	0 (0.0)	15 (33.3)	
	3(6.7)	5 (11.1)	

SD- Standard deviation

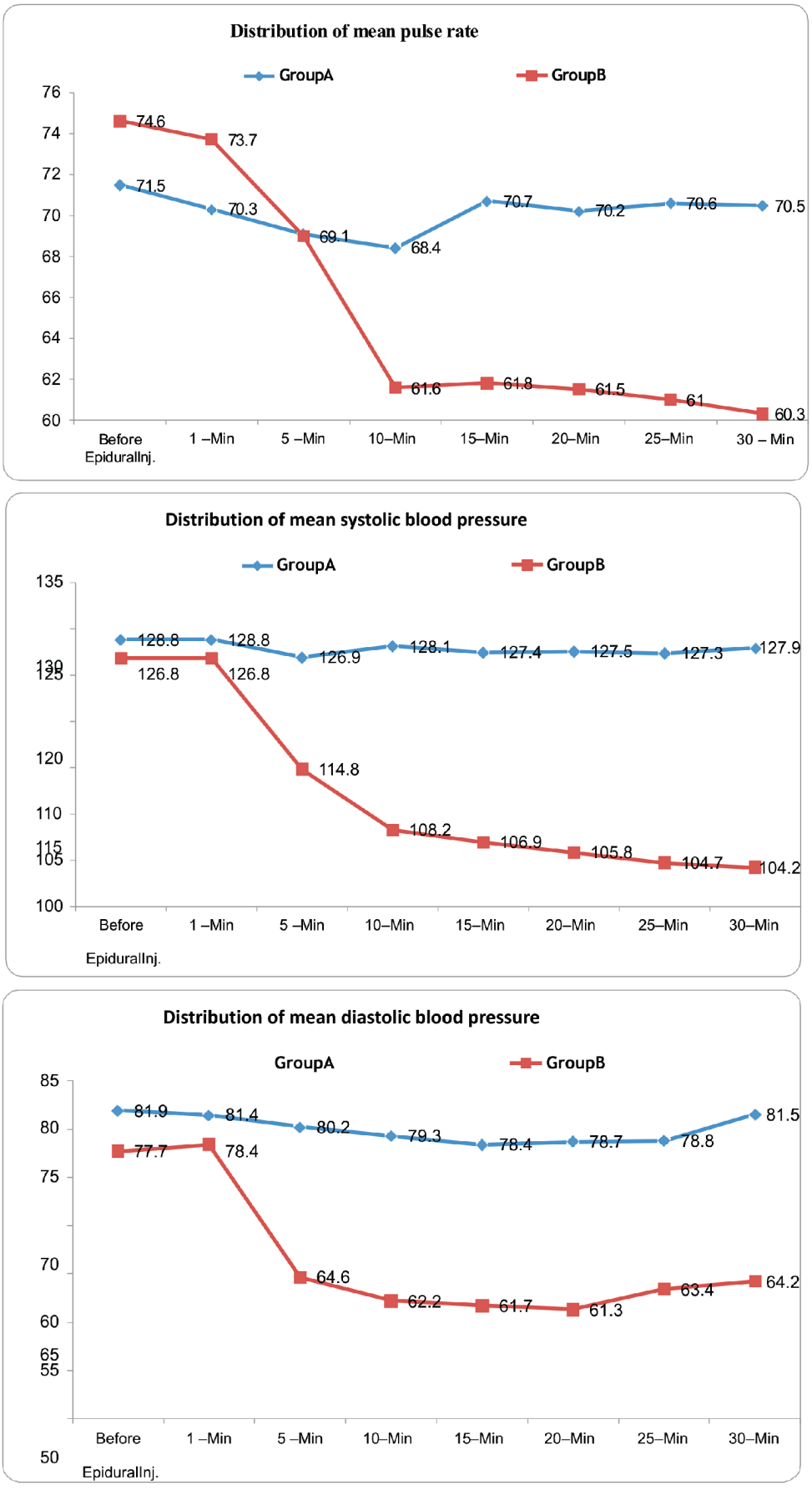

Fig 2 : Distribution of mean pulse rate, mean systolic blood pressure and mean diastolic blood pressure between two groups.

DISCUSSION

In the present randomized controlled study, time of onset of sensory block and motor block, time required for two segment regression, time for post-operative analgesia and incidence of untoward side effects were significantly higher in clonidine group as compared to magnesium sulfate group. Clonidine produced prolonged duration of anesthesia with sedation.

Time to achieve T6 block was 11.80 ± 3.2 m and 16.9 ± 3.4 m*(P*<0.05) for bupivacaine and magnesium sulfate group Vs bupivacaine and clonidine group respectively as reported by Ghatak et al., [7] Husain [8] reported that time to achieve T6 block was 10.8±3.2 m and 13.6 ±3.7 m (P<0.001)for bupivacaine and magnesium sulfate group Vs bupivacaine and clonidine group respectively. Roy et al.,[4] reported that time to achieve T6 block was14.0±2.1 m and 18.0±2.6 m (P<0.001)for bupivacaine and magnesium sulfate group Vs bupivacaine and clonidine group respectively. Pradhan et al., [9] reported that time to achieve T6 block was 6.5±2.5 m and 8.2±2.8 m (*P*<0.05) for bupivacaine and magnesium sulfate group Vs bupivacaine and clonidine group respectively. Our study substantiated these findings. In our study time required to achieve motor blockade till modified bromage scale-3 was significantly lower in group A (20.3 ±1.4 m) than group B (25.5±1.0 m). Pradhan et al.,[9] reported that the time taken to achieve complete motor blockade was lower in magnesium sulphate and bupivacaine group (15.4±6.8 m) than bupivacane and clonidine group (19.1±5.3 m), but this finding was not statistically significant (p=0.06). In the present research, clonidine group had significantly slower onset of motor blockade than magnesium sulfate group (P value is <0.001).

In the present research, time interval between epidural injection and regression of sensory blockade by two segment was significantly longer in the clonidine group (188.8±5.3 m) than magnesium sulphate group (166.4±7.8m). The time from epidural injection to two segment regression was significantly higher (*P*<0.05) in clonidine group (145.3 ± 27.7 m) than in magnesium group (130.3 ± 33.9 m) as reported by Ghatak et al.,[7]The time from epidural injection to two segment regression was significantly higher (*P*=0.0002)in clonidine group (140.6± 10.2m) than in magnesium sulfate group (130.5±9.8 m) as reported by Pradhan et al., [9]

Roy and Mrunalini [4] reported that the time for first top up was longer in bupivacaine and clonidine group than bupivacaine and magnesium sulfate group at 133.6±7.5 m, and 130.4±9.8 m respectively (p<0.05). The time from epidural medication to first epidural top up was maximum (180.3 ± 30.0 m) in bupivacaine and clonidine group followed by bupivacaine and magnesium sulfate group (161.7 ± 30.1 m) as reported by Ghatak et al.,[7] The difference among groups was statistically significant (*P*<0.05). The time to first rescue top up was 350.7±25.8 m and 315.2±24.8m for bupivacaine and clonidine Vs bupivacaine and magnesium sulfate group respectively (p=0.0001) as reported by Pradhan et al.,[9] In the present study the time for first top up was significantly longer (p=0.001) in bupivacaine and clonidine group than bupivacaine and magnesium sulfate group at 457.6±19.2 m, and 82.9±36.8 m respectively.

In the present research, there was no statistically significant difference in hemodynamic parameters (blood pressure and heart rate) between the two groups till 5 minutes. Mean heart rate, mean systolic blood pressure, and mean diastolic blood pressure post-operatively at 10 minutes, 15 minutes, 20 minutes, 25 minutes and 30 minutes were significantly higher in Group A compared to Group B. Eisenach et al reported that 150 µg clonidine decreased arterial blood pressure by 18% and reduced heart rate by 5% to 20%. [10]

In the present study, nausea was observed in 5/45 (11.1%) and 3/45 (6.7%) patients in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate groups respectively. Shivering was observed in 7/45 (15.6%) and 4/45 (8.9%) patients in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively. Sedation was observed in 15/45 (33.3%) and 0/45 (0.0%) in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively. Pradhan et al.,[9] reported vomiting in 4/30 (13.3%) and 7/30 (23.3%) in bupivacaine and clonidine group Vs bupivacaine + magnesium sulfate group respectively (p= 0.317), shivering in 2 (6.7%) and 4/30 (13.3%) in bupivacaine and clonidine group Vsbupivacaine and magnesium sulfate group respectively (p= 0.389), sedation in 8 (26.7%) and 1/30 (3.3%) in clonidine and bupivacaine group Vs magnesium sulfate and bupivacaine group respectively (p= 0.03), and headache in 3 (10.0 %) and 1/30 (3.3%) in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively (p= 0.605). Roy and Mrunalini [4] reported nausea and vomiting in 3/30 (10.0%) and 2/30 (6.7%) in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively (p= 0.127), shivering in 10 (33.3%) and 0/30 (0.0%) in bupivacaine and clonidine group Vsbupivacaine and magnesium sulfate group respectively (p= <0.001), and sedation in 9 (30.0%) and 0/30 (0.0%) in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively (p= <0.001). Ghatak et al [7] reported nausea and vomiting in 6/30 (20.0%) and 2/30 (6.7%) in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively (p= 0.165), shivering in 7/30 (23.3%) and 0/30 (0.0%) in bupivacaine and clonidine group Vsbupivacaine and magnesium sulfate group respectively (p= 0.022), and sedation in 7/30 (23.3%) and 0/30 (0.0%) in bupivacaine and clonidine group Vs bupivacaine and magnesium sulfate group respectively (p= < 0.001).

Postoperative hypomagnesaemia is prevented by perioperative magnesium supplementation; so also incidence of postoperative shivering is reduced.[3] Intrathecal administration of clonidine 150 µg failed to prevent post-spinal shivering was observed byJeon et al.,[11] When clonidine is used in conjunction with opioids for post-operative analgesia, sedation is mostly associated with it. Neurologic injury is not caused even if larger doses of magnesium sulphate were inadvertently administered into the epidural space. [12] A transient motor block followed by a complete resolution without neurological deficit at long-term follow-up was reported by Lejuste even though 100 mg of magnesium sulphate was administered in trathecally inadvertently. [13] In the present study, shivering, sedation and nausea was significantly less in magnesium group compared to clonidine group.

LIMITATIONS

We have observed patients for only 30 minutes. Further studies with larger sample size and more duration of observations are needed to validate our results.

CONCLUSIONS

Time of onset of sensory block and motor block, time required for two segment regression were significantly less in magnesium

sulphate group whereas time for post-operative analgesia was significantly higher in clonidine group. Untoward side effects were significantly less in magnesium sulphate group. Clonidine produced prolonged duration of anesthesia with sedation. It is desirable that more studies should be conducted taking larger dose of magnesium with larger sample size.

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