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Research Article

The Effectiveness of Intra-Articular Injection of Hypertonic Saline in Pain Control and Function of Patients with Knee Osteoarthritis

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Abstract

Background: The aim of this study was to report the effectiveness of intra-articular injection of hypertonic saline in pain reduction and functional improvement in patients with knee osteoarthritis (OA).
Methods: Patients with knee pain and dysfunction who fulfilled the American College of Rheumatology criteria and whose illness was sub-acute or chronic were enrolled. We performed a single intra-articular injection of 5 cc of hypertonic (5%) saline solution. Measured outcomes were Visual Analogue Scale (VAS) score and Knee Injury and Osteoarthritis Outcome Score (KOOS) evaluated before and 1 month after intervention.
Results: A total of 28 patients with mean age of 66.3 years were surveyed. Overall, study participants reported clinically and statistically significant reduction in VAS and KOOS subscales for symptoms, pain, function, daily living, sports, recreational activities, and quality of life in one month of follow-up with respect to the patients' mean baseline scores (by 24.47%, 42.74%, 54.96%, 43.78%, and 63.63%, respectively). Although obese patients [body mass index (BMI) ≥30 kg/m^2] showed less improvement in terms of pain, sports, and quality of life subscales of KOOS, compared with non-obese patients (BMI < 30 kg/m^2); VAS score difference was not significant.
Conclusion: Intra-articular injection of hypertonic saline yields a statistically and clinically significant short-term pain reduction and functional improvement of patients with knee OA.

Keywords: Knee; Osteoarthritis; Injections; Intra-Articular Injections

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Background

Knee osteoarthritis (OA) is a prevalent degenerative condition with functional impairment which is the result of mechanical stress against the knee joint. World population aging and increased incidence of obesity highlights this issue (1). In 2009, the fourth most common cause of hospital admission in the United States (US) was OA with the annual cost of 42.3 billion dollars (1). The prevalence of OA differs among various populations from 2.8% in the Philippines to 19.3% in some rural regions of Iran (2).

Stiffness, pain, crepitus, and swelling inside the knee are the most common symptoms of knee OA which can occasionally lead to severe limb deformity. Clinical manifestation and more specific radiological features are two main arms of diagnosis (3).

There is no distinctive treatment for knee OA; however, multiple pharmacological options are available including oral selective and non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, chondroitin sulfate, glucosamine, topical products, and so on, which can reduce pain and improve performance (4). Although these drugs might be beneficial in a short-term period, to date, there is not any study showing that such interventions could alter the underlying disease (5). Also, non-pharmacological interventions such as orthotics or assistive devices, exercise, and physical agent modalities including superficial or deep heat and electrotherapeutic agents could be beneficial. Total knee replacement (arthroplasty) is the treatment of choice in advanced stages of knee OA (6). Various intra-articular injections, including corticosteroids, saline, dextrose, hyaluronic acid (HA), autologous blood, platelet-rich plasma (PRP), butolinium toxin (BTX) (7), and ozone (O2-O3) injection are valuable options for patients who do not respond to conservative treatment and are not simultaneously candidate for arthroplasty (8).

Although intra-articular injection of normal saline was formerly labeled in multiple clinical trials as the "placebo effect", surprisingly, based on the results of some recent studies, saline was considered as a potentially effective treatment option for knee OA (9, 10). According to a meta-analysis of 13 cohorts studies, for the therapeutic effectiveness of normal saline intra-articular injection, improvements in pain and performance were detected through 6 months (11).

The mechanism of action behind common prolotherapy is not completely understood. However, current theory holds that the injected irritant materials, especially hypertonic ones, cause initiating a local inflammatory cascade following cell shrinkage, which triggers the release of growth factors and collagen deposition (12, 13). Hypertonic saline as an inexpensive and safe choice with mentioned effects could be an appropriate selection.

Herein, we aimed to report the effectiveness of intra-articular injection of hypertonic saline in pain and function of patients with knee OA.

Methods

Design and Setting

In this clinical trial, clinical criteria of the American Rheumatologic Association were used for diagnosis of sub-acute or chronic knee OA. Patients were recruited from physical medicine and rehabilitation clinics of AJA University of Medical Sciences, Tehran, Iran, from June 2019 to August 2019 after checking for inclusion and exclusion criteria.

Eligibility Criteria

The inclusion criteria were adult patients with moderate or moderate to severe OA (grade 3 and 4 based on Kellgren-Lawrence radiological classification) and pain refractory to pharmacologic or physical agents through 1 month before injection with informed consent. Patients with secondary arthritis or rheumatologic diseases, with the history of joint replacement or recent intra-articular injection of other agents, history of oral or systemic corticosteroid intake 2 weeks before injection, and history of anticoagulation therapy use were excluded from the study.

Baseline Assessments

For the baseline assessments, we recorded a detailed medical history and physical examination with special attention to time since pain complaint. We recorded patient weight and height at the time of enrollment. Body mass index (BMI) was calculated according to the formula: weight (kg)/length^2 (m^2).

Intervention

A physiatrist performed a single intra-articular injection of 5 cc of 5% hypertonic saline solution (solution with a concentration of sodium chloride) under sterile conditions using a 23-gauge needle. Hypersaline brand medication was used from Shahid Ghazi pharmaceutical company (Tehran, Iran).

The method of the intra-articular injection of the knee was based on degree of the access to joint space according to the plane radiography (infero-medial, medial, or lateral approach). 500 mg acetaminophen was prescribed in cases of severe pain and patients were requested not to use NSAIDs after injection. They were also advised refusing physical therapy participation during the 1-month follow-up period because of its confounding role on research results. Moreover, patients were educated for strengthening exercise for quadriceps, hip adductors, hip abductors, and stretching exercise for calf and hamstring muscles after injection to do for a week post-injection.

Outcome Measures

Baseline demographic data such as age, gender, and BMI were collected. Side of knee pain, duration of pain, and the severity of knee OA was interpreted based on the Kellgren-Lawrence Grading. The knee pain was graded using Visual Analogue Scale (VAS) score. We used Knee Injury and Osteoarthritis Outcome Score (KOOS) to evaluate symptoms, pain, function, daily living, sports, recreational activities, and quality of life in patients with knee OA. The patients were assessed for these measures at the time of first injection and 4 weeks later. Additionally, we checked for strengthening exercise compliance at follow-up session.

Ethics Approval and Informed Consent

Before project participation, the aims of the study and potential risks were explained to all the patients orally and written informed consents were obtained. The study procedure was according to the ethical standards of Helsinki Protocol and it was approved by the Ethics Committee of AJA University of Medical Sciences (code: IR.AJAUMS.REC.1398.003) and is registered in Iranian Registry of Clinical Trials (IRCT) (no. IRCT 20190309042989N1).

Data Analysis

Means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables were calculated to describe overall summary statistics of patient characteristics and baseline patient-reported outcome measures. The improvement percentage was calculated by dividing the change from baseline after 4 weeks into the baseline score (baseline score - week 4 score/baseline score), and multiplying it by 100. T-test was used for comparing means of before/after injection and obese/non obese data. The analyses were performed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA). P-values less than 0.05 were considered significant.

Results

In total, 28 patients were evaluated in this study. The mean age was 66.30 ± 8.50 years (range: 46 to 86 years). Patients' characteristics including demographic information and baseline patient-reported outcome measures, are shown in table 1. All participants demonstrated exercise adherence during first week after injection.

Table 1. Demographic distribution and comparison of clinical variables in the three groups before treatment

Variable	Total number of patients	Value	Min	Max
Age (year)	28	66.30 ± 8.50	46	86
BMI (kg/m^2)				
<30		15 (53.57)	NA	NA
≥30		13 (46.43)	NA	NA
Kellgren-Lawrence osteoarthritis grade				
3		14 (50.0)	NA	NA
4		14 (50.0)	NA	NA
Baseline KOOS				
Symptoms	27	5.08 (1.16)	2.43	7.29
Pain	27	3.51 (0.95)	2.11	5.22
Function	27	2.82 (0.94)	1.00	4.65
Sport	27	2.33 (1.14)	1.00	4.20
Quality of life	27	1.87 (1.01)	1.00	4.00
Baseline VNS score	27	8.44 (1.69)	5.00	10.00

Data in the value column are presented as mean ± standard deviation (SD) or number and percentage

BMI: Body mass index; NA: Not available; KOOS: Knee Injury and Osteoarthritis Outcome Score; VNS: Visual Numeric Scale

Overall, study participants reported clinically and statistically significant reduction in KOOS subscales for symptoms, pain, function, daily living, sports, recreational activities, and quality of life in one month of follow-up with respect to the patients' mean baseline scores. KOOS subscales of symptoms, pain, function, daily living, sports, recreational activities, and quality of life were reduced by 24.47%, 42.74%, 54.96%, 43.78%, and 63.63% in one month, respectively ($P < 0.05$ for all comparisons). Reported changes in the 5 domains of KOOS are shown in table 2.

The most considerable improvement from baseline was seen in quality of life of patients. The Visual Numeric Scale (VNS) score was significantly decreased from 8.67 ± 1.43 to 6.21 ± 2.04 in one month ($P < 0.001$).

Table 2. Changes in Knee Injury and Osteoarthritis Outcome Score (KOOS) and Visual Numeric Scale (VNS) scores over time

Outcome measure	Time	Mean ± SD	95% CI	P-value	Change from baseline	Percent change from baseline
VNS	Baseline	8.67 ± 1.43	7.77-9.11	< 0.001	-2.46	28.37
	1 month	6.21 ± 2.04	5.34-7.07			
KOOS symptoms	Baseline	5.19 ± 1.13	4.62-5.54	< 0.001	1.27	24.47
	1 month	6.46 ± 1.24	5.94-6.99			
KOOS pain	Baseline	3.51 ± 0.95	3.13-3.89	0.002	1.50	42.74
	1 month	5.01 ± 2.11	4.18-5.85			
KOOS function	Baseline	2.82 ± 0.94	2.44-3.19	0.001	1.55	54.96
	1 month	4.37 ± 2.17	3.52-5.23			
KOOS sport	Baseline	2.33 ± 1.14	1.88-2.78	0.007	1.02	43.78
	1 month	3.35 ± 1.98	2.57-4.13			
KOOS quality of lif	Baseline	1.87 ± 1.01	1.47-2.27	0.003	1.19	63.64
	1 month	3.06 ± 1.57	2.43-3.68			

VNS: Visual Numeric Scale; KOOS: Knee Injury and Osteoarthritis Outcome Score; SD: Standard deviation; CI: Confidence interval

Baseline KOOS subscales did not significantly differ between obese and non-obese patients (P > 0.05). Table 3 demonstrates that obese patients (BMI ≥30 kg/m^2) showed worse improvement in terms of pain, sports, and quality of life subscales of KOOS, compared with non-obese patients (BMI < 30 kg/m^2); however, changes in VNS score did not show any difference between obese and non-obese patients after one month.

Table 3. Relative improvement in Knee Injury and Osteoarthritis Outcome Score (KOOS) and Visual Numeric Scale (VNS) scores over time based on body mass index (BMI)

	BMI (kg/m^2)		P-value
	< 30	≥30	
VNS	37.52	34.71	0.828
KOOS symptoms	30.42	3.24	0.131
KOOS pain	87.30	33.12	0.042
KOOS function	77.69	57.79	0.368
KOOS sport	84.29	37.21	0.043
KOOS quality of life	87.30	58.15	0.006

Data are presented as percentage
BMI: Body mass index; VNS: Visual Numeric Scale; KOOS: Knee Injury and Osteoarthritis Outcome Score

Discussion

Our results showed that intra-articular injection of hypertonic saline yielded a statistically and clinically significant improvement in pain and performance of patients with knee OA 1 month after the injection.

Several clinical features prove knee OA as an inflammatory condition. The deposition and further release of microcrystals from articular cartilage might be the possible mechanism which leads to changes in synovial membrane. The severity of joint damage depends on the amount of hydroxyapatite crystals (9). The efficacy of intra-articular injection of corticosteroids in OA seems minimal compared with other inflammatory conditions such as rheumatoid arthritis (RA) and shows less benefit in the treatment of these patients compared with saline injection (14).

Recently published studies have suggested that intra-articular injection of saline might represent a notable therapeutic effect in OA rather than placebo effect with apparent symptomatic improvement (15). Our results agree with a favorable improvement in patients' function and pain after injection of saline.

There are many rationales for potential beneficial effects of saline intra-articular injection. First, hypertonic saline attenuates neutrophil activation which is reversible by using normal concentrations of saline. Moreover, hyperosmolarity reduces 3 of the 6 pro-inflammatory cytokines [Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES), monocyte chemoattractant protein-1 (MCP-1), and interferon-inducible protein-10 (IP-10)]. Finally, proteoglycans and especially aggrecans form joint cartilage which will break down to various degrees in the different stages of OA resulting in release of sodium ions that could be prevented by hypertonic saline injection (9).

Despite total improvement in KOOS and VNS scores, obese patients revealed more functional impairment and pain compared with non-obese participants. Previous literature also clarified that higher BMI increased pain in general and specifically chronic musculoskeletal pain (16). Our results reemphasize the importance of weight loss for pain management of patients with OA. Obesity places more mechanical force on knee joint and is also associated with decreased physical activity which subsequently leads to decreased muscle strength, inadequate resistance exercise, and increased pain in obese individuals.

Our data suggest that intra-articular injection of saline will notably relieve the pain associated with knee OA. In recent years, neuropathic pain has been introduced to be prominent in patients with OA which is the result of extensive and repetitive nociceptive input from articular peripheral pain receptors and transmitted to the dorsal horn of the spinal cord neurons. This fact that saline helped to reduce nociceptive pain in our patients might question its use as a placebo in clinical trials with pain as primary outcome measure.

We presented interesting results on using hypertonic saline as a cost-effective treatment option for patients with knee OA for the first time; however, we faced some limitations. The sample size in our study was small due to patient loss for follow-up, so we did not interpret statistically non-significant findings and emphasized statistically significant ones. We did not include a control group for comparison of the results which keeps the placebo effect being mentioned. In addition, our data were mostly based on subjective self-reported tools. More assessments such as articular cartilage thickness measurement using imaging techniques or articular liquid laboratory analysis for inflammatory or growth factors measurement are recommended for objective confirmation. The other extra articular causes of pain such as ligamentous ones are not evaluated in this study and could influence our results.

Conclusion

This study addressed the potential beneficial effect of intra-articular injection of saline on pain and function of patients with symptomatic knee OA. Further randomized controlled trials (RCTs) with comparison group are suggested to confirm our findings.

Conflict of Interest

The authors declare no conflict of interest in this study.

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