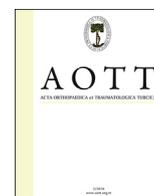




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The effects of intra-articular levobupivacain versus levobupivacain plus magnesium sulfate on postoperative analgesia in patients undergoing arthroscopic meniscectomy: A prospective randomized controlled study



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ABSTRACT

Objective: The aim of this study was to compared the effectiveness of intraarticular levobupivacain with levobupivacain and magnesium sulfate.

Methods: In this prospective randomized double blinded study, 96 patients (67 male, 29 female; age range: 18–65 years) with ASA (American Society of Anesthesiologist) score I and II, who had undergone arthroscopic meniscectomy operation, were divided to 3 groups that had postoperative analgesia with intra-articular saline injection (control group), levobupivacain injection (L group) or levobupivacain and magnesium sulfate injection (LM group). Patients were compared with postoperative VAS (Visual Analog Score) score during rest and activity, opioid analgesic need, non-opioid analgesic need and other medication needs.

Results: Postoperative VAS scores during rest and activation at early postoperative period were significantly lower at LM group when compared with L group and lower than control group at all time periods. Opioid analgesic need, non-opioid analgesic need and other medication needs for non-pain symptoms were lower at LM group when compared with L and control groups at all time periods.

Conclusion: Intraarticular magnesium sulfate plus Levobupivacain injection is a safe and effective method for post operative pain management after arthroscopic meniscectomy.

Keywords: Intra-articular injection, Magnesium sulfate, Levobupivacain, Postoperative analgesia, Chondrocyte apoptosis, Pain management, Arthroscopic meniscectomy

Level of Evidence: Level I, Therapeutic study

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Introduction

Arthroscopic meniscectomy operation is an outpatient orthopedic surgery procedure. Patient satisfaction and outpatient surgery can only be obtained with effective postoperative analgesia.

Early postoperative analgesia can be obtained with opioid analgesics, non-opioid analgesics, local analgesics and neuraxial blockers.¹

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Multimodal pain management (oral, intravenous, peripheral blocks) is the common method for postoperative pain management after arthroscopic knee surgeries. Recent papers recommend multimodal intra-articular cocktails instead of multimodal pain management due to its side effects like nausea, vomiting, sedation, acute gastric irritation, itching, urinary retention, respiratory depression and partial motor block.^{2,3}

Neuraxial block is not the choice for postoperative pain management after small surgical procedures because of its side effects like urinary retention, prolonged motor block, headache and epidural hematoma. Intra-articular local anesthetic injections are effective but lasts for a short time. Side effects of systemic drugs restricts single drug usage.

Levobupivacain (Chirocaine 0,5% levobupivacaine hydrochloride 5 mg/ml, 10 ml Abbot) is an effective local anesthetic for intra-

articular use but it has been shown to disrupt chondrocyte membrane activity and this effect is dose dependent.^{4,5} Magnesium sulfate acts as an NMDA (N-Methyl-D-Aspartate) receptor antagonist. There are a few studies that report magnesium sulfate increase the analgesic effect of levobupivacain but we couldn't find a study comparing the effectivity of intra-articular levobupivacain with levobupivacain and magnesium sulfate.

We hypothesized that magnesium sulfate when used as an adjunct to levobupivacain intra articularly may produce equally or better analgesia in arthroscopic meniscectomy operations with lower dose of levobupivacain in order to decrease local anesthetic related chondrocyte damage.

Material and method

Ninety-six patients (46 female, 50 male), 18–65 years of age with ASA (American Society of Anesthesiologist) score I and II, undergoing arthroscopic meniscectomy operation between 4/2013 and 3/2014 were included into the study. Patients were assigned

randomly to one of three groups using an Excel (Microsoft, Redmond, WA, USA)-generated randomization table (Group L: levobupivacain group, n = 32; Group LM: levobupivacain plus magnesium sulfate, n = 32; Group C: control group, n = 32) Flow chart of the study is shown in Fig. 1.

Informed consent was obtained from all patients and ethical committee approval was taken from the institution's ethical committee. All patients were informed about the VAS score system and PCA (Patient controlled analgesia) devices. Initial evaluation of patients was performed with physical examination including assessment of active and passive range of motion (ROM) and evaluation of joint line tenderness, stability of collateral and cruciate ligaments, patellar compression test and lower extremity alignment. Radiographic evaluation was performed with MRI. Patients who had knee instability due to cruciate and/or collateral ligaments injuries; cartilage damage requiring surgical interventions; and lower extremity mal-alignment due to congenital, acquired or traumatic lower extremity deformities, were excluded.

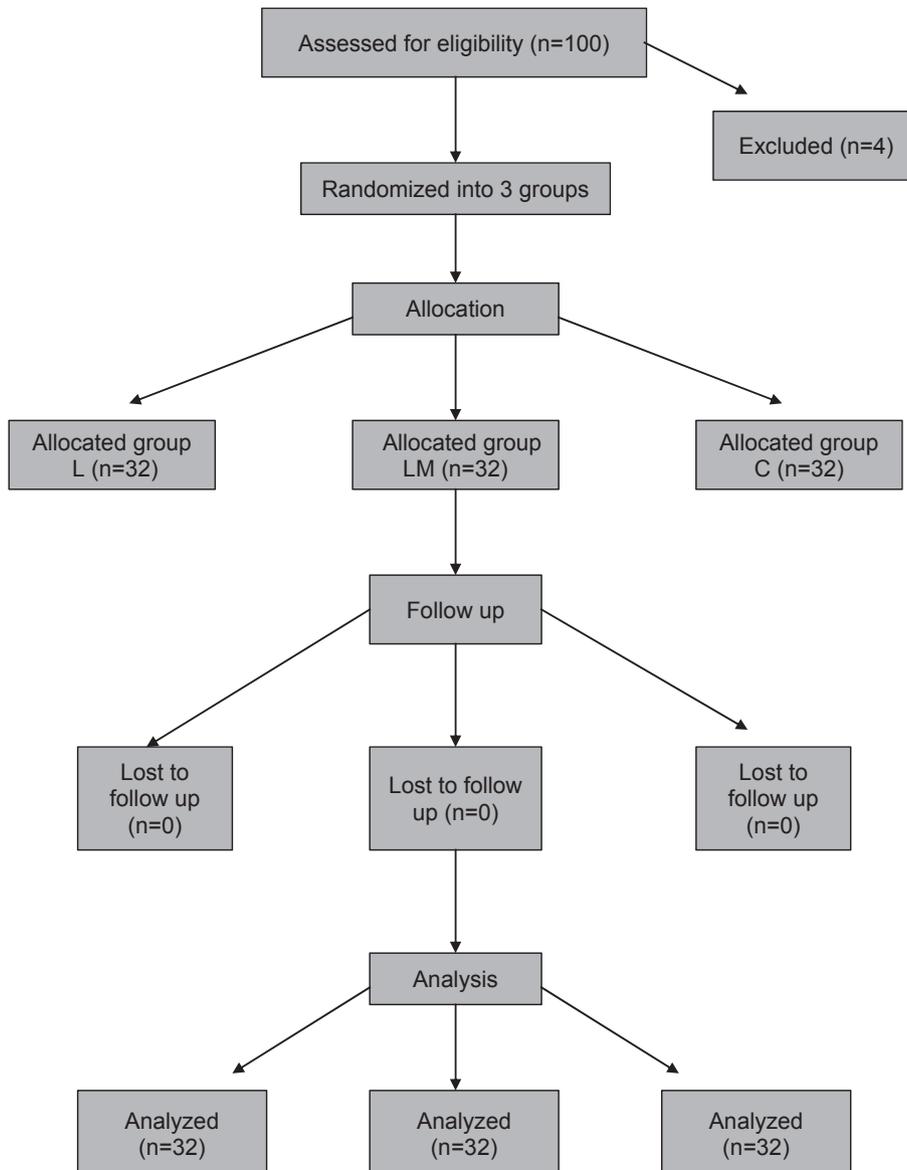


Fig. 1. Flow chart.

Patients who need an additional procedure to meniscectomy and who had an injury to the same knee last month were also excluded. Other exclusion criteria were allergy to levobupivacain or magnesium sulfate, regular analgesic use or analgesic use 1 day before surgery, cardiovascular, hepatic, renal, neurologic, allergic or endocrine diseases, pregnancy and nursery, deafness, alcohol or drug abuse.

Patients in L group received 100 mg (10 ml) of levobupivacain intraarticularly, patients in LM group received 50 mg (5 ml) of levobupivacain and an additional 1,5 g magnesium sulfate (10 ml) intraarticularly. In order to reach identical appearance and same volume of the study drugs 5 ml of normal saline was added to 10 ml levobupivacaine in Group L patients. Group C patients received 15 ml of normal saline intraarticularly.

On arrival at the operating room, standard anesthetic monitors were applied. Anesthesia was induced with iv propofol (2–3 mg/kg) and fentanyl (1–1,5 µg/kg). Tracheal intubation was facilitated with iv rocuronium (0,6 mg/kg). After tracheal intubation all patients received iv 8 mg dexamethasone. Normocapnic mechanical ventilation was performed after intubation. General anesthesia was maintained with sevoflurane (1 minimum alveolar concentration) in 40% oxygen/NO₂ mixture.

Patients were operated by the same surgical team under general anesthesia with pneumatic tourniquet control. Standard anterolateral and anteromedial arthroscopy portals were used during the surgery. All meniscal tears which were not able to be repaired were partially excised with shaver and punches. Meniscal repair cases were also excluded. Drugs were prepared by the pharmacy department, and given to the blinded investigators. The patients, anesthesiologists (with the exception of the primary author), statistician, and observers were all blinded to the study groups.

Drugs were injected intra operatively after the surgery under pneumatic tourniquet. 100 mg of levobupivacain was used at L group, 50 mg of levobupivacain and an additional 1,5 g magnesium sulfate was used at LM group. 1 g intravenous paracetamol was to patients prior to intra-articular injections.

Postoperative analgesia was provided with a patient controlled analgesia with iv tramadol (5 mg/mL) (2 ml bolus and 10 min lockout interval without basal infusion). As a rescue analgesic patients with VAS>4 received diclofenac 75 mg im.

Hemodynamic parameters, VAS scores, tramadol hydrochloride use and rescue analgesic use were recorded at postoperative 0th (as soon as the patient became cooperative), 1th, 2nd, 4th, 6th, 12th and 24th hours during rest and activity. All patients were mobilized with full weight bearing at postoperative 4th hour and VAS scores were recorded. Isometric terminal extension and ROM exercises were begun at the same time.

SPSS (Statistical Package for Social Sciences) for Windows 15.0 statistic software was used for data analysis.

While evaluating the findings obtained from the study, SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis To compare VAS scores between the groups Kruskal Wallis test, to compare to the tramadol use between the groups one-way ANOVA and Tukey's HSD test were used. Pearson Chi-squared and Fisher Exact test was used to compare the opioid related side effects and rescue analgesic use between the groups. Significance was evaluated at $p < 0,05$.

For the power analysis of the study, when we considered $\Delta:1$ SD:0,34, the number of determined samples of each group was detected as 30 for Power: 0,80, $\beta:0,20$ ve $\alpha:0,05$.

Results

Mean age of the patients was $41,20 \pm 10,96$ (18–65). Mean BMI was $27,0 \pm 3,94$ kg/m² (18,62–39,56 kg/m²). There were no

statistical significant difference between groups for demographic data and body mass index ($p > 0,05$) (Table 1).

In first 4 h postoperatively group L and Group LM patients had significantly lower VAS scores compared to control group. Throughout this period VAS scores of group LM were lower than the group L. After 4 h group L and LM patients had lower VAS scores compared to control group but there was no statistically difference between group L and LM patients throughout the 4–24 h time interval (Table 2, Graph 2).

During mobilization group L and LM patients had lower VAS scores compared to control group and LM patients had significantly lower VAS scores than the patients in group L (Graph 1).

Total tramadol hydrochloride use was lower in L and LM groups compared to control group (Table 3).

Post operative tramadol hydrochloride consumption was lower in group L and LM compared to control group and except the 8 h postoperatively (Graph 3).

LM group patients consumed lower tramadol hydrochloride than the L group in all measurement times.

Rescue analgesic use was lower in L and LM groups compared to control group in the first 2 h but no difference was found between group L and LM (Table 4).

There was no statistically significant difference between 3 groups for additional complaints at 1st, 2nd, 4th and 6th hours postoperatively (Table 4).

When compared with L and control groups, VAS scores (during rest and activity) and total analgesic use (24 h) were statistical significantly lower. There were also lower side effects (nausea, vomiting, respiratory depression) at LM group when compared to other groups because of lower opioid use and lower pain resulting a comfortable postoperative period. No postoperative effusions were seen postoperatively.

Table 1
Demographic data and body mass index.

	LM group	L group	Control	^a p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	43,06 ± 13,19	40,06 ± 9,24	40,47 ± 10,19	0,499
BMI (kg/m ²)	27,90 ± 4,54	29,79 ± 3,27	36,31 ± 3,86	0,257
	n (%)	n (%)	n (%)	^b p
Male	22 (%68,8)	24 (%75)	21 (%65,6)	0,708
Female	10 (%31,3)	8 (%25)	11 (%34,4)	

^a Oneway ANOVA test.

^b Pearson Chi-Square test: * $p < 0,05$.

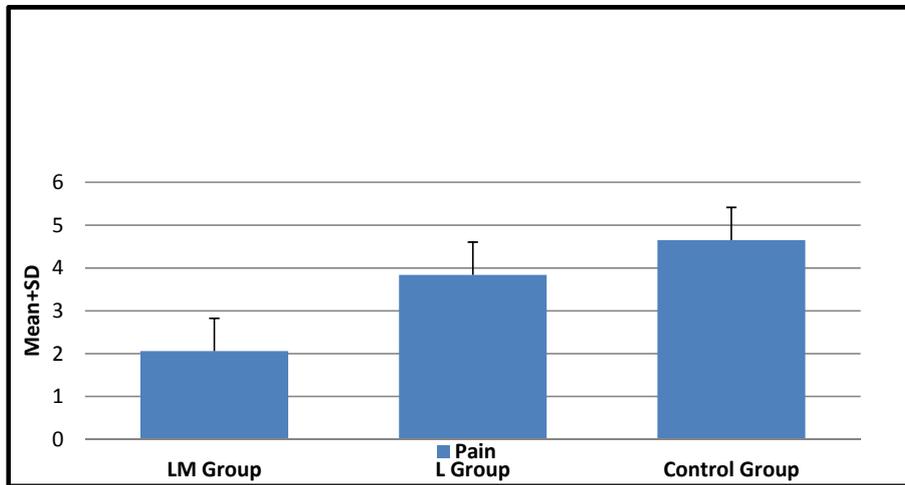
Table 2
VAS scores.

Pain	LM group	L group	Control	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Mobilisation	2,06 ± 0,95 (2)	3,84 ± 0,71 (4)	4,65 ± 1,40 (4,5)	0,001**
0 h	0,78 ± 0,91 (0,5)	1,87 ± 1,24 (2)	2,81 ± 1,76 (2)	0,001**
1 h	0,47 ± 0,84 (0)	1,75 ± 1,41 (1)	2,59 ± 1,54 (2)	0,001**
2 h	0,56 ± 0,76 (0)	1,15 ± 1,19 (1)	3,65 ± 2,24 (4)	0,001**
4 h	0,65 ± 1,03 (0)	1,0 ± 1,68 (0)	2,72 ± 1,63 (2)	0,001**
6 h	0,59 ± 0,95 (0)	1,06 ± 1,29 (0,5)	1,63 ± 1,26 (1)	0,001**
8 h	0,47 ± 0,67 (0)	0,72 ± 0,96 (0)	0,87 ± 0,66 (1)	0,047*
12 h	0,25 ± 0,51 (0)	0,22 ± 0,49 (0)	0,69 ± 0,69 (1)	0,002**
24 h	0,03 ± 0,18 (0)	0 ± 0 (0)	0,31 ± 0,47 (0)	0,001**

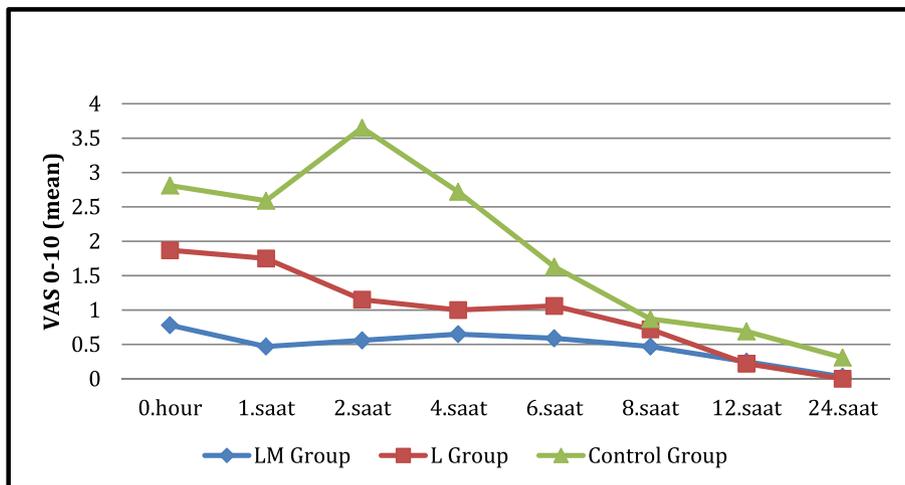
Kruskal Wallis test: ** $p < 0,01$, * $p < 0,05$.

Discussion

It is well known that intraarticular local anesthetics have negative effects on chondrocytes and to decrease this damage we



Graph 1. Pain during mobilization.



Graph 2. Pain scale.

Table 3
Tramadol Hydrochloride use.

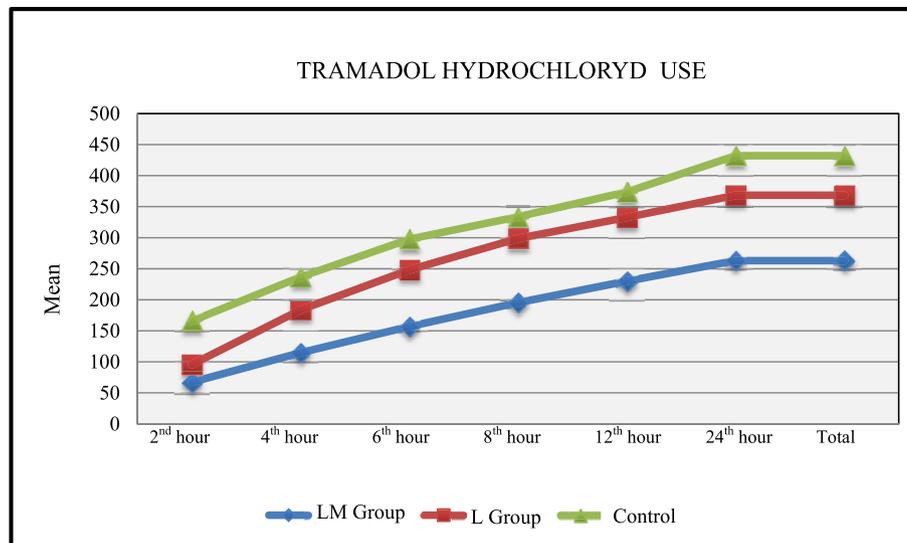
Tramadol hydrochloride	LM group Mean ± SD	L group Mean ± SD	Control Mean ± SD	p
2 h	67,19 ± 25,93	95,63 ± 37,15	165,94 ± 43,24	0,001**
4 h	114,69 ± 42,27	183,75 ± 62,98	236,87 ± 65,82	0,001**
6 h	156,88 ± 48,02	248,13 ± 60,93	297,81 ± 66,47	0,001**
8 h	195,31 ± 54,12	298,75 ± 67,09	333,75 ± 47,29	0,001**
12 h	230,0 ± 61,96	332,81 ± 62,64	373,75 ± 69,03	0,001**
24 h	263,13 ± 73,41	368,44 ± 66,68	432,19 ± 71,24	0,001**
Total	263,13 ± 73,41	368,44 ± 66,68	432,19 ± 71,24	0,001**

Oneway ANOVA test: **p < 0,01.

used magnesium sulfate as an adjunct to decrease the levobupivacaine dose. In this study we showed that magnesium sulfate added to intraarticular levobupivacaine produces better analgesia even with lower dose of levobupivacaine.

Effective postoperative analgesia affects postoperative hospitalization time, patient satisfaction and results of surgery. Insufficient analgesia causes delayed mobilization, longer hospitalization times and lowers patient satisfaction.⁶ Opioid analgesics can be used as effective postoperative analgesics but side effects can be as irritating as pain itself when used after outpatient surgeries.²

Local anesthetic agents are widely used intra-articular for postoperative analgesia. Levobupivacain is a *l*-isomer of bupivacain and it is preferred because of its lower cardio toxicity and better safety margin.⁷ There are studies showing good results of combination of levobupivacain with other agents like tramadol, fentanyl, ketamine, dexmedetomidine, midazolam, morphine, larnoksicam and magnesium for intravenous or intra-articular injections.^{3,8–17} Magnesium sulfate has also been used alone or as a combination with other analgesics for postoperative analgesia.^{8,9,18,19}



Graph 3. Tramadol hydrochloride use.

Table 4
Rescue analgesic use and opioid related side effects.

		LM Group	L Group	Control	p
		n (%)	n (%)	n (%)	
Analgesic	1 h	2 (%6,3)	3 (%9,4)	10 (%31,3)	^a 0,011*
	2 h	2 (%6,3)	6 (%18,8)	19 (%59,4)	^a 0,001**
	4 h	1 (%3,1)	3 (%9,4)	7 (%21,9)	^b 0,074
	6 h	1 (%3,1)	1 (%3,1)	4 (%12,5)	^b 0,359
	8 h	0 (%0)	1 (%3,1)	0 (%0)	^b 1000
	24 h	0 (%0)	0 (%0)	0 (%0)	^b 1000
Opioid related side effects	1 h	0 (%0)	2 (%6,3)	4 (%12,5)	^b 0,160
	2 h	2 (%6,3)	6 (%18,8)	9 (%28,1)	^a 0,071
	4 h	0 (%0)	4 (%12,5)	3 (%9,4)	^b 0,156
	6 h	1 (%3,1)	1 (%3,1)	2 (%6,3)	^b 1000
	8 h	0 (%0)	0 (%0)	0 (%0)	^b 1000
	24 h	0 (%0)	0 (%0)	0 (%0)	^b 1000

^a Pearson Chi–Square test.

^b Fisher's Exact test: **p < 0,01 *p < 0,05.

Magnesium sulfate acts as an antagonist of NMDA receptors that has a major role at acute pain. There are studies showing that NMDA receptors also present at peripheral tissues like skin, muscle and joints.^{20–22}

In our study we see that, when compared with L group, patients of LM group had lower pain scores at early and late postoperative periods, particularly at postoperative 4th hour, when the patients have most opioid related side effects.

Additionally, opioid use at postoperative 2nd, 4th, 6th, 8th, 12th and 24th hours were significantly lower at ML group thus resulting to less opioid side effects and the need of additional medications for these side effects. Less need to analgesics decreases the overall cost of the treatment and effort of medical professionals.

Non-opioid analgesics as rescue analgesics use was also significantly lower at LM group. Gastrointestinal side effects of NSAID's and uncomfortable intramuscular injections can be safely prevented with an effective postoperative analgesia method like intra-articular levobupivacain and magnesium sulfate combination.

There are several studies showing that when compared with single use, lower doses of local anesthetics can act same when combined with other agents for intra-articular injections.^{8,23} Similar to the literature, we find that, lower dose of levobupivacain can act more efficiently with the combination of magnesium sulfate.

This phenomenon can be described by the synergistic acting mechanism of these agents both at peripheral and central use.²⁴ With the combination with magnesium sulfate, levobupivacain can be used %50 less with the same effect.

There are studies showing the negative effects of local anesthetic agents on chondrocytes when used intraarticularly.^{25–28} These findings guide local anesthetic choice for intra-articular injections.

Ian et al showed that, local anesthetics disrupt chondrocyte membrane integrity during intra-articular injections and this negative effect correlates with the dose used.^{29,30} Another study showed that chondrocyte count significantly decreases 6 weeks after intra-articular injections.³¹ E. Jacobson et al showed that intra-articular injection of 100 mg levobupivacain has a better analgesic effect than 50 mg levobupivacain but dose dependent negative effects of levobupivacain on chondrocytes were not considered.³²

Baker et al showed that combination of local anesthetic agents with hyaluronic acid lowers the chondrocyte damage when compared with local anesthetics alone.³³

In our study we saw that, combination of levobupivacain with magnesium sulfate increase the analgesic effect even with half dose of levobupivacain resulting less negative dose dependent effects on chondrocytes.

In contrast to local anesthetic agents, magnesium sulfate has a positive influence on chondral regeneration. Recent studies showed that %10, %20 and %50 solutions of magnesium sulfate has the same effect like saline when used on human chondrocyte cell cultures.^{19,34–36} Another study showed that magnesium sulfate inhibits P-NR1 and chondrocyte apoptosis thus prevents chondral injury.³⁷ Magnesium sulfate also acts as an anti-inflammatory agent with systemic and local immune modulatory effects.^{36,37}

The major limitations of this study were the lack of an additional group with magnesium sulfate injections alone, cost analysis of the hospitalization time and assessment of patient satisfaction.

We conclude that, except from the synergistic effect of magnesium sulfate with levobupivacain, anti-inflammatory effect of magnesium sulfate can be another reason for the lower analgesic need and lower pain scores of the patients in LM group. Therefore, intra articular magnesium sulfate plus Levobupivacain injection is safe and effective to use in post operative pain management of patients undergoing arthroscopic meniscectomy.

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