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SCIENTIFIC ARTICLE

Effects of intraarticular tramadol, magnesium and ketamine on postoperative pain in arthroscopic meniscectomy

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KEYWORDS
Intraarticular analgesia;
Ketamine;
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Abstract
Objective: Postoperative pain control is important in terms of early recovery and rehabilitation in arthroscopic meniscectomy. For this purpose, we aimed to compare the effects of intraarticular tramadol, magnesium, and ketamine with combinations of pericapsular bupivacaine on postoperative pain and recovery in arthroscopic meniscectomy.
Methods: Ninety patients who underwent arthroscopic meniscectomy were enrolled in the study. Group T was given tramadol, Group K was given ketamine, and Group M was given magnesium reconstituted intraarticularly, and all groups received periarticular bupivacaine. Comparisons were made in terms of the patients' postoperative Visual Analogue Scale scores with and without movement, need for additional analgesics, first analgesic time, mobilization times, adverse effects, and satisfaction with the analgesics.
Results: The Visual Analogue Scale scores were lowest in Group T at 0 minutes, and were higher in the 15th and 30th minutes and 1st, 2nd, and 6th hours. Visual Analogue Scale values with movement were found to be high in Group M at 0 and 15 minutes, but they were found to be higher in group T in the 30th minute, 1st, 2nd and 6th hour. The groups were similar in terms of postoperative additional analgesic use, number of analgesic use, and satisfaction with analgesics; however, the first analgesic time was earlier in Group M, and the first mobilization time was earlier in Group K.

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Conclusion: Intraarticular ketamine enables early mobilization and less need for additional analgesics, it also provides a better analgesic effect in comparison with intraarticular tramadol and magnesium.

PALAVRAS-CHAVE
Analgesia intra-articular;
Cetamina;
Tramadol;
Magnésio;
Artroscopia de joelho

Efeitos de tramadol, magnésio e cetamina por via intra-articular sobre a dor pós-operatória em meniscectomia artroscópica

Resumo
Objetivo: O controle da dor pós-operatória é importante para recuperação e reabilitação precoces em meniscectomia artroscópica. Portanto, nosso objetivo foi comparar os efeitos de tramadol, magnésio e cetamina administrados por via intra-articular em associação com bupivacaína pericapsular sobre a dor e a recuperação após meniscectomia artroscópica.
Métodos: Noventa pacientes submetidos à meniscectomia artroscópica foram incluídos no estudo. O Grupo T recebeu tramadol, o Grupo K recebeu cetamina e o Grupo M recebeu magnésio em doses reconstituídas por via intra-articular e todos os grupos receberam bupivacaína por via periarticular. As avaliações foram feitas mediante comparação dos escores em escala visual analógica no pós-operatório dos pacientes em movimento e em repouso, necessidade de analgésicos adicionais, tempo até a primeira necessidade de analgésico, tempo de mobilização, efeitos adversos e satisfação com os analgésicos.
Resultados: Os escores da escala visual analógica foram menores no minuto zero e maiores nos minutos 15 e 30 e nas horas 1, 2 e 6 no Grupo T. Os escores da escala visual analógica em movimento foram maiores nos minutos zero e 15 no Grupo M e maiores no minuto 30 e nas horas 1, 2 e 6 no Grupo T. Os escores dos grupos foram semelhantes em relação à necessidade de analgésico adicional no pós-operatório, ao consumo de analgésico e à satisfação com os analgésicos, mas os tempos até a primeira necessidade de analgesia e até a primeira mobilização foram mais curtos nos grupos M e K, respectivamente.
Conclusão: A administração intra-articular de cetamina permite mobilização precoce e diminui a necessidade de analgésicos adicionais, além de proporcionar um melhor efeito analgésico em comparação com tramadol e magnésio por via intra-articular.

Introduction

Arthroscopic meniscectomy is one of the most frequently performed ambulatory surgeries. Therefore, aggressive pain control in the early postoperative period becomes highly important in terms of early recovery and rehabilitation.[1] Many different anesthetic techniques and medicines (e.g., local anesthetic, opioids, Non-Steroidal Anti-Inflammatory Drugs – NSAIDs) have been used for pain control in these surgeries. Agents used for this purpose should both control pain effectively and have minimal adverse effects.[2] However, despite several studies that aimed at finding the ideal treatment and technique, no conclusion has yet been drawn on this issue.

Tramadol, which is one of the opioids used for analgesic purposes in arthroscopic surgeries, demonstrates an analgesic effect due to its opioid agonist effect and preventive interaction for the withdrawal of noradrenaline and serotonin in the central nervous system. Some studies demonstrated that tramadol might have a local anesthetic-type effect in minor operations, similar to that of lidocaine on the sodium channel of axons.[3,4] Due to these features, intraarticular tramadol has frequently been used intraarticularly in knee arthroscopies.[2,5–7] As to ketamine, with its effects on the N-Methyl D-Aspartate (NMDA), opioid, and muscarinic receptors, it is known to be a strong analgesic that has both systemic and peripheral (skin, muscle, knee-joint) effects.[8] Due to these features, intraarticular ketamine has been used in knee arthroscopies.[9] Magnesium is an NMDA receptor blocker, and is mainly used in eclampsia, headache, and acute migraine attacks.[8] Recent studies reported that due to its systemic and local analgesic effects, magnesium has been frequently used in postoperative pain protocols in arthroscopic surgeries.[10,11] However, no research has been conducted regarding the superiority of intraarticular use of tramadol, ketamine, and magnesium – which also have local effects – over each other in terms of analgesia, recovery, and adverse effects.

The purpose of this study was to compare the effects of intraarticular tramadol, magnesium, and ketamine with

combinations of pericapsular bupivacaine in outpatient arthroscopic meniscectomy in terms of postoperative pain and recovery.

Methods

Ninety patients who were aged between 30 and 70 years, American Society of Anesthesiologists (ASA) Status I–II, and who were scheduled to undergo elective knee arthroscopy meniscectomy surgery were prospectively enrolled in the study after receiving ethics committee approval and signed informed consent from the patients. Patients who had severe cardiac disease, kidney failure, liver failure, Body Mass Index (BMI) $\geq 30\,kg.m^{-2}$, those who used α-methyl dopa, clonidine, β-blockers, calcium channel blockers due to hypertension; those with neuromuscular disease; patients who were allergic to the drugs investigated; those who received opioid or NSAID analgesics up to 24 hours before surgery; and patients who did not want to participate were not included in the study. In addition, patients who used analgesics other than the recommended pain killers after discharge from hospital were excluded.

During the preoperative visit, all patients were informed about using Visual Analogue Scale (VAS) scores from 0 to 10, where 0 = no pain, and 10 = unbearable pain, and 30 minutes before the operation they were given $0.05\,mg.kg^{-1}$ intravenous (IV) midazolam premedication. In the operating room, the patients were monitored in a standard way via electrocardiogram, noninvasive blood pressure, capnography, and with pulse oximetry. The general anesthesia induction was performed with propofol $2\,mg.kg^{-1}$ and fentanyl $0.1\,\mu g.kg^{-1}$, which was followed by placement of a laryngeal mask; during the procedure, spontaneous breathing of the patients was enhanced. Anesthesia management was provided with 1 MAC of sevoflurane (Primus, Drager), 50% O_2 and N_2O, and no additional analgesics were given throughout the surgery.

Ninety patients were randomly assigned to three groups using the closed envelope method such that three groups of thirty patients were formed. The skin incision of the portals was closed and no tourniquet was used, and the groups were formed by administering 100 mg tramadol in Group T, $1\,mg.kg^{-1}$ ketamine in Group K, and 1.5 g 10 mL 10% magnesium in Group M, which was administered intraarticularly and diluted in 20 mL of saline. In addition, a 10 mL periarticular injection of 0.5% bupivacaine was administered to all groups. All surgical procedures were performed by a single surgeon by opening two standard arthroscopic portals. The injections were made by a surgeon who was blinded to the contents, and the evaluations were also made by a different anesthetist who did not know about which injection had been administered.

All patients' VAS scores with and without movement (0 mins, 15th min, 30th min, 1st hr, 2nd hr, and 6th hr), use of additional analgesics at the hospital (20 mg lornoxicam administered to 4 patients with VAS ≥ 4), time of first analgesic (paracetamol) within the first 24 hours after discharge from hospital (scored as 1 = none, 2 = 15 min, 3 = 30 min, 4 = 1 hour, 5 = 2 hours, 6 = 6 hours) and the number of analgesics, if any, were questioned by calling the patient. In addition, the patients' postoperative medicine adverse effects (nausea, vomiting, dizziness, rash, hallucination, somnolence, diarrhea, cramps, weakness, flushing), mobilization time (1 = 0–2 hours, 2 = 2–4 hours, 3 = 4–6 hours, 4 = 6–8 hours, 5 = 8–10 hours) and satisfaction with analgesia (1 = poor, 2 = good, 3 = excellent) were recorded.

All data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 11.5 (SPSS Company, Chicago, IL, USA). The *t*-test was used for comparing group means and the Chi-square or Fisher test was used to compare percentages. Statistical analyses used an ordinary ANOVA test for intra-group differences with post hoc test when $p < 0.05$ and the Mann–Whitney *U* test for intergroup differences. Differences in group demographic characteristics were tested using Student's *t*-test or the contingency table Chi-square test for categorical measures. A *p*-values <0.05 were considered statistically significant. Sample size was estimated using pain scores as the primary variable. Assuming an SD of 1 cm, we calculated that a group size of 30 patients would be sufficient to detect a difference of 1 cm on the VAS at an alpha threshold of 0.007 with 90% power. A *p*-value lowers than 0.05 was considered statistically significant and adjusted to a value of 0.007 when multiple comparisons were performed, according to Bonferroni.

Results

After obtaining local Ethics Committee approval for the study and written informed consent from the patients, when the demographic data of patients were compared, the gender sex distribution was 12 females and 18 males in all groups. An analysis of the age distribution showed that the average age was 45.7 ± 12.1 years in Group K, 45.2 ± 14.1 years in Group T, and 43.0 ± 10.5 years in Group M, and there were no statistically significant differences between the groups. BMI was found to be statistically similar across the groups. In addition, an analysis of ASA scores showed that ASA I/II grades were 23/7 in Group K, 22/8 in Group T, and 18/12 in Group M, which indicated statistically similar values (Table 1).

An analysis of the patients' intra-operative parameters showed that the total amount of crystalloid solution given and duration of anesthesia and surgery were statistically similar (Table 2).

Postoperative 0th and 15th minute VAS scores with/without movement indicated statistically significant differences with the highest pain score in Group M compared with the other groups. Thirtieth minute, 1st, 2nd and 6th hour VAS scores with/without movement in Group T were found to have significantly higher pain scores compared with Groups K and M. In addition, pain scores with/without movement at 0th, 15th, and 30th minutes were lowest in Group K and at Group M in the 1st, 2nd, and 6th hours (Table 3).

Regarding postoperative adverse effects, there were no statistical differences in nausea and vomiting between the groups at 0th, 15th, and 30th minutes, and the 1st, 2nd, and 6th hour. Postoperative hallucination was seen only in Group K and demonstrated significant differences compared with the other two groups (Table 4). None of the patients demonstrated any adverse effects such as dizziness, rash, somnolence, diarrhea, cramps, weakness, and flushing.

Table 1 Demographic data findings.

	Group K ($n = 30$)	Group T ($n = 30$)	Group M ($n = 30$)	p
Sex (F/M), n	12/18	12/18	12/18	0.999
Age (years) mean ± SD	45.7 ± 12.1	45.2 ± 14.1	43.0 ± 10.5	0.679
BMI ($kg.m^{-2}$)mean ± SD	27.8 ± 5.8	28.9 ± 5.7	28.9 ± 5.7	0.161
ASA (I/II), n	23/7	22/8	18/12	0.329

Among three groups $p > 0.05$.
F, female; M, male; BMI, Body Mass Index; ASA, American Society of Anesthesiologists Classification.

Table 2 Intra-operative data findings.

	Group K ($n = 30$)	Group T ($n = 30$)	Group M ($n = 30$)
Anesthesia duration (min), mean ± SD	52.0 ± 12.8	48.7 ± 13.3	51.7 ± 8.9
Surgery duration (min), mean ± SD	34.7 ± 8.4	30.6 ± 9.8	33.3 ± 2
Total crystalloid given (mL), mean ± SD	401.7 ± 122.8	397.3 ± 217.4	340.7 ± 106.2

Among three groups $p > 0.05$.

Table 3 Postoperative VAS scores.

	Group K ($n = 30$)	Group T ($n = 30$)	Group M ($n = 30$)
VAS with movement 0th min, mean ± SD	0.1 ± 0.3[b]	0.6 ± 1.7[b]	5.2 ± 3.2
VAS with movement 15th min, mean ± SD	0.3 ± 1.6[a]	3.9 ± 3.9	4.8 ± 3.2[c]
VAS with movement 30th min, mean ± SD	0.8 ± 2.1[a]	4.0 ± 3.4	1.7 ± 2.0[a]
VAS with movement 1st hr, mean ± SD	1.1 ± 2.2[a]	3.4 ± 2.9	0.1 ± 0.6[a]
VAS with movement 2nd hr, mean ± SD	0.6 ± 1.3[a]	2.6 ± 2.8	0[a]
VAS with movement 6th hr, mean ± SD	0.3 ± 1.2[b]	1.9 ± 2.3[b]	0
VAS without movement 0th min, mean ± SD	0.0 ± 1.2[b,a]	0.0 ± 0.4[b]	4.5 ± 3.1
VAS without movement 15th min, mean ± SD	0.3 ± 1.6	2.8 ± 3.4[c]	4.2 ± 2.8[c]
VAS without movement 30th min, mean ± SD	0.5 ± 1.6[a]	3.0 ± 3.3	1.6 ± 2.6[a]
VAS without movement 1st hr, mean ± SD	0.6 ± 1.6[a]	2.3 ± 2.6	0.2 ± 0.9[a]
VAS without movement 2nd hr, mean ± SD	0.4 ± 1.0[a]	1.5 ± 1.9	0[a]
VAS without movement 6th hr, mean ± SD	0.4 ± 1.4	1.0 ± 1.7	0[a]

VAS, Visual Analogue Scale.
[a] $p < 0.05$, when compared with Group T.
[b] $p < 0.05$, when compared with Group M.
[c] $p < 0.05$, when compared with Group K.

In the postoperative period, patients using additional analgesia and the mean number of additional analgesics used were statistically similar, but the first time of additional analgesic intake was earlier in Group M than in the other groups. The number of patients with pain at the 24th hour and analgesic satisfaction were similar, whereas the Group K was mobilized earlier (Table 5).

Discussion

Outpatient surgery procedures are defined as a patient staying in hospital for less than 12 hours following surgery, and knee arthroscopic surgeries are one of the most frequently conducted outpatient surgeries in many countries.[12] In all outpatient surgeries, postoperative pain is the most important contraindication that prevents discharge from hospital.[12] In addition, similar to many studies, choice of medicine to be used for postoperative analgesics and avoidance of opioid medicine, which has important adverse effects, have directed us to use local infiltration methods.[12] Pain in arthroscopies is caused by the stimulation of free nerve endings and afferent nociceptors and release of inflammatory factors such as bradykinin, histamine, and serotonin from damaged cells.[1] Nociceptive activity is associated with primary hyperalgesia, and pain and inflammation mediators disseminate pain from the incision to wider areas.[1,2,5] Therefore, exposure to agents that have local effects and portal incisions and surrounding capsular areas have been proven to provide more effective analgesia in postoperative pain.[5] Hence, we aimed to identify and compare intraarticular administration of tramadol, ketamine, and magnesium, with combinations of periarticular bupivacaine in terms of their analgesic effects, postoperative adverse effects, postoperative mobilization and satisfaction, and postoperative analgesic requirements by administering both weak opioid and non-opioid medications in terms of their analgesic effects, postoperative

Table 4 Analysis of postoperative nausea, vomiting, and hallucination.

	Group K ($n=30$)	Group T ($n=30$)	Group M ($n=30$)
Nausea 0th, *n* (%)	0 (0)	1 (100)	0 (0)
Nausea 15th min, *n* (%)	1 (50)	1 (50)	0 (0)
Nausea 30th min, *n* (%)	2 (40)	3 (60)	0 (0)
Nausea 1st hr, *n* (%)	2 (100)	0 (0)	0 (0)
Nausea 2nd hr, *n* (%)	1 (50)	1 (50)	0 (0)
Nausea 6th hr, *n* (%)	0 (33)	0 (33)	0 (33)
Vomiting 0th min, *n* (%)	0 (33)	0 (33)	0 (33)
Vomiting 15th min, n (%)	1 (100)	0 (0)	0 (0)
Vomiting 30th min, *n* (%)	1 (100)	0 (0)	0 (0)
Vomiting 1st hr, *n* (%)	2 (100)	0 (0)	0 (0)
Vomiting 2nd hr, *n* (%)	1 (100)	0 (0)	0 (0)
Vomiting 6th hr, *n* (%)	0 (33)	0 (33)	0 (33)
Hallucination, *n* (%)	30 (100)[a]	0 (0)	0 (0)

[a] $p < 0.05$ with Chi-square test in three groups.

adverse effects, postoperative mobilization and satisfaction, and postoperative analgesic requirements.

Use of both pericapsular bupivacaine and intraarticular analgesics in arthroscopic meniscectomy operations has been proven to be more effective in pain control and have effects that reduce postoperative adverse effects such as nausea, sedation, hypotension, rash, diplopia, and respiratory depression.[1] Therefore, local anesthetics have been frequently used with the infiltration method in arthroscopic operations.[2] Bupivacaine, one of the local anesthetic medicines, shows its effects by enabling the formation of action potentials in the neuronal membrane and/or preventing their spread, thus enabling afferent nociceptive blockage.[13] Therefore, all groups in this study were administered periarticular bupivacaine; this way, without harming articular chondrocytes, we aimed to increase the analgesic effect and decrease the adverse effects of intraarticular medication.

Intraarticular medicine injection is almost routine practice for postoperative pain control after knee arthroscopies.[5] A number of studies have been conducted on the combinations of many medicines and practices and their effectiveness.[1,2,5–7] Besides its peripheral analgesic effects, tramadol is a weak opioid that increases the function of the descending tramadol peripheral by enabling the activation of opioid receptors and inhibition of 5 hydroxytryptamine and noradrenalin reuptake.[2] A study found that 0.25% bupivacaine added to 100 mg of tramadol resulted in lower VAS pain scores, longer analgesia, and less additional analgesic need without causing adverse effects in the postoperative 24 hour compared with groups in which these medicines were used alone.[5] In our study, it was found that despite the satisfaction of all patients in each group about postoperative analgesia, the effect of intraarticular 100 mg tramadol, apart from in the early period, was higher in the VAS scores with and without movement in comparison with the ketamine and magnesium groups. In addition, although previous research showed that tramadol enabled early mobilization, our study showed that the ketamine group was mobilized earlier than both the tramadol and the magnesium group.

Ketamine NMDA interacts with serotonergic and adrenergic receptors and has analgesic activity apart from its anesthetic effect.[8] As an NMDA receptor antagonist, the intraarticular administration of ketamine, which has antinociceptive effects on both peripheral and central pain pathways, is frequently applied as a non-opioid analgesic. Several publications have shown that adjuvant use of ketamine with local anesthetics in knee arthroscopy provided rapid onset of movements and better analgesia.[14] The present study also found that intraarticular ketamine provided better analgesia than tramadol and magnesium by requiring less additional analgesics. However, it should be kept in mind that adverse effects may be encountered due to systemic absorption of high-dose intraarticular ketamine.[15] Patients hallucinating due to high doses of intraarticular ketamine presents a disadvantage in terms of discharge. However, if the more potent S (+)-ketamine form instead of R (−)-ketamine is used, which we used in our study, less ketamine can be given to reduce hallucinations, agitation, disorientation, pain, and anxiety.[16] In addition, this adverse effect can be present during administration but rapidly dissipates upon termination of treatment and low-dose of ketamine and/or by adding a benzodiazepine or an alpha-2-receptor agonist. The occurrence of adverse effects is limited and often well-tolerated by the patient. Despite the hallucination adverse effects, earlier mobilization was achieved in the ketamine group compared with the tramadol and magnesium groups. However, although there were fewer adverse effects when 0.5 $mg.kg^{-1}$ intraarticular ketamine was administered, it may not provide better analgesia than intraarticular bupivacaine.[17]

Although the peripheral anti-nociceptive effect of magnesium induced by voltage-dependent NMDA antagonism has not been fully identified, it is known that NMDA blockage of

Table 5 Analysis of postoperative analgesia and mobilization.

	Group K ($n=30$)	Group T ($n=30$)	Group M ($n=30$)
Patients who used additional analgesia, *n* (%)	25 (31.3)	29 (36.3)	26 (32.5)
Time of first analgesic (hour), mean ± SD	3.5 ± 1.6[a]	4.2 ± 1.9[a]	1.9 ± 0.5
Number of additional analgesics, mean ± SD	1.5 ± 1.1	1.6 ± 0.9	1.7 ± 1.0
Patients with pain on 24th hour, *n* (%)	1 (33.3)	2 (66.7)	0 (0)
Satisfaction about analgesia, mean ± SD	2.4 ± 0.5	2.2 ± 0.5	2.2 ± 0.5
Time of mobilization (hour), mean ± SD	1.6 ± 0.6	1.9 ± 0.6[b]	1.9 ± 0.2[b]

[a] $p < 0.05$, when compared with Group M.
[b] $p < 0.05$, when compared with Group K.

receptors decreases the excitability of the nociceptive input terminal in the C-fibers of the NMDA receptor blockade.[18] Calcium channel inhibition is also considered to be effective in the analgesic effect of magnesium.[19] Magnesium, which is known to reduce postoperative analgesic requirement,[10] has parenteral, oral, rectal, subcutaneous, transdermal, and intranasal administration use for this purpose.[20] A study reported that intraarticular magnesium was more effective than many intraarticular combinations.[21] Our this study found that intraarticular magnesium provided better analgesia than tramadol. Although it had similar analgesic results to the group given ketamine, additional analgesic use was found to be higher compared with the other two groups. In addition, adverse effects such as dizziness, somnolence, diarrhea, cramps, weakness, flushing, which are mainly seen in the use of systemic magnesium, were not observed in our intraarticular magnesium use.

Intraarticular ketamine was administered as 1 $mg.kg^{-1}$, as with doses of similar studies, and we similarly found that ketamine-containing combinations provided better analgesia.[22,23] However, further studies[24] suggested that intraarticular ketamine might be toxic to chondrocytes. The results of the in vitro study by Ozturk et al. may not be fully reflected in clinical practice because of the increased dilution of ketamine with the further increase of intraarticular fluid with portal hollies, intraarticular ketamine dilution to 20 mL, and only single-dose administration. Also, cell culture studies may lack several enzyme mechanisms, they are not embedded in their surrounding tissue and important cell repair mechanisms may be absent when used in vitro.[25] However, we believe that new studies to determine the dose of intraarticular ketamine to provide the best analgesia with minimal dosing will further reduce possible chondrotoxic effects.

A limitation of this study is that postoperative the patients' VAS scores, complications, and analgesic requirements were assessed for the first postoperative 24 hours only. The lack of investigation of different doses of intraarticular ketamine that provide less but sufficient analgesia limits our ability to study.

Summary

In conclusion, given that ketamine enables better postoperative analgesia, intraarticular ketamine in arthroscopic meniscectomies seems to be preferable agent despite unwanted effects such as hallucinations. However, like in all outpatient surgeries, arthroscopic surgeries should also involve maintenance of research for an ideal medication that is less harmful, has fewer adverse effects, but is more effective in analgesia through both medicine and dose and method studies.

Conflicts of interest

The authors declare no conflicts of interest.

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