ANALGESIC REQUIREMENTS FOR PATIENTS UNDERGOING LOWER EXTREMITY ORTHOPEDIC SURGERY

The Effect of Combined Spinal and Epidural Magnesium

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Abstract

Background: Polypharmacological approach is the most common practice to treat perioperative pain, as no single agent has yet been identified to specifically inhibit nociception without associated side effects[1]. Opioids such as Fentanyl is commonly added to local anesthetics to produce spinal and epidural anesthesia. However, significant adverse effects, such as pruritus, respiratory depression, hemodynamic instability and occasionally severe nausea and vomiting, may limit their use[3,4,5]. Our present study was designed to assess the effectiveness of using combined intrathecal and epidural magnesium (Mg) in reducing intra-and postoperative analgesic requirements and improving the quality of analgesia.

Method: Eighty patients ASA I, II, III who scheduled for lower extremity orthopedic surgery were included in the study. Patients were randomly allocated to one of two groups, 40 patients each. The Control Group: patients received intrathecal 10 mg of Bupivacaine 0.5% (2 ml), plus 25 µg of Fentanyl (0.5 ml), plus 0.9% NaCl solution (1 ml) and an epidural infusion of 0.9% NaCl at a rate of 5 ml/hr. The Magnesium Group: patients received intrathecal 10 mg of Bupivacaine 0.5% (2 ml), plus 25 µg of Fentanyl (0.5 ml), plus 50 mg of 5% Mg (1 ml) and an epidural infusion of 2% Mg at a rate of 100 mg/hr (5 ml/hr).

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Results: Intrathecal Mg prolonged fentanyl analgesia as indicated by increased duration of anesthesia in the Mg group, and thus improving the quality of spinal anesthesia. The effectiveness of the postoperative analgesia was confirmed by markedly lower perioperative analgesic requirements (38.3 % less than the Control group), the patient's low VAS score, the longer time for the patients first requirements of post-operative analgesia in the Mg group.

Conclusion: For lower extremity orthopedic procedure, supplementation of spinal anesthesia with combined intrathecally injected and epidurally infused Mg, considerably reduced the perioperative analgesic requirements without any side effects.

Key words: Intrathecal, epidural, magnesium, perioperative pain.

Introduction

Effective treatment of peri-and post-operative pain represents an important component of postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential decrease in perioperative morbidity. Polypharmacological approach is the most common practice to treat perioperative pain, as no single agent has yet been identified to specifically inhibit nociception without associated side effects[1].

Different techniques and drugs were studied in order to prolong the duration of regional anesthesia and achieve postoperative pain relief[2]. Opioids such as Fentanyl are commonly added to local anesthetics to produce spinal and epidural anesthesia. However, significant adverse effects such as, pruritus, urinary retention, respiratory depression, hemodynamic instability and occasionally severe nausea and vomiting, may limit their use[3,4,5]. Diverse classes of drugs such as epinephrine[7], clonidine[8], and neostigmine[9] have been added to intrathecal opioid in attempts to prolong analgesia and reduce the incidence of adverse events[10] observed when opioid are used.

Adding Magnesium, on the other hand, may improve the quality and increase the duration of spinal anesthesia[6]. Magnesium, which is the fourth most plentiful cation in the body, proved to have antinociceptive effects in animal and human model of pain[11,12]. Its effect is primarily based on the regulation of calcium influx into the cell, that is natural physiological calcium antagonism and antagonism of N-methyl-p-aspertate (NMDA) receptors[2]. This effect has promoted the investigation of magnesium as an adjuvant for perioperative analgesia. Studies concerning the different route of magnesium sulfate administration, may improve anesthetic and analgesia quality[13,14]. Whatever the route of administration, intravenous, intrathecal or epidural, the true site of action of magnesium is probably at the spinal cord NMDA receptors[15,16,17]. To obtain a meaningful and clinically effective action of Mg, direct intrathecal Mg injection will be a preferable route. This intrathecal route has been shown to be clinically safe in human[6,18] and its safety profile has been evaluated in several experimental settings, including histopathologic analysis[19,20]. Some clinical studies proved the effective analgesic property of Mg as an adjunct to intrathecal opioid analgesia[6,18]. Other clinical study proved that using epidural Mg reduce postoperative analgesic requirement[21].

The present report is a randomized study designed to assess the effectiveness of using combined intrathecal and epidural Mg in reducing intra-and postoperative analgesic requirements and improving the quality of analgesia in patients undergoing lower extremity surgery.

Patients and Methods

After procuring the informed patient consent, 80 patients ASA I, II III scheduled for lower extremity orthopedic surgery (either knee arthroscopy or scheduled for bone surgeries) were included in the study. Exclusion criteria included any significant coexisting disease, including hepatorenal, any contraindication to regional anesthesia, such as local infection or bleeding disorder, long term opioid use, a history of chronic pain, age younger than 18 years old, mentally unable to handle PCA, allergy to

any of the study medication, or preoperative blood Mg levels outside the normal range (1.6-2.6 mg/dl). During the preoperative assessment, all enrolled patients were informed about the study objectives and protocol, and were shown how to use a visual analogue scale (VAS) and the patient controlled epidural analgesia (PCEA) device.

Patients were randomly allocated to one of two groups, 40 patients each. Control Group: patients received intrathecal 10 mg of isobaric Bupivacaine 0.5% (2 ml), plus 25 µg of Fentanyl (0.5 ml), plus 0.9% NaCl solution (1 ml). Total intrathecally injected volume is 3 ml. Epidural infusion of 0.9% NaCl at a rate of 5 ml/hr. Magnesium Group: patients received intrathecal 10 mg of Bupivacaine 0.5% (2 ml), plus 25 µg of Fentanyl (0.5 ml), plus 50 mg of 5% Mg (1 ml). Total intrathecally injected volume is 3 ml. Epidural infusion of 2% Mg at a rate of 100 mg/hr (5 ml/hr). 5% Mg was prepared by taking 1 ml of 50% Mg and diluted to 10 ml of preservative free sterile water. 2% Mg was prepared by taking 1 ml of 50% Mg and diluted to 25 ml of preservative free sterile water.

All patients were equipped with a PCEA device and the initial settings of a demand bolus dose of Fentanyl 5 ml (5 µg/ml) with no background infusion, lockout interval 20 minutes, and 4 hr limit of 30 ml (150 µg Fentanyl). The continuous epidural infusion of either saline or Mg was connected to epidural catheter hub with a y-set. After establishing an i.v. access, a preload of 500 ml of 0.9% sodium chloride was given. All patients had a combined spinal-epidural anesthesia through a Portex Combined Spinal/Epidural Minipack with lock Pencil point Needle (Portex, Hythe, Kent, UK). The epidural space was identified at L3-L4 or L4-L5 using a loss of resistance technique.

A 26 G pencil point spinal needle was placed through the Tuohy needle into the subarachnoid space, until it returns clear CFS. After intrathecal injection, the spinal needle was withdrawn, and a single-orifice epidural catheter was inserted cranially, 4-6 cm into the epidural space and then secured. The catheter was then connected to infusion pump (Grasby, 3200) that was disconnected after 24 hours. Surgery Started at least 20 minutes after the intrathecal injection. During surgery, sensory and motor block,

mean blood pressure (MBP), Heart rate (HR), respiratory rate (RR), and oxygen saturation (SPO_2), were recorded every 5 minutes.

Hypotension was defined as 30% decrease of the baseline. Hypotension was treated with i.v. fluid bolus of 500 ml of lactated ringer's solution followed by i.v. ephedrine if required. Tachycardia was defined as HR >100 beats/min and bradycardia was defined as <50 beats/min.

Onset, duration and the highest level of sensory and motor block were recorded. The onset of sensory block was defined as the time between injection of IT anesthetic and absence of pain, assessed by pinprick. Motor block was assessed by the modified Bromage scale (0, no motor loss; 1 inability to flex the hip; 2, inability to flex the knee; 3, inability to flex the ankle). The highest level of sensory and motor block was evaluated every 5 minutes for 20 minutes after injection.

Pain score using the VAS from 0 to 10 (0, no pain at all; 10, maximum imaginable, pain) was recorded 5 minutes before intrathecal injection, after the start of surgery and subsequently every 15 minutes until surgery was complete, then at 4-h intervals for 24 hours. A resting pain of ≤3 was considered satisfactory pain relief. If the VAS exceeded 3, Fentanyl bolus was given intravenously to relieve pain. Number of patients with intraoperative inadequate analgesia that required supplementary rescue analgesia were recorded.

Patients' first requirement for postoperative epidural analgesia was recorded. That was defined as the time from the completion of surgery until the time of first use of rescue medication by PCEA. Total Fentanyl consumption administered via the PCEA was recorded throughout the 24-h study period. Sedation was assessed on a four-point scale[22]; 0: awake and alert, 1: mildly sedated, aroused by shaking, 3: deeply sedated, difficult to be aroused by physical stimulation.

Patients were evaluated for the side effects related to epidural drugs (drowsiness, respiratory depression, nausea, vomiting). Adverse events related with the drugs and epidural catheter was recorded throughout surgery and 24 hours after.

Statistical Analysis

The data are expressed as mean and standard deviation. Paired and unpaired Student t-test was used for each parameter for within and between group comparisons. Differences in hemodynamics within each group are analyzed using repeated measure ANOVA with Dunnet test for post-hoc analysis. Visual Analogue Score, Sedation Score, and incidence of side effects were analyzed using the Chi Square test. All statistical analysis was done using Excel and SPSS package.

Results

Demographic Data

There were no significant intergroup differences in patients' ages, weight, height, type or duration of surgery (Table 1).

Table 1
Demographic data (mean ± SD)

	Control Group	Magnesium Group
Age (years)	51.3 ± 17.6	52.2 ± 20.8
Sex (female/male)	19/21	18/22
Weight (Kg)	69.4 ± 11.9	70.9 ± 8.8
Height (cm)	163.4 ± 11.2	164.5 ± 7.9
Type of surgery (arthroscopic/bone)	18/22	23/17
Duration of surgery (min)	114.9 ± 45.7	117.1 ± 33.4

Cardio-respiratory variables

The mean blood pressure and the mean heart rate were significantly lower 5 minutes after the intrathecal injection of drugs in both groups, but there were no significant difference between the two groups (Table 2). There were no difference between groups as regard to SPO_2 and respiratory rate $P>0.05$.

Table 2

Hemodynamic data (mean ± SD)

Time	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Mean Blood Pressure (MBP)										
● Control Group	85 ± 14*	70 ± 10	72 ± 18	73 ± 11	69 ± 15	74 ± 11	70 ± 7	71 ± 9	71 ± 13	75 ± 8
● Mg Group	84 ± 12*	68 ± 13	72 ± 7	70 ± 9	70 ± 8	71 ± 14	68 ± 12	70 ± 8	71 ± 11	71 ± 12
Mean Heart Rate (MHR)										
● Control Group	92 ± 9*	84 ± 13	83 ± 12	80 ± 10	83 ± 9	84 ± 14	83 ± 11	83 ± 9	83 ± 10	82 ± 15
● Mg Group	92 ± 15*	81 ± 11	82 ± 10	82 ± 15	81 ± 16	81 ± 16	82 ± 9	83 ± 9	80 ± 17	80 ± 7

T1 = baseline value, T2, T3, T4, T5 = 5, 10, 15, 20 min after intrathecal injection of drugs, and T6, T7, T8, T9, T10 = 2, 4, 8, 12, 24 hours post-operatively.

* Significant difference from baseline value within group ($P<0.05$).

Characteristics of spinal block

The onset and time to reach highest level of sensory and motor blocks were significantly delayed in the Mg group compared to Control, $P<0.05$. Duration of spinal anesthesia was defined as the period from spinal injection to the first occasion when the patient complains of pain in the post-operative period (Table 3). Duration of anesthesia was statistically significant longer in the Mg group compared to Control, $P<0.05$.

Table 3

Characteristics of the axial block (Mean ± SD)

	Control Group	Magnesium Group
Sensory Block		
● Onset	12.5 ± 3	16 ± 3.3*
● Duration	90 ± 9.6*	100.8 ± 10.9
● Time to reach highest level of sensory block (min)	13.1 ± 2.5	16.8 ± 2.7*
Motor Block		
● Onset	7.2 ± 1.6	9.5 ± 2.7*
● Time to reach highest level of motor block (min)	14.6 ± 3.3	18.4 ± 3*
● Complete recovery of motor block (min)	144.3 ± 15.9	146.8 ± 14.4
Duration of spinal anesthesia (min)	164.4 ± 16.9	182.8 ± 19.1*

* Significant difference between the two groups.

Analgesia

None of the patients in both groups required supplemental analgesia intraoperatively. Time to first analgesic requirement time was significantly longer in the Mg group compared to the Control group, 79 vs. 43.85 min.

There was significantly less total epidurally infused Fentanyl consumption in the Mg group compared to the Control group in 24 hours, 252 vs. 409 μg.

Sedation and pain Score

Visual Analogue Scale (VAS): Patients were assessed for VAS at T1 (baseline), T2 (after the start of surgery) and subsequently T3, T4, T5, T6 (every 30 minutes until surgery was complete), T7-T10 (4-h intervals for 24) (Table 4). Although VAS was lower ion the Mg group but not statistically significant difference between the two groups P>0.05.

Table 4

VAS in the two groups

Time	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Control Group	2(1-4)	0(0-6)	0(0-4)	0(0-4)	0(0-6)	0(0-7)	2(0-9)	4(0-8)	4(0-9)	3(0-9)
Mg Group	3(1-4)	0(0-5)	0(0-6)	0(0-6)	0(0-4)	0(0-6)	1(0-6)	3(0-8)	4(0-7)	2(0-8)

Data are Median (range).

Sedation Score: Patients were assessed for Sedation Score at T1 (baseline), T2 (after the start of surgery) and subsequently T3, T4, T5, T6 (every 30 minutes until surgery was complete), T7-T10 (4-h intervals for 24) (Table 5). The two groups were comparable with no statistically significant difference between them P>0.05.

Table 5

Sedation score between groups

Time	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Control Group	0(0-1)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-1)	1(1-1)
Mg Group	1(0-1)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-1)	1(1-1)	1(1-1)

Data are Median (range).

Adverse Effects

There were statistically significant lower incidence of PONV and prutitus in the Mg group compared to Control (P<0.05). None of patients in both groups suffered from respiratory depression or drowsiness (Table 6).

Table 6

Number of side effects in the two groups

	Control Group	Mg Group
PONV	9(22.5)	4(105)*
Respiratory Depression	0%	0%
Drowsiness	0%	0%
Prutritus	25(62.5%)	15(37.5%)*

* Significant difference between the two groups.

Discussion

In this prospective, randomized, controlled trial, evidence was provided that patients receiving combined spinal-epidural anesthesia for lower extremity orthopedic operations, adjuncts of intrathecal (50 mg) and epidural (100 mg/hr) magnesium sulphate reduced peri-operative analgesic requirements relative to patients receiving combined spina-epidural anesthesia alone.

The use of large doses of opioid may increase the incidence of side effects, especially in elderly patients. The aim of intra-and post-operative analgesic management must be to provide adequate analgesia without side effects. The co-administration of opioid with drugs that would reduce analgesic consumption will be beneficial for intra-and post-operative pain management[21]. 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[11,23].

Mg, which is NMDA receptor antagonist, and a physiological calcium channel blocker, has analgesic properties in acute and chronic pain conditions. These effects encouraged the co-administration of Mg as an

adjuvant agent to reduce intra-and post-operative analgesic requirements[13]. Intrathecal and epidural Mg can provide a low-cost, simple change in clinical anesthesiology practice, leading to significant decrease in patient's peri-operative analgesic needs.

There were no significant differences in the hemodynamics (MBP, HR, RR, and SPO_2) between the two groups in the doses used indicating minimal or no serious side effects on the patients by using either technique $P>0.05$.

Intrathecal Mg prolonged fentanyl analgesia as indicated by the increased duration of anesthesia in the Mg group, and thus improving the quality of spinal anesthesia. This finding was comparable with others[18,6] that demonstrated that intrathecal Mg prolongs the duration of spinal opioid analgesia in human. One major finding in this study was that the group treated with combined intrathecally and epidurally infused Mg had markedly lower peri-operative analgesic requirements (38.3% less than the Control group).

The significant decrease in Fentanyl use obtained in this trial is comparable with other studies[21,6] that proved that intrathecal and epidural Mg prolong fentanyl analgesia and reduce postoperative analgesic requirement.

The effectiveness of the postoperative analgesia was further confirmed by the patient's low VAS score, longer time for the patient's first requirements of post-operative analgesia, and the comparable sedation score in the Mg group compared to the control group.

This finding is different from some studies[15,25] which suggests that Mg is not that effective in anesthesia. Their finding can be explained by the different route of Mg administration (intravenous) they used, which may lead us to the fact that the true site of action of Mg is spinal cord NMDA receptors[16,17,18].

The safety of intrathecal and epidural Mg administration has been evaluated in animal[11,12] and human[21,18] studies that concluded that Mg seems to have a good safety profile with no serious side effects. This is

comparable to our study where there were no side effects related to the drug used and even less side effects caused by less fentanyl used e.g. less PONV and less prutitus in the Mg group compared to the control group.

The dose of Mg used intrathecally was based on data from another study[18] that found that 50 mg Mg potentiate fentanyl analgesia without increasing the side effect. While the epidural dose of Mg was driven from human study[24] that found that 100 mg/hr reduced postoperative analgesic requirement of morphine without side effects.

Conclusion

For lower extremity orthopedic procedure, supplementation of spinal anesthesia with combined intrathecally injected and epidurally infused Mg, considerably reduced the perioperative analgesic requirements without any side effects.

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