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Evaluation of single epidural bolus dose of magnesium sulphate as an adjuvant to fentanyl for postoperative analgesia in total knee replacement surgery

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Abstract

Background: Magnesium has antinociceptive effects in animal and human models of pain. Magnesium has been used as an adjuvant by various routes, including intravenous, intrathecal and epidural in different dosage regimens. Forty patients undergoing Total Knee Replacement surgery were enrolled to receive either fentanyl (Group F) or fentanyl plus magnesium sulphate (Group FM) post operatively for epidural analgesia. Ventilatory frequency, heart rate, blood pressure, pain assessment using a visual analogue scale (VAS), sedation scores and fentanyl consumption were recorded in the postoperative period. This is a prospective, randomized, controlled study designed to assess the efficacy of single bolus administration of Magnesium epidurally as an adjuvant to epidural fentanyl for postoperative analgesia taken in National Institute of Medical Science, Jaipur. **Materials and Methods:** 40 Patients of ASA grade I and II aged 20 to 60 years of either gender undergoing Total Knee replacement surgery enrolled in study received combined spinal epidural anaesthesia with 4 ml of 0.5% hyperbaric bupivacaine intrathecally. After surgery patients were randomized into group F (epidural fentanyl 50µg in 10ml saline) and Group FM (epidural magnesium 75 mg along with fentanyl 50µg in 10 ml saline). Rescue analgesic is provided by Intravenous Tramadol if VAS score >4. Patient's first analgesic requirement time and duration of analgesia were recorded. The groups were similar with respect to haemodynamic and respiratory variables, sedation, pruritis, and nausea. Co-administration of magnesium for postoperative epidural analgesia results in a reduction in fentanyl consumption without any side-effects. **Result:** 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. The duration of analgesia was significantly longer for Group FM compared to Group F. The frequency of rescue analgesics required in postoperative period in group FM was significantly less than that in Group F. **Conclusion:** The administration of magnesium as an adjuvant to epidural fentanyl for postoperative analgesia results in significantly lower VAS with prolonged duration of analgesia as compared to epidural fentanyl alone. Thus, Epidural magnesium was found to reduce the use of postoperative analgesia without increases in side.

Keywords: Epidural, Magnesium, N-methyl-d-aspartate receptor, Post-operative pain, Rescue analgesia.

INTRODUCTION

Providing postoperative pain relief is a challenge for anesthesiologists. Postoperative epidural analgesia after combined spinal epidural (CSE) anesthesia is one of the accepted techniques [1]. Various adjuvants in addition to opioids have been used epidurally to prolong analgesia and reduce the incidence of adverse events observed when opioids are used alone [1]. N-methyl-d-aspartate (NMDA) receptors present in dorsal horn of spinal cord have a role in the modulation of central sensitization of noxious stimulus [2]. Calcium influx is thought to be the primary mechanism by which NMDA receptors act [1]. Calcium channel blockers and NMDA receptor antagonist have shown to be beneficial in preventing initiation of pain. Magnesium, a divalent cation, through noncompetitive mechanism blocks the NMDA receptor in a voltage-dependent manner and results in natural calcium antagonism [3]. Various animal and human studies have shown that magnesium possesses antinociceptive action. Magnesium has been used as an adjuvant by various routes, including intravenous, intrathecal, and epidural in different dosage regimens [4,5]. The role of epidural anesthesia and analgesia in reducing the incidence and severity of perioperative physiologic derangements, in addition to relieving pain has been reported in several studies [6-9]. Various adjuvants in addition to opioids have been used epidurally to prolong analgesia and

reduce the incidence of adverse events observed when opioids are used alone [1]. N-methyl-d-aspartate (NMDA) receptors present in dorsal horn of spinal cord have a role in the modulation of central sensitization of noxious stimulus [2]. Calcium influx is thought to be the primary mechanism by which NMDA receptors act [2]. Calcium channel blockers and NMDA receptor antagonist have shown to be beneficial in preventing initiation of pain. Magnesium, a divalent cation, through noncompetitive mechanism blocks the NMDA receptor in a voltage-dependent manner and results in natural calcium antagonism [3]. Various animal and human studies have shown that magnesium possesses antinociceptive action. Magnesium has been used as an adjuvant by various routes, including intravenous, intrathecal, and epidural in different dosage regimens [4,5]. The role of epidural anesthesia and analgesia in reducing the incidence and severity of perioperative physiologic derangements, in addition to relieving pain has been reported in several studies [6-9]. Various adjuvants in addition to opioids have been used epidurally to prolong analgesia and reduce the incidence of adverse events observed when opioids are used alone [10].

Because of its greater liphophilic nature, fentanyl offers some advantages for epidural analgesia. The rapidity of analgesic effects of epidural fentanyl administration and relatively short duration of action makes it the drug of choice for postoperative acute pain [11]. Magnesium, the non-competitive NMDA antagonist, administered intrathecally or epidurally, is proved to prolong the duration of spinal opioid analgesia [12].

Co-administration of epidural magnesium for postoperative epidural analgesia has provided a pronounced reduction in patient controlled epidural fentanyl consumption without any side-effects [13]. On the basis of these evidences, a study was undertaken to compare the effects of epidural fentanyl and fentanyl plus magnesium on duration of analgesia, hemodynamic stability and side effects in patients.

Aims and Objectives: Aim of our study is to evaluate the analgesic efficacy of single bolus dose of magnesium sulphate as an adjuvant to epidural fentanyl for postoperative analgesia.

MATERIALS AND METHODS

The present study was a Prospective, randomized double blind comparative study. After obtaining institutional ethics committee approval, written and informed consent, 40 patients of ASA grade I and II aged 20-60 years of either gender, undergoing orthopaedic total knee replacement surgeries were enrolled for the study. Thorough pre-anaesthetic evaluation and investigations were carried out to find out any associated systemic illness.

Exclusion Criteria: Patients for whom central neuraxial block was contraindicated and those with history of reaction to study drugs, on analgesic therapy and calcium channel blockers, major hepatic, renal or cardiovascular dysfunction were excluded from the study.

Patients were briefed before operation on visual analogue pain scale (Table 1). They were advised overnight fasting and pre-medicated with 0.5mg oral Tab Alprazolam at night. On arrival at the operating room, electrocardiogram, non- invasive blood pressure and pulse oximeter monitoring were started. Baseline pulse rate, blood pressure (systolic, diastolic and mean), and oxygen saturation were noted. An intravenous access was established and all the patients were preloaded with lactated Ringer's solution (10ml/kg body weight).

Table 1: Visual analogue score

Visual analogue score: 0 – 10	
No pain	2
Little pain	2
Considerable pain	2
Lot of pain	2
Worst pain	2

Under all aseptic precautions, patient received CSE anaesthesia. The epidural space was identified at L3-L4 or L4-L5 space using a loss of resistance technique. Dural puncture was performed by a needle-through-needle technique with a Whitacre 26G needle and 4ml of 0.5% hyperbaric Bupivacaine was injected into Intrathecal space. Epidural catheter was threaded 4cms in addition to the distance of epidural space and fixed with adhesive plaster on patients back. Sensory block was assessed bilaterally by using pinprick method with short bevelled needle. Motor block was evaluated using modified Bromage scale (Table 2).

Table 2: Showing modified bromage scale

0	No motor block
1	Inability to raise extended legs
2	Inability to flex knees
3	Inability to flex ankle joints

An epidural test dose of 45mg Lignocaine and 1:200000 Adrenaline in a volume of 3ml was administered.

When surgery was complete, patients were randomized by computer generated random number assignment into 2 groups of 20 each. After surgery patients were shifted to post anaesthesia care unit and Group F (n-20) Patients received epidural fentanyl 50µg in 10ml normal saline. Group FM (n-20) received epidural magnesium 75mg along with fentanyl 50µg diluted in isotonic saline to a total of 10ml. The drug was prepared by an independent investigator who was not involved in the peri-operative management of the patient. Fentanyl was prepared from an ampoule containing 50µg/ml, whereas magnesium dose was prepared from an ampoule containing 50% magnesium (500 mg / ml) which was diluted to 5% in 10ml normal saline and 1.5ml was administered. Patients were monitored postoperatively for vitals, VAS score for pain and any other side effects such as excessive sedation, pruritis, post-operative nausea vomiting (PONV), urinary retention and respiratory depression. Sedation was assessed on RAMSAY SEDATION SCORE (Table 3). All the patients were observed for any neurological complications until 24 hrs after surgery. Postoperative monitoring was recorded Regular intervals. If the patients need analgesia, rescue analgesic (Intravenous Tramadol 50 mg) is given.

Table 3: Ramsay sedation score

LEVEL 1-anxious and agitated or restless or both
LEVEL 2-cooperative and oriented
LEVEL 3-responds to commands only
LEVEL 4-6 patient asleep, responds to light glabellar tap or loud auditory stimulus
LEVEL 4 –Brisk response
LEVEL 5 – Sluggish response
LEVEL 6 –No response

Statistical Analysis

Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2008).

Kruskul Wally's chi square was used to test the significance of relationship. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

The groups were comparable with respect to age, gender (Table 4) (Figure 1). The duration of surgery was comparable in both the groups (159±22.5 min in Group F vs 163±20.6 min in Group FM (p=0.473) (Table 5).

Table 4: Showing age and gender distribution

Group	FM	F	'P'
Age in yrs	39.2±9.9	40.2± 8.4	0.7341 Not significant
Sex Male Female	 90% 10%	 90% 10%	 1.0 Not significant

Table 5: Showing comparison of duration of analgesia

Variable	Group F	Group FM	p Value
Duration of Analgesia (mint)	164±17.1	340 ± 28.8	0.001

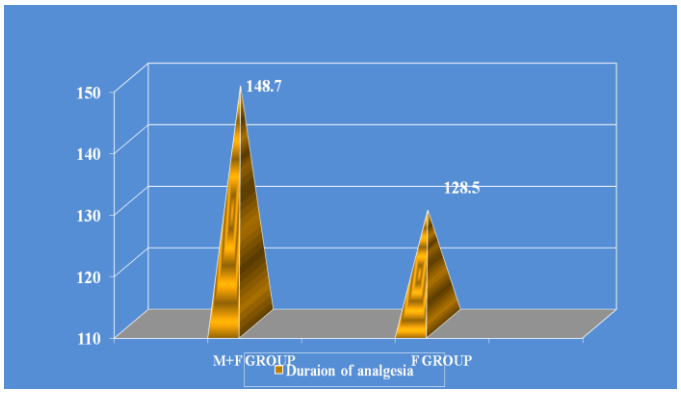

Figure 1: Duration of analgesia (in minutes)

The sensory and motor block level were comparable prior to administration of epidural drugs in the 2 groups (p=0.7 and 0.52 respectively).

The duration of analgesia after the epidural drug administration was significantly longer for Group FM 340±28.8 minutes, compared with Group F (164±17.1min (p=0.001) (Table 6).

Table 6: Analgesia duration

Variable	FM Group	F Group	"P"
Duration of analgesia (in minutes)	148.7 ± 34.4	128.5 ± 28.7	0.0295 Significant

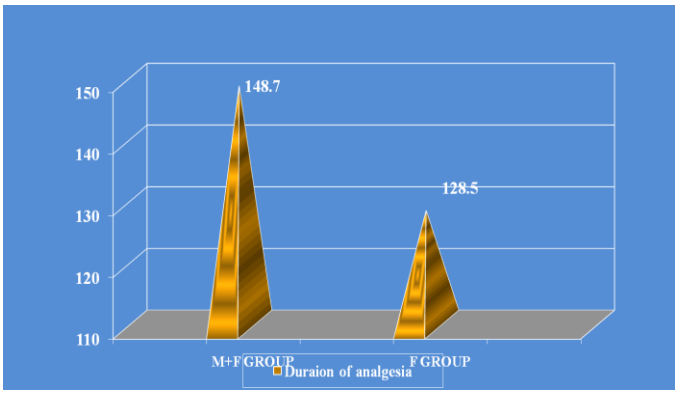

Figure 2: Duration of analgesia (in minutes)

The frequency of rescue analgesic (intravenous tramadol 50mg) required in postoperative period in Group FM was significantly less than in Group F (Table 7), (Figure 3). Postoperative pulse rate, systolic, diastolic and mean blood pressure were comparable in both groups and statistically insignificant (p>0.05).

Table 7: Showing VAS scoring

Time	Group F	Group FM	p value
0 min	2.7 ± 1.0	3.1 ± 1.3	0.3126 Not significant
30 min	0.65 ± 0.49	0.15 ± 0.37	0.0014 Significant
1h	0.8 ± 0.4	0.2 ± 0.41	0.0013 Significant
2h	3.4 ± 0.68	2.75 ± 0.96	0.0271 Significant
3h	3.95 ± 0.22	3.4 ± 0.88	0.0214 Significant

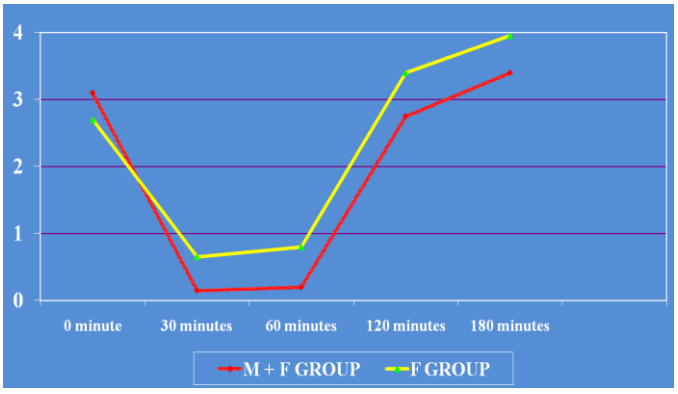

Figure 3: Visual analogue scale

There was no incidence of hypotension or bradycardia in either of the group postoperatively. There was no incidence of respiratory depression in either of the groups. No patients experienced excessive sedation (median sedation score 0 in both the groups), PONV or pruritis. Two patients each in both the group had urinary retention (p=1).

DISCUSSION

The results of present study show that a single bolus dose of epidural magnesium (75mg) as an adjuvant to epidural fentanyl (50µg) results in prolonged duration of analgesia as compared with epidural fentanyl (50µg) alone. Also VAS was lower in the study group as compared with

control group. Concomitant administration of magnesium also reduces the requirements of rescue analgesic with no increased incidence of side effects.

Noxious stimulation leads to the release of neurotransmitters, which bind to various subclasses of excitatory amino acid receptors, including NMDA receptors. NMDA receptor signaling may be important in determining the duration of acute pain [14]. Therefore, NMDA receptor antagonists play a role in the prevention and treatment of post-injury pain. Magnesium blocks calcium influx and non-competitively antagonizes NMDa receptor channels. Magnesium can have an effect on pain when used alone, but it has also been shown that it potentiates the analgesic properties of opioids [15].

In this way the co-administration of magnesium with fentanyl prolongs fentanyl analgesia. In our study 75 mg dose of epidural magnesium in Group FM resulted in lower VAS scores at 30 mins, 1, 2 and 3 hrs postoperatively and our observation coincided with study of Biliar et al. The frequency of rescue analgesia requirement was lower in Group FM in 24 hr study period and our observation coincided with study of Arcioni *et al* [16] who studied the effect of combined intrathecal and epidural infusion of magnesium sulphate supplementation. They concluded that supplementation of spinal anesthesia with combined intrathecal and epidural magnesium significantly reduces patient's postoperative analgesic requirements. The concern of neuromuscular blockade after epidural magnesium administration is emphasized in literature but no impact was noted on motor function in our study when magnesium was administered epidurally (as suggested by modified Bromage score) [17].

Also neurologic outcome after inadvertent administration of larger doses of intrathecal and epidural magnesium has been studied and no neurologic deficit has been reported [18,19]. There were no increased incidences of side effects in magnesium group, although 2 patients in both the groups complained of urinary retention which might have resulted from epidural administration of fentanyl [20]. Thus in present clinical study epidurally administered magnesium is shown to prolong the duration of fentanyl analgesia without significant side effects.

CONCLUSION

We conclude that the administration of epidural magnesium (75 mg) as an adjuvant to epidural fentanyl (50µg) for postoperative analgesia resulted in prolonged duration of analgesia when compared with epidural fentanyl (50µg) alone. Concomitant administration of magnesium also reduces the requirement for rescue analgesic with no increased incidence of side effects.

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