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Randomized Controlled Trial

Ultrasound-guided Shoulder Intraarticular Ozone Injection Versus Pulsed Radiofrequency Application for Shoulder Adhesive Capsulitis: A Randomized Controlled Trial

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Background: A diseased shoulder due to pain, stiffness, or weakness negatively affects patients' quality of life and their ability to carry out activities of daily living. Adhesive capsulitis is a disease characterized by shoulder pain and global limitation of movement in the shoulder joint. Many interventions have been proposed for the treatment of primary adhesive capsulitis. The current study compares the effect of ultrasound-guided intraarticular injection of ozone versus steroid versus intraarticular application of pulsed radiofrequency.

Objectives: The primary outcome of the current study was to compare the improvement in the Visual Analog Scale (VAS) after the 3 treatment modalities. The secondary outcomes included functional improvement measured by the Shoulder Pain and Disability Index (SPADI) and level of inflammatory biomarkers measured by serum intercellular adhesion molecule (ICAM-1) and high-sensitivity C-reactive protein(hs-CRP).

Study Design: The current study is a prospective, double blinded, randomized controlled trial. We employed a double blinding technique for both the patients and the outcome assessors.

Setting: Our study was carried out at the Medical Research Institute, Alexandria University, Egypt, after approval of the local ethical committee (IORG0008812). The study was registered in the "clinical trials library for protocol registration and results system" with number NCT04724317.
The study included 45 patients with a diagnosis of primary adhesive capsulitis.

Methods: Patients were randomly assigned to 3 equal groups: steroid group, ozone group, and pulsed radiofrequency group. Pain and global shoulder functions were assessed using the VAS at rest and with movement, range of motion (ROM), and the SPADI. Moreover, ICAM-1 and hs-CRP were measured as inflammatory markers.

Results: The results of the current study reveal that all patients in all groups have had a statistically significant improvement after their intervention regarding pain, disability, ROM, and inflammatory markers. Pairwise comparisons revealed that improvement of the VAS during movement had a statistically significant improvement starting from the second week and continuing to the fourth and eighth week. VAS during rest had a significant improvement starting from follow-up week one in the steroid group. Moreover, improvement in the ROM and SPADI scores started from the second week follow-up. Percent improvement was calculated for each group and there was a statistically significant difference between groups in VAS at rest and ROM in the pulsed radiofrequency group compared to the steroid group.
Regarding inflammatory markers, both ICAM-1 and hs-CRP had a significant improvement after all 3 interventions with no statistically significant difference among the groups.

Limitations: This study is a single-center study. A shortage of previously published data, and heterogeneity in the published methodology of the 3 interventions limited our discussion data for comparison with the previous literature.

Conclusion: Ultrasound-guided shoulder joint intraarticular injection of steroid, ozone, or pulsed radiofrequency application all result in a significant improvement in pain, disability, and ROM in primary adhesive capsulitis. They can be used as an effective treatment modality for this condition.

Comparing groups statistically, the pulsed radiofrequency group had a more delayed, but statistically better long-term improvement compared to the other 2 groups.

Key words: Adhesive capsulitis, pulsed radiofrequency, ozone, shoulder, glenohumeral joint, pain, hs-CRP, triamcinolone acetonide

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A diseased shoulder due to pain, stiffness, or weakness negatively affects patients' quality of life and their ability to carry out their daily activities. Adhesive capsulitis (AC), first described in 1872, is defined as "a condition of varying severity characterized by a gradual development of global limitation of active and passive shoulder motion where radiographic findings other than osteopenia are absent" (1,2). The estimated incidence of AC is 2–5% of the total population once per lifetime (3). Bilateral joint affection can occur in 20–30% of cases (4).

The pathophysiology of AC is a combined inflammatory and fibrotic process with elevated inflammatory cells, interleukin (IL)-1a, IL-1b, tumor necrosis factor (TNF)-α, cyclooxygenase (COX)-1 and COX-2 (5,6). Recent studies have shown elevated intercellular adhesion molecule (ICAM) -1 in patients with AC. ICAM-1 is a transmembrane protein present in endothelial cells and leukocytes. It has a role in leukocyte-endothelial migration (7).

Adhesive capsulitis is classified as primary or secondary. Primary idiopathic AC is a diagnosis of exclusion of all causative diseases of the secondary subtype (4,8). Secondary AC can follow a severe articular injury, or as a complication of shoulder joint surgeries, either open or arthroscopic.

Other associated systemic diseases include thyroid disease, Dupuytren disease, and other autoimmune disorders (4). Theoretically, the stages of AC are classified according to the clinical presentation. In the first stage, patients complain of pain increasing at night with a preserved range of motion (ROM). The second stage is characterized by stiffness with mild loss of both axillary fold, while the third stage is characterized by a profound global loss of ROM with progressive loss of both axillary fold. Stage 4 is characterized by persistent stiffness with minimal pain indicating synovitis relief (2,4).

A diagnosis of AC depends on the exclusion of all other pathologies of a painful stiff shoulder joint. External rotation is usually the first affected movement. During active movement, pain is worse during capsule stretch at the end of motion. Passive joint movements are limited with firm endpoints in the late stages of the disease (8).

Radiologically, plain x-ray films are usually negative except for osteopenia, which may be present secondary to joint disuse (2). Magnetic resonance imaging may be positive for capsular thickening, pericapsular inflammatory changes, or a decreased glenohumeral joint space (8). Dynamic sonographic examination may reveal capsular thickening or limited supraspinatus ligament sliding movement.

As there are no clear guidelines for a management algorithm for adhesive capsulitis, treatment should be tailored according to the patient's condition (8,9). Treatment options include nonoperative and operative modalities. Nonoperative options include physical therapy, pharmacological therapy, and intraarticular or extraarticular injection. Operative modalities are manipulation under anesthesia and arthroscopic or open capsulotomy.

Pharmacological therapy includes nonsteroidal anti-inflammatory drugs to relieve pain but they have no direct relation to ROM improvement (8). Systemic steroids have failed to show significant long-term improvement in pain scores, ROM, or disability scores. However, intraarticular steroid injection offers faster and better symptomatic relief in comparison to systemic steroids (10).

The radiofrequency (RF) technique was first introduced to clinical practice in the early 1950s as a continuous RF technique. This was followed by pulsed radiofrequency (PRF) in 1998, that limits the thermal effect to a nondestructive temperature (11). PRF generators produce oscillating pulses of 420–500 kHz, 45-volt amplitude for 20 milliseconds, followed by a 480 milliseconds silence period. This allows time for heat absorption in the tissues to a maximum temperature of 42° (11,12).

Ozone (O_3) is a colorless unstable gas with a characteristic smell that consists of 3 oxygen atoms bound together in a cyclic structure. In 1834, Schoenbein isolated ozone and reported its oxidant and disinfectant properties (13). The introduction of certified O_3 generators has allowed for wider ozone uses and medical applications (14).

Many theories have been stated to explain the exact mechanism of ozone action. To date, immune modulation, anti-inflammatory effect, circulatory stimulation, and analgesic effect are the most evident theories (15). The oxidative effect of ozone injection

includes increased production of nitric oxide (NO), adenosine, and prostaglandins. These mediators have a positive role in the vasodilatation process and thus improve tissue circulation.

Objectives

Our study aimed to evaluate the efficacy of ultrasound-guided shoulder intraarticular ozone injection versus PRF application compared to intraarticular steroid injection in patients with idiopathic adhesive capsulitis. The primary outcome was the improvement in the visual analog scale (VAS). The secondary outcomes include functional improvement measured by the Shoulder Pain and Disability Index (SPADI) and improvement in the level of inflammatory biomarkers measured by serum intercellular adhesion molecule-1 (ICAM-1) and high-sensitivity C-reactive protein (hs-CRP).

Methods

Study Design and Population

We conducted a prospective randomized controlled double-blinded trial at Medical Research Institute, Alexandria University, Egypt, after approval of the local ethical committee (IORG0008812). The study was registered in the "clinical trials library for protocol registration and results system" with the number NCT04724317. This study meets the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (16).

Forty-five patients were included in the trial. They ranged in age from 30 to 65 years, were diagnosed with primary shoulder AC, and had a history of inadequate response to a trial of conservative therapy for at least 4 weeks. Exclusion criteria were patients with secondary AC, central poststroke neuropathic pain, rheumatoid arthritis, current shoulder fracture or trauma, local tumor, reported coagulopathy, or allergy to medications used in the trial. The recruitment period extended from March 2021 through November 2021 (Fig. 1). An Informed written consent was taken from all participants.

Sample Size, Randomization, and Blinding

The sample size was calculated using GPower soft-

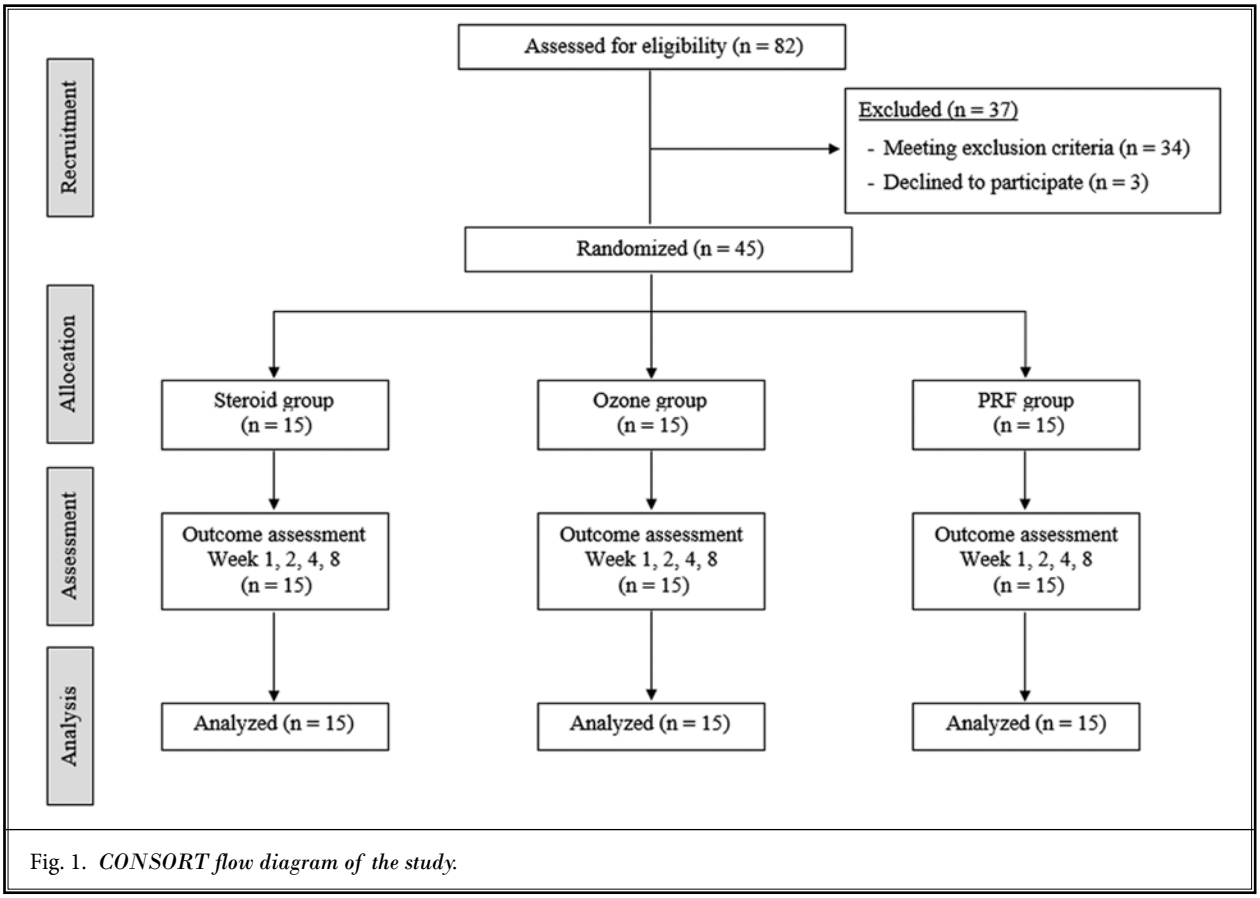


Fig. 1. *CONSORT flow diagram of the study.*

ware version 3.1.9.2 (Heinrich Heine University). Adopting a power of 95% to detect a standardized effect size of 1.591 in the VAS at 2 months postintervention, the anticipated difference between groups = 2, and a level of significance of 95% (α = 0.05), the minimum required sample size was found to be 12 patients per group. The sample size was increased to 15 patients per group to control for withdrawal bias. Randomization was done using computerized, variable-sized, blocks. Blinding was employed for the patients and the outcome assessors.

Procedures

All patients underwent proper history taking, a standard shoulder examination, and documented baseline VAS score, SPADI, and ROM. The VAS score was documented during movement (VASm), and during rest (VASr). Interventions were carried out in the operating theater for proper monitoring and sterilization. A blood sample for baseline ICAM-1 and hs-CRP was taken before the intervention.

Interventions were done with the patient in a lateral semiprone position with the affected shoulder facing up. The glenohumeral space was optimized by arm internal rotation and adduction across the chest. A Sonosite® S-Nerve™ ultrasound machine (FUJIFILM Sonosite, Inc.) was used with a high-frequency linear probe (7-14 MHz). The posterior approach for ultrasound-guided shoulder injection was adopted after identifying the humeral head, joint capsule, labrum, glenoid, infraspinatus, and deltoid muscles. Needle paths went from inferomedial to superolateral, targeting the subcapsular endpoint adjacent to the labrum (Fig. 2).

Patients were categorized into 3 equal groups. In the steroid group, patients were treated with an intraarticular injection of 5 mL of 0.125% bupivacaine added to 40 mg triamcinolone. In the ozone group, patients were treated with an intraarticular injection of 5 mL of 0.125% bupivacaine followed by a 10 mL of an oxygen-ozone mixture (15 µg/mL). The oxygen-ozone mixture was produced using a Longevity® EXT50 ozone generator (Longevity Resources [Note: Although the company is closed, the device is available for use in our institution for research purposes]). In the PRF group, patients were treated with a shoulder intraarticular injection of 5 mL of 0.125% bupivacaine followed by an intraarticular PRF application using a 10 cm needle - 10 mm active tip (NeuroTherm) for 4 minutes (17). A NeuroTherm® NT2000iX RF machine was used for the procedure.

Outcome Measures

Patients were treated as day-case patients and were observed in the pain department for 2 hours posttherapy. The VAS, ROM, and any complications were recorded before discharge. Follow-up visits were planned at weeks one, 2, 4, and 8 in which reassessment was done for VASr, VASm, SPADI, and ROM. A blood sample for ICAM-1 and hs-CRP was taken during the last follow-up visit.

Statistical Analysis

Data were collected and fed to the computer using IBM SPSS Statistics 25.0 (IBM Corporation). The Kolmogorov-Smirnov test revealed significance in the distribution of most variables, so nonparametric statistics were adopted. Data were described using minimum, maximum, median, 95% CI of the median, and 25th to 75th percentile.

Categorical variables were described using frequency and percentage. Comparisons were carried out between more than 2 independent subgroups using the Kruskal-Wallis test. Comparisons were carried out between 2 studied subgroups using the Wilcoxon signed rank test. Comparisons were carried out among related samples by Friedman's test. Post-hoc pair-wise comparisons were carried out using the Dunn-Šidák test for multiple comparisons. Significant values have been adjusted by the Bonferroni correction for multiple tests.

Results

The 3 studied groups were comparable regarding demographic data, affected side, and hand dominance (Table 1).

VASm and VASr scores had no significant difference among the studied groups at baseline, at discharge, and at the first, second, and fourth weeks of follow-up (P = 0.998, 0.381, 0.573, 0.493, and 0.495 for VASm respectively, and P = 0.824, 0.216, 0.505, 0.904, and 0.141 for VASr respectively). After 8 weeks, scores were significantly better in the PRF group (P = 0.024, and 0.01 for VASm and VASr).

The analysis of repeated measures within each group showed a statistically significant difference in each group (P < 0.001). Using the post-hoc test, there was a statistically significant improvement in all groups before discharge, and in the second, fourth, and eighth week of follow-up compared to the preintervention value. The steroid group was the only one to show a significant difference in week one regarding VASr score (Figs. 3,4).

The VASm and VASr percentage change (%) was calculated for each patient by comparing the preinjection value with the end-of-study value. Both had a significant difference among the 3 studied groups (P = 0.045, and 0.013 respectively). Using the post-hoc test, the VASm had no statistically significant difference between groups, while the VASr had a significant difference between the steroid and PRF groups (Fig. 5).

ROM had no statistical difference among the studied groups at baseline (P = 0.891), and in the first week (P = 0.227). It had a statistically significant difference in the second, fourth, and eighth weeks (P = 0.041, 0.022, and < 0.001, respectively) all in favor of the PRF group, followed by the ozone group and then the steroid group. The analysis of repeated measures within each group showed a statistically significant improvement after each intervention (P < 0.001). Using the post-hoc test, there was a significant improvement in all groups in the second, fourth, and eighth weeks when compared to the baseline value.

The percentage change in ROM had a statistically significant difference among the studied groups (P = 0.005). Using the post-hoc test, there was a statistically significant difference between the steroid and PRF groups (Fig. 6).

Pain and disability components of the SPADI had no statistical difference among the studied groups at baseline, after one week, 2 weeks, 4 weeks, and 8

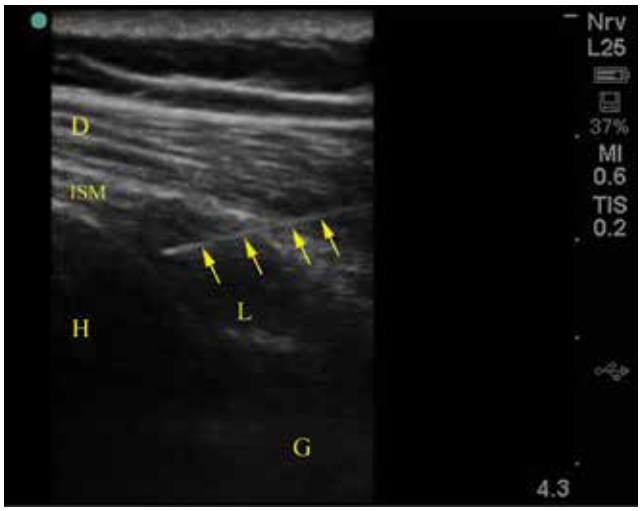


Fig. 2. *Ultrasound-guided posterior approach for glenohumeral joint injection.*
D, deltoid; ISM, infraspinatus m; H, humerus; G, glenoid; L, labrum. Arrows indicate needle pathway from medial to lateral.

Table 1. *Demographic and clinical characteristics of the studied groups.*

Characteristics	Steroid Group (n = 15)	Ozone Group (n = 15)	PRF Group (n = 15)	*P* value
Age (years) median (IQR)	42.00 (39.00-52.00)	48.00 (39.00-54.00)	46.00 (38.00-57.00)	0.838
Gender				
Men	3 (20.00%)	3 (20.00%)	7 (46.67%)	0.217
Women	12 (80.00%)	12 (80.00%)	8 (53.33%)	
Affected side				
Right	10 (66.67%)	9 (60.00%)	8 (53.33%)	0.757
Left	5 (33.33%)	6 (40.00%)	7 (46.67%)	
Dominant hand				
Nondominant	6 (40.00%)	6 (40.00%)	7 (46.67%)	0.913
Dominant	9 (60.00%)	9 (60.00%)	8 (53.33%)	
Pain intensity				
VASm median (IQR)	7.00 (6.00-9.00)	7.00 (6.00-8.00)	7.00 (7.00-8.00)	0.998
VASr median (IQR)	3.00 (3.00-5.00)	3.00 (2.00-4.00)	4.00 (3.00-4.00)	0.824
QOL				
SPADI Pain median (IQR)	54.00 (38.00-68.00)	60.00 (48.00-66.00)	62.00 (52.00-76.00)	0.831
SPADI Disability median (IQR)	57.50 (40.00-68.75)	53.75 (48.75-65.00)	60.00 (52.50-67.50)	0.846
ROM median (IQR)	50.00 (43.00-55.00)	49.00 (43.00-55.00)	45.00 (45.00-52.00)	0.891
ICAM-1 (pg/mL) median (IQR)	642.50 (572.70-672.20)	601.80 (559.60-648.20)	623.20 (581.40-672.40)	0.402
CRP (mg/L) median (IQR)	1.90 (1.46-2.41)	1.70 (1.53-2.49)	1.90 (1.23-2.87)	0.943

IQR, interquartile range; QOL, quality of life; VASm, Visual Analog Scale during movement; VASr, Visual Analog Scale during rest; CRP, C-reactive protein; ROM, range of motion; ICAM-1, intercellular adhesion molecule; SPADI, Shoulder Pain and Disability Index

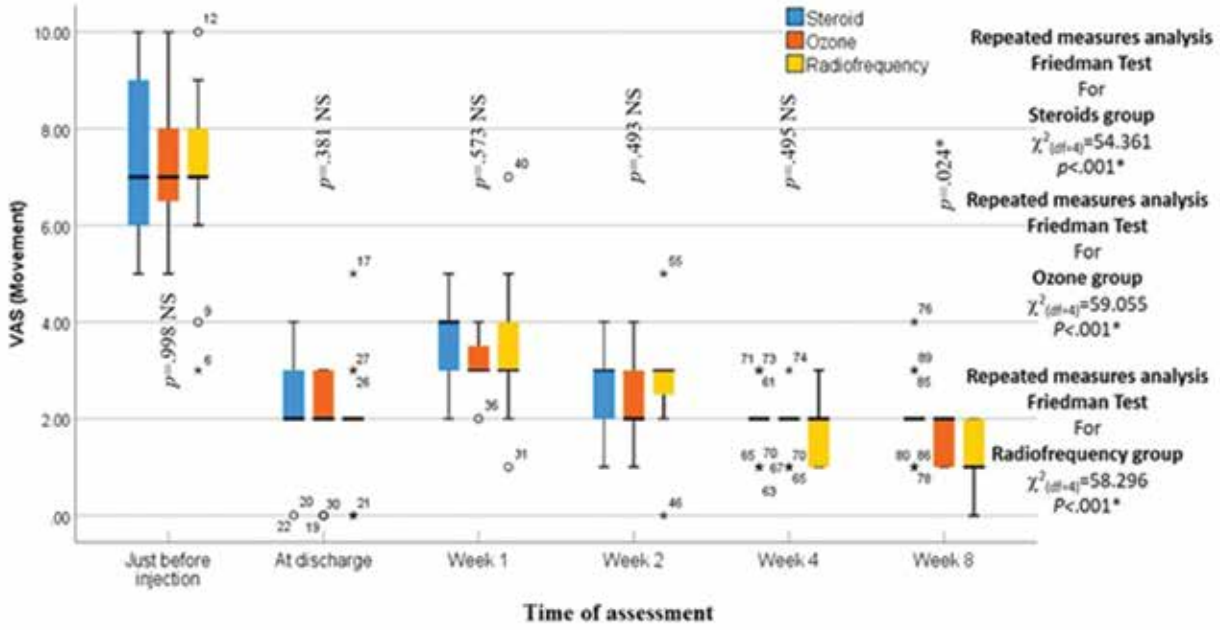


Fig. 3. *Visual Analog Scale during movement score.*

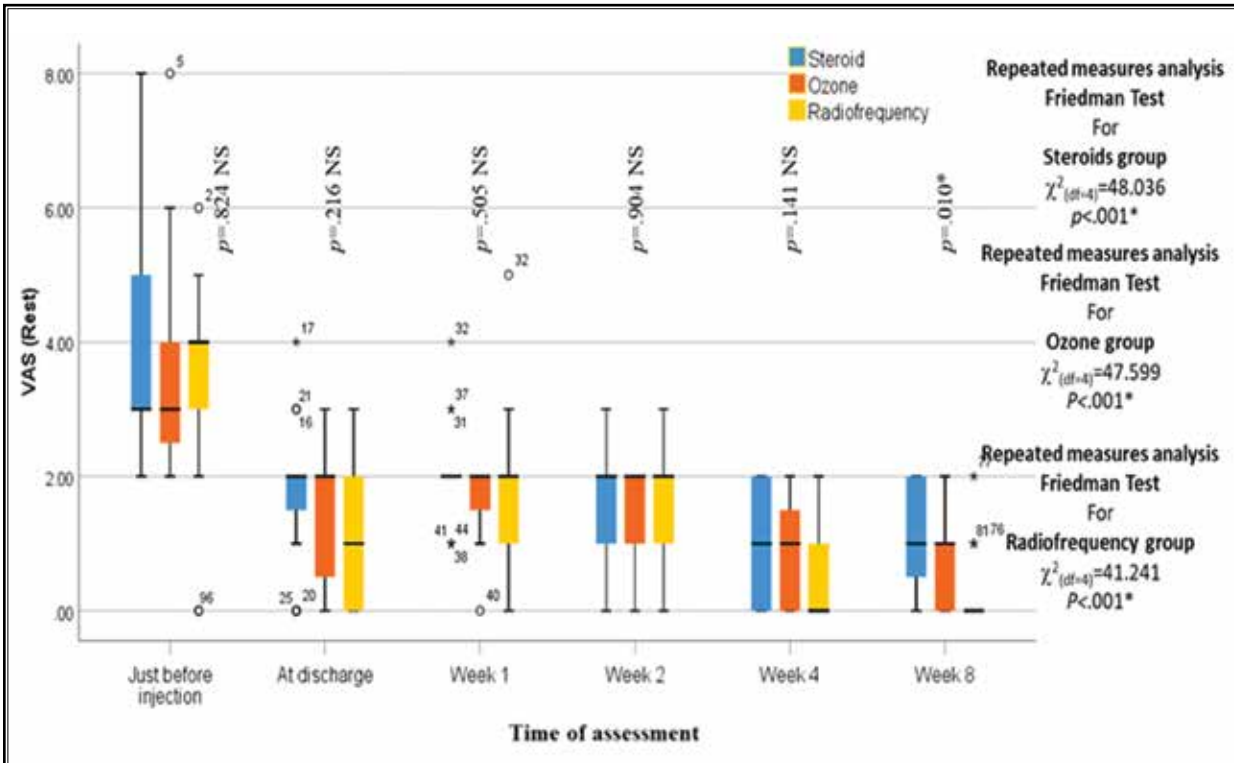


Fig. 4. *Visual Analog Scale during rest score*

weeks (P = 0.831, 0.907, 0.878, 0.831, and 0.241 respectively for pain, and P = 0.846, 0.776, 0.772, 0.553, and 0.094 respectively for disability) (Figs. 7,8). The analysis of repeated measures for both components of SPADI within each group showed a statistically significant improvement after each intervention (P < 0.001). Using the post-hoc test, there was a statistically significant improvement in all groups in the second, fourth, and eighth weeks when compared to the baseline value.

The percentage change of both components of the SPADI did not show any statistically significant difference among the studied groups (P = 0.119, and 0.306 respectively). ICAM-1 level (pg/mL), and hs-CRP level (mg/L) had no statistical difference among the studied groups at baseline and at the end of the study (P = 0.402, and 0.071 respectively for ICAM-1, and 0.943, and 0.061 respectively for hs-CRP). Within each group, the analysis of repeated measures showed a statistically significant improvement in both ICAM-1 and hs-CRP levels between the 2 different points of measurement in all groups (P = 0.001) (Fig. 9).

Discussion

In the current study, VASm and VASr scores showed nearly the same pattern of improvement starting from the second week throughout the follow-up period. The exception was in the steroid group which showed a more rapid improvement starting from the first week. This can be explained by the rapid anti-inflammatory effect of an intraarticular steroid injection.

In 2020, a systematic review and meta-analysis was published by Zhang and colleagues (18), discussing the efficacy of nonsurgical treatment strategies for a frozen shoulder. They concluded that an intraarticular steroid injection provided short- to medium-term pain relief (one-6 months) in patients suffering from a painful freezing phase. This benefit was not significant over a longer period of follow-up (i.e., > 6 months) (18). Similarly, McKean and colleagues (19) published data evaluating the effect of a glenohumeral steroid injection through the rotator interval. They reported a significant early improvement in VAS throughout the follow-up period (24 hours – 5 months) (19).

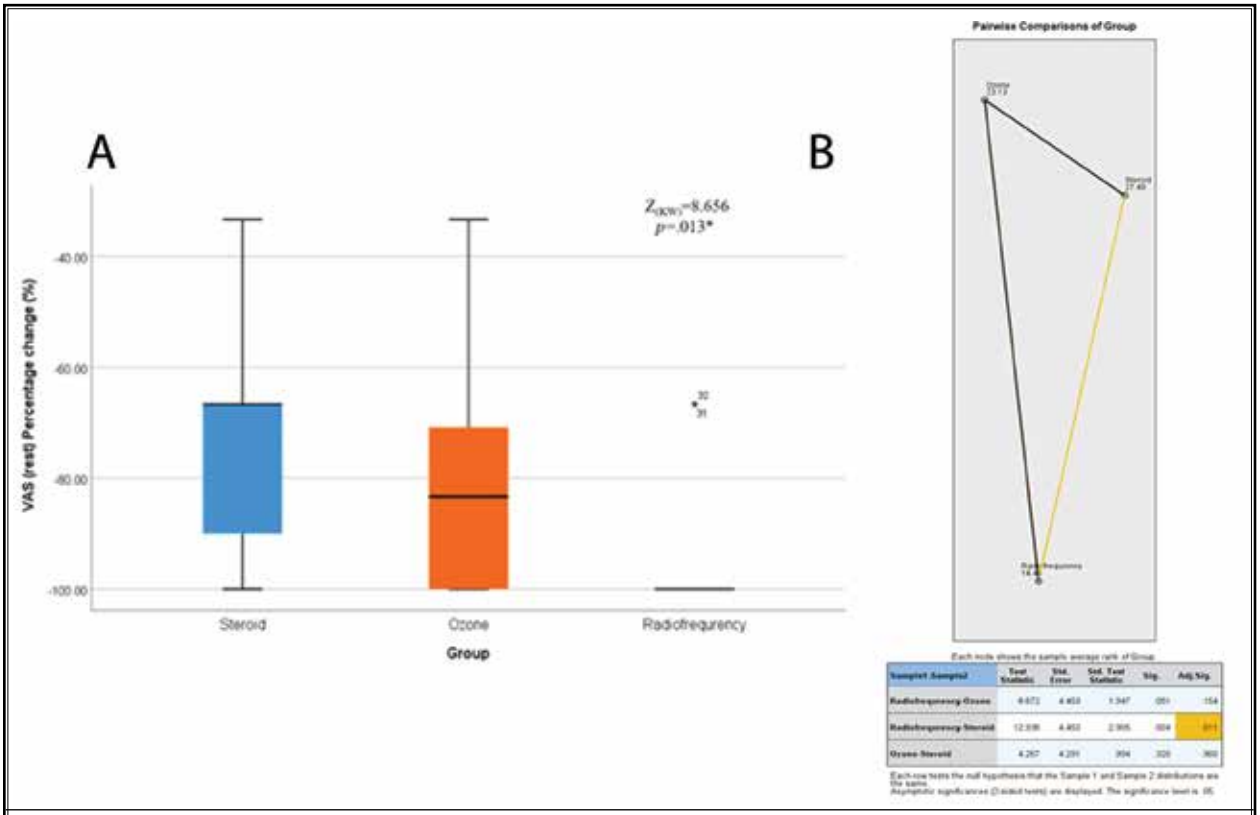
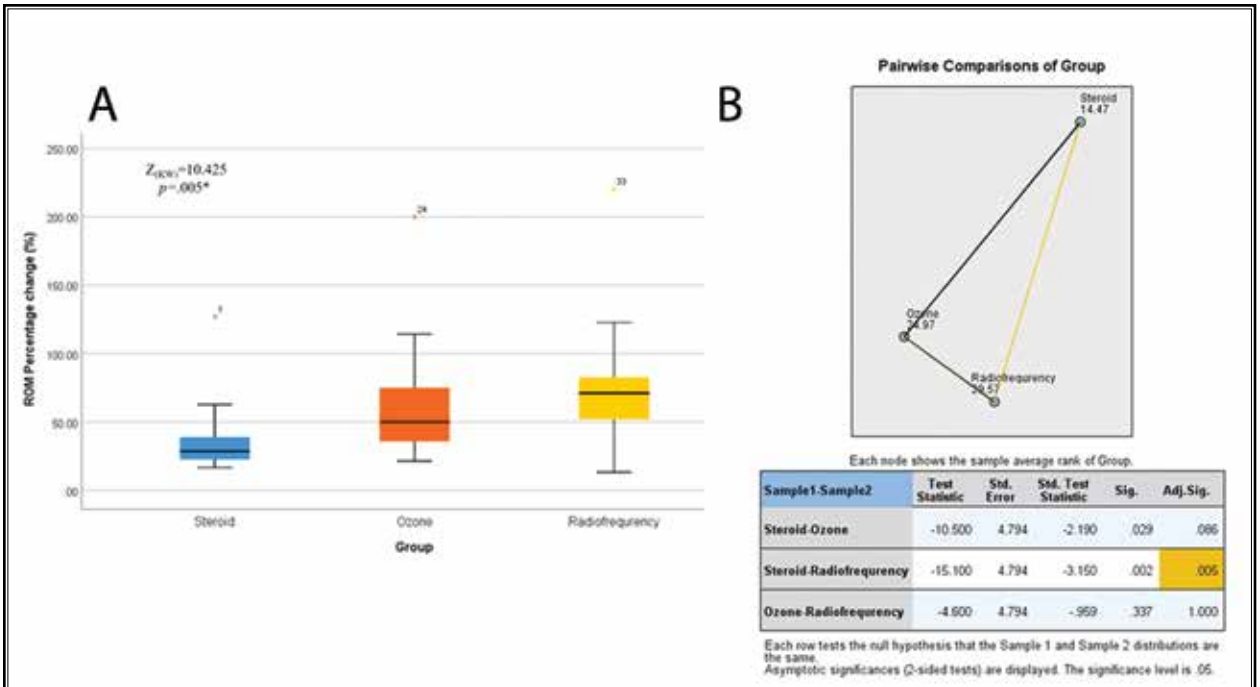


Fig. 5. *Visual Analog Scale during rest percentage change.*



Sample1-Sample2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj.Sig.
Steroid-Ozone	-10.500	4.794	-2.190	.029	.086
Steroid-Radiofrequency	-15.100	4.794	-3.150	.002	.005
Ozone-Radiofrequency	-4.600	4.794	-.959	.337	1.000

Fig. 6. *Range of movement percentage change.*

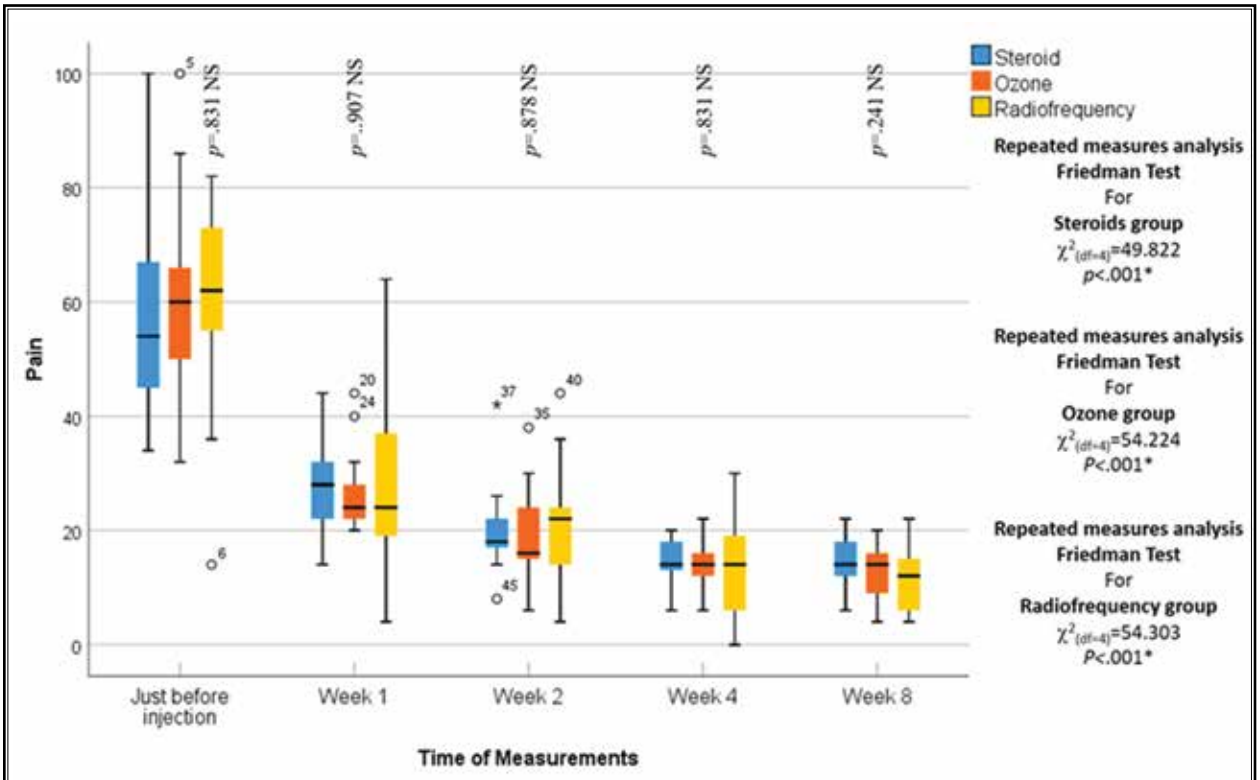


Fig. 7. *Pain component of Shoulder Pain and Disability Index.*

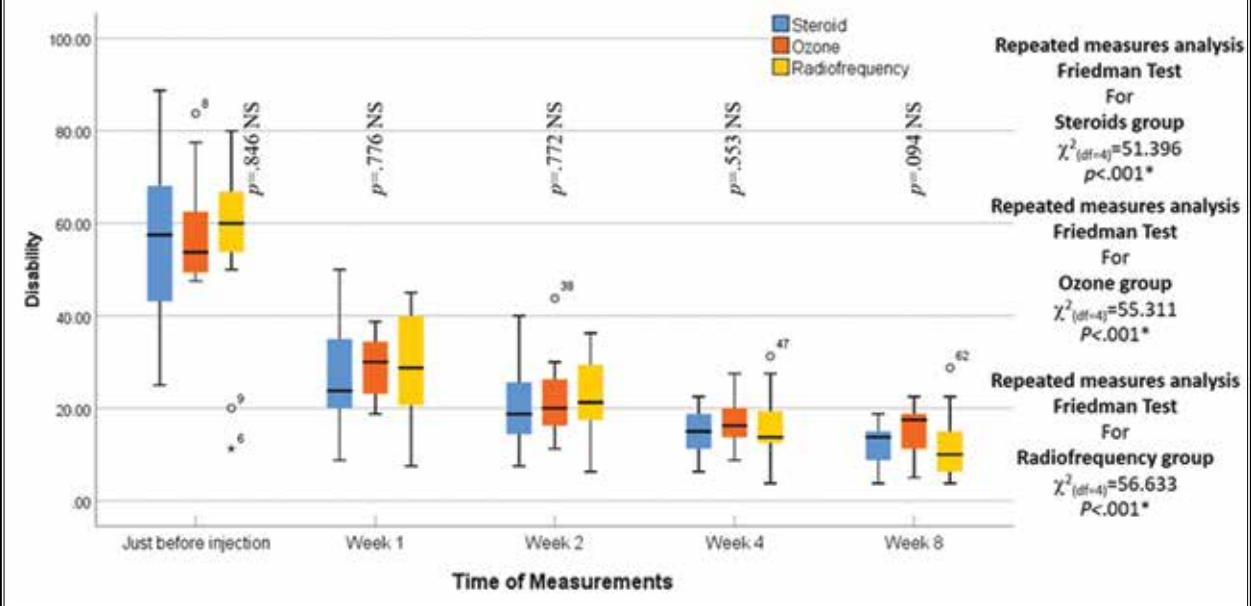


Fig. 8. *Disability component.*

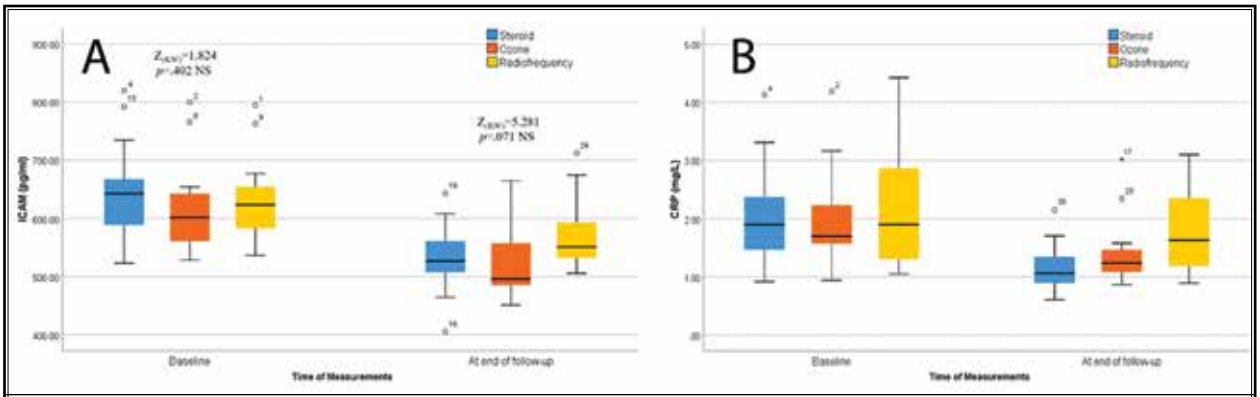


Fig. 9. *Intercellular adhesion molecule (ICAM)-1 level.*

Intraarticular ozone injections have been documented to improve pain and disability associated with many articular pathologies. In 2015, Hashemi and his colleagues (20) published a randomized controlled trial (RCT) that evaluated intraarticular ozone therapy in knee osteoarthritis. They reported a significant improvement in the VAS in the ozone group at the end of the follow-up period (20). The reduction in pain reported after ozone injection can be explained by the destruction of algogenic substances, serotonin alteration, and bradykinin inactivation (21). Locally, ozone injection suppresses pain by direct oxidation of pain receptors and pain mediators. Also, local inhibition of apoptosis and phagocytosis plays an analgesic role (14).

In 2019, an RCT was published by Babaei-Ghazani and colleagues (22), comparing the effect of steroid injection to ozone intraarticular injection in patients with shoulder impingement. They reported a more rapid response to the steroid injection after at 2 weeks postinjection. They reported a delayed improvement in the ozone group in the period of 2 weeks – 2 months postinjection (22). In comparison to our study, the end of follow-up results f favored the steroid group (60.4% reduction in VAS) compared to the 37% reduction in the ozone group.

In our study, intergroup comparisons regarding VASm and VASr scores showed a significant difference at week 8, with the greatest improvement in the PRF group compared to the other 2 groups. This indicates a more delayed improvement in the PRF group that can be explained by its immune modulatory effect due to suppression of pro-inflammatory cytokines (23).

The exact mechanism of action of PRF is still debatable. PRF can produce subcellular, microscopic lesions on neurons in a volume around the electrode, possibly resulting in a reduction of afferent pain signals (24). The modulatory effect of PRF has been reported after intraarticular application, causing a reduction in pain signaling. Rapid improvement is attributed to suppression of both C-fiber response and synaptic transmission while long-term improvement is attributed to an immune modulation response due to suppression of pro-inflammatory cytokines (23,25).

The overall percentage improvement in VASm had no statistical difference among the studied groups as measured by the post-hoc test. Conversely, VASr showed a significant improvement in the PRF group compared to the steroid group. This improvement can be explained by the neuromodulation effect of the PRF affecting the C-fibers' nerve endings of the joint capsule that initiate the resting baseline pain sensation (12,25).

Regarding ROM, our saw a significant improvement starting from the second week. In the systematic review published by Zhang and colleagues (18), they reported a significant improvement in ROM in patients who did not have diabetes mellitus who received an intraarticular steroid injection for the treatment of frozen shoulder. The same results were published by McKean et al (19) in which they reported improvement in ROM after a rotator interval injection extending for 2 months of follow-up.

In the RCT published by Kim and colleagues (26), they reported a significant improvement in passive ROM after a glenohumeral injection with both low- and high-dose triamcinolone acetonide (20 mg vs 40 mg); there was no significant difference between the groups at the end of the follow-up period.

Despite limited published data, ozone injection has been reported to improve ROM. Seyam and his colleagues (21) reported an improvement in ROM after an oxygen-ozone injection. They suggested a new mechanism of action for ozone therapy as it may has a muscle relaxant effect helping in the treatment of AC (21). In a case report by Benvenuti (27), improvement was reported in active ROM after a weekly session of ozone injection for 3 weeks.

Intraarticular application of PRF has been reported to improve joint mobility. Filippiadis and colleagues (23) reported improved mobility in 88.6% of their patients after intraarticular PRF for 10 minutes followed by 60 mg sodium hyaluronate viscosupplementation.

In a comparative study carried out by Babaei-Ghazani and his colleagues (22), they found a significant comparable improvement within both steroid and ozone groups regarding adduction, flexion, and internal rotation.

Comparing the 3 studied groups regarding ROM in our study, there was a significant difference at weeks 2, 4, and 8 with greater improvement in the PRF group, followed by the ozone group, and then the steroid group. In this study, we emphasize that improvement was progressive, and ROM median value was improved in the PRF and ozone groups across the time of assessment. There were no available previous data to compare our results with. This progressive improvement can be explained by extended anti-inflammatory and immune-modulatory effects for both treatment modalities.

In our study, SPADI was used to assess the improvement in quality of life during the postintervention period. A SPADI score is subdivided into a pain component and a disability component; each is calculated as a percent value. Both components of the SPADI showed a significant improvement from the second week of follow-up.

In 2020, an RCT was published (28) comparing the effect of intraarticular steroid injection (methylprednisolone 80 mg) to hydrodilatation in patients with adhesive capsulitis. Results showed a significant improvement in SPADI in the steroid injection group (28).

In 2013, Schianchi and his colleagues (12) published a review about the application of PRF for the treatment of joint pain. They postulated that the application of PRF influences the production of pro-inflammatory cytokines rather than its effect being confined to neurons and nerve endings (12).

The Babaei-Ghazani study (22), found a greater improvement in the SPADI score in their steroid group patients compared to the ozone group. These results can be explained by their approach of injecting the subacromial subdeltoid bursa, which is different from our approach for intraarticular glenohumeral injection (22).

In the current study, serum ICAM-1 and hs-CRP,

as biological markers for adhesive capsulitis, were measured before intervention and at the end of the follow-up period (i.e., after 8 weeks). Both markers had a significant improvement after the interventions.

In 2013, Kim and his colleagues (7) investigated the role of ICAM-1 in adhesive capsulitis in a case-control study. Their results showed a significant increase in serum ICAM-1 level in adhesive capsulitis and diabetes mellitus. Moreover, they detected a significantly higher level of tissue ICAM-1 in the shoulder capsule and synovial fluid in cases of adhesive capsulitis. They also reported a significant downregulation of gene expression of ICAM-1 in cultured cells after 3 days of steroid treatment in patients with adhesive capsulitis (7).

In a review published by Bui and colleagues (29), they reported the role of ICAM-1 in regulating the permeability of endothelial cells in healthy and inflamed tissues. This role can be explained by regulating the intracellular calcium level and regulating cytokine production. The effect of high-level serum ICAM-1 was shown to promote a pro-inflammatory response in many disease conditions (29).

High-sensitivity CRP (hs-CRP) was found to be more sensitive to detect the inflammatory process at a lower level than the standard measurement of CRP (30). Elevated hs-CRP has been associated with many orthopedic and musculoskeletal diseases, including shoulder pain. In a case-control study, Park and colleagues (31) reported a strong association between the level of hs-CRP and idiopathic adhesive capsulitis after controlling other variables in a multivariable logistic regression model.

Limitations

The current study is a single-center study. After a review of the literature, the current study is the first RCT comparing the efficacy of intraarticular steroid injection (as a gold standard treatment modality) to intraarticular ozone and PRF. There are limited data available for comparison in the discussion. Moreover, the available data have a marked heterogeneity in the methodology used during interventions.

Conclusion

This study investigated the effect of different nonsurgical modalities for the treatment of idiopathic adhesive capsulitis. The results show a more promising, but delayed, effect for both ozone and PRF for the treatment of idiopathic AC when compared with steroid injection. Steroid injection was superior at the onset of pain relief at rest (VASr) starting from week one postintervention.

In contrast, the PRF and ozone groups had better VASr and VASm scores at week 8 postintervention. Improvement in SPADI was significant after the 3 intervention modalities with no significant difference among them regarding pain and disability components. Similarly, ICAM - 1 and hs-CRP were significantly improved at the end of the follow-up period with no significant difference among groups.

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