Randomized Controlled Trial

Comparison Between Multisite Injection and Single Rotator Interval Injection of Corticosteroid in Primary Frozen Shoulder (Adhesive Capsulitis): A Randomized Controlled Trial

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Background: Steroid injection is a commonly used conservative treatment for primary frozen shoulder (PFS), but the optimal injection site remains undetermined.

Objectives: We conducted a prospective randomized controlled trial of multisite combined injection (MCI) vs single rotator interval injection (SRI).

Study Design: A randomized double-blinded controlled trial.

Setting: Center for Joint Surgery, Department of Orthopaedic Surgery, the Second Affiliated Hospital of Chongqing Medical University.

Methods: Sixty-four patients with PFS were randomly assigned to 2 groups. The experimental group received MCI in the rotator interval, intraarticular, and subacromial bursa; the control group received an SRI. Both groups were injected with one mL of 40 mg triamcinolone acetonide and 4 mL of 2% lidocaine. The injection process was completed under ultrasound guidance. Follow-up points were 4, 8, and 12 weeks postinjection. The outcome measures included the Visual Analog Scale (VAS) score, the American Shoulder and Elbow Surgeons (ASES) score, the Constant-Murley Shoulder (CMS) score, passive range of motion of the shoulder, and patient satisfaction rating.

Results: Thirty patients in the MCI group and 29 patients in the SRI group were included in the data analysis. All the outcomes in the 2 groups were significantly better postinjection than preinjection. The MCI group had a lower VAS score than the SRI group at 4 weeks (3.1 ± 1.2 vs 4.3 ± 1.6) and 8 weeks (2.2 ± 1.2 vs. 3.4 ± 1.2) ($P < 0.05$). Compared with the SRI group, the MCI group had a significant improvement in flexion and abduction ($P < 0.01$). Additionally, the ASES and CMS scores in the MCI group were better than those in the SRI group at 4, 8 and 12 weeks ($P < 0.01$).

Limitations: Limitations include the sample size of this study is small and a that it was conducted at a single-center.

Conclusions: Both MCI and SRI effectively alleviated pain and restored range of motion in patients with PFS. However, the MCI group had obviously lower early pain scores, better flexion and abduction, and better function scores than the SRI group; no additional adverse events were observed.

Key words: Primary frozen shoulder, adhesive capsulitis, steroid injection, rotator interval, intraarticular, subacromial bursa

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Frozen shoulder (FS), also known as "adhesive capsulitis," is a common chronic musculoskeletal disease with an undetermined onset and long duration. It has an incidence of 2%-5% in the general population (1). The prevalence rate is higher in patients with type 1 diabetes mellitus and thyroid diseases (2). Although it is considered a self-limiting disease, the symptoms usually last for several months or even longer in the recovery process. Unfortunately, some patients still have some residual joint stiffness that remains, which seriously affects the work and life of patients (3).

According to the pathogenesis of FS, there are 2 main categories (4): 1) primary: insidious onset and unknown etiology; 2) secondary: mainly caused by trauma or surgery with long-term upper limb immobilization. Waninger, et al (5) proved that the injection of a vaccine into the deltoid muscle can also lead to FS. In addition to the undefined mechanism, the pain and limited movement symptoms of primary frozen shoulder (PFS) seriously affect shoulder function (6).

Local steroid injection is one of the most used nonsurgical treatments for PFS (7,8). An early local injection can reduce synovial inflammation, reduce pain, and accelerate early functional recovery (9,10). Although local injections are being increasingly used, clinicians have yet to find the optimal injection site (11). In 2020, high-quality literature (12) revealed that an intraarticular injection into the glenohumeral joint is recommended for patients with PFS. Some scholars have also recommended a subacromial bursa (SA) injection as the first choice (13).

In a prospective randomized controlled trial (RCT), Sun, et al (14) demonstrated that in patients with PFS, a single rotator interval injection (SRI) of steroids, rather than a single IA or a single SA, was better for improving range of motion (ROM) and Visual Analog Scale (VAS) scores at 4, 8, and 12 weeks. The rotator interval (RI) is used to describe weak areas in the soft tissue in the anterior and upper part of the shoulder joint (15). Its boundary shape on the coronal plane is similar to a triangle. The upper edge of the RI is the leading edge of the supraspinatus tendon, the lower edge is the upper edge of the subscapularis tendon, the base of the triangle is the root of the coracoid process, and the apex is the insertion of the coracohumeral ligament in the intertubercular sulcus of the humerus.

The RI is a novel injection site, and its contents include the coracohumeral ligament, the superior glenohumeral ligament, the anterior joint capsule and the IA region of the long head tendon of the biceps (16). Although studies have proven that combined IA and SA injections can achieve better clinical efficacy, we found that there is no comparative study on multisite combined injection (MCI) and SRI (17).

As the number of patients with PFS increases, scholars are focusing on identifying the optimal site for a local steroid injection (18,19). RI is an undoubtedly recommended single injection site (20). However, it is still controversial whether MCI into the RI has better clinical efficacy. If there is no obvious advantage of MCI, SRI will greatly reduce the related costs and operation time. If MCI can relieve pain and improve ROM better than SRI, it should be promoted in clinical practice. Therefore, we performed an RCT to compare the efficacy of MCI (RI+IA+SA) and SRI in patients with PFS for pain, ROM, functional score, and adverse events. It was hypothesized that MCI is the optimal injection method.

Methods

Study Type

This single-center, open, single-blind, prospective RCT was conducted in the outpatient department of our research center from June 2021 through December 2022. All patients signed an informed consent form before participating and voluntarily accepted random grouping. The study was approved by the ethics committee in our hospital and was registered with the Clinical Trial Registration Center (ChiCTR: http://www.chictr.org.cn) (Registration No.: ChiCTR2100050203) before the start of the trial. The protocol was designed following CONSORT (Consolidated Standards of Reporting Trials) guidance.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) patients aged ≥ 18 years old with unilateral shoulder pain, limited shoulder movement, and who were diagnosed with PFS; 2) patients with a duration of pain ≤ 9 months and a VAS score for shoulder pain ≥ 3; 3) patients with a movement restriction, which was defined as passive movement of the affected shoulder joint that is limited by more than 30° on at least 2 motion planes when compared with that of the opposite side; and 4) patients who underwent routine shoulder x-ray and magnetic resonance imaging (MRI) examinations to exclude rotator cuff tears, calcified tendinitis, and osteoarthritis.

Exclusion criteria were: 1) patients with shoulder pain secondary to rheumatic disease, trauma, or infectious arthritis; 2) patients who received a corticosteroid

injection on the affected side within the previous 3 months; 3) patients with a diagnosis of frozen shoulder in both shoulders; and 4) patients with an inability to understand and cooperate with the investigators or provide informed consent.

Sample Size Estimation:

Before randomization, a prospective power analysis was used to estimate the sample size. Based on our preliminary study of 20 patients, it was found that the difference in the American Shoulder and Elbow Surgeons (ASES) score between the MCI group and the SRI group was 12 points, and the SD was 15 points. After accepting an α risk of 0.05 and a β risk of 0.2 in a bilateral contrast, it was found that 26 patients were needed for each group. Moreover, assuming that the loss rate would be 20% (21), at least 32 patients were needed in each group.

Randomization Method

First, a data expert used a computer to generate a column of random numbers from 1 to 64, which were equally divided into 2 groups. The first group represented the MCI group and the second group represented the SRI group. After signing the informed consent form, the patients were included in the MCI group or the SRI group according to the corresponding matching serial number. The operator only performed injection therapy and did not participate in the follow-up or data analysis. Follow-up measurements and data analysis were performed by other researchers. Because the injection site of the MCI group was different from that of the SRI group, patients could not be completely blinded.

Treatment Process

All the patients were locally injected by a trained joint surgeon (MN) to exclude any differences caused by different operators. The MCI group received one mL of 40 mg triamcinolone acetonide plus 4 mL of 2% lidocaine and 5 mL of normal saline, totaling 10 mL mixed liquid in a 10 mL syringe. The SRI group received one mL of 40 mg triamcinolone acetonide plus 4 mL of 2% lidocaine, totaling 5 mL mixed liquid in a 5 mL syringe. The injection site was identified by running a 16G intravenous needle. Our detailed injection steps follow.

MCI group: As described by Koraman et, al (21) and Sun, et al (14), the patient was in the sitting position. 1) Rotator interval: Rotate the upper limb of the affected side as far as possible to improve external rotation and elbow flexion. Under the guidance of ultrasound, the needle was passed through the skin from the outside to the inside to the coracohumeral ligament; the angle between the needle and the coronal plane was approximately 30°. Then, approximately 4 mL of the mixture was penetrated into the coracohumeral ligament along the long axis. 2) Subacromial bursa: Under the guidance of ultrasound, we passed the needle through the skin from the lateral part of the acromion and parallel to the horizontal plane into the subacromial bursa, then approximately 3 mL of the mixture was injected. 3) Intraarticular: The upper limbs of the affected side were folded in front of the chest to the opposite shoulder so that the posterior shoulder joint was fully opened. Under ultrasound guidance, the needle was directed toward the coracoid process and passed through the skin and joint capsule. After no effusion was found, approximately 3 mL of the mixture was injected into the IA region (Fig. 1).

SRI group: Approximately 5 mL of the mixture was permeated around the coracohumeral ligament as described above.

All patients had to stay in the hospital outpatient room for at least 20 minutes to in order to detect

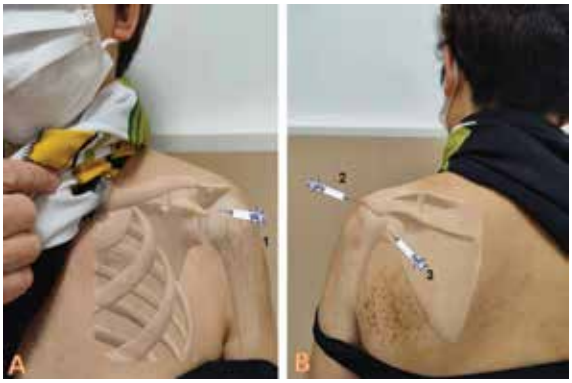

Fig. 1. *Schematic diagram of multisite injection of left shoulder joint. A: Schematic diagram of the front. The first site is the rotator interval. The patient was in a sitting position with elbow flexion 90° and forearm external rotation. The biceps longhead tendon and the coracohumeral ligament were found under ultrasound guidance, and the needle was inserted around the coracohumeral ligament for injection. B: Schematic diagram of the posterior, the patient was in a sitting position with elbow flexion 90° and forearm internal rotation. The second site is the subacromial space. Syringe needle enters from the lateral side of the acromial. The third site, the intraarticular, enters from the medial and inferior part of the posterolateral acromion. All the above operations were completed under the guidance of ultrasound.*

and record any postinjection acute adverse reactions, including dizziness, skin flushing, and local bleeding. Late adverse events, including menstrual disorder, infection, personality change, and skin pigmentation, were also examined during follow-up. Postinjection, the same rehabilitation manual (Supplementary 1) was issued to guide patients through 12 weeks of shoulder functional exercises (22). Any extra drugs and physiotherapy were prohibited.

Outcome Indicators

The results were collected before treatment and at 4, 8 and 12 weeks postinjection. The main indicators were the VAS score and passive ROM (flexion, abduction, internal rotation, and external rotation). The secondary indicators were ASES score, Constant-Murley Shoulder score (CMS), and complications. In addition, in accordance with a previous study (23), satisfaction evaluation was conducted for shoulder pain and function improvement at 4 weeks postinjection. If the symptoms were reduced to less than 50% of the initial symptom, it was termed "Good." If the symptoms improved by < 50%, a slight improvement was considered and marked as "Fair." If the symptoms showed no signs of improvement, they were marked as "Poor."

Data Analysis

IBM SPSS Statistics 25.0 (IBM Corp) was used for statistical analysis. The normality of the data was tested by the Kolmogorov–Smirnov test. The quantitative data conforming to a normal distribution are expressed as the mean ± SD and the qualitative data are expressed as percentages. Repeated-measures analysis of variance (ANOVA) was performed to define the overall effect of the measurements at different time points within the group. The differences in continuous variables between the 2 groups were analyzed by the independent sample t test or the Mann–Whitney U test (for nonnormal data), and the dichotomous variables and rank data between the 2 groups were analyzed by the Fisher's exact test. A P value < 0.05 was considered statistically significant. We used intention-to-treat to analyze the follow-up data.

Results

Patient Characteristics

A total of 90 patients met the inclusion criteria, but only 32 patients in each group signed informed consent forms and underwent the injection procedure. However, during the follow-up, 2 patients in the MCI group were lost to follow-up because of a job transfer and choice of surgery. Three patients in the SRI group were lost to follow-up because of choosing other treatments. Finally, 30 patients in the MCI group and 29 in the SRI group entered the data analysis phase (Fig. 2). The baseline characteristics, including age, gender, body mass index (BMI [kg/m^2]), duration, VAS score, shoulder ROM, ASES and CMS scores, were similar across both groups (Table 1).

VAS

The results showed that VAS scores were improved in both groups at postinjection follow-up when compared with the baseline measurements. This significant change lasted up to 12 weeks (P < 0.05). In addition, the VAS scores in the MCI group at 4 weeks (3.1 ± 1.2 vs 4.3 ± 1.6) and 8 weeks (2.2 ± 1.2 vs 3.4 ± 1.2) were significantly lower than those in the SRI group (P < 0.05). However, there was no significant difference at 12 weeks (P = 0.36) (Table 2).

ROM

At 4 weeks postinjection follow-up, passive ROM in the 2 groups was improved compared to preinjection and further improved over time (P < 0.05). Flexion and abduction in the MCI group were significantly better than that in the SRI group at 4, 8, and 12 weeks postinjection (P<0.01). There was no significant difference in internal rotation or external rotation between the 2 groups (P > 0.05), but internal rotation in the MCI group was better at 8 weeks (MD[what is this abbreviation?] = 5.2; P < 0.05) (Table 3).

Functional Outcomes

The results show that the pretreatment-to-4 week improvement in ASES and CMS scores was statistically significant in both groups and that functional outcomes improved over time (P < 0.05). Importantly, the ASES and CMS scores in the MCI group were significantly higher than those in the SRI group at 4, 8, and 12 weeks postinjection (P < 0.05) (Table 4).

Degree of Satisfaction and Complications

In terms of the satisfaction rating at 12 weeks, the results show that 25 patients in the MCI group marked "Good," 5 marked "Fair," and 0 marked "Poor." In the SRI group, 18 patients marked "Good," 11 marked "Fair," and 0 marked "Poor." However, there was no significant difference in the degrees of satisfaction be-

tween the 2 groups (P = 0.059) (Table 5).

At the same time, one patient in the MCI group and one patient in the SRI group presented with symptoms of palpitation and sweating; both patients recovered completely after rest. Apart from this, no complications were observed in either group.

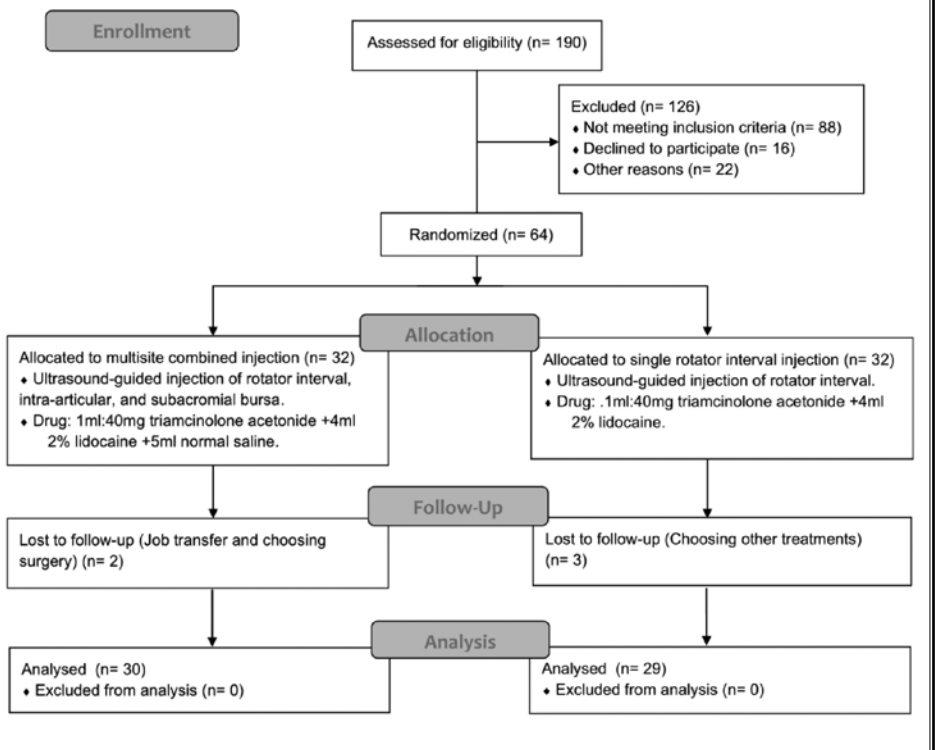

Fig. 2. *CONSORT flow chart.*

Discussion

To our knowledge, this is the first prospective, randomized controlled study to investigate MCI including RI, IA and SA, vs SRI in patients with PFS. The results show that both the MCI group and the SRI group significantly improved their pain scores, functional scores, and ROM posttreatment. However, the main finding of the study was that the MCI group had their pain scores reduced to optimal levels earlier than the SRI group (P < 0.05), and their relief remained up to 8 weeks. There was no significant difference in pain scores at 12 weeks.

At the same time, the recovery of abduction and flexion activity was faster and better in the MCI group (P < 0.05), reaching 147° for abduction and 155° for flexion at 12 weeks. In addition, ASES and CMS scores in the MCI group were consistently better than those in the SRI group at 4, 8, and 12 weeks postinjection (P < 0.05). Although there was no significant difference in satisfaction ratings between the 2 groups (P > 0.05), the percentage of patients in the MCI group who were very satisfied was still higher than that in the SRI group (83% vs 62.1%). In addition, only one patient in each group developed related complications. These results prove that MCI has bet-

Table 1. *Comparison of baseline characteristics between the 2 groups.*

	MCI Group (n = 30)	SRI Group (n = 29)	Statistical Tests	P Value
Age (years)	56.7 ± 12.1	58.6 ± 11.0	t = -0.628	0.53
Height (cm)	159.1 ± 6.9	158.9 ± 6.4	t = 0.137	0.89
Weight (kg)	60.1 ± 4.6	60.4 ± 9.5	t = -0.136	0.89
BMI (kg/m^2)	23.8 ± 2.0	23.8 ± 2.8	t = -0.055	0.96
Pain duration (month)	3.3 ± 1.6	3.7 ± 1.3	t = -0.953	0.35
Women/men	19/11	19/10	χ^2 = 0.031	0.86
Left/right shoulder	18/12	20/9	χ^2 = 0.517	0.47
Diabetes/ non-diabetes	8/22	8/21	χ^2 = 0.006	0.94
VAS score	6.7 ± 1.2	6.8 ± 1.3	t = -0.178	0.86
CMS score	37.7 ± 7.7	38.4 ± 6.7	t = -0.399	0.69
ASES score	33.8 ± 8.3	33.9 ± 8.2	t = -0.067	0.95
Flexion (0-180°)	86.3 ± 25.7	87.6 ± 20.3	t = -0.207	0.84
Abduction (0-180°)	81.9 ± 15.5	83.6 ± 22.6	t = -0.336	0.74
External rotation (0-90°)	25.0 ± 10.8	26.1 ± 6.6	t = -0.486	0.63
Internal rotation (0-90°)	35.8 ± 8.8	34.6 ± 11.4	t = 0.459	0.65

Abbreviations: MCI: multisite combined injection; SCI: single rotator interval injection; BMI: body mass index; VAS: visual analog scale; CMS: Constant-Murley shoulder; ASES: American Shoulder and Elbow Surgeons.

ter clinical efficacy than SRI on the basis of operational safety.

Patients with PFS commonly present with shoulder pain and limited active and passive shoulder movement without having any prior history of trauma, infection, or surgery. The pathologic changes of patients with PFS include initial aseptic inflammation around the joint capsule, followed by proliferation of myoblasts and fibroblasts, proliferation of type I and III collagen, adhesion of the synovial membrane, and then thickening and contracture of the joint capsule and the soft tissue around the joint (24). Therefore, the joint space becomes narrow, and the glenohumeral joint volume decreases significantly (25).

FS usually occurs in 3 overlapping stages: the first is the freezing stage, lasting from 10 to 36 weeks; followed by the frozen stage lasting from 4 to 12 months; and finally the thawing stage, lasting from 12 to 42 months (26). The first stage of frozen shoulder is characterized by significantly increased shoulder pain and gradually decreased shoulder ROM (26). Considering the special pathological characteristics of FS, the early application of steroid hormones has been proven to be effective in treating pain directly caused by inflammation (27,28). In addition to conservative treatment, scholars believe that injecting steroids and local anesthetics into the joint after manipulation therapy conducted under anesthesia, or arthroscopic capsular release, can also reduce inflammation and pain to a great extent (29).

Therefore, the goals of timely and effective intervention in the early stage of PFS are to avoid inflamma-

Table 3. *Comparison of passive range of motion between the 2 groups.*

Outcomes	Before Treatment	4 Weeks	8 Weeks	12 Weeks
Flexion (0-180°)				
MCI group	86.3 ± 25.7	128.3 ± 18.6*	143.0 ± 15.6*	147.3 ± 12.6*
SRI group	87.6 ± 20.3	112.7 ± 17.2*	130.1 ± 16.2*	135.5 ± 15.3*
P value	0.84	0.001	0.003	0.002
Abduction (0-180°)				
MCI group	81.9 ± 15.5	137.7 ± 13.6*	151.5 ± 10.2*	155.5 ± 8.4*
SRI group	83.6 ± 22.6	119.2 ± 20.3*	134.7 ± 18.1*	142.8 ± 15.4*
P value	0.74	< 0.001	< 0.001	< 0.001
External rotation (0-90°)				
MCI group	25.0 ± 10.8	48.1 ± 10.5*	51.7 ± 9.5*	55.7 ± 9.4*
SRI group	26.1 ± 6.6	46.3 ± 11.9*	53.4 ± 11.7*	56.4 ± 12.3*
P value	0.63	0.54	0.53	0.81
Internal rotation (0-90°)				
MCI group	35.8 ± 8.8	54.6 ± 9.7*	62.1 ± 8.3*	66.4 ± 7.4*
SRI group	34.6 ± 11.4	53.9 ± 11.7*	56.9 ± 11.5*	65.1 ± 14.2*
P value	0.65	0.81	0.048	0.67

Abbreviations: MCI: multisite combined injection; SCI: single rotator interval injection; * represents $P < 0.05$ compared with the last time point in the group.

Table 2. *Comparison of VAS scores between the two groups.*

	Before Treatment	4 Weeks	8 Weeks	12 Weeks
MCI group	6.7 ± 1.2	3.1 ± 1.2*	2.2 ± 1.2*	1.9 ± 1.2*
SRI group	6.8 ± 1.3	4.3 ± 1.6*	3.4 ± 1.2*	2.2 ± 1.3*
P value	0.86	0.003	< 0.001	0.36

Abbreviations: MCI: multisite combined injection; SCI: single rotator interval injection; * represents $P < 0.05$ compared with the last time point in the group.

Table 4. *Comparison of functional scores between the 2 groups.*

Outcomes	Before Treatment	4 Weeks	8 Weeks	12 Weeks
ASES score				
MCI group	33.8 ± 8.3	76.5 ± 8.0*	83.7 ± 8.8*	87.7 ± 5.7*
SRI group	33.9 ± 8.2	60.8 ± 12.3*	72.2 ± 10.1*	80.7 ± 7.0*
P value	0.95	< 0.001	< 0.001	< 0.001
CMS score				
MCI group	37.7 ± 7.7	68.0 ± 9.0*	72.9 ± 8.1*	78.9 ± 5.3*
SRI group	38.4 ± 6.7	60.6 ± 9.5*	67.9 ± 8.6*	74.3 ± 7.9*
P value	0.69	0.003	0.023	0.01

Abbreviations: MCI: multisite combined injection; SCI: single rotator interval injection; CMS: Constant-Murley shoulder; ASES: American Shoulder and Elbow Surgeons.
* represents $P < 0.05$ compared with the last time point in the group.

Table 5. *Comparison of satisfaction levels between the 2 groups at 12 weeks.*

Degree	MCI group (30)	SRI group (29)	$P = 0.059$
Good	25	18	
Fair	5	11	
Poor	0	0	

Abbreviations: MCI: multisite combined injection; SCI: single rotator interval injection.

tion and further exacerbation of symptoms. Steroid injection, as one of the preferred nonsurgical treatment methods, has been accepted by patients because of its good effectiveness, quick symptom relief, and low cost.

There is still much controversy over the optimal injection site. Sun, et al (14) proved in a prospective RCT in 2018 that their SRI group had more significant improvement in pain score, ROM, and function score than their single IA group or their single SA group; the worst results were in their SA group. Cho, et al (30) demonstrated that combined IA and SA injections improved activity more significantly than either IA or SA alone. In 2021, Koraman, et al (21) conducted a prospective RCT in which the experimental group was injected at multiple sites, including the RI, IA, posterior inferior joint capsule, SA and posterior superior joint capsule. The control group received a single IA injection. The injection drugs were triamcinolone and bupivacaine. The multisite group had better ROM outcomes than the IA group at one, 3, and 6 months. However, injection at the posterior superior joint capsule easily damages the suprascapular nerve, and the RI was not the optimal site in the control group, so the clinical significance is modest.

In addition, if there are too many injection sites, the learning curve is long, which is not conducive to widespread clinical application. Therefore, we plan to explore whether an RI+IA+SA combined injection is a safe and alternative method and whether it leads to earlier recovery and better shoulder function than an RI alone injection. Kim, et al (31) found there were no significant differences in ROM or functional scores between patients who received high-dose triamcinolone acetonide (40 mg/mL) and patients who received low-dose triamcinolone acetonide (20 mg/mL). Considering the potency and solubility of triamcinolone acetonide, the injection volumes of MCI and RI in our study were 10 mL and 5 mL, respectively.

Our study found that although there was no difference between internal rotation and external rotation, the early improvement in VAS score and functional score of the MCI group was more significant than that of the SRI group. In the early stage of PFS, the coracohumeral ligament in the RI becomes a thickened bundle (32), thus leading to limited external rotation as the main symptom in the early stage. Biopsy material from the RI also showed chronic inflammation and fibrous hyperplasia (25). MRI has also shown an increased number of blood vessels and thickened coracohumeral ligaments in RI (33). During shoulder arthroscopic release, inflammatory changes in the RI have also been observed, including hyperemia and edema in part of the biceps long head tendon (34).

However, the coracohumeral ligament is more involved in shoulder external rotation, extension, and internal rotation in the abduction position while standing. This ligament is relatively relaxed during abduction and flexion, which explains why SRI is not better than MCI in improving abduction and flexion activities. In addition, the joint capsule has been clearly proven to be a key location in the development of PFS (35). During shoulder arthroscopic surgery for PFS, we can see a significant reduction in the joint luminal volume and a large amount of synovial inflammation and hyperplasia in the field of vision.

Finally, the SA should not be ignored. Although there is no clear evidence to prove that the SA is related to PFS, recent studies have shown that increased cytokines can be detected in the SA of patients with PFS (36), and significantly increased fluid accumulation and vascular shadow can also be seen on MRI (37). Some studies have proven that steroid injections into the SA and IA can achieve similar clinical efficacy (30,38). These results suggest that SA may be a potential lesion site of PFS. Therefore, we speculated that the RI, IA, and SA are all important lesion sites of PFS, and that a multisite injection would reduce inflammation inside and outside the joint capsule, thus suggesting that an MCI can achieve better clinical efficacy than an SRI.

As an adequately powered RCT to explore MCI (RI+IA+SA) vs SRI, the deviation risk of this study was small, and the results are highly reliable. Our study provides an available and efficacious combination of injection sites. However, the results proved that there is no significant difference in external rotation between the 2 groups. In the early stage of FS, inflammation may be mainly concentrated around the coracohumeral ligament in the RI. Therefore, we believe that patients with isolated limited external rotation should only receive an injection in the RI. For patients with special symptoms, a personalized injection program can be developed.

However, our study has some limitations that deserve attention: 1) the follow-up period of 12 weeks was short, and the duration of PFS was long, so it is still unclear whether an MCI injection can promote long-term relief from PFS; 2) both type I, type II diabetes mellitus, and thyroid disease are risk factors for PFS and are associated with a poor prognosis. Due to the small number of patients included, this study did not exclude

these patients or conduct a subgroup analysis on these patients; 3) the injection doses used and medications administered to the 2 groups were different; 4) our study mainly explored the optimal injection site for PFS, but there is still no unified standard for the optimal composition or dosage of mixed drugs (39). More high-quality studies are needed to explore this in the future so that clinicians can reference it in practice.

Conclusion

Both MCI and SRI effectively reduced pain and improved ROM in patients with PFS. However, the MCI group had better early pain scores, better flexion and abduction, and better function scores than the SRI group, without an additional adverse event. Therefore, MCI is an effective and feasible treatment method in patients with PFS.

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Supplementary 1 A detailed home exercise program

Internal and external rotation exercise	The patient stands with back against the wall or lies with back on the bed. Put arms close to lateral body. Bend elbow, and take the elbow point as the fulcrum to carry out internal rotation exercise and external rotation exercise of the diseased shoulder joint.
Flexion exercise	The patient stands facing the wall, slowly climbs up the wall with the diseased side's fingers, raises the upper limbs as high as possible, makes a mark on the wall, and then slowly returns to the original place, repeatedly, gradually increase the height according to recovery time.
Abduction exercise	The patient's upper limbs droop naturally, with arms straighten and palms down, slowly abduct, lift up with force, stop for 2 minutes after reaching the top, and then return to the original place.
Internal rotation exercise	The patient stands naturally. In the posture of internal rotation and backward extension of the diseased side's upper limb, the healthy side pulls the diseased side's hand or wrist, and gradually pulls to the healthy side and upward.
Extension exercise	The patient stands naturally. In the posture of internal rotation and backward extension of the upper limb on the diseased side, bend the elbow and wrist, touch the spine spinous process with the abdomen of the middle finger, and then stay still from bottom to top as much as possible. After 2 minutes, slowly return to the original place, repeatedly, gradually increase the height according to recovery time.

Note: After injection, these patients participated in a self-exercise program composed of flexion, abduction, external rotation and internal rotation under mild active training. Patients slowly repeated the training methods 15-20 times in 15 minutes at a frequency of three times a day. In addition, instruct the patient to gently stretch the shoulder within the tolerance range, but avoid over stretching.