ORIGINAL ARTICLE

Comparison of the Effect of Intra-articular Injection of Methylprednisolone Alone and in Combination with Combined Ketamine in Pain Reduction in Patients with Knee Osteoarthritis

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Abstract

Background and Objective: Pain is a common complaint in knee osteoarthritis (OA) and the main cause of functional disabilities among middle-aged and older persons. The conventional treatments are medications, administered in long-term and are costly with significant side effects. Therefore, it is necessary to develop new efficient therapeutic approaches part icularly those ones that allow the patients to continue their work. The present study aimed to comparatively investigate the pain relieving efficacy of intra-articular injection of methylprednisolone alone and combined ketamine-methylprednisolone in patients with knee OA. **Materials and Methods:** This is a double-blind clinical trial conducted on patients with knee OA. Seventy patients were randomly divided into two treatment groups (each group 35 cases aged 40-73 years old) of control and case groups. The control group received 40 mg methylprednisolone and 1 ml of distilled water and the case group received 40 mg of methylprednisolone along with ketamine (0.5 mg/kg) intra-articularly. The pain perceived by the patients was assessed using a visual analog scale (VAS) (at three-time points: Before injection, 1 month, and 3 months after injection). The amount of pain reduction was compared pre- and post-injection in each group and between the two groups. **Results:** The pain reduction in the control and case groups was the same at the 1st month. The pain VAS score in the control group at the 3 month follow-up showed gradually increased. **Conclusion:** The VAS pain score showed a higher level of stability in the reduction of pain intensity in case group and these people experienced the reduction in the severity of pain for a longer time.

Key words: Ketamine, methylprednisolone, osteoarthritis, pain

INTRODUCTION

Osteoarthritis (OA) is a common musculoskeletal disorder and the leading cause of disability with several morbidities and constraints imposing significant healthcare and occupation burdens.[1] During the OA development, all anatomic element joints including cartilage, bone, synovium, joint capsule, and muscles around the joint are involved.[2] Distinguishing features of OA are bone remodeling, destruction of the cartilage, synovial inflammation, and loss of joint function, and finally, genu varum will occur. Radiographical changes and pain caused by OA start from about 35 years old which is mainly activity dependent.[3] With the progression of OA, pain will be more intensive and movement restrictions will also be more intensive.[4]

OA is the leading cause of 90% of cases of the knee and the hip replacement surgeries worldwide.[5] The population of Iran, like other Asian countries, is currently becoming old

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quickly. It is estimated that the ratio of the population aged over 65 years in developing countries doubles to the year 2040 (from 6.8% in 2008 to 16.2% in 2040).[6]

The aforementioned changes in developed countries gradually happened with respect to the social and economic progress have taken place but in Asian countries takes place within 2-3 decades (e.g. in Singapore, the population over 65 years increase to about 316% in 2040).[7]

Due to the quality of lifestyle in Iran, the knee arthritis has a very high prevalence and causes several problems for Iranians. Since the usual treatments in the form of long-lasting medications are costly and expensive for patients, and also, the lack of treatment causes morbidity and disability to earn a living on a daily basis, so it is necessary to adopt new and effective therapeutic measures as much as possible to provide the field for patients to back to work and to avoid additional costs.

In addition to adjusting the daily activities, using pharmacological treatments, particularly, nonsteroidal anti-inflammatory drugs have a major role in the treatment of patients and can be used as oral, injection, or topical administrations. Due to side effects of this group of drugs, care should be taken in recommendation for these drugs. Physical therapy also has a major role in reducing the pain and increasing the functional abilities of the patients.

Currently, different therapeutic methods are prescribed for the management of knee OA. Almost, in all of these approaches, the patients are advised to adjust their daily habits and activities and avoid the long-term flexion of the knee.[8]

Performing an intra-articular injection also is one of the appropriate and effective ways in the reduction of pain in patients in which several drugs, such as steroids, are used. For some patients with OA, total joint replacement surgery is a final treatment solution that is a costly treatment with significant potential restrictions on their life.[9]

Like other sodium salts, methylprednisolone is a water soluble drug and can be administered as injection. This drug is similar to adrenal corticosteroids and has anti-inflammatory effects. By inhibiting the enzymes of cyclooxygenase and lipooxygenase, these drugs stop the release of relevant mediators.

By reduction of inflammatory mediators, swelling and effusion are decreased and range of motion will increase. In addition, reducing these mediators will reduce the pain by decreasing pain receptor stimulations.[10]

Ketamine is an inhibitor for N-methyl-D-aspartate and inhibits it non-competitively and inhibits calcium and sodium entry. This material is water soluble and can be used orally or injectably.

This is a dissociative drug and its major effect is on the limbic system. Because of its water solubility, the drug effects will appear rapidly. This medication has a stimulative effect on the cardiovascular system. Probably due to the effect of inhibition on the cell stimulation, this drug reduces pain. After performing arthroscopic surgery of the knee, the analgesic effect of this drug was investigated and acceptable results were obtained.[11,12]

Therefore, the present study was aimed to comparatively investigate the pain relieving efficacy of intra-articular injection of methylprednisolone alone and combined ketamine-methylprednisolone in patients with knee OA.

MATERIALS AND METHODS

This was a double-blind case–control clinical trial conducted on patients with knee OA. Seventy patients were randomly divided into two treatment groups (each group 35 cases aged 40-73 years old) of control and case groups. The patients were classified into control and case groups and studied. These two groups were selected as possible as in terms of age, sex, as well as underlying diseases.

The first basic design of the study was to intra-articularly injection of distilled water in the control group and ketamine in case group. However, this injection was associated with the possibility of an intra-articular infection and lack of therapeutic effects of distilled water in these patients. Moreover, because of observing the ethical issues and failure to impose the risk of infection to patients, it was decided to use methylprednisolone and a combination of ketamine-methylprednisolone, respectively, in the control group and the case group.

The patients were visited in an orthopedic clinic, and after the definitive diagnosis of knee OA, they were divided into two groups based on the radiographic and clinical findings. The two groups were selected to be matched as much as possible in age, gender, and disease characteristics. The amount of the pain intensity of each patient was measured and recorded using a VAS. On this score, the pain intensity of the patient is assessed visually and based on the patient's self-reports [Figure 1].

Forty mg methylprednisolone (Aburaihan Pharmaceutical Co., Iran) and 1 ml of distilled water were injected into the controls intra-articularly. 40 mg methylprednisolone and 0.5 mg/kg ketamine were intra-articularly and simultaneously injected into the cases. All injections were done by compliance with the full sterility condition and after checking out and recording vital signs of heart rate, systolic and diastolic blood pressure, and electrocardiogram and pulse oximetry for patients. It should be noted that the physician who injected the drug and the patient was blinded on the type of medication administered, and the drugs were prepared by someone else.

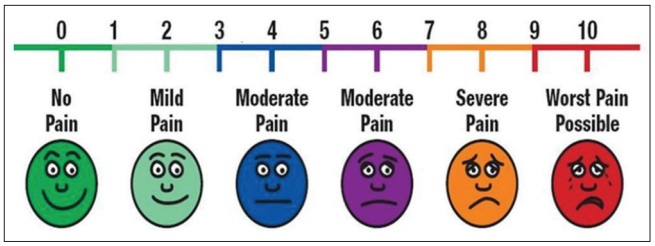

Figure 1: Visual analog scale used in this study to score the pain intensity of patients

After performing the injections, the patients were made under the auspices for about 2 h in terms of possible side effects, including nausea, dizziness, blood pressure changes, and changes of consciousness.

During this assessment, most of the patients were released without any problem. During the period of assessment, the patients were banned from taking any other medication that had an analgesic effect. Moreover, if they used drug, they were excluded. After a month, all patients were visited again and based on the VAS score, the amount of their pain intensity was measured and recorded again. The above steps also were done again during 3 months after the injection. In this study, the inclusion criteria were:

1. The existence of OA of the knee based on the clinical and radiographical criteria
2. Medicinal treatment failed, at least for a month
3. Normal knee anatomy and the absence of rheumatologic disorders
4. The age range of 40-75 years old.

And the exclusion criteria for patients from this study were as follows:

1. Simultaneous consumption of an analgesic drug during evaluation
2. The lack of access to the patient and failure to perform a follow-up based on the specified program
3. Rheumatic disease or history of trauma to the knee or damage to meniscus or knee ligaments
4. Drug addiction
5. Clotting disorders
6. Local infections.

Information about each patient was checked. The VAS changes were measured and then statistically analyzed.

Some of the findings relating to patients in the group receiving methylprednisolone-ketamine group are presented in Table 1.

Some of the findings relating to patients in the group receiving methylprednisolone are presented in Table 2.

The experimental procedures of this study including clinical examinations, drug injections, and the outcome assessments were performed in the Ahvaz Razi Hospital, an affiliated Hospital to Ahvaz Jundishapur University of Medical Sciences (AJUMS), Iran. All of the experimental procedures of this study were approved by the Local Ethics Committee of AJUMS, Ahvaz, Iran (Registration Code: AJUMS. REC.1393.320) that are in accordance with the ethical standards and regulations of studies involved in human beings of the Declaration of Helsinki (1964). After the enrollment and before the start of the experimental procedures, the researchers clearly explained the aim and objectives of the study, procedures, and their possible benefits and side effects to the patients. Then, all participants filled and signed written consent form for their participation in the study.

Table 1: VAS score in case group

ΣVAS_3-VAS_1	ΣVAS_3-VAS_1	Number of patients	VAS_0
0.17	−4.70	0	2
SD: 0.57	SD: 1.29	0	4
		14	6
		19	8
		1	10

VAS_0: Immediately after intervention, VAS_1: 1-month follow-up, VAS_3: 3-month follow-up. SD: Standard deviation, VAS: Visual analog scale

Table 2: VAS score in case group

ΣVAS_3-VAS_1	ΣVAS_1-VAS_0	Number of patients	VAS0
0.645	−4.96	0	2
SD: 1.08	SD: 1.25	0	4
		14	6
		16	8
		1	10

VAS_0: Immediately after intervention, VAS_1: 1-month follow-up, VAS_3: 3-month follow-up. SD: Standard deviation, VAS: Visual analog scale

RESULTS

At the end of the assessment, based on the inclusion and exclusion criteria, 34 patients in the case group and 31 patients from the control group could be studied, and the final results were presented based on their findings. Most of the patients did not report a major complaint as the side effects of the injection. Only one patient was admitted for observation due to severe dizziness and was released the next morning. In both the control and case groups, after injection, the amount of pain relief at the 1-month follow-up had a statistically significant reduction, and the changes in the VAS score indicated pain reduction that indicated the influence of injections in both groups.

The two groups showed no significant difference in the intensity of the perceived pain scores indicating that

adding ketamine did not enhance the analgesic effect of methylprednisolone in the 1st month.

Assessments at the 3-month follow-up on the pain scores showed that some of the patients in the control group experienced significantly increased pain compared to the pain score at the 1-month follow-up. This increase showed that the effect of methylprednisolone declined after 3 months, and patients' pain was stronger again.

The results of the statistical analysis in the case group show that after doing injections, the pain has been reduced significantly in the 1st month. The amount of reduction of the intensity of the pain in the 1st month in this group is almost equivalent to the control group, and adding the ketamine has not had any enhancing effect on the intensity of pain relief. However, the 3-month survey shows that unlike the controls in this group the analgesic effect still remains and a more effect can be seen in this group than in the control group. The statistical results of the case group show that VAS in the 1-month and the 3-month courses has not had any significant change. Therefore, adding ketamine to methylprednisolone has stabilized analgesic effect of methylprednisolone, or the effect of this drug has been applied to delay and decrease pain independently. Considering the short period of study of patients, it is necessary to check the above effect for a longer time.

DISCUSSION

In previous studies, the influence of ketamine on pain relief for patients with partial meniscectomy has been proven, and in all these patients, a surgical procedure has been done on the knee; on the other hand, in the previous studies, the effect of corticosteroid has been proven.[11] For example, by injecting corticosteroids (20 mg, triamcinolone) and comparing it with placebo in the 48 patients with OA, Dieppe *et al.* established its impact on the reduction of pain and tenderness.[13] In a double-blind prospective study, On 60 patients with arthroscopic surgery, Didom Dal observed that the consumption of sedative medicine in those, who have received 0.5 mg/kg of intra-articular ketamine, has been less than control group.[14] In a study conducted by Borner *et al.,* 68 patients were classified in four groups that bupivacaine (10 ml of 0.25%), intra-articular ketamine, (0.9% NaCl to 10 cc 0.25 mg/kg), intravenous ketamine (0.25 kg/mg), and 10 ml (0.9% NaCl) was given to the first, second, third, and fourth groups, respectively.[15]

At the end of the study, the control group who received intra-articular ketamine alone had a significant pain reduction compared with other people.[16] It should be noted that in a study conducted by Huang *et al.*, on patients with arthroscopic surgery, no significant effect of ketamine was observed.

This study was for the effect of ketamine in patients with OA of the knee. In these patients, no surgical procedure was done on the knee joint, and this treatment is considered as outpatient one. The prescription of this medication is not generally associated with significant side effects and is on the outpatient basis. While its 1-month effect in keeping with methylprednisolone does not cause exacerbation of analgesic effect, but due to it, it brings longer analgesic effect. It is recommended that patients with severe arthritis and resistant to other treatments, who are not a good candidates for surgery to avoid pharmaceutical side effects and reduce the dosage of other medicines, use intra-articular ketamine.

One of the confounding factors and limits of this study that needs to pay attention is to advise patients not to use other analgesic medications during the period of investigation. However, due to convenient access to medication by patients and on the other some local beliefs, the use of local remedies can alter the results of the survey. On the other hand, many patients without coordination may use their previous medications. Since, in the case group, two drugs were simultaneously prescribed, so the probability of the effect of those two drugs on together should not be overlooked. It seems that another study in compliance with the principles of medical ethics and by providing the two groups of patients should be carried out. In the control group, an inert material such as distilled water should be injected and ketamine should be injected in the case group. If the above study is unable to do, we can select just a group of patients for injecting intra-articular ketamine.

CONCLUSIONS

This study indicates that ketamine affects the OA pain and prolongs the analgesic period in the patients. In the case group, the results of VAS in the 3-month benchmark represent the prolonged period of painlessness. Although proof of independent ketamine or analgesic effect in keeping with methylprednisolone in this study is not evident, this study indicates that new treatments with fewer side effects can be used in the treatment of OA instead of traditional medicines. The study can underlie other similar studies with the help of other drugs. Considering that the study was prospective and blind clinical trials, its results can be used as the basis for similar studies.

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