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Original Research Paper

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"TO ASSESS THE ROLE AND TO COMPARE THE EFFICACY OF MAGNESIUM SULPHATE AND CLONIDINE AS AN ADJUVANT IN EPIDURAL BUPIVACAINE IN PATIENTS UNERGOING LOWER ABDOMINAL AND LOWER LIMB SURGERIES"

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ABSTRACT

Objective: We conducted this clinical study to assess the adjuvant effects magnesium sulfate (Mgso4) and clonidine when administered epidurally with bupivacaine.

Methods: A total of 90 American Society of Anesthesiology (ASA) grade I and II patients undergoing lower abdominal and lower limb surgeries were enrolled to receive either magnesium sulphate (Group B) or clonidine (Group C) along with epidural bupivacaine for surgical anaesthesia. All patients received 19 ml of epidural bupivacaine 0.5% along with 50 mg magnesium in group B, 150 mcg clonidine in Group C, whereas in control group (Group A), patients received same volume of normal saline

Results: Onset of anaesthesia was rapid in magnesium group (Group B). In group C there was prolongation of duration of anaesthesia and sedation with lower VAS score, but the incidence of shivering was higher. The groups were similar with respect to haemodynamic variables, nausea and vomiting.

Conclusion: The current study establishes magnesium sulphate as a predictable and safe adjunct to epidural bupivacaine for rapid onset of anaesthesia and clonidine for prolonged duration of anaesthesia with sedation

KEYWORDS :

INTRODUCTION

Regional anaesthesia is a safe, inexpensive technique, with the advantage of prolonged postoperative pain relief. Effective treatment of postoperative pain blunts autonomic, somatic, and endocrine responses. It has become common practice to use a polypharmacological approach for the treatment of postoperative pain, because no drug has yet been identified that specifically inhibits nociception without associated side-effects.[1]

Research continues concerning different techniques and drugs that could prolong the duration of regional anaesthesia and postoperative pain relief.

Magnesium, the fourth most common cation in the body, has postsynaptic N-methyl D-aspartate (NMDA) calcium channel blocker properties, and has been used successfully to potentiate opioid analgesia and to treat neuropathic pain in animals [5]. It has antinociceptive effects in animal and human models of pain.[2 3] Tramer et al. did the first clinical study demonstrating that the administration of magnesium sulfate in the perioperative period was associated with less analgesic requirements in the postoperative period[6].

Other studies examined different routes of magnesium administration such as the intravenous or the intrathecal route, and were found to improve anesthetic and analgesic quality[7].

Epidural magnesium was found to reduce the use of postoperative analgesia without any side effects[8,9].

Clonidine is centrally acting partial α2 adrenergic agonist with selectivity ratio 200 : 1.[4] It inhibits voltage gated Na+ channels and suppresses the generation of action potentials in tonic firing dorsal horn neurons, causing analgesia.[10] It produces antinociception by stimulating postsynaptic α2 adrenergic receptors in the dorsal horn of spinal cord. This mimics the effects of nor-adrenaline which is released from the descending inhibitory pathways in the central nervous system. Thus, decreased activity of second-order neurons and wide dynamic range neurons in the dorsal horn occurs,[10,11] which in turn attenuates the input from peripheral nociceptive Aδ and C fibers.

METHODS AND MATERIAL

INCLUSION CRITERIA

- Patient of 18-60 year of either gender
- A.S.A physical status I or II with ±20% of ideal body weight

EXCLUSION CRITERIA

- Contraindication to central neuraxial blockade
- History of adverse reaction to any study medication
- history of analgesic use,
- chronic pain syndrome
- Communication difficulties that would prevent postoperative assesment

TYPE OF STUDY

Prospective, Randomised, double blind study.

After obtaining institutional ethical committee approval and written informed consent, 90 patients undergoing elective lower abdominal and lower limb surgeries were randomly allocated in to 3 groups by block randomization method, where one patient had every chance to get allocated in any group by lautery method.

Group A (control group): bupivacaine 0.5% (19 ml) + saline 0.9(1 ml).

Group B: bupivacaine 0.5% (19 ml) + magnesium sulphate 50 mg (in 1 ml 0.9% saline)

Group C: bupivacaine 0.5% (19 ml) + clonidine 150 mcg (1 ml).

Intravenous fluid loading with 20 ml/kg of Ringer's lactate solution was given. Patients were then placed in the sitting position, and local anesthesia infiltration of skin and subcutaneous tissues was done at the level of L2–3 or L3–4 with 2–3 mL of lidocaine 2%.

Then, the epidural space was localized with the loss of resistance to air technique using an 18-gauge Tuohyneedle.

A 20 G epidural catheter was then advanced for 3 to 5 cm into the epidural space. Correct placement of epidural catheter was verified

with a test dose of 3 ml epidural lignocaine 2% with adrenaline (1 : 2,00,000)

The patients were then divided randomly into following three group 30 in each group according to the epidural medications.

Sensory block was assessed bilaterally by using analgesia to pin prick with a short hypodermic needle in midclavicular line.

Motor blockade was assessed by using modified Bromage scale

0: no motor block;
1: inability to raise extended legs;
2: inability to flex knees;
3: inability to flex ankle joints.[12]

Monitoring consisted of heart rate, noninvasive arterial blood pressure and SpO2 measurements in three groups preoperatively, intraoperatively and during shifting.

Hypotension was defined as systolic blood pressure <90 mmHg or >30% decrease in baseline values. Tachycardia was defined as heart rate >100/min and bradycardia was defined as heart rate <60/min.

Sedation was assessed on a four point scale[8]

(Grade 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).

The patients were asked to evaluate their pain on standard 100 point visual analogue pain scale (VAS)

0 = no pain,
VAS 100 = worst possible pain.

In the event of pain, (VAS ≥40), both intraoperatively as well as postoperatively, a bolus of epidural bupivacaine 0.25% (8 ml) was administered by the anaesthesiologist inside the operation theatre and the nursing staff in the recovery room.

Time to two segment regression to first epidural top up requirement and occurrence of adverse effects, if any, were recorded.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS for windows 15.0. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Parametric data were compared using analysis of variance (ANOVA) within group comparisons at different time intervals assessed by using paired t-test.

All the categorical data were compared by using chisquare test. A sample size of 20 patients per group was needed to detect an intergroup difference of at least 20% (α= 0.01, two-sided, power = 90%) with two sample t-test.[9]

A value of $P<0.05$ was considered stastically significant.

RESULTS

There were no differences in age, height, body weight, body mass index (BMI) between the groups [Figure 1]. These groups were similar in the maximal dermatome height achieved. No difference in the quality of sensory and motor block before and during the surgery was noted between groups.

Systolic, diastolic arterial blood pressures, heart rates and oxygen saturations remained stable, and there was no significant difference between the groups. Systolic arterial blood pressures were similar in this period [Figure 2].

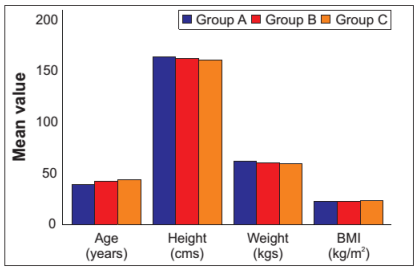

Figure 1: Patient characteristics in the three groups. Data are given as mean (SD)

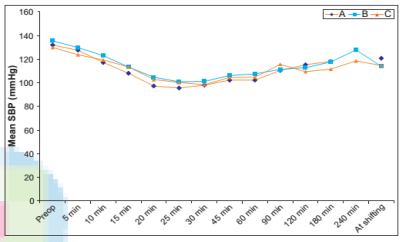

Figure 2: Systolic arterial blood pressures (SAP) in the operative period. There were no significant differences between groups. Data are given as mean (SD)

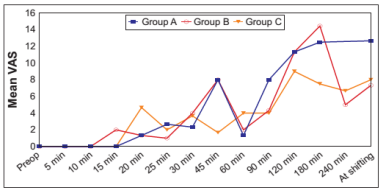

Figure 3: Intergroup comparison of intensity of operative pain as measured using a VAS at different time intervals. The difference in intensity of operative pain between groups was statistically significant at 45 minutes ($P < 0.05$) by using two-way repeated-measures analysis of variance (ANOVA). Data are given as mean (SD)

Time to achieve T6 block was least in epidural magnesium adjuvant group (12.20 ± 3.45 minutes) and highest (19.73 ± 3.29 minutes) in control group, whereas it was 17.53 ± 4.33minutes in clonidine group of patients.

The difference between the groups was statistically significant. (F = 19.546; P<0.05).

Wide variation in pain scores were seen throughout the study period. However, statistically significant intergroup differences were seen only at 40 minutes.

At this time, clonidine group showing significantly lower pain scores as compared with control group and magnesium group [Figure 3].

The time from epidural medication to first epidural top up was maximum (183.33 ± 28.65minutes) in clonidine group followed by magnesium group (159.67 ± 32.40 minutes) and with a minimum (149.36 ± 37.80 minutes) in control group of patients. The differences among groups were significant (P<0.05).

The time from epidural medication to two segment regression ranged from 122.10 ± 27.08 minutes in control Group (Group A) to 144.24 ± 27.74 minutes in clonidine Group (Group C), with an intermediate value (131.33 ± 33.96 minutes) in magnesium Group (Group B) patients. The differences in time from epidural medication to two segment regression among groups were not statistically significant (P>0.05) [Table 1].

Shivering occurred in five (16.66) control group and seven (23.33) clonidine group patients, whereas no patients in magnesium group (Group B) suffered from shivering during this study. The differences among groups were statistically significant (P<0.05)

Sedation was observed in eight patients (26.66%) in clonidine group (Group C), which is statistically significant (P<0.05) [Table 2].

Variables	Group A Mean	SD	Group B Mean	SD	Group C Mean	SD	P value
Time taken to achieve T6 block (min)	19.73	3.29	12.20	3.45	16.93	4.33	<0.001*
Time to 1st epidural top-up (min)	149.36	37.8	159.67	32.4	183.33	29.97	0.047
Time to 2nd segment regression (min)	122.10	27.08	131.33	33.94	144.24	27.74	0.129

Table-2

Complications	Group A	Group B	Group C	P value
Hypotension	24	19	22	0.389
Bradycardia	6	4	10	0.162
Nausea, vomiting	2	2	6	0.165
Shivering	5	0	7	0.022
Sedation	0	0	8	<0.001

DISCUSSION

This study shows that addition of magnesium, a competitive NMDA antagonist, as adjuvant to epidural bupivacaine fasten the onset of block and establishment of epidural block upto T6 level.

With addition of clonidine, centrally acting α2 agonist prolongs duration of anaesthesia along with significant sedation.

Zand et al.[13]showed that the time to onset of sensory block in L1 was 17.12 ± 2.18 minutes in group of patients receiving a total of 18 ml plain 0.5% bupivacaine, and their study time to onset of sensory block in T10 was 24.9 ± 2.54 minutes. Our study also shows onset to T6 level was 17.92 ± 3.29 minutes in control group. Early onset may be due to use of a test dose of 3 ml epidural lignocaine 2% with adrenaline (1:2,00,000).

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 sensitization such as wind-up and long-term potentiation in the spinal cord in the response of cells to prolonged stimuli.[14] Central sensitization has an important role in pain perception and is considered to be one of the mechanisms implicated in the persistence of postoperative pain.[15] NMDA receptor signaling may be important in determining the duration of acute pain.[16] Therefore, NMDA receptor antagonists may play a role in the prevention and treatment of post-injury pain. Magnesium blocks calcium influx and non-competitively antagonizes NMDA receptor channels.[17] Non-competitive NMDA receptor antagonists can have an effect on pain when used alone, but it has also been shown that they can reveal the analgesic properties of opioids.[18]

Clonidine induces dose-dependent spinal cord antinociception, mainly through stimulation of α2- adrenoceptors in the dorsal horn, mimicking the activation of descending inhibitory pathways.[19]

Motor and Sensory blockade are enhanced by clonidine. The effects of clonidine on the prolongation of nerve blockade are clearly dosedependent.[20]

We also found in our study that the time gap between initial epidural medication and the time to first epidural top up was highest(183.33 ± 28.65minutes) in clonidine group followed by magnesium group (159.67 ± 32.40 minutes) and with a minimum (149.36 ± 37.80 minutes) in control group of patients. The differences among groups were statistically significant(P<0.05).

After neuraxial or systemic administration, clonidine affects arterial blood pressure in a complex manner because of opposing actions at multiple sites. The α2-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 5to 20%, and concluded that epidural clonidine does not induce haemodynamic instability. In our study, we have also not found statistically significant arterial blood pressure differences in among the three groups.

In the magnesium group no patient suffered from shivering during this study, whereas shivering occurred in five (16.66%) patients belonging to control group and seven patients (23.3%) belonging to the clonidine group. The differences among groups were statistically significant (P<0.05). Perioperative magnesium supplementation prevents postoperative hypomagnesaemia and decreases the incidence of postoperative shivering.

Sedation is a side effect frequently associated with the use of clonidine in postoperative analgesia, often in conjunction with opioids.[21]

In our study sedation was observed in eight patients (26.66%) in clonidine group (Group C), which is statistically significant (P<0.05) A bolus dose of epidural clonidine more than 100 mcg may cause significant sedation [22] But lower doses of clonidine will not cause significant sedation.[23]

Our study has the limitation of only one dose-response evaluation. We preferred to use a smaller dose of magnesium that would not cause any side-effects. In two cases reported by Goodman et al.,[24] larger doses (8.7 g, 9.6 g) of magnesium inadvertently administered into the epidural space did not cause any neurologic injury. Also another report described an inadvertent intrathecal injection of 1000 mg of magnesium producing a transient motor block followed by a complete resolution and no neurological deficit at long-term follow-up.[25]

One of the main differences of this study from ours is the route of administration and the second difference is the higher doses of magnesium they used in rabbits.

We feel that further studies should address different dosages of magnesium with larger number of patients and different surgical settings to establish our findings.

CONCLUSION

Addition of magnesium with bupivacaine in epidural produces rapid onset of anaesthesia without any side-effects, and addition of clonidine to epidural bupivacaine produces prolonged duration of anaethesia with sedation.

The results of the present investigation suggest that magnesium may be a useful alternative as an adjuvant to epidural

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