Original Research Article

Clinical evaluation of adding solitary dose of magnesium to fentanyl on post-operative analgesia during combined spinal epidural technique for hip replacement procedures

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ABSTRACT

Background: Numerous receptors such as NMDA have evolved in the management of post-operative pain which can be antagonized effectively before the initiation of painful stimuli. The analgesic property of Magnesium is primarily related to the regulation of calcium influx and antagonism of N-methyl-D-aspartate (NMDA) receptors distributed throughout the central nervous system. This study was designed to evaluate if addition of magnesium to epidural fentanyl as pre-emptive solitary dose could prolong post-operative analgesia during combined spinal epidural anesthesia in elective hip replacement surgeries.

Methods: A total of 63 adult consented ASA grade I and II patients aged between 40 and 70 years of either sex, who met the inclusion criteria for hip replacement surgery, were randomized to receive either epidural fentanyl (Group I) or combined epidural magnesium sulphate and fentanyl (Group II). Both the groups subsequently received subarachnoid block with 0.5 % heavy bupivacaine. Intraoperative hemodynamic, subarachnoid block characteristics and 24 hours post-operative analgesia was evaluated.

Results: There was significant delay in two dermatome regression for the combined fentanyl magnesium group (149.07±6.48 min) compared to fentanyl alone group (121.23±2.92 min). The post-operative VAS score was statistically lower for the combined fentanyl magnesium group (lowest:0.7±0.4 at 4th hr, highest: 2.9±0.3 at 20th hr) compared to fentanyl alone group (lowest:1.86±1.7 at 5th hr, highest: 3.37±0.9 at 4th hr). There was highly significant difference in average time to first epidural top up and 24hrs epidural top up consumption between fentanyl alone group (264.83±34.08min, 2.8±0.5) and combined fentanyl magnesium group (398±69.5min, 1.43±0.5). Total epidural top ups were 84 in fentanyl alone group and 43 in combined fentanyl magnesium group. Hemodynamic parameters were stable in both groups.

Conclusions: Pre-emptive co-administration of magnesium sulphate as a solitary dose to epidural fentanyl in CSE technique prolongs the duration of post-operative analgesia, reduce the requirement of epidural top up and provide stable hemodynamic perioptatively compared to epidural fentanyl alone.

Keywords: Combined spinal epidural(CSE), Fentanyl, Magnesium sulphate

INTRODUCTION

The increasing demand for hip arthroplasty and replacement surgery over the last decade has sparkled the evolution of many innovative anesthetic techniques with the objective to provide effective pain relief and focus has now shifted to regional based techniques. Pre-incisional or precisely known as pre-emptive analgesia prevents the initiation of events that result in central nervous system excitability has been accepted as an
important aspect of multimodal pain management strategy.\textsuperscript{1,2,3} Besides local anesthetics, diverse variety of drugs have been used as adjuncts. For instance these comprise opioids, clonidine, epinephrine, ketamine, sodium bicarbonate, neostigmine and anticholinesterases.\textsuperscript{4,9}

These adjuvants can be given in epidural space prior to the surgical incision to effectively modify the postoperative analgesia. Innumerable inherent pain control network or receptors exist in substantia gelatinosa of spinal cord where these acts to provide antinociception. Noxious stimuli such as postoperative pain often leads to release of excitatory neurotransmitters such as glutamate and aspartate, which bind to several sub classes of excitatory amino acid receptors, including N-Methyl D-Aspartate (NMDA) receptors.\textsuperscript{10} NMDA is a membrane protein that regulates the influx of sodium and calcium ions into the cell and the efflux of potassium ions thus initiating central sensitisation and wind up.\textsuperscript{11} Thus NMDA receptor signals can be a key in determining the duration and intensity of post-operative pain. Magnesium ions block the NMDA channels non-competitively in a voltage-dependent way.\textsuperscript{12,13} In this way magnesium can play a pivotal role in pain signal modulation at substantia gelatinosa of spinal cord.

We hence forth designed a prospective, randomized, double blind clinical study to investigate the efficacy of preemptive epidural magnesium as solitary dose when added to fentanyl to investigate if this combination had any effect on various parameters such as sensorimotor block characteristics and postoperative analgesia given concomitantly with hyperbaric bupivacaine 0.5% in subarachnoid block during hip replacement surgery.

\textbf{METHODS}

After approval from ethical committee of institution, 63 ASA grade I and II patients, between 40-70 years age scheduled for elective hip replacement surgery of maximum duration 180 minutes, under sequential combined spinal epidural (CSE) block were enrolled in this study.

Patient with ASA status $\geq$ ASA III, with Known allergy to local anesthetics or study drugs, history of neuropathic or chronic pain or bleeding diathesis, on psychotropic drugs, local sepsis, previous spinal surgery and severe spinal deformity like kyphoscoliosis, ankyloses or spondylisis, severe cardiac, renal, hepatic, pulmonary, hematologic, neuromuscular disease, patient for revision surgery, with ongoing analgesic therapy and calcium channel blockers and who had inadvertent dural puncture during epidural space detection were excluded from the study.

All patients underwent preoperative evaluation which included history, physical examination and biochemical investigations before enrollment and their basic data was recorded. The observer was blinded about the groups and dose and dilution of the study drugs received by the patients.

\textbf{Allocation of study groups and randomization}

All 63 patients include in this study were randomized into two comparable equal groups, using a computer-generated random number assignment in sealed opaque envelopes that were opened just before entry in the study. The study drugs were prepared by an anesthesiologist who was no further involved in the investigation. These were as follows:

- **Group I** (n=30) received epidural Fentanyl (1ml=50 mcg) + 9 ml normal saline.

- **Group II** (n=30) received epidural Fentanyl (1ml=50 mcg) + Magnesium sulphate (0.5ml=50mg) + 8.5ml normal saline. 0.5ml (50mg) magnesium sulphate was collected from 10ml solution prepared after diluting 50% magnesium sulphate 2ml (1000mg) in 8 ml normal saline. Thus, a total volume of epidural drug was 10ml in both the groups.

The protocol defined primary end points for this study were sensori-motor block characteristic and the perioperative pain while hemodynamics were the secondary outcome. Both the patient and the observer were unaware of the groups.

\textbf{Study procedure and anesthetic technique}

Prior to surgery, patients were made familiar to epidural technique and 11-point visual analogue scale (VAS score 0: no pain;10: worst pain). On arrival at the operating room, electrocardiogram for heart rate, non-invasive blood pressure and SpO2 by pulse oximeter were monitored and baseline parameters including respiratory rate and urinary output were noted. All the patients were preloaded with 500 ml lactated Ringer's solution 30 minutes prior to the block. All the patients were assigned to one of the two groups, as per the randomization. Brownridge’s sequential double needle-double interspace CSE technique was performed in all patients.

Under all aseptic precautions, lumbar CSE technique was established with the Portex Epidural Minipack system 1 containing 18.0 G Tuohys needle and 20.0 G epidural catheter in sitting position. L2-L3 or L3-4 interspace was chosen.

Epidural space was identified by air filled loss of resistance syringe attached to Tuohy’s needle and epidural catheter was negotiated upto 4.0cm mark into the epidural space. After negative aspiration of CSF and blood an epidural test dose (3.0ml 2.0% lignocaine with adrenaline 1:200000) was given to rule out incidental vascular invasion. An increase in heart rate of $>$20-30 beats/min within 60 seconds indicated intravascular
position. Under this circumstance, procedure was shifted to lower space. The prepared study drug was subsequently injected in the epidural space.

Through a level lower than the epidural space, subarachnoid block was established with 26 G Quincke’s spinal needle and 3.5ml of 0.5% hyperbaric bupivacaine was injected after identifying the space by free flow of cerebrospinal fluid. The epidural catheter was secured at the back with sponge and adhesive tape. The patient was then laid supine for block to establish. Throughout the procedure, all patients received supplemental oxygen 3L/min via face mask. On achieving minimum block level for sensory dermatome of at least T10, further lateral positioning for the operative procedure was permitted for surgery to commence. The time (T=0) was taken after completion of subarachnoid block. Also, duration of effective analgesia (time of first dose of epidural top-up at VAS 4.0) and total consumption of epidural top-up (10.0ml of 0.125% bupivacaine) in 24 hrs post-operatively were observed.

The hemodynamics changes, heart rate and mean blood pressure, respiratory rate, level of sedation by Ramsay sedation scale and any side effects or complications, if any during the perioperative period were recorded. Ramsay sedation score (1-6): 1: Anxious, agitated, or restless; 2: Cooperative, oriented, tranquil and alert; 3: Responds to commands; 4: Asleep but brisk response to light glabellar tap/loud auditory stimulus; 5: A sleep, sluggish response to light glabellar tap/loud auditory stimulus; 6: A sleep, no response.

### Statistical analysis

The analysed data was expressed as mean±SD. Qualitative demographic data for categorical variables was analyzed using the χ2-test, whereas statistical comparison for numerical variables such as VAS, modified Bromage scale and hemodynamic parameter was performed by independent sample t-test. Block characteristics were compared using Mann Whitney U test. The data was evaluated on SPSS version 16 and entered on MS excel 2010. The sample size was based on 30 min difference in mean duration of sensory and motor blockade between the group for type I error of 0.01 and power of 90%. A p-value <0.05 was considered statistically significant.

### RESULTS

The demographic profile was comparable with no statistically significant difference between the groups (Table 1).

The onset of sensory and motor block in the two groups were comparable. However, there was significant delay in the two-dermatome regression of the block for the group II (p<0.001). Also, there is delay in the first epidural top up at VAS score 4 for the group II whereas group I reached VAS score 4.0 earlier as reflected in first epidural top up received at 264.83±34.08 mins. More top up doses were consumed in group I (84) compared to group II (43) (p<0.001) (Table 2).

### Table 1: Demographic profile and duration of surgery.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>ASA grade (I/II)</th>
<th>Duration of surgery (min)</th>
<th>Male:Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td>58.30±8.7</td>
<td>159.20±6.7</td>
<td>17/13</td>
<td>139.67±18.9</td>
<td>15/15</td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td>55.36±8.9</td>
<td>160.30±7.1</td>
<td>18/12</td>
<td>140.70±17.9</td>
<td>16/14</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.204</td>
<td>0.539</td>
<td>0.069</td>
<td>0.829</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Sensorimotor block characteristics in both the groups.

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset time sensory block at T10 level (min)</td>
<td>2.38±0.2</td>
<td>2.45±0.3</td>
<td>0.209</td>
</tr>
<tr>
<td>Highest sensory level attained</td>
<td>159.20±6.7</td>
<td>T6</td>
<td>T7</td>
</tr>
<tr>
<td>Two segment regressions from highest level(min)</td>
<td>121.23±2.92</td>
<td>149.07±6.48</td>
<td>0.0001</td>
</tr>
<tr>
<td>Onset time of motor block (min)</td>
<td>4.13±0.5</td>
<td>4.27±0.7</td>
<td>0.376</td>
</tr>
<tr>
<td>Time for motor block to Bromage scale 3(min)</td>
<td>8.20±0.6</td>
<td>8.33±0.8</td>
<td>0.479</td>
</tr>
<tr>
<td>Motor block regression to Bromage scale 0(min)</td>
<td>246±18.3</td>
<td>244±15.2</td>
<td>0.646</td>
</tr>
<tr>
<td>Average Time to first epidural top up(mins)</td>
<td>264.83±34.08</td>
<td>398±69.55</td>
<td>0.0001</td>
</tr>
<tr>
<td>Average epidural top up consumption in 24 hrs</td>
<td>2.8±0.5</td>
<td>1.43±0.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Post-operatively, the average VAS score was higher in group I (highest 3.37±0.9 at 4th hour, p<0.0001) compared to group II (highest 2.8±1.3 at 6th hour, p=0.007) (Figure 1). Mean arterial pressure recorded at different time interval were comparable between the two groups (Figure 3).
Occurrence of adverse effects such as pruritus, nausea, vomiting, hypotension, bradycardia and headache were observed in both the groups. Pruritus was the most common side effect. Headache was least common, with one patient each in both the groups. None of the patients in the study groups suffered from respiratory depression, shivering and drowsiness (Figure 4).

**DISCUSSION**

The present study has evaluated the clinical efficacy and safety of adding magnesium sulphate to fentanyl in the lumbar epidural space and assessed its effects on the subarachnoid block in hip replacement procedures. The mean duration of sensory analgesia was prolonged as was evident by delayed regression of block when fentanyl was combined with magnesium sulphate in the epidural space. Moreover, this combination produced remarkable achievement in controlling postoperative pain as evident by fewer epidural top ups required in combined group. The hemodynamics were relatively stable in both the groups. Thus, magnesium sulphate can safely be administered during the combined spinal epidural anesthesia.

We used 50mg dose of magnesium sulphate which has been less than what Sonali Banwait et al, used in their study to evaluate the application of a single epidural bolus dose of magnesium (75mg) given postoperatively as an adjuvant to epidural fentanyl (1µg/kg) for postoperative analgesia in sixty patients undergoing total hip replacement surgery under CSE anaesthesia where 2.5mL of 0.5% hyperbaric bupivacaine intrathecally was given.14 The mean duration of analgesia after epidural drug administration was significantly longer for group FM (340±28.8 min) compared with group F (164±17.1

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**Figure 1: Average VAS score.**

**Figure 2: Frequency distribution of epidural top ups in two groups.**

**Figure 3: Mean arterial blood pressure.**

**Figure 4: Various adverse effects.**
min), while in present study the corresponding values were 398±69.55 min and 264.83±34.08 mins respectively. This difference could be attributable to much higher intrathecal dose used in our study.

Bilir et al, performed a randomised double blind study where he administered fentanyl in one group (Group F) in bolus dose of 25µg and magnesium sulphate 50 mg combined with same dose of fentanyl epidurally (Group FM).\(^{15}\) In group FM the initial epidural bolus dose was followed by continuous infusion of 100mg/day magnesium sulphate at a total volume of 24mL, for 24 hours. In this study hyperbaric bupivacaine 0.5% 1.5mL was injected intrathecally in both the groups. Pain assessment was done byVAS score at 30min, then at 1, 2, 4, 8, 12 and 24hours in the postoperative period. They found no significant difference in the sensori-motor block characteristics.

All the patients were connected to PCEA (patient controlled epidural analgesia) device with an initial setting of a demand bolus dose of 25µg fentanyl (5µg/mL) with no background infusion and a lockout interval of 20min with 4hour limit of 30mL (150µg fentanyl). In group F, patients received epidural saline at the rate of 1mL/h for 24hours with another infusion pump. Whereas in group FM, magnesium sulphate 50mg in 5ml volume as a bolus dose, was given which was followed by continuous epidural infusion of 100mg at a total 24mL volume for 24hour. The continuous epidural infusion of saline or magnesium was connected to epidural connector hub with a y-set. It was commenced in the recovery room while the block was still effective. Patients in group F were observed to have higher VAS scores at the outset of postoperative period but this difference in the groups were statistically significant only at first hour after surgery. After the first hour although the VAS scores were higher for the fentanyl group but the difference between the two groups was not statistically significant.

This insignificance could be due to the inclusion of Fentanyl-PCEA device in the postoperative period in their study; while in our study, VAS scores were significantly lower in combined group. One plausible explanation to this could be due to non-inclusion of Fentanyl-PCEA device in our study. Moreover, patients were randomised into two groups after the completion of surgery in Bilir’s study whereas in our study patients were randomised into two groups for the administration of study drugs through epidural catheter before the institution of subarachnoid block.

PV Shiva compared the sensory and motor block characteristics in fifty patients undergoing elective lower limb and abdominal surgeries. In this randomised comparative clinical study, spinal anaesthesia with 2.5cc of 0.5% hyperbaric bupivacaine was given.\(^{16}\) When the sensory block regressed to L1 level, patients were administered either 50µg of epidural fentanyl (Group F) or 50µg of epidural fentanyl plus 50mg of magnesium sulphate (Group FM). During the evaluation, it was found that time taken to achieve highest sensory level was comparable in both the groups. Also, the time for regression to L1 (118.8±13.41 min in group F and 119.6±17.85 min in group FM) was comparable. While in our study, the time to two-dermatome regression was slow in the combined fentanyl magnesium group (149.07±6.48min) as compared to fentanyl group (121.23±2.92 min) which was highly significant statistically. This difference between our study and that of PV Shiva can be explained by the fact that we administered the study drug, that is fentanyl and combined fentanyl and magnesium before the subarachnoid block. Whereas in the study of PV Shiva, the same dose of drug was administered only once the sensory level regressed to L1 level after the subarachnoid block.

Moreover, we diluted the study drug in 10ml distilled water whereas in that study, the study drug was diluted in 6ml of normal saline. The volume of hyperbaric bupivacaine given intrathecally in Shiva’s study was lower (2.5ml) compared to higher dose (3.5ml) in our study. This can contribute to much faster regression in Shiva’s study compared to our study. This can possibly explain for delayed regression of the sensory block observed in our study. The sensory block regressed to L1 level much faster in study done by PV Shiva.

Abir Hassan Aly Kandil et al, carried out a prospective randomized double blind study in 60 patients undergoing lower limb orthopedic surgery with the enrollment to receive either 0.5% bupivacaine or 0.5% bupivacaine plus magnesium sulphate 50mg as an initial dose followed by a continuous infusion of 10 mg/hr as epidural analgesia.\(^{17}\) After the completion of surgery, all patients were given 2µg/mL fentanyl and 0.03% bupivacaine using PCEA device. The PCEA was programmed to deliver 2.5mL/hr infusion with a bolus dose of 1.5ml on demand. The lockout interval between boluses was 6min. The PCEA bolus volume was titrated according to the analgesic effect or appearance of side effects. As regards the hemodynamics, there was no significant difference between the two groups. The findings of these studies match with the changes observed in the present study.

The mean blood pressure and the sedation scores were comparable between the two groups as observed in various studies such as that of Bilir, PV Shiva, Ramadan Shabana, Abir Kandil and Sonali Banwait.\(^{18}\) There were no reports of neurological complications associated with the use of magnesium in the present study. Occurrence of other side effects in our study were minor. The incidence of hypotension and bradycardia were reported higher for groups by Kandil et al, with incidence of hypotension 16.7% in the control group and 13.3% for the magnesium group could be due to use of
continuous infusion of epidural magnesium and use of epidural fentanyl in PCEA device.

CONCLUSION

It can be concluded that magnesium when co-administered with epidural fentanyl prolongs the duration of spinal analgesic effects of epidural fentanyl and subarachnoid block with no effects on ventilation or spinal cord. Magnesium as solitary dose combined with epidural fentanyl in CSE technique besides providing preemptive and preventive analgesia has analgesic sparing effect with pronounced reduction in the epidural top up consumption. It can be suggested that as an adjuvant, it is safe to administer magnesium to opioid analgesic in combined spinal epidural technique.

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Ethical approval: The study was approved by the Institutional Ethics Committee of Subharti university

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