Original Article

Effect of intra-articular hyalase, Ketorolac, marcaine and triamcinolone, versus Ketorolac, marcaine and triamcinolone for reducing knee joint pain other than joint replacement

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Abstract

Introduction: Knee pain is one of the causes of physiological complications in patients with osteoarthritis of the knee. It is necessary to provide a solution to reduce pain in these patients. Our study aimed to compare the effect of intra-articular hyalase, ketorolac, marcaine, and triamcinolone versus ketorolac, marcaine, and triamcinolone for reducing knee joint pain after knee surgery. **Methods:** This clinical study was performed on 30 candidates for knee surgery other than knee replacement from 2019 to 2020. The patients were randomly divided into two groups: hyalase, ketorolac, marcaine, and triamcinolone (group 1) and ketorolac, marcaine, and triamcinolone (group 2). The patient's pain score was recorded by the Numeric Rating Scale (NRS) and range of motion (ROM) at the end of the first week, the end of the first month, and the end of the third month as well as the sixth month and the twelfth month after surgery. **Results:** The mean age of the patients was 42.3 years. On average, the group receiving hyalase (first group) received about 30% better scores and had less pain ($P < 0.05$). In the first week, first month, and third month, no significant difference was observed between the two groups. But the pain scores for the first and second groups were 3.1 and 4.5 during the sixth to twelfth months, respectively ($P < 0.05$). Moreover, the increase in ROM during the sixth to twelfth months was significantly higher in the group receiving hyalase ($P < 0.05$). **Conclusion:** Adding hyalase to ketorolac, marcaine, and triamcinolone could improve pain control in the short and long term and this could be capable of reducing the need for additional drugs.

Keywords: Hyalase, intra-articular injection, ketorolac, knee joint pain

Introduction

Many people in the world suffer from knee problems every year, and the number of these patients is expanding despite the increase in the elderly population in Iran. In many cases, people with knee problems need knee surgery.[1,2] It has been reported that a high percentage of people experience severe pain after knee surgery, and some patients experience this pain for months. These pains can cause short-term and even long-term physiological and respiratory complications, increased blood pressure, heart rate, sympathetic stimulation, decreased respiratory power, decreased lung volume, atelectasis, and lung infections.[3] In addition to physiological problems, knee pain also affects a patient's sense of well-being and quality of life.[4,5]

Range of motion (ROM) disturbance is another complication of osteoarthritis that causes the patients to have limited activity

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even after knee surgery.[6] Decreased ROM in patients with long-term knee osteoarthritis also has limitations.[7] There are many strategies for controlling pain, one of the most important of which is opioids, but there are conflicting findings of opioids, where some studies have identified opioids as good pain controllers, but some have listed several side effects for them. Intra-articular injection of marcaine can significantly reduce the pain following knee aspiration in people with osteoarthritis of the joint, but in the long run, does not control pain well.[8,9] Furthermore, morphine is capable of reducing pain by affecting the central nervous receptors but nausea, vomiting, constipation, drowsiness, respiratory depression, and hypotension in higher doses have caused the doctors to use alternative medicines or drugs for decreasing the dosage of morphine.[9]

Non-steroidal anti-inflammatory drugs (NSAIDs) are other commonly used drugs that play an effective role in pain control.[10] Ketorolac is one of the NSAIDs that have minimal gastrointestinal side effects. It is recommended to reduce postoperative pain and the use of narcotic analgesics.[11] Combining non-steroidal anti-inflammatory drugs with narcotics can be more effective in controlling pain.[12,13]

Another compound that has recently received attention is hyalase. The analgesic effect of this drug has been proven by its addition to drug combinations. Another reason for using hyalase is its effectiveness in controlling low-back pain after spinal cord surgery. Hyalase had a significant effect on pain index in patients at different times after surgery by reducing pain in the receiving groups but alone was not sufficient to reduce pain and patient comfort. Studies have considered paying attention to hyalase as a new strategy in reducing postoperative pain.[14-16] Regarding the importance of pain relief in patients undergoing knee surgery and the importance of providing the best pain reliever, we investigated a new drug combination in reducing knee pain. This study aimed to compare the effect of intra-articular hyalase, ketorolac, marcaine, and triamcinolone versus ketorolac, marcaine, and triamcinolone for reducing knee joint pain after knee surgery.

Materials and Methods

Study design

This clinical study was performed on the candidates for knee surgery, except for knee replacement from 2019 to 2020 in the clinic of the Bu Ali Hospital in Sari. The patients were randomly admitted to the study considering the inclusion criteria. The sample size was calculated in each group to be 17 based on the study by Sun *et al.* ($\alpha = 0.05$, statistical power of 90% and 10% probability of loss).

During the study, the patients' informed consent was obtained and ethical issues were observed.

Inclusion and exclusion criteria

The inclusion criteria included a willingness to participate in the study, American society of anesthesiologists (ASA) classes I and II, ages between 20 and 60 years, patients who underwent knee surgery other than knee replacement, people with chronic diseases, unwillingness to participate in the study, fasting, respiratory problems, and individuals with a history of psychotropic drugs and people with a history of psychotropic drugs and allergies to the drugs used.

Procedure

The eligible patients were divided into two groups of hyalase, ketorolac, marcaine, and triamcinolone (group 1) and ketorolac, marcaine, and triamcinolone (group 2) by simple random sampling upon entering the operating room.

After entering the operating room, the patients underwent hemodynamic and respiratory monitoring throughout the sedation period. This monitoring was performed under the supervision of an anesthesiologist according to the outpatient monitoring instructions, including continuous monitoring of heart rate, respiration rate, and percentage of peripheral blood oxygen by a pulse oximeter. Intermittent and non-invasive measurements of systolic and diastolic blood pressure were performed. All these criteria were recorded in a double-blind trial at intervals, 30 and 60 min later for each patient in a separate form by the anesthesia nurse who was unaware of the medication regimen used in each group. Fluid administration was performed through a 20G face angiocatheter. The patients underwent surgery using general anesthesia. The induction of anesthesia in all the patients of the two groups was performed equally using propofol 2 mg/kg (low-chain molecular type), fentanyl 3 μg/kg (Abu Reihan Company), and muscle relaxant 0.5 mg (Rasht Company).

An anesthesiologist injected the drugs according to the type of group of each patient. All the patients were intubated with an appropriately-sized endotracheal tube. During the operation, the amount of bleeding and other discharge parameters were assessed. The patient's pain score was measured by the Numeric Rating Scale (NRS) and knee ROM in the case groups by a goniometer. The center of the goniometer was on the outside of the femur, its upper arm was parallel to the long axis of the femur and toward the greater trochanter and its lower arm was parallel to the long axis of the fibula and toward the external ankle. The variables were recorded at the end of the first week, the end of the first month, the end of the third, sixth, and twelfth months. Finally, the data were categorized for statistical analysis.

Data analysis

To compare knowledge and performance in the studied groups, SPSS software version 22 was used. For descriptive purposes, descriptive indices, central indices, and dispersion were used. An independent t-test was used to achieve the analytical goals. A significant level of 0.05 was considered to be statistically significant.

Results

The demographic findings showed that the mean age of the patients in the first and second groups was 42.7 and 43.1 years,

respectively. The two groups were equal in terms of gender, age, and weight**.** The two groups were in the same condition in terms of the hemodynamic factors. The comparison of the hemodynamic variables at the beginning of entering the operating room before sedation in the two groups showed no significant difference between the two groups before the intervention ($P > 0.05$) [Tables 1 and 2].

The mean pain scores in the first and second groups were determined to be 3.56 ± 0.93 and 4.48 ± 0.84, respectively. The first group received about 30% better scores and had less pain. The difference between the two groups was statistically significant [$P < 0.05$; Table 3].

The amount of pain in both groups was reduced during the follow-up period and the lowest amount of pain was observed in both groups 12 months after surgery. The comparison of the mean postoperative pain intensity between the two groups did not show significant differences during the first week, the end of the first month, and the end of the third month ($P < 0.05$). But the pain score was 3.1 and 4.5 for the first group and second group from the sixth to the twelfth month, respectively. The first group had a more effective role in improving pain than the second group when the pain score in this group showed a significant decrease ($P < 0.05$).

The percentage of the range of motion changes during the sixth and twelfth months in the two groups were statistically significant. The changes in the range of motion in the first group receiving hyalase increased by 3.9% during the sixth month, compared with 5.2% in the twelfth month. A decrease in ROM was found in 15% of the patients who did not receive hyalase, but the ROM was within the normal range in the patients receiving hyalase [Table 4].

Table 1: Individual variables

Variable	SD±Mean		*P*
	Frist group	Second group	
Age	42.72±2.46	43.1±2.46	0.24
Sex	8.7	7.8	0.15
Weight (kg)	77.57±2.46	79.29±7.48	0.35

Table 2: Hemodynamic variables

Variable	SD±Mean		*P*
	Frist group	Second group	
Pulse count	107.43±11.33	109.5±10.46	0.18
Systolic blood pressure	114.67±8.46	112.34±9.46	0.23
Diastolic blood pressure	68.12±4.55	66.39±5.17	0.54
Number of breaths	20.17±2.46	21.34±2.46	0.14

Table 3: Comparison of the mean pain intensity during follow-up

Postoperative pain	Groups		*P*
	Frist group	Second group	
Average pain score	3.56±0.93	4.48±0.84	0.04
The first week	4.12±0.84	4.58 ± -0.59	0.12
first month	4.04±0.76	4.37±0.49	0.23
Third month	3.79±0.63	4.22±0.64	0.08
The 6 month	3.26±0.69	4.12±0.87	0.01
Twelfth month	3.12±0.75	4.08±0.89	0.009

Table 4: Comparison of ROMs during follow-up

ROM postoperative ROM (degree)	Groups		Percentage of range of motion changes	*P*
	Frist group	Second group		
The first week	121.32±13.19	120.24±8.19	1.1	0.33
first month	119.09±7.31	120.16±7.32	0.9	0.43
Third month	124.79±6.31	123.22±8.71	1.2	0.25
The sixth month	133.26±9.69	126.72±11.07	3.9	0.03
Twelfth month	139.32±8.75	125.98±8.65	5.2	0.01

Discussion

In the present study, injections of steroids, hyaluronidase, ketorolac, marcaine, and triamcinolone were considered as an effective treatment for reducing knee joint pain other than joint replacement. The pain scores were different in the studied groups. The mean pain score in the first group (hyaluronidase, ketorolac, marcaine, and triamcinolone) showed a lower score than the second group (ketorolac, marcaine, and triamcinolone) and was significantly more effective in reducing pain.

Similar studies in Iran have shown that the visual analog scale (VAS) score in the group receiving hyaluronidase was significantly lower than the group receiving lidocaine and bicarbonate. In addition, the patients in the hyaluronidase group experienced a greater reduction in the weeks before the injection, after the injection, in the second and fourth weeks, indicating the permanent effect of this drug on the reduction of pain.[15] In 2021, Lee *et al*.[16] examined the combination of hyalase and triamcinolone for sedation and shoulder pain. The results showed that both drug groups were effective in reducing the pain scores in patients, but there was a significant reduction in the pain scores without the need for treatment in the combination group of hyalase and triamcinolone, which was consistent with the present study.

The findings of our study showed that the scores for the first and second groups were 3.1 and 4.5, respectively. The first group had a more effective role in improving pain than the second group and the pain score in this group showed a significant decrease.

A study by Kim *et al*.[17] showed that interlaminar lumbar epidural injection (ILEI) for failed back surgery syndrome treated with triamcinolone and hyaluronidase showed longer-term effectiveness to reduce pain. Their findings showed that hyalase alone had little effect on pain, but when combined with other opioids, a significant effect on VAS and oswestry disability index (ODI) was observed. Also, after 12 weeks, only patients in the group receiving hyaluronidase and the epidural drug had a significant effect on reducing VAS and ODI.

In the present study, a combination of anti-inflammatory and anesthetic drugs was used, and the combined effect of these drugs on pain and sedation has been proven in previous studies.[18-20] The study by Reuben *et al*.[21] showed that patients receiving lidocaine with ketorolac experienced significantly less pain during surgery. In another study, the addition of dexmedetomidine to ketorolac further reduced the postoperative pain scores and increased satisfaction compared to its addition to paracetamol.[22] Also, the duration of analgesia was longer in the group receiving the anti-inflammatory compound.[23] However, in the present study, their analgesic efficacy was evaluated by adding hyalase to the combination of these drugs, suggesting the efficacy of adding this compound during the study and for long periods.

Hyaluronidase has been recognized in many studies as an effective substance in reducing pain. The findings revealed that hyaluronidase was capable of increasing the absorption of drugs in the tissue and reduced tissue damage during drug injection. Furthermore, hyaluronidase has become an important drug to reduce complications and adverse outcomes after knee surgery by reducing the pain process.[24,25] A study found that the group receiving NSAIDs experienced significantly longer analgesia after surgery and that their number of pain sensations was lower during recovery. It was shown that these drugs with systemic absorption can play a role in controlling the cyclooxygenase and reducing pain.[21]

Many other studies have confirmed that the use of intravenous NSAIDs with other opioids could be effective in delaying the onset of postoperative pain, but pain control is still an important issue.[21,26,27] In 2017, Germán *et al*.[28] reported that multidisciplinary management using NSAIDs or paracetamol could be capable of improving the safety and quality of analgesia and reducing the need for drugs, but offering new solutions is also of great importance. The present study, in addition to the use of NSAIDs and narcotics, introduced the use of hyalase for reducing pain, which, in general, showed effective results in reducing pain in patients undergoing knee surgery.

Overall, our findings showed that patients receiving hyalase not only experienced significant pain relief but also had better ROM during the sixth and twelfth months than those who did not receive hyalase. There was a decrease in ROM in 15% of the patients who did not receive hyalase, but ROM was within the normal range in patients receiving hyalase. Increased postoperative ROM indicated the effective role of hyalase in reducing adhesion and subsequent increase in the knee range of motion.

In the present study, no obvious side effects were observed in the hyaluronidase group. Of course, allergic reactions are one of the most common side effects of hyaluronidase, which are mostly local,[29] but systemic reactions may occur in rare cases. Since most allergic reactions to hyaluronidase are short term, it is recommended that low-dose injection tests can be performed before use.

Conclusion

In the present study, the mean pain score at almost all different times after surgery in the hyalase group (group 1) was significantly lower than the other group, indicating the effective role of adding hyalase in increasing analgesia.

Decreased adhesion and subsequent increase in ROM recovery was another important finding of the present study, indicating the effectiveness of hyalase on the range of motion. Overall, pain in the first group showed a significant reduction during the sixth and twelfth-month- follow-up periods. Further studies are needed to be performed in longer follow-up periods with larger sample size.

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Conflicts of interest

There are no conflicts of interest.

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