J Anesth (2009) 23:508–512
DOI 10.1007/s00540-009-0822-8

Journal of
Anesthesia

A comparison of intra-articular magnesium and/or morphine with bupivacaine for postoperative analgesia after arthroscopic knee surgery

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Abstract
Purpose. Both magnesium and morphine provide enhanced patient analgesia after arthroscopic knee surgery when administered separately via the intra-articular route. Magnesium sulfate amplifies the analgesic effect of morphine. This study was designed to compare the analgesic effects of intra-articular magnesium and morphine, with bupivacaine, when used separately and in combination.
Methods. Eighty patients undergoing arthroscopic menisectomy were randomized blindly into four intra-articular groups: group B+Mor+Mg received 20 ml 0.25% bupivacaine, morphine 2 mg, and magnesium 150 mg; group B+Mor received 20 ml 0.25% bupivacaine and morphine 2 mg; group B+Mg received 20 ml 0.25% bupivacaine and magnesium 150 mg; and group B received 20 ml 0.25% bupivacaine. Pain scores at rest and during movement, analgesic duration, and total analgesic consumption were recorded.
Results. Group B+Mor and group B+Mg patients had equally effective postoperative analgesia. Group B+Mor+Mg patients had significantly reduced visual analogue scale (VAS) values both at rest and during movement and significantly increased time to first postoperative analgesic request, as well as significantly reduced total analgesic consumption, compared with the other groups.
Conclusion. Intra-articular administration of magnesium sulfate or morphine, with bupivacaine, had comparable analgesic effects in the doses used. Their combination provided more effective postoperative analgesia than either drug alone.

Key words Analgesia · Postoperative · Analgesic technique · Intra-articular · Pharmacology · Magnesium sulfate · Morphine

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Received: April 15, 2009 / Accepted: July 13, 2009

Introduction

Knee arthroscopy is a very common procedure. Many different methods have been used in efforts to provide adequate analgesia after surgery [1–3]. Intra-articular (IA) bupivacaine provides enhanced postoperative analgesia after arthroscopic knee surgery [4,5]. Morphine has been combined with bupivacaine to augment analgesia [6]. More recently, magnesium sulfate has been shown to provide analgesia when administered into the knee joint after arthroscopy [7]. Magnesium sulfate amplifies the analgesic effect of morphine in different experimental models of pain [8]. No clinical studies have examined the analgesic effect of magnesium sulfate and morphine in combination when administered intra-articularly. We hypothesized that the combination of IA magnesium sulfate and morphine would provide more significant analgesia than either drug alone.

Therefore, this double-blind, prospective, randomized study was conducted to compare the analgesic effects of IA magnesium sulfate and morphine, with bupivacaine, when used alone and in combination, after arthroscopic meniscectomy.

Patients, materials, and methods

After obtaining local Ethics Committee approval and written informed consent for the study, 80 patients were scheduled to undergo elective arthroscopic meniscectomy of the knee by a single surgeon. Patients were eligible for participation if they were older than 18 years, and were American Society of Anesthesiology (ASA) physical status I or II. The exclusion criteria included daily intake of nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids, relevant drug allergy, and the need for postoperative intra-articular drainage. Before the operation all patients received instructions for using

a 10-cm visual analogue scale (VAS) with 0 = no pain, to 10 = the worst imaginable pain.

Patients received general anesthesia, in adherence with the study protocol. No premedication was given. After the placement of routine monitors, anesthesia was induced with 2 μg·kg^{-1} IV fentanyl, 2 mg·kg^{-1} IV propofol, and maintained with 60% N_20 in O_2 and 1% to 2% inspired isoflurane. Patients breathed spontaneously via a laryngeal mask airway for the duration of the procedure. No other supplementary analgesic medication was given during the operation after the first dose of fentanyl. Before surgical incision, a pneumatic tourniquet at a pressure of 300 mmHg was applied to all patients. At the end of the operation, patients were assigned, in equal numbers, to one of four treatment groups in a double-blinded, randomized manner; group B+Mor+Mg received 20 ml 0.25% bupivacaine, morphine 2 mg, and magnesium 150 mg (MgSO4; 10% solution); group B+Mor received 20 ml 0.25% bupivacaine and morphine 2 mg; group B+Mg received 20 ml 0.25% bupivacaine and magnesium 150 mg (MgSO4; 10% solution); and group B received 20 ml 0.25% bupivacaine. The study solution, supplied in a coded syringe, was injected into the knee joint through the arhroscope at the end of the surgery, 10 min before the tourniquet release.

Pain scores both at rest and during movement (active flexion of the knee) were recorded by a blinded observer in the post-anesthesia care unit (PACU) at 1 and 2 h after injection of the study drug. Patients received IV fentanyl (25 μg every 5 min as needed) in the PACU if they experienced pain.

On discharge from the hospital, patients were instructed to take one Solpadine tablet (500 mg paracetamol, 30 mg caffeine, and 8 mg codeine; Glaxo SmithKline, Brentford, UK) every 3 h if they required an analgesic. Patients were given a data sheet and were asked to record the first time they required additional analgesia (oral analgesics) and the total analgesic requirement during the initial 24 h after surgery, and they were also asked to rate their VAS pain scores at rest and during movement 24 h after surgery. Analgesic duration was considered as the time from IA injection of the study drug to the first requirement for supplemental analgesics. Patients were contacted by telephone the day following surgery for an interview, to evaluate postoperative pain and analgesic requirements. Patients were also monitored for arterial pressure, heart rate, and sedation; side effects (nausea, vomiting, or pruritus) were also recorded.

Patients were discharged when they were oriented to time and place, were able to void, had stable vital signs, and could ambulate with the assistance of crutches. Discharge time was classified as the time from the end of surgery until the patients met the discharge criteria.

Statistical analysis

An SPSS (SPSS, Chicago, IL, USA) statistical software package was used for data analysis. Descriptive statistics included means and SD for quantitative measures, while *n* was used for categorical measures. Analysis of variance (ANOVA) was used to compare pain scores in the four different groups, and the least significant difference method was used for the pairwise comparison of means at each time. The time to first analgesic dose and the 24-h analgesic requirement were analyzed using one-way ANOVA. Post-hoc comparisons were made using the Tukey test. We used χ^2 analysis for the comparison of categorical data. A P value below 0.05 was considered significant. The following assumptions were made for the power analysis performed prior to the investigation: (i) for the pain scores, a 50% difference in pain scores; (ii) for the analgesic consumption, a difference of two tablets per 24 h; and (iii) for the time to first analgesic, a difference of 3 h. With these assumptions, a power of 90%, and using an alpha of 0.05/6 (because there were six possible comparisons among the four groups), the pain score comparison required the largest number of patients. This number was 15 patients per group. The power analysis performed at the conclusion of the study, using an alpha of 0.05/6 and given 20 patients per group, revealed a power that was greater than 90% [2].

Results

All the patients completed the study protocol. There were no significant differences between the four treatment groups with regards to age, weight, height, sex, and ASA status, or in the duration of surgery or discharge time (Table 1). No patient experienced hypotension (mean arterial pressure ≤ 20% of baseline), hypoxemia (peripheral oxygen saturation [$S_{P_{O_2}}$] ≤ 90%), or bradycardia (heart rate ≤60 bpm). No side effects were reported during the first 24 h after surgery. None of the patients required pain therapy while in the PACU.

Postoperatively, at 1, 2, and 24 h, VAS pain scores at rest and during movement were significantly lower in group B+Mor+Mg compared with the scores in group B ($P < 0.001$) or groups B+Mor and B+Mg ($P < 0.01$). VAS pain scores were significantly lower in groups B+Mor and B+Mg compared with those in group B ($P < 0.01$). There were no significant differences in VAS pain scores at rest and during movement between group B+Mor and group B+Mg at 1, 2, or 24 h (Fig. 1.).

Group B+Mor+Mg had a significantly longer time to first analgesic request (947 ± 194 min) than group B (320 ± 105 min; $P < 0.001$), group B+Mor (645 ± 168 min;

$P < 0.001$), or group B+Mg (610 ± 154 min; $P < 0.001$). Groups B+Mor and B+Mg had a significantly longer time to first analgesic request than group B ($P < 0.001$). There was no significant difference in analgesic duration between groups B+Mor and B+Mg (Fig. 2).

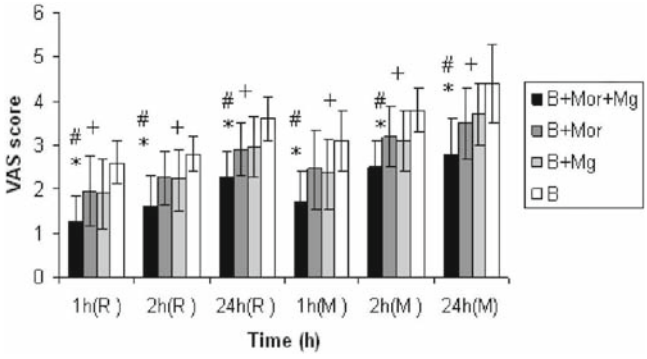

Fig. 1. Postoperative pain scores (means ± SD). *Bars* represent mean visual analogue score (*VAS*) at 1, 2, and 24 h after surgery, at rest (*R*) and, during movement (*M*). *B+Mor+Mg*, combination of bupivacaine, morphine, and magnesium; *B+Mor*, combination of bupivacaine and morphine; *B+Mg*, combination of bupivacaine and magnesium; *B*, bupivacaine. $^{*}P < 0.001$ vs group B; $^{\#}P < 0.01$ vs groups B+Mor and B+Mg; $^{+}P < 0.01$ vs group B

The number of Solpadine tablets consumed over the 24-h study period was significantly lower in group B+Mor+Mg (1.7 ± 0.9) than in group B (4.4 ± 1.4; $P < 0.001$), group B+Mor (3.0 ± 1.2; $P < 0.01$), or group B+Mg (3.1 ± 1.0; $P < 0.01$). There was significantly lower analgesic consumption in group B+Mor and group B+Mg than in group B ($P < 0.01$). There was no significant difference in analgesic consumption between groups B+Mor and B+Mg (Fig. 3).

Discussion

In attempts to improve recovery from arthroscopic knee surgery, research has been directed at new techniques for postoperative analgesia. The results of the present study showed a comparable analgesic effect from the individual IA administration of both magnesium and morphine, with bupivacaine, in the doses used. The addition of magnesium to morphine and bupivacaine provided more effective analgesia than either agent alone. Patients in the group that received IA magnesium and morphine had a longer analgesic duration and lower 24-h analgesic consumption than

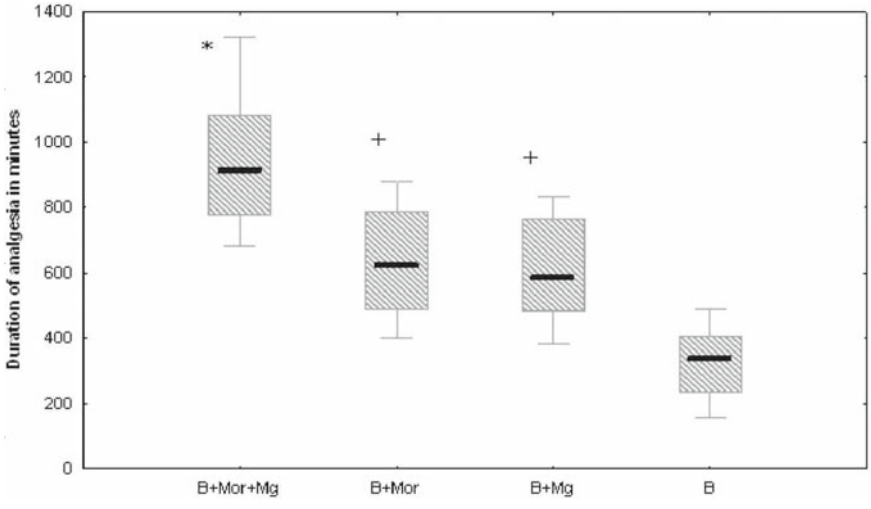

Fig. 2. Duration of analgesia in the four groups. *B+Mor+Mg*, combination of bupivacaine, morphine, and magnesium; *B+Mor*, combination of bupivacaine and morphine; *B+Mg*, combination of bupivacaine and magnesium; *B*, bupivacaine. The *boxes* represent the 25th–75th percentiles, the *horizontal lines* are the medians, the *extended bars* represent the 5th-95th percentiles. $^{*}P < 0.001$ vs groups B+Mor, B+Mg, and B; $^{+}P < 0.001$ vs group B

Table 1. Patient demographics and surgical data

	IA Bupivacaine/ Morphine/Magnesium (B+Mor+Mg)	IA Bupivacaine/ Morphine (B+Mor)	IA Bupivacaine/ Magnesium (B+Mg)	IA Bupivacaine (B)
Age (years)	34 ± 9	33 ± 8	36 ± 6	35 ± 7
Weight (kg)	73 ± 5	75 ± 6	74 ± 7	72 ± 8
Height (cm)	172 ± 9	169 ± 7	171 ± 8	173 ± 10
Sex (M/F)	17/3	17/3	18/2	16/4
ASA (I/II)	18/2	19/1	17/3	18/2
Duration of surgery (min)	42 ± 7	39 ± 9	40 ± 8	41 ± 8
Discharge time (min)	129 ± 15	134 ± 18	132 ± 17	138 ± 20

Data are presented as means ± SD or numbers ($n = 20$ in each group)
IA, intra-articular; ASA, American Society of Anesthesiology

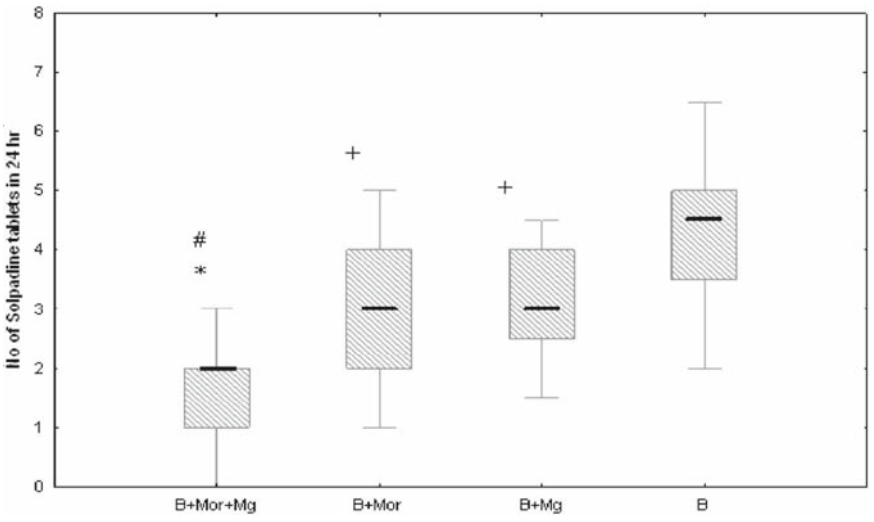

Fig. 3. Analgesic consumption in the four groups [number of Solpadeine tablets (Glaxo SmithKline) in 24 h]. *B+Mor+Mg*, combination of bupivacaine, morphine, and magnesium; *B+Mor*, combination of bupivacaine and morphine; *B+Mg*, combination of bupivacaine and magnesium; *B*, bupivacaine. The *boxes* represent the 25th–75th percentiles, the *horizontal lines* are the medians, the *extended bars* represent the 5th–95th percentiles. $^{*}P < 0.001$ vs group B; $^{\#}P < 0.01$ vs groups B+Mor and B+Mg; $^{+}P < 0.01$ vs group B

either the group with IA magnesium or the group with IA morphine.

The analgesic effect of IA morphine has been well described. Most studies have demonstrated a beneficial effect when morphine is administered via the IA route [9,10]. Peripheral opioid-binding sites have been identified in synovial tissue, indicating that analgesia is locally mediated [3]. A systematic review of the peripheral analgesic effects of IA morphine [11] demonstrated a definite analgesic effect and reported that a systemic effect of intra-articularly administered morphine could not be completely ruled out.

Magnesium sulfate has been shown to provide postoperative analgesia when injected into the knee joint after arthroscopic surgery. Bondok and Abd El-Hady [7] found that IA administration of magnesium sulfate 500 mg at the end of arthroscopic knee surgery improved postoperative pain scores, increased the time to first rescue analgesic request, and decreased the need for other analgesic medications. Magnesium is a physiological calcium channel blocker. Calcium is required for the release of various neurotransmitters and substances implicated in nociceptive pain [12]. Magnesium blocks N-methyl-D-aspartate (NMDA) receptors in a voltage-dependent way, and the addition of magnesium produces a dramatic reduction of NMDA-induced currents [13]. Studies have identified NMDA receptors peripherally in the skin [14], muscles [15], and knee joints [16], and found that they play a role in the sensory transmission of noxious signals. NMDA receptor antagonists have been shown to effectively alleviate pain-related behavior in animal models as well as in clinical situations [17,18]. The safety of IA magnesium sulfate was tested in an unpublished animal study conducted on rats and then in an in vitro animal study conducted by Egerbacher et al. [19], and no side effects were detected.

The present study showed that the administration of magnesium along with bupivacaine via the IA route resulted in a significant improvement in analgesia compared with bupivacaine alone; the analgesic effect was comparable to that of IA morphine with bupivacaine in the doses used. Recently, El Sharnouby et al. [20] demonstrated that magnesium sulfate 1000 mg combined with bupivacaine produced a reduction in postoperative pain when given intra-articularly, in comparison to either bupivacaine or magnesium alone, or to saline placebo.

The important finding of the present study is the demonstration that the combination of magnesium and morphine along with bupivacaine provides more effective postoperative analgesia compared with that provided by either drug alone. NMDA receptor antagonists can enhance the analgesic properties of opioids [21]. Although the exact mechanism of the interaction between the NMDA receptor complex and opioid antinociception has not been fully elucidated, previous studies have shown a synergistic interaction between magnesium and morphine with respect to antinociception. Begon and colleagues [8] reported that magnesium amplified the analgesic effect of low-dose morphine in different experimental models of pain. In another study, by McCarthy and colleagues [22], the addition of magnesium sulfate to morphine in an intrathecal infusion provided better analgesia than morphine alone in normal rats. Kroin et al. [23] demonstrated that acute bolus dosing of intrathecal magnesium sulfate produced dose-dependent potentiation of the antinociceptive effect of morphine to noxious thermal stimulation in normal rats and mechanical stimulation at an incisional pain site; these investigators reported that magnesium could potentiate opioid analgesic effects by both central and peripheral mechanisms. In human investigations,

Unlugene et al. [24] reported that the addition of magnesium or ketamine to morphine for IV patient-controlled analgesia led to a significantly lower consumption of morphine. Ryu and colleagues [25] showed that IV magnesium sulfate improved the quality of postoperative analgesia and significantly reduced morphine consumption in patients undergoing gynecological surgery.

In the present study, a lower dose of magnesium sulfate (150 mg [$MgSO_4$; 10%]) was used in comparison with the doses used in previous studies [7,20]. Bilir et al. [26] found that the epidural administration of magnesium 150 mg in 24 h provided a pronounced reduction in patient-controlled epidural fentanyl consumption without any side effects. The low dose used and absence of side effects usually described after the systemic administration of magnesium suggest a local analgesic effect of IA magnesium sulfate. However, a systemic analgesic effect of intra-articularly administered magnesium cannot be ruled out.

Further studies are required to compare the analgesic effect of parenteral versus intra-articular injection of different doses of magnesium sulfate and to evaluate the safety of its use on intra-articular cartilage.

In conclusion, the IA administration of magnesium or morphine, with bupivacaine, had comparable analgesic effects in the doses used. The combination of magnesium and morphine along with bupivacaine provided more effective postoperative analgesia compared with that provided by either drug alone. In the group that received magnesium and morphine along with bupivacaine there was an increased time to first postoperative analgesic request and a decreased need for postoperative analgesics compared with these parameters in the other groups.

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