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The Analgesic Effect of Single Dose of Intrathecal Magnesium Sulfate

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Background: Intrathecal (IT) magnesium has antinociceptive effects on animals and has been reported to prolong spinal opioid analgesia in humans. This study examined the effect of IT magnesium on spinal anesthesia and postoperative epidural analgesia.

Methods: Sixty patients undergoing total knee replacement were enrolled in this study. Before the IT injection of 0.5% isobaric tetracaine (10 mg), group C and group M received 0.9% saline or 50% magnesium sulfate 0.1 ml, respectively. The epidural solution for postoperative analgesia contained 0.2% ropivacaine (100 ml) only in group M, and 0.2% ropivacaine plus morphine (50μg/ml) in group C. The verbal rating scale (VRS) scores for pain, sensory block level, intensity of motor block and side effects were recorded at 5, 60, and 120 minutes after the IT injection and at 1, 12 and 36 hours after surgery in the post-anesthesia care unit (PACU).

Results: The VRS score at 120 minutes after the IT injection were lower in group M than in group C ($P < 0.05$). There were no differences in the VRS scores and the use of supplemental analgesics at the postoperative period. The incidence of PONV, pruritus and urinary retention was significantly lower in group M than in group C at 12 and 36 hours after surgery.

Conclusions: IT magnesium can be used as a local anesthetic adjuvant to strengthen the analgesic effect of spinal local anesthesia and to intensify the analgesic effect of epidural local anesthesia for postoperative pain control to the extent of 5 mg epidural morphine. **(Korean J Anesthesiol 2007; 52: S 72～6)**

Key Words: epidural opioid, intrathecal magnesium, local anesthetic.

INTRODUCTION

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation. It has numerous physiological activities including activation of enzymes involved in energy metabolism, protein synthesis, regulation of vasomotor tone, neurotransmission and signaling.[1,2] Magnesium sulfate ($MgSO_4$) has been used as a pharmacological agent in a variety of clinical situations such as tachyarrythmia, myocardial and neuronal ischemia, asthma, and seizures in preeclampsia.[3] Magnesium also has antinociceptive effects in animal and human pain models.[3-5] These effects are primarily based on the regulation of calcium influx into the cell, natural physiologic calcium antagonism,[2] and antagonism of the N-methyl-D-aspartate (NMDA) receptor.[6]

Although some clinical reports[3,4] have demonstrated antinociceptive effects of systemically administered $MgSO_4$, results are not consistent.[7,8] There are considerable evidences that intrathecally administered magnesium has antinociceptive effects in animals.[5,9,10] In addition, the safety profile has been evaluated, including histopathological analysis.[11] In the first randomized human study of intrathecal (IT) magnesium as an antinociceptive modulator, the addition of IT magnesium, acting as a noncompetitive NMDA antagonist, has shown prolongation of the analgesic effect of opioids in spinal analgesia.[12] Magnesium has also been shown to potentiate the analgesic effect of bupivacaine when co-administered intrathecally in rats.[13] However, no clinical study has examined the effect of IT $MgSO_4$ with local anesthetics in humans.

We therefore conducted a prospective, randomized, controlled clinical trial to investigate the effect of intrathecally co-admin-

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istered magnesium and local anesthetics on the intensity, block level, and duration of spinal anesthesia, and the epidural local anesthetics intensifying effect of IT magnesium on postoperative epidural analgesia in patients undergoing total knee replacement (TKR).

MATERIALS AND METHODS

The hospital ethics committee approved this study and informed consent was obtained from all patients. Sixty patients with ASA physical status 1 and 2 undergoing elective TKR were included. All combined spinal-epidural (CSE) procedures were done by the same experienced anesthesiologist. All patients underwent TKR by the same surgeon.

Patient characteristics and duration of surgery were comparable between the groups (Table 1).

Patients were excluded from participation for any contraindication to regional anesthesia, a history of opioid medication or magnesium treatment, allergy to morphine, magnesium and local anesthetics, or significant coexisting diseases (hepatic, renal or cardiovascular diseases). Patients were randomized using a sealed envelope system to receive IT $MgSO_4$ or IT placebo. Each group contained 30 patients. Before surgery, patients were instructed on the use of the patient controlled epidural analgesia (PCEA) device and the VRS (verbal rating scale) for pain assessment.

Patients received 500-1,000 ml of intravenous balanced salt solution and were placed in left lateral position for a CSE procedure. An 18-gauge Tuohy needle, 8.89 cm (Portex, New Hampshire, USA) was introduced via a midline approach into the L3-4 vertebral level epidural space using loss of resistance technique. A 27-gauge, 11.9 cm Whitacre tip spinal needle was placed through the Tuohy needle, and subarachnoid placement was confirmed by free flow of cerebrospinal fluid.

Table 1. Patient Characteristics and Duration of Surgery

	Group C (n = 30)	Group M (n = 30)
Sex (M/F)	2/28	1/29
Age (yr)	66.2 ± 5.7	67.8 ± 7.3
Height (cm)	154.9 ± 6.8	153.9 ± 4.9
Weight (kg)	64.3 ± 8.0	58.4 ± 10.0
Duration of surgery (min)	78.5 ± 18.5	76.9 ± 21.0

Values are mean ± SD except sex, which are number of patients. Group C: patients receive 0.5% isobaric tetracaine (10 mg) with 0.9% saline (0.1 ml) intrathecally and then patient controlled epidural analgesia (PCEA) with 0.2% ropivacaine plus morphine (50μg/ml) for postoperative analgesia, Group M: patients receive 0.5% isobaric tetracaine (10 mg) with 50% magnesium sulfate (0.1 ml, 50 mg) intrathecally and then PCEA with 0.2% ropivacaine only for postoperative analgesia.

Patients and anesthesia providers were blinded to the treatment group and an independent researcher prepared the first study solution containing 0.1 ml of 0.9% saline for group C or preservative free-50% magnesium sulfate (50 mg, Masi 50%®, Huons, Seoul, Korea) for group M. Prior to IT injection of 2 ml (10 mg) 0.5% isobaric tetracaine (Pantocainsterile®, Daihan Pharm., Seoul, Korea), first study solution was given. The spinal needle was removed and a 20-gauge, closed end, multiport catheter was inserted 4-5 cm cephalad within the epidural space, and the patient was placed in supine position. Electrocardiogram and arterial oxygen saturation were monitored continuously and the non-invasive blood pressure was recorded every 5 minutes until the end of the surgical procedure, and then every 10 minutes until recovery. Intravenous crystalloids, or colloids, and small doses of ephedrine were used to maintain mean arterial pressure within 20% of baseline. If the patient complained of pain during surgery, a 5-7 ml bolus of supplemental 2% lidocaine was administered via the epidural catheter.

Scores for pain, upper level of loss of cold sensation, intensity of motor block, and somnolence were recorded at 5, 60, and 120 minutes after the IT injection. Pain level was assessed by VRS scores scaled from 0 to 10 (0 = no pain, 10 = the worst pain imagined). The upper level of loss of cold sensation was assessed at the midclavicular line using an alcohol swab bilaterally. The intensity of motor block was graded as 0 (none) = full flexion of knees and feet; 1 (partial) = just able to move knees; 2 (almost complete) = able to move feet only; and 3 (complete) = unable to move feet or knees. Somnolence was categorized as 1 = fully awake; 2 = somnolent and responds to call; 3 = somnolent and no response to verbal stimulation; and 4 = asleep and responds to only painful stimulation.[12]

In the postanesthesia care unit (PACU) epidural analgesia was started using the PCEA technique with silicone balloon infuser (Accufuser Plus®, Woo Young Med., Paju, Korea) containing the second study solution made by the researcher who prepared the first study solution, after parameters 120 minutes post-IT injection were checked. The second study solution

Table 2. Pain Scores, Upper Sensory Level, Intensity of Motor Block and Somnolence Score

	Elapsed time from spinal anesthesia	Group C (n = 30)	Group M (n = 30)
VRS	5 min	0	0
	60 min	0	0
	120 min	1.7 ± 2.9	0*
Upper sensory level	5 min	T7 (T3-12)	T8 (T4-L1)
	60 min	T6 (T3-12)	T6 (T3-12)
	120 min	T6 (T4-12)	T6 (T3-12)
Motor block	5 min	2.7 ± 0.6	2.5 ± 0.6
	60 min	3.0 ± 0.0	2.9 ± 0.4
	120 min	3.0 ± 0.0	3.0 ± 0.0
Somnolence score	5 min	1.0 ± 0.2	1.0 ± 0.2
	60 min	1.3 ± 0.5	1.4 ± 0.6
	120 min	1.0 ± 0.0	1.1 ± 0.4

Values are mean ± SD, except for upper sensory level, which are median (range). VRS: verbal rating scale, Group C: patients receive 0.5% isobaric tetracaine (10 mg) with 0.9% saline (0.1 ml) intrathecally and then patient controlled epidural analgesia (PCEA) with 0.2% ropivacaine plus morphine (50μg/ml) for postoperative analgesia, Group M: patients receive 0.5% isobaric tetracaine (10 mg) with 50% magnesium sulfate (0.1 ml, 50 mg) intrathecally and then PCEA with 0.2% ropivacaine only for postoperative analgesia. *P < 0.05 compared with group C.

consisted of 0.2% ropivacaine mixed, with morphine sulfate 5 mg (50μg/ml) in group C and 0.5 ml normal saline in group M. Balloon pump infuser setting included 2 ml/hr for continuous infusion and 0.5 ml for bolus dose with a 15 minutes lockout period for postoperative 36 hours. Patients with VRS score higher than 5 were given meperidine 25 mg intramuscular (IM) as rescue analgesia. Each patient was interviewed at 1 hour after arrival on PACU, at 12, and 36 hours post-operation by an investigator blinded to patient group. Pain intensity at rest and on the operated leg movement by VRS scores, the occurrence of postoperative nausea and vomiting (PONV), pruritus, urinary retention and somnolence were assessed. The presence of motor or sensory complications was assessed 6 weeks after TKR as a routine postoperative evaluation by the surgeon who was blind to the study group.

Preliminary study indicated that with 30 patients per group, the study would have a 90% chance (β = 0.9) of detecting a difference, at a 5% level of significance, of at least 1.6 VRS score at 120 minutes after IT injection.

Statistical analysis was performed using the statistical package for social sciences statistical software (SPSS 10.0, USA). Demographic data were compared using the unpaired t-test. The VRS score, sensory level, motor score and somnolence score were analyzed using the Mann-Whitney U-test. The incidence of post-operative adverse events was analyzed using Fisher's exact test. Results are expressed as mean ± SD, median (range) or number of patients. A P value of less than 0.05 was considered statistically significant.

Table 3. Pain Scores and Number of Rescue Analgesia in Postoperative Period

	Postoperative period	Group C (n = 30)	Group M (n = 30)
VRS_R	at PACU	0.1 ± 0.7	0.1 ± 0.6
	12 hr	5.0 ± 3.4	3.7 ± 3.0
	36 hr	4.1 ± 2.4	4.3 ± 2.5
VRS_M	12 hr	6.0 ± 3.0	6.5 ± 2.4
	36 hr	7.2 ± 2.4	6.9 ± 2.1
No. of rescue analgesia per each patient	at PACU	0.7 ± 0.6	0.9 ± 0.8
	12 hr	0.5 ± 0.8	0.4 ± 0.6
	36 hr	0.4 ± 0.7	0.2 ± 0.5

Values are mean ± SD. VRS_R: verbal rating scale at rest, PACU: postanesthesia care unit, VRSM: verbal rating scale on movement, No. of rescue analgesia; frequency of rescue analgesia (25 mg meperidine, IM). Group C: patients receive 0.5% isobaric tetracaine (10 mg) with 0.9% saline (0.1 ml) intrathecally and then patient controlled epidural analgesia (PCEA) with 0.2% ropivacaine plus morphine (50μg/ml) for postoperative analgesia, Group M: patients receive 0.5% isobaric tetracaine (10 mg) with 50% magnesium sulfate (0.1 ml, 50 mg) intrathecally and then PCEA with 0.2% ropivacaine only for postoperative analgesia.

RESULTS

The VRS scores at 120 minutes after IT injection were significantly lower in group M than group C (P < 0.05)(Table 2). All group M patients reported lasting analgesic effects up to 120 minutes after IT injection. Intraoperative supplemental 2% lidocaine was requested via the epidural catheter in only one patient of group C.

There were no differences in the VRS scores at rest and on movement and in supplemental analgesic use between two groups at PACU, 12, and 36 hours post-operation (Table 3). The infuser became empty, which took average time of 43.4 ± 6.3 hrs in group M and 43.3 ± 5.4 hrs in group C. There was no significant difference between the two groups.

Table 4. Postoperative Side Effects

	Postoperative period	Group C (n = 30)	Group M (n = 30)
Nausea (%)	at PACU	3.3	6.7
	12 hr	60.0	16.7*
	36 hr	40.0	10.0*
Vomiting (%)	at PACU	0	0
	12 hr	40.0	10.0*
	36 hr	10.0	0*
Pruritus (%)	at PACU	0	0
	12 hr	66.7	10.0*
	36 hr	33.1	16.7*
Urinary retention (%)	at PACU	0	0
	12 hr	16.7	6.7*
	36 hr	13.3	0*
Somnolence (%)	at PACU	3.3	3.3
	12 hr	0	0
	36 hr	3.3	0

Values are the percentage of patients. PACU: postanesthesia care unit. Group C: patients receive 0.5% isobaric tetracaine (10 mg) with 0.9% saline (0.1 ml) intrathecally and then patient controlled epidural analgesia (PCEA) with 0.2% ropivacaine plus morphine (50μg/ml) for postoperative analgesia, Group M: patients receive 0.5% isobaric tetracaine (10 mg) with 50% magnesium sulfate (0.1 ml, 50 mg) intrathecally and then PCEA with 0.2% ropivacaine only for postoperative analgesia. *P $<$ 0.05 compared with group C.

At 12 and 36 hours post-operation, PONV, pruritus and urinary retention incidence was significantly lower in group M than group C (P $<$ 0.05)(Table 4). There was no significant difference between two groups in incidence of somnolence during the whole study period.

No patient in either group had any sensory or motor complication on routine postoperative evaluation 6 weeks after TKR.

DISCUSSION

This study demonstrated that 50 mg of IT magnesium, as a noncompetitive NMDA antagonist, improved spinal analgesic effect of local anesthetic up to 2 hours. Even though group M PCEA solution contained only local anesthetic agent whereas group C PCEA solution was added morphine, there was no difference in the intensity of postoperative epidural analgesia between the two groups.

At doses used in this study, intrathecally administered $MgSO_4$ has been reported to prolong the duration of spinal opioid analgesia without increasing adverse events in parturiants.[12] In this previous human study, the dose of magnesium was based on data from a rat model of postoperative pain in which morphine antinociception was potentiated with 188μg of IT magnesium.[10] Based on the relative differences in CSF volume and body weight between human and rat, the 188μg was conservatively extrapolated to 50 mg. In rats, repeated IT injections of 9.2 mg/kg iso-osmolar $MgSO_4$ produced transient motor and sensory block similar to that of 2% lidocaine with complete recovery and benign clinical consequences.[11] In a canine study, 3 mg/kg (45-60 mg) IT $MgSO_4$ before thoracic aortic cross-clamping did not produce neurological deficit or spinal cord abnormalities whereas adverse neurological outcome and an ischemic-injury pattern on histopathological examination were seen in control group.[14] If the 45-60 mg IT magnesium dose which is protective of the spinal cord in dogs were extrapolated by comparing the relative CSF volumes (approximately 12 ml versus 120 ml), this represent a 450-650 mg dose in human. Comparatively, the dosage of IT magnesium used in this study is 10% of a dose shown to be nontoxic in dogs. Lejuste[15] described the inadvertent IT injection of 1,000 mg of magnesium, producing a dense motor block followed by complete resolution within 90 minutes, with no neurological deficit at long-term follow-up.

Other various intrathecal adjuvants such as NMDA antagonists, clonidine, and neostigmine have been assessed as possibilities for improved pain relief without side effects.[16-18] Of these, magnesium, as calcium antagonist and NMDA receptor blocker, has also the promising antinociceptive effects.[2,6]

In the previous clinical studies, the perioperative intravenous (IV) administration of $MgSO_4$ has shown the equivocal results. Some clinical studies have demonstrated antinociceptive effects for systemically administered $MgSO_4$ on the assumption that magnesium acts on NMDA receptors located in the spinal cord.[3,4] Whereas, no decrease in postoperative analgesic consumption was observed in a randomized clinical trial using IV magnesium (bolus and infusion). IV magnesium for modulation of antinociception via NMDA channel antagonism is insufficient blood-brain barrier penetration to achieve effective CSF concentration.[8,19] Considering these factors, recent studies have focused on the antinociceptive effect of IT magnesium.[9,10,12]

According to the human study of IT magnesium, conducted in labor analgesia, the median analgesic duration of 25μg fentanyl was 60 minutes, which was prolonged to 75 minutes with

addition of 50 mg IT magnesium.[12] Perioperative application of IV magnesium has been reported to reduce morphine consumption during the first 48 hours after surgery in patients undergoing abdominal hysterectomy with general anesthesia.[3] According to the results of this study, IT magnesium performed more dense sensory block up to 120 minutes. There were no differences in the VAS scores and additional acquired analgesics between group M and group C for the whole study period. Initially, the control group was designed to receive only local anesthetics via PCEA and IT normal saline prior to 0.5% tetracaine of spinal anesthesia. However, VAS at resting on postoperative 12 hr was 7.9 ± 0.9 in control group, in contrast with 3.7 ± 3.0 in group M. In addition, 4 of 6 in control group refused the epidural solution. Because of this intractable pain, we discarded the initially designed control group. After then, morphine was added to PCEA (group C). We could not differentiate whether these results were induced by either prolongation of spinal local anesthetics or some preemptive analgesic effect due to IT magnesium as an NMDA receptor antagonist. However, we obviously demonstrated that single IT magnesium might be as effective as postoperative epidural morphine 5 mg during the whole study period.

This study is limited by the use of a long acting spinal anesthetic, so it may have overshadowed any true analgesic benefits of IT magnesium. To evaluate the effect of IT magnesium as adjuvants of spinal local anesthetics, it would have been helpful to test patients until complete regression of spinal anesthetic with the more frequent interval.

In conclusion, IT magnesium co-administered with local anesthetics, both strengthened the analgesic effects of the intraoperative spinal local anesthetics, and postoperative epidural analgesia. IT magnesium might be considered as a local anesthetic adjuvant and to intensify postoperative epidural local anesthetics.

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