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Comparison of efficacy of intra-articular morphine and steroid in patients with knee osteoarthritis

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Abstract

Introduction: Primary therapeutic aim in treatment of osteoarthritis of the knee is to relieve the pain of osteoarthritis. The aim of this study was to compare the efficacy of intra-articular triamcinolone with intra-articular morphine in pain relief due to osteoarthritis of the knee in the elderly population.

Materials and Methods: Patients between 50 and 80 years of age were randomized into three groups. Group M received morphine plus bupivacaine intra-articularly, Group T received triamcinolone plus bupivacaine intra-articularly, and Group C received saline plus bupivacaine intra-articularly. Patients were evaluated before injection and in 2nd, 4th, 6th, and 12th weeks after injection. First-line supplementary analgesic was oral paracetamol 1500 mg/day. If analgesia was insufficient with paracetamol, oral dexametopfen trometamol 50 mg/day was recommended to patients.

Results: After the intra-articular injection, there was statistically significant decrease in visual analog scale (VAS) scores in Groups M and T, when compared to Group C. The decrease of VAS scores seen at the first 2 weeks continued steadily up to the end of 12th week. There was a significant decrease in Groups M and T in the WOMAC scores, when compared to Group C. There was no significant difference in the WOMAC scores between morphine and steroid groups. Significantly less supplementary analgesics was used in the morphine and steroid groups.

Conclusion: Intra-articular morphine was as effective as intra-articular triamcinolone for analgesia in patients with osteoarthritis knee. Intra-articular morphine is possibly a better option than intra-articular steroid as it has lesser side effects.

Key words: Injection, knee, morphine, osteoarthritis, triamcinolone

Introduction

Osteoarthritis of the knee is one of the most frequent forms of arthritis, especially in the elderly population, and is a major cause of pain and disability.^[1,2] Underlying cause of the disease is degradation of cartilage and its presents clinically is pain, stiffness, limited mobility of the involved joint. Main symptom of osteoarthritis of the knee is pain; therefore, primary aim is to relieve the pain.^[3,4] Intra-articular opioids are used in addition to steroids.^[5-7]

Morphine and endogenous opioids (enkephalins, dynorphins, and β -endorphins) stimulate δ -, κ -, and μ -opioid receptors. or/and β -endorphins) stimulate sigma, kappa-, and μ -opioid receptors. Activation of all three main receptors has biological effects, which are mediated primarily via central nervous system.^[8,9] After discovery of opioid receptors in peripheral nerve terminals, opioids were administered locally. Antinociceptive and anti-inflammatory effects of morphine have been demonstrated.^[10,11] In chronic arthritis patients, intra-articular morphine injection provides analgesia, which is equivalent to dexamethasone. It is also possible that intra-articular morphine may have some anti-inflammatory actions.^[5]

There is no other study which compares long-term clinical effects of intra-articular morphine with dexamethasone in osteoarthritis of the knee in the literature. We aimed to compare intra-articular triamcinolone with morphine through a 12-week-period.

Materials and Methods

After the approval, of local ethical committee, written informed consent was obtained from each included patient. A double blind,

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prospective, randomized, and controlled trial was conducted on different modes of intra-articular analgesia in patients suffering from osteoarthritis knee. The inclusion and exclusion criteria were as per Table 1. Patients were randomized by the closed-envelope technique into three groups. Namely, Group M (morphine), Group T (steroid), and Group C (control).

In the supine position, the knee was flexed and a roll was placed under it. Under strict asepsis, a 1½-inch 25 G needle was placed between the patella and femoral condyle in the middle of the medial edge of patella. Local anesthetic was not used to the injection site. In Group M patients, morphine 5 mg (½ ml) with bupivacaine 20 mg (4 ml) and ½ ml saline (5 ml volume) was given intra-articularly. In Group T patients, triamcinolone acetonide 40 mg (1 ml) with bupivacaine 20 mg (4 ml) was given intra-articularly (5 ml volume). In Group C patients, 1 ml saline plus 20 mg bupivacaine (4 ml) was given intra-articularly (5 ml volume). Since the solutions were in different colors, sticker was used to cover injectors to hide to ensure blinding. Injections were administered by another blinded investigator. Patients were observed for 1 h after the injection. The knee was wrapped with compressive elastic bandage. Cold application was performed. After discharge, if there was persistent pain, patients were advised to take 1 g paracetamol orally three times daily. If there was persistent pain despite paracetamol, dexketoprofen trometamol 50 mg/daily orally was advised and its intake recorded.

Pain severity was evaluated according to visual analog scale (VAS), by the same blinded physician, before injection, and in 2nd, 4th, 6th and 12th weeks after injection. The following parameters were recorded at every visit:

1. VAS scores at daily activities only for the injected knee (0 = no pain and 10 = worst and most severe pain ever).
2. According to the Turkish version of WOMAC (Western Ontario and McMaster Universities) scale,^[15] which contains 24 questions [Table 2], pain scores were evaluated according to WOMAC-P and WOMAC-S. WOMAC is a new multidimensional, self-administered health status instrument for patients with osteoarthritis of the hip or knee.
3. Incidence of side effects, if any, such as itching, paresthesia, urinary retention, nausea-vomiting, dizziness-vertigo, and rash were recorded.

The SPSS 17.0 software program was used for statistical analysis. Efficacy of treatment was evaluated for each group using VAS, WOMAC-P, WOMAC-S, and WOMAC-F scores. Initial values and values in 2nd, 4th, 6th, and 12th weeks were analyzed with ANOVA one-way variance analysis. One-way ANOVA analysis was performed by post-hoc tests, Bonferroni correction. $P < 0.016$ was considered

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 50 and 80 years	Serious systemic diseases
Diagnosis of osteoarthritis of the knee according to American College of Rheumatology (ACR) criteria ^[12]	Secondary arthritis according to Osteoarthritis Research Society criteria ^[14]
Grades 3-4 according to Kellgren-Lawrence classification ^[13]	Allergy of drugs to be used
Laboratory evaluations within normal range	Bleeding diathesis
Complete blood cell count	Symptomatic osteoarthritis of the knee requiring treatment
Erythrocyte sedimentation rate	Previous history of intra-articular injection (hyaluronic acid, ozone therapy, corticosteroids, etc.)
C-reactive protein	Not responded adequately to treatment with acetaminofen or NSAIDs drugs
Rheumatoid factor	
Blood urea nitrogen	
Creatinine	
Alkaline phosphatase	
Alanine aminotransferase	
Aspartate aminotransferase	
Calcium	
Phosphorus	
Serum electrolytes	
Knee pain > 3 months	
Pain severity between 4 and 10 on the Visual Analog Scale	

Table 2: WOMAC scale questionnaire

Pain Questions

Walking on a flat surface
Going up or down stairs
At night while in bed
Sitting or lying
While standing
Stiffness questions:
How severe is your knee joint stiffness after wakening in the morning?
How severe is your knee stiffness after sitting, lying or resting later in the day?
Difficulty in function questions:
Descending stairs
Ascending stairs
Rising from sitting
Standing
Bending to the floor/pick up an object
Walking on a flat surface
Getting in/out of car
Going shopping
Putting on socks/stockings
Lying in bed (turning over, maintaining hip position)
Getting in/out of bath
Sitting
Getting on/off toilet
Heavy domestic duties (moving heavy boxes, scrubbing floors etc.)
Light domestic duties (cooking, dusting etc.)

as significant. Then, efficacy of three groups was compared with each other using variance analysis of repeated measures. Supplementary analgesic consumption was evaluated with chi-square test. $P < 0.05$ was accepted as statistically significant.

Results

A total 82 patients were recruited, but 9 out of them were excluded later as they did not come for follow-up. There was no significant difference of demographic data between groups [Table 3].

The VAS baseline values in the three groups were not significantly different ($P > 0.05$). VAS scores of the control group had no significant change over 12 weeks of time. The morphine and steroid groups had significantly decreased VAS scores at every visit over 12 weeks. The morphine and steroid groups were compared with each other, and their scores were similar ($P > 0.05$). Variance analysis of repeated measurements revealed decreased VAS scores of both morphine and steroid groups than the control group and this decrease continued until the end of 12th week [$P < 0.001$, Figure 1].

WOMAC pain, stiffness and, function scores were compared using one-way ANOVA. VAS scores of morphine and steroid groups were significantly decreased in 2nd, 4th, 6th, and 12th weeks [$P < 0.001$, Figure 2]. In three groups, there was a significant different compared in terms of the WOMAC baseline values ($P > 0.05$). Morphine and steroid groups were compared with each other using variance analysis of repeated measurements, and their WOMAC scores were also similar in 2nd, 4th, 6th, and 12th weeks [$P > 0.05$, Figure 2].

Patients in the morphine and steroid groups needed significantly lesser NSAID supplementation than patients in the control group. However, all patients of the control group needed NSAID supplementation and paracetamol. The morphine group had significantly lower NSAID consumption than steroid group ($P = 0.036$). No side effect was recorded for any patient during the conduct of this study.

Discussion

This study presents 12-week follow-up of 82 patients with osteoarthritis of the knee. We found that intra-articular morphine and triamcinolone had high analgesic efficacy. Intra-articular morphine had no side effects as observed in previous studies.^[5,6] No patient in this study had any adverse effects during 12 weeks. We used two different measurement methods (VAS and WOMAC) to assess

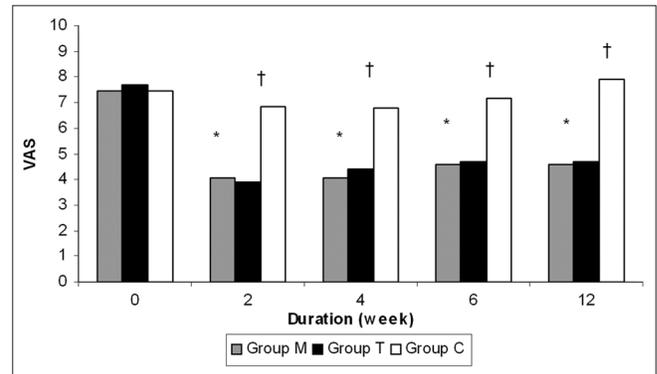


Figure 1: VAS scores versus time in the groups.*Significance of Group M versus Group T, $P > 0.05$. †Significance of Group M and Group T versus Group C, $P < 0.000$

Table 3: Demographic features of the three groups

Baseline characteristics	Group M (n = 23)	Group T (n = 25)	Group C (n = 25)	P value
Age, years	67.9 ± 7.8	68.6 ± 7.3	70.7 ± 7.7	0.420
Gender				
Males/females, n	3/20	4/21	7/18	0.372
Weight, kg	78.1 ± 13.6	77.8 ± 14.9	74.3 ± 9.6	0.635
Height, cm	163.4 ± 5.9	159.8 ± 7.8	161.9 ± 8.3	0.836
Education, years				
Illiterate	15	16	17	0.955
5 years	8	7	8	
Occupation				
Housewife	20 (86.9%)	21 (84%)	18 (72%)	0.340
Kellgren/Lawrence				
Grade 3	14	16	18	0.701
Grade 4	9	9	7	
Concomitant analgesic use				
Paracetamol	16	20	25	0.015*/0.404†
NSAID	6	14	25	0.000*/0.036*

Values are the mean ± SD, NSAID = Dexametopfen trometamol, $P > 0.05$ not significant. *Chi-square significance of Group M and Group T versus Group C. †Chi-square significance of Group M versus Group T.

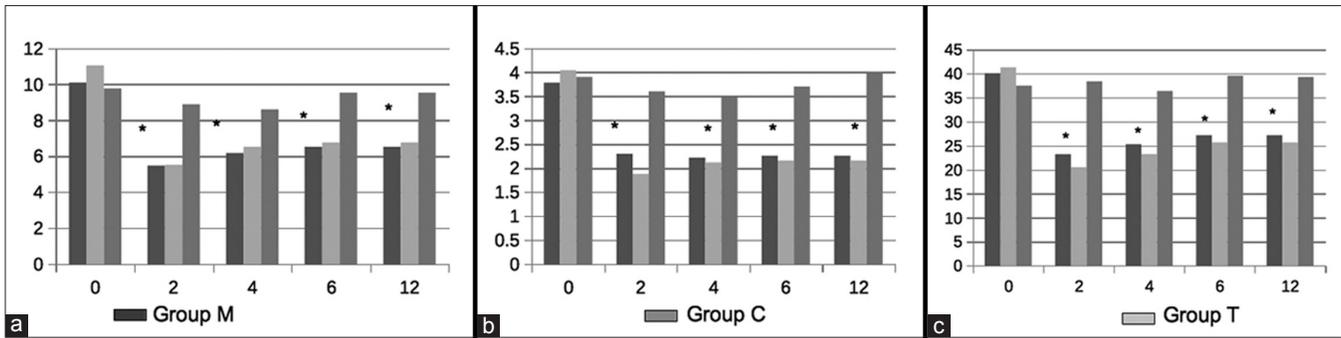


Figure 2: WOMAC scores versus time in the groups. (a) WOMAC - pain (0–20 point), (b) WOMAC - stiffness (0–8 point), and (c) WOMAC - function (0–68 point). *Significance of Group M and Group T versus Group C, $P < 0.000$

pain relief and functional improvement of the knee joint in this study.

The exact mechanism of analgesic and anti-inflammatory effect of intra-articular morphine is not known yet. Probably, opioid receptors of peripheral nerve terminals are activated.^[9,11] Opioid receptors are synthesized at dorsal root ganglions and transferred to nerve terminals via axonal route. When these receptors are stimulated, both endogenous and exogenous opioid peptides are activated simultaneously inside inflammatory cells.^[10] Local opioid-dependent analgesic actions are more pronounced in inflamed tissues than noninflamed tissues. This may be because of increased coupling with G-proteins, and/or may be associated with the increased number of exposed opioid receptors (which are exposed after degradation of perineural barriers and passage of agonists).^[8,16]

Intra-articular steroid and morphine were compared in chronic arthritis patients for relief of pain severity and both were found to provide pain relief for 2–6 days.^[5] We too found that intra-articular morphine provided long-term pain relief in patients with osteoarthritis.^[6,7] Morphine may inhibit the nociceptive sensitization or excitation of peripheral sensory neurons and development of long-term excitatory effects in spinal cord (wind-up) proinflammatory reflex mechanisms.^[11]

Low blood flow of the knee joint together with low clearance of synovial fluid may contribute to long-lasting analgesic effect. The long-term analgesic effect may also be due to low lipid solubility of morphine with low absorption rate. Morphine metabolites too have an analgesic effect. Furthermore, morphine has cellular pro-proliferative effects, which may be associated with cartilage regeneration and regulation of chondrocyte growth.^[8]

Instead of systemic absorption, morphine was shown to stay inside the knee joint after intra-articular injection. In a study, comparing same doses of intra-articular with intravenous morphine, significantly different plasma levels were found. Intra-articular morphine has significantly lower systemic

side effects, such as nausea-vomiting, dizziness-vertigo, constipation, dependency-abuse, compared to systemic administration.^[5]

Studies have shown that demographic features have a role in effectiveness of morphine, in treatment of both acute and chronic pain. Clinical presentation and side effects of opioids are affected by demographic features as well.^[17-19] Patients in our study were of low socioeconomically and educational status. However, the compliance of patients was good and increased because their pain stopped a few minutes after intra-articular injections. All injections are performed by the same experienced doctor at the first attempt. Nine patients were excluded from as they did not come for follow-up examinations.

There is a minimal risk of injury to joint with single-shot corticosteroid injection. On the other hand, long-term triamcinolone injection may lead to harmful consequences to joint cartilage.^[20] Long-term and repeated intra-articular steroid injections may lead to serious side effects of systemic steroids.^[21-23] The most feared consequence is steroid-induced arthropathy and joint sepsis.^[2,24,25] Every injection causes some degree of anxiety to the physicians performing it.^[26] However, one study suggests that there are no adverse effects, to anatomical structures of the knee joint, of steroid injections at 3 month intervals within 2 years.^[3] Lipid necrosis, dermal atrophy, depigmentation, and subcutaneous tissue atrophy are minor local complications seen near the injection site. Malposition of the needle may cause these minor local complications.^[21] Easy-one-shot injection is performed with 1½-inch 25 G needle directly without any risk of malposition.

Intra-articular analgesic drug administration helps reduce consumption of oral analgesic/anti-inflammatory drugs. Our control group had insufficient level of analgesia with paracetamol, and their VAS/WOMAC scores were high; therefore, we had to give dexketoprofen trometamol to these patients in addition to paracetamol. The morphine and steroid groups had significantly lower consumption of other analgesics

and their pain scores were low.^[5] All of the included patients refused arthroscopic debridement and/or knee prosthesis operations. They had to use NSAID for longer terms and were prone to their gastrointestinal side effects. NSAID complication costs are at least three times higher than the cost of intra-articular steroid injections.^[24]

In conclusion, intra-articular morphine has comparable efficacy with intra-articular triamcinolone injection in pain relief. Nevertheless, further studies are needed for evaluation of dosage and effectiveness in different and /or larger patient populations in order to confirm these results.

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