



ORIGINAL ARTICLE

# Analgesic effect of intra-articular magnesium sulphate compared with bupivacaine after knee arthroscopic meniscectomy

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## KEYWORDS

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**Abstract** This work aimed to evaluate the analgesic efficacy of intra-articular injection of magnesium sulphate (4%) compared with equivalent volume of bupivacaine (0.5%) after outpatient knee arthroscopic meniscectomy. Forty patients were randomly assigned to two groups. Group M ( $n = 20$ ) received intra-articular magnesium sulphate 4%, group B ( $n = 20$ ) received bupivacaine (0.5%). Analgesic effect was evaluated by analgesic duration, and by measuring pain intensity at 1, 2, 4, 6, 12, 24 h both at rest and on knee movement to 90°. The primary outcome variable was pain intensity on the VAS at 1, 2, 4, 6, 12, 24 h post arthroscopy at rest and on movement (flexion of knee to 90°), although the magnesium group had lower time weighted averages (TWAs) at rest and on movement, these TWAs were not statistically significant. The median duration of post-operative analgesia was significantly longer in the patients treated with magnesium sulphate (528 min) than in the bupivacaine group (317 min) ( $p < 0.0001$ ), with less number of patients needing supplementary analgesia in magnesium group (8/20) than those of the bupivacaine group (16/20) ( $p < 0.022$ ). Also analgesic consumption was significantly lower in the magnesium sulphate group ( $p < 0.002$ ). We concluded that the use of magnesium sulphate is rational and effective in reducing pain, and is more physiological and shortens convalescence after outpatient arthroscopic meniscectomy, however our hypotheses that analgesic efficacy of intra-articular isotonic magnesium sulphate would be superior to intra-articular local anaesthetic cannot be supported with this study.

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## Introduction

Knee arthroscopy is a common orthopedic practice usually performed on an outpatient basis [1]. Arthroscopy has spared patients from large incisions and decreased morbidity compared with those of open procedures, but it has not eliminated pain [2]. One of the most important aspects to be considered is

that the patients, who will be discharged shortly after surgery, must be provided with an analgesic treatment that is both effective and safe [3].

Most of the intra-articular structures of the knee including the synovial tissue, the anterior fat pad and the joint capsule, have free nerve-endings that are capable of sensing painful stimuli and producing severe pain [4,5].

Previous studies [1,3,6–18] have investigated a wide variety of intra-articular local anaesthetics, opioids and systemic non-steroidal anti-inflammatory drugs (NSAIDs). Intra-articular (IA) local anaesthetics are often used for control of pain after arthroscopic knee surgery due to their direct blockade of the nociceptive pain response at the site of administration, with minimal systemic absorption. However the mean duration of analgesia provided by local anaesthetics is short and patients may need supplementary analgesia, possibly delaying patient discharge. To overcome this, the search continues for various drugs looking for an ideal analgesic technique which is site-specific, long lasting, easily administered and has a high therapeutic index with minimal adverse reactions [9].

A relatively new approach for peripheral pain control is to use magnesium sulphate. Magnesium has been investigated as an adjuvant agent for intra- and postoperative analgesia as it can block calcium influx and non-competitively antagonize N-methyl D-aspartate (NMDA) receptor channels [19]. Magnesium sulphate has been used successfully to potentiate opioid analgesia; this encouraged its use after major lumbar orthopedic surgery [20]. Recent studies have found that intra-articular injection of magnesium sulphate is effective for postoperative analgesia when compared with saline (control) in arthroscopic knee surgery [10,15].

The present investigation should help to test an acceptable, effective alternative intra-articular analgesic with a long duration of analgesia after knee arthroscopic meniscectomy and to introduce some modification to minimize the risk of potential chondrocyte damage from previous suggested concentrations.

Our aim was to evaluate the analgesic efficacy of intra-articular injection of magnesium sulphate 4% compared with equivalent volume of bupivacaine (0.5%) after knee arthroscopic meniscectomy. Our hypotheses was that analgesic efficacy of intra-articular isotonic magnesium sulphate would be superior to intra-articular local anaesthetic.

## Patients and method

We carried out a prospective randomized and double blinded study. A total of 40 adult consecutive patients who had been diagnosed with torn meniscus and were candidates to arthroscopic meniscectomy with American Society of Anaesthesiologists (ASA) physical status physical status classes I and II were included in the study, after obtaining hospital ethics committee approval, and informed written consents.

*Exclusion criteria* comprised patients who were on chronic use of NSAID, opiates, calcium channel blockers, corticosteroids, tricyclic antidepressant, or in the presence of psychiatric disorders, history of gastric or duodenal ulcers, hypersensitivity to NSAIDs, consumption of analgesics within 24 h of surgery, pregnancy, breast-feeding, liver or renal disease, or hypersensitivity to local anaesthesia.

Before the operation, all patients received detailed instructions for using a 100-mm Visual Analogue Scale (VAS) score with 0 = no pain, to 100 = the worst imaginable pain.

Patients were randomized using a random number generator to one of the following regimens: group M ( $n = 20$ ) received 20 ml of magnesium sulphate 4% (800 mg; 8 ml of magnesium sulphate 10% and 12 ml of distilled water, Osmolarity is 320 mOsm/L), and group B ( $n = 20$ ) received 20 ml 0.5% bupivacaine after completion of arthroscopy and 10 min prior to tourniquet release. An independent anaesthesiologist who did not participate in the study prepared the study medication.

## Anaesthetic regimen

Induction of anaesthesia was achieved by fentanyl  $1 \mu\text{g kg}^{-1}$ , propofol  $2 \text{ mg kg}^{-1}$ , and atracurium  $0.5 \text{ mg kg}^{-1}$ . Endotracheal intubation was performed and mechanical ventilation was applied. Anaesthesia was maintained by sevoflurane 1% in a gas mixture of oxygen (40%) and nitrous oxide (60%). Depth of anaesthesia was maintained by increasing or decreasing sevoflurane percentage taking hemodynamic changes as indicators.

At conclusion of surgery, inhalation anaesthetics were discontinued and muscle relaxant was reversed by neostigmine sulphate  $0.05 \text{ mg kg}^{-1}$  and atropine sulphate  $0.02 \text{ mg kg}^{-1}$ . There were no complications related to anaesthesia or analgesic used.

## Surgical procedure

Once the patient had been anaesthetized, the tourniquet was inflated, the surgical field was sterilized, and a standard arthroscopy technique was performed through an anterolateral and anteromedial portal. Partial meniscectomy was performed. The respective drug was injected into the joint after the portals had been stitched to prevent extravasation at the end of surgery, 10 min before tourniquet deflation and this was taken as the start time of the study. A compression bandage was applied, and the tourniquet was removed.

## Pain assessment

The primary outcome measure (post-arthroscopy pain) was assessed at rest and on movement of the knee to  $90^\circ$  by visual analogue pain score (VAS) as 0 mm is no pain and 100 mm is worst imaginable pain. A rescue dose of tramadol 50 mg intravenously was available as a postoperative analgesia at the patient's request or when the VAS value was higher than 40. The patients were discharged if they met home-readiness criteria that included orientation to time and place, stable vital signs, absence of nausea and vomiting, adequate control of pain, and ability to void and ambulate. Discharge time was classified as the time from the end of surgery until the patients met the discharge criteria. On discharge, patients were given diclofenac 50 mg tablets to be taken if needed.

## The following parameters were recorded

Age, sex, weight, ASA status, and duration of surgical procedure (tourniquet time), were recorded.

Pain was recorded by the patients as they were given a data sheet and were asked to rate their pain intensity on the VAS at 1, 2, 4, 6, 12, 24 h post arthroscopy at rest and on movement (flexion of knee to  $90^\circ$ ). Finally, the patient recorded VAS

value after leg elevation 10 times, and when walking up and downstairs after 24 h from the arthroscopy.

The time of first patient need for analgesia (duration of postoperative analgesia) was measured from time of completion of surgery until first requirement of analgesic (Rescue Dose). After discharge, Patients were asked to record when they needed the first analgesic, also they were asked to record if they needed supplementary analgesia and the total amount of oral diclofenac consumption in the subsequent 24 h, and presence of any undesirable effects.

Finally the presence of knee effusion at the 10th day, time to return to work and time to become pain free were recorded.

### Statistical analysis

Data were analyzed using computer statistical software system STATA version 9. Continuous variables were tested for normality. The baseline participants' characteristics information, duration of surgical procedure, and discharge time analgesic duration were analyzed using two-tailed unpaired *t*-tests. Gender distribution was compared using Fisher's exact test. Between group differences in pain scores were analyzed by unpaired *t* test (primary outcome measure). The time weighted averages (TWAs) of the visual analogue scale at rest and on movement were calculated. The calculation was made by plotting the pain scores of the two compared groups across time (1 h till 24 h) then the Area-Under-the-Curves (AUCs) for the two groups were computed. *t*-Test was utilized to compare the TWAs.

The need for analgesia was compared using Fisher's exact test. Multiple secondary outcome measures included the total diclofenac consumption, and analgesic duration were not normally distributed, hence Mann-Whitney *U*-test was used to compare this variable across the two groups. Descriptive data were expressed as mean (SD), median (25–75th percentiles), or participants number (%). Sample size was estimated using pain scores as the primary variable. Assuming a SD of 10 mm, the minimum needed sample size to detect a difference of 10 mm on the VAS at an alpha threshold of 0.05 with 80% power is 34. So each group should include at least 17 patients. Therefore, we included 20 patients per group.

### Results

All 40 patients completed the study; Patient characteristics are presented in (Table 1). There were no statistical differences between both groups in terms of age, weight, ASA status, gender, tourniquet time and pre arthroscopy VAS at rest and on knee movement (Table 1).

Although the VAS values (both at rest and on knee movement to 90°) of the patients treated with magnesium sulphate tended to be lower than those of the bupivacaine group, the differences were not statistically significant (Table 2). Magnesium group had lower time weighted averages (TWAs) at rest and on movement, these TWAs were not statistically significant (Table 3).

The median duration of postoperative analgesia (range) was significantly longer in the patients who received magnesium sulphate 528 (480–570) min than in the patients in bupivacaine group 317 (223–371) min ( $p < 0.0001$ ) Fig. 1.

None of the patients in the magnesium sulphate group needed analgesia during hospital stay before discharge, but (6/20) patients in bupivacaine group needed analgesia ( $p = 0.02$ ).

The participants who took magnesium sulphate were less likely to take postoperative additional oral analgesia in the next 24 h after the arthroscopy (8/20) than those of the bupivacaine group (16/20) [Fisher's Exact test  $p = 0.022$  RR = 0.50 (95% CI = 0.280–0.893)]. Also total median oral diclofenac consumption was significantly lower in the magnesium sulphate group 0 (0–87.5) mg than in bupivacaine group 100 (50–150) mg ( $p = 0.002$ ) (Table 4).

Hospital stay averaged 4.5 h, and discharge time was not different between magnesium group (264 min  $\pm$  17) and bupivacaine group (271  $\pm$  24 min) ( $p = 0.279$ ). There was no significant difference between both groups regarding pain at leg lift 10 times or at walking stairs at 24 h, also at time to become pain free and time to return to work, although the values tend to be lower in the magnesium sulphate group (Table 5). Only one patient in each group developed knee effusion that was resolved within 1 week. We reported no need for hospital re-admission after discharge and no side effects related to intra-articular injection in both groups.

### Discussion

The principal finding of this investigation is that there was no significant difference between the two groups as regards the primary outcome measure (postoperative pain scores) between both groups, however, analysis of the secondary outcome measures showed that intra-articular administration of magnesium sulphate (4%, 800 mg; 8 ml of magnesium sulphate 10% and 12 ml of distilled water, Osmolarity is 320 mOsm/L) at the end of arthroscopic meniscectomy is more effective than intra-articular bupivacaine as evidenced by a significantly longer analgesic duration in the magnesium sulphate group (528) min than in the patients in bupivacaine group (317) min. The participants who took magnesium sulphate were less likely to take

**Table 1** The baseline characteristics of the magnesium (M) group and bupivacaine (B) group.

	Group M ( $n = 20$ )	Group B ( $n = 20$ )	<i>p</i> Value
Age (y)	31.10 (7.90)	32.20 (9.62)	0.70
Weight (kg)	82.00 (8.10)	80.15 (8.60)	0.49
Surgery Duration (min)	45.80 (9.98)	45.40 (11.03)	0.91
Male	17 (85.00%)	18 (90.00%)	1.00
ASA I/ASA II	15/5	16/4	1.00
Pre VAS at rest (mm)	11.70 (4.52)	10.30 (3.93)	0.44
Pre VAS on movement (mm)	15.50 (5.71)	15.00 (4.30)	0.80

Values are mean (SD) or number (%).

**Table 2** Comparison of the resting VAS and VAS on knee movement to 90° across the groups at the different time periods.

	VAS at rest						VAS with knee movement to 90°					
	1 h	2 h	4 h	6 h	12 h	24 h	1 h	2 h	4 h	6 h	12 h	24 h
Group M (n = 20)	19.05 (7.00)	16.55 (6.13)	16.35 (6.58)	15.80 (6.36)	20.65 (7.56)	24.40 (10.89)	26.35 (7.06)	22.85 (6.18)	21.35 (6.10)	21.30 (6.13)	25.10 (7.51)	28.10 (13.67)
Group B (n = 20)	21.80 (7.89)	17.80 (7.37)	17.30 (3.28)	18.00 (4.72)	24.25 (8.26)	28.05 (13.74)	30.60 (6.47)	23.80 (5.20)	24.20 (7.00)	22.80 (5.16)	31.50 (11.83)	34.95 (15.70)
<i>p</i> <sup>a</sup> Value	0.25	0.60	0.60	0.22	0.19	0.36	0.06	0.60	0.20	0.41	0.07	0.23

Values are mean (SD).

<sup>a</sup> Bonferroni adjustment was used.

**Table 3** Comparison of the time weighted averages (TWAs) of the visual analogue scale at rest and on movement across the groups.

	Group (M) TWA (SD)	Group (B) TWA (SD)	<i>p</i> Value
VAS at rest	24.77 (06.72)	29.55 (08.94)	0.09
VAS on movement	19.84 (06.24)	22.77 (06.83)	0.22

postoperative additional oral analgesia in the next 24 h after the arthroscopy (8/20) than those of the bupivacaine group (16/20), finally magnesium sulphate group participants required significantly lower dose of supplementary analgesia in the first 24 h after surgery than in bupivacaine group, which may be explained by the more prolonged action of magnesium.

The absence of statistically significant differences between both groups in measures of pain (VAS at rest, VAS on movement and time to return to work and time to become pain free) may be explained by the availability of analgesia on demand which may lead to a converging of pain scores, as differences in pain are translated into differences in behaviour and analgesic consumption.

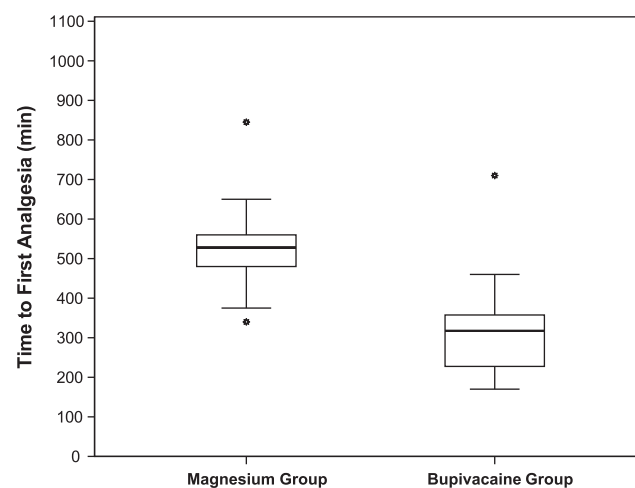
Evaluation of the level of postoperative pain in a relatively minor arthroscopic surgery with an expected mild pain is difficult. The most commonly accepted method is the Visual Analogue Scale VAS for assessing analgesia and the need to take additional analgesics as a rescue dose [3,7,9–10,13,18]. Various factors have been implicated in pain after arthroscopy and the effectiveness of intra-articular analgesia. These include preoperative pain scores, duration of anaesthesia, type of surgery, volume injected, time of intra-articular injection relative to tourniquet deflation, pain assessment in rest and movement, whether the study performed as an outpatient case or not. All these factors make the large number of studies difficult to compare [12].

In the design of this study we attempted to use best practice in performance and analysis, as the comparison of VAS at rest and on knee movements, by stressing the joint, the degree of pain and adequacy of analgesia are better assessed. Such testing has been recommended for the assessment of postoperative pain, especially when assessing outpatients for discharge home [7,12,17–18]. Neuroaxial block can affect the pain scores in the early postoperative time so we used general anaesthesia with endotracheal intubation with short acting anaesthetic duration (propofol, fentanyl, sevoflurane and N<sub>2</sub>O), with which the patients became fully conscious within 30 min after recovery from anaesthesia.

Also we released the tourniquet 10 min after intra-articular injection, as this confounding variable may affect the analgesic

efficacy of intra-articular substance as noticed by Whitford et al. [21] who observed that keeping the tourniquet inflated for 10 min provided superior analgesia and decreased the need for supplementary analgesics compared with releasing the tourniquet immediately after intra-articular injection. It is possible that by increasing the time-interval between intra-articular injection and tourniquet release, the local tissue-binding to receptors can be increased, enhancing the analgesic effect.

Magnesium sulphate is a widely used drug with good safety and efficacy for many indications including eclampsia, cardiac arrhythmias, acute severe asthma and perioperative as one of the analgesic and opioid saving drug. Mg<sup>2+</sup> preparations are usually well tolerated even when given at large dosages and are considered to be safe as reported by Koinig et al. [22] who used magnesium sulphate 50 mg kg<sup>-1</sup> intravenously and



**Fig. 1** The analgesic duration in minutes in the both groups. The box represents the 25–75th percentiles, and the median is represented by the solid line. The extended bars represent two standard deviation. Magnesium group had a significantly longer time to first analgesic request (rescue dose) than bupivacaine group ( $p < 0.0001$ ).

**Table 4** Comparison of the total postoperative analgesic intake across the groups.

	Group M ( <i>n</i> = 20)	Group B ( <i>n</i> = 20)	<i>p</i> Value
Number of patients requiring analgesia at hospital	0 <sup>a</sup>	6 (30%)	0.020
Number of patients requiring supplementary analgesia at home	8 (40%) <sup>a</sup>	16 (80%)	0.022
Diclofenac consumption (mg)	0 <sup>b</sup> (0–87.5)	100 (50.0–150.0)	0.002

<sup>a</sup> No. (%).<sup>b</sup> Median (25–75th percentiles).**Table 5** Comparison of hospital stay, pain at leg lift and walking, and the time to become pain free and time to return to work across the groups.

	Group (M) <i>n</i> = 20	Group (B) <i>n</i> = 20	<i>p</i> Value
Hospital stay (min)	264 (17)	271 (24)	0.28
Pain at leg lift	32.60 (13.48)	36.20 (13.32)	0.06
Pain at walking stairs	29.45 (12.90)	34.15 (12.58)	0.54
Time to become pain free (days)	5.60 (2.4)	7.50 (3.1)	0.07
Time to return to work (days)	10.70 (2.6)	12.70 (3.9)	0.06

Values are mean (SD).

implicated that the perioperative administration of IV magnesium sulphate reduces intra- and postoperative analgesic requirements without serious adverse reactions.

Experimental and clinical data from acute and chronic pain situations demonstrate an effect of magnesium on the pain threshold, which is clinically apparent postoperatively as a reduction of analgesic requirements [22]. In our study, the analgesic efficacy of intra-articular magnesium sulphate is evident even after decreasing the osmolarity of the magnesium sulphate solution to be nearly isotonic instead of the previous work of Bondok and Abd El-Hady [10] who used hyperosmolar solution (550 mOsm/L). This may prevent any potential harmful effect of hyperosmolar solution on the cartilage or nerve fibres intra-articularly.

Patients in magnesium group did not need analgesic before discharge, became pain free and returned home 1.9 days earlier than patients in group bupivacaine with less need for supplementary analgesia is important and points to more effective analgesic action of magnesium sulphate and that it extends longer than the 24 h which was the limit of the study. Although these differences were not statistically significant, it may have a relevant clinical significance, this suggests further studies to test its validity.

The current study has some limitations. First of all, the plasma concentrations of the drugs were not measured and chondrotoxic effects of the drugs were not tested however study by Baker et al. [23] showed that magnesium sulphate exerts a less toxic effect on monolayer chondrocyte culture than local anaesthetic, they showed no significant difference between the magnesium sulphate and normal saline treatments suggesting that magnesium sulphate is no more detrimental to chondrocyte viability than arthroscopic fluid that may explain the earlier return to work. Second, the obtained results are not generalizable since we use it in arthroscopic meniscectomy only, and elderly and children were not included. Although the analgesic effect of intra-articular magnesium sulphate is proved; the debate is about the proper concentration and osmolarity which needs further investigations to explore its

effect after arthroscopy. Finally, before translating the result of this study into clinical practice, the possible side effects of magnesium systemic absorption particularly in patients with impaired renal function or high risk patients, should be considered carefully.

## Conclusion

The study findings indicate that following outpatient arthroscopic knee surgery, the use of magnesium sulphate is rational and effective in reducing pain, and is more physiological and shortens convalescence after outpatient arthroscopic meniscectomy, however Our hypotheses that analgesic efficacy of intra-articular isotonic magnesium sulphate would be superior to intra-articular local anaesthetic cannot be supported with this study.

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