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Original Article

Therapeutic effect of shoulder arthroscopic release on frozen shoulder and its effect on fibrogenic cytokines and inflammatory factors

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Abstract: Objective: To investigate the therapeutic effect of shoulder arthroscopic release on primary frozen shoulder and its effect on the expressions of fibrogenic cytokines and inflammatory factors. Methods: A total of 60 patients with frozen shoulder treated in our hospital from July 2014 to July 2017 were enrolled, including 30 patients who underwent arthroscopic treatment (A group) and 30 patients who received intra-articular injection of medicine under B-scan ultrasonography (B group). Meanwhile, fifteen non-frozen shoulder patients who underwent examinations of shoulder joint fluid were selected as control group (C group). The Visual Analogue Scale (VAS) pain score and Constant shoulder score of A group and B group before treatment and one month after treatment were recorded and compared. Shoulder joint fluid of C group, A group and B group were collected before treatment and one month after treatment respectively with the guidance of B-scan ultrasonography. The cytokines such as interleukins-6 (IL-6), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), interleukins-1 (IL-1) and tumor necrosis factor-α (TNF-α) were detected to compare the differences in the scores of the two treatment methods and the correlation between these cytokines and the frozen shoulder, so as to further confirm the therapeutic effect and possible mechanism of the two treatment methods. Results: There was no significant difference in VAS pain score or Constant shoulder score between the two groups before treatment; while after treatment, the VAS pain score of A group was more markedly reduced than that of B group and the Constant shoulder score was more distinctly promoted than that of group B (both $P<0.05$). Before treatment, the concentrations of IL-6, TGF-β, VEGF, IL-1 and TNF-α in A group and B group were significantly higher than those in C group; while after treatment, all cytokines were remarkably decreased and patients in group A showed more decreases than those in B group (all $P<0.05$). Hence, the changes of cytokines were positively correlated with VAS pain score and negatively associated with Constant shoulder score. Conclusion: The therapeutic effect of shoulder arthroscopy on frozen shoulder is evidently better than that of intra-articular injection of medicine, which may be related to a further reduction of the concentrations of IL-6, TGF-β, VEGF, IL-1 and TNF-α.

Keywords: Frozen shoulder, arthroscopy, cytokines

Introduction

Frozen shoulder, also known as omarthritis, whose main feature is progressive shoulder pain and limited joint activity, predominantly occurs in the elderly especially in elderly women [1]. It can be divided into primary frozen shoulder and secondary frozen shoulder. So far, the mechanism of primary frozen shoulder is still unclear, but some studies reported that it might be related with metabolic diseases, genetic factors, environmental factors, etc. [2, 3]. Secondary frozen shoulder can be seen in shoulder surgeries or traumas like humerus fractures, clavicle fractures and shoulder dislocations. Numerous treatments for frozen shoulder have evolved. With the development of minimally invasive surgery, it has become increasingly popular for the treatments of various diseases, such as gallbladder, liver, appendix and other viscera surgeries under laparoscope, lung or mediastinum disease operations with thoracoscope, knee examination and knee osteoarthritis under knee arthroscope. Therefore, the application of shoulder arthroscopy has become a newly developed treatment for

frozen shoulder. This article aims to provide a clinical basis for arthroscopic treatment of frozen shoulder by comparing the effect between shoulder arthroscopy and intra-articular injection of medicine. Some studies have found that inflammatory factors such as interleukins-1 (IL-1), interleukins-6 (IL-6), tumor necrosis factor-α (TNF-α), fibrogenic cytokines like transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF) are all highly expressed in the capsule of shoulder joint in patients with frozen shoulder [4-6]. Thus, confirmation has been made that there is an association between these cytokines and the development of frozen shoulder. Thereby, we explore the expressions of these cytokines in the articular fluid of patients with frozen shoulder before and after treatment, to further prove whether they are related to the development of frozen shoulder or not.

Materials and methods

General data

Sixty patients with frozen shoulder treated in Shengli Oilfield Central Hospital of Dongying City, Shandong Province, from July 2014 to July 2017 were recruited as the study subjects. Inclusion criteria: (1) Patients met the diagnostic criteria for primary frozen shoulder, did not undergo surgical treatment and no other procedures or conservative treatments had been performed within two weeks [7]; (2) Patients were in stage I-II according to Neviasar staging for frozen shoulder with a duration of 6-12 months, and could tolerate conventional surgery, medication, rehabilitation [8, 9]; (3) Patients aged from 45 to 55 years old; (4) Patients volunteered for surgery, medication and follow-up rehabilitation as well as good compliance; (5) Patients' straight X-ray showed normal shape of joint space and humerus in shoulder joint and the outlet of supraspinatus muscle. Exclusion criteria: (1) Patients with secondary frozen shoulder; (2) Patients had a history of shoulder joint and ipsilateral arm injuries or surgeries; (3) Patients had a poor function of heart, lung and brain, associated with chronic diseases like diabetes mellitus; (4) Patients were allergic to injected medicine; (5) Patients had hematologic diseases or coagulation abnormalities; (6) Patients were diagnosed with rheumatoid arthritis or articular tumors. Concurrently, fifteen non-frozen shoulder patients like the ones with joint tuberculosis, rheumatic arthritis and gouty arthritis, aged from 45 to 55 years old, who underwent joint fluid examination in our hospital, were selected. The exclusion criteria were as same as mentioned above (1-5). The study was approved by the Medical Ethics Committee. All patients were aware of the possible risks of treatments and that alternative treatments were to be performed if clinically ineffective. Informed consents were obtained.

Study subject

Patients aged 45-55 years included 32 females and 28 males with primary frozen shoulder and a duration of 6-12 months. Patients were randomly assigned into two groups by computer after numbering, including arthroscopic treatment group (A group) and injection of medicine under B-scan ultrasonography group (B group); while fifteen non-frozen shoulder patients were recruited as control group (C group). No apparent differences were found in group A and group B in general information such as age, sex, duration of disease, severity of disease, and disease stage. Besides, there was no evident difference in age and sex among three groups.

Treatment

Arthroscopy: Patients in group A received arthroscopic treatment, in which patients under general anesthesia received procedures by the same group of surgeons. A beach chair position was taken by patients. A small amount of saline was injected into the joint cavity to expand the joint capsule using 18G puncture needle, which could reduce the injury to humeral cartilage in time of arthroscopy. The blood pressure was controlled in 90-95/60-65 mmHg. Arthroscopy was placed 1-3 cm below the posterior horn of the acromion through the posterior direction of the coracoid process. Into the joint cavity and subacromial bursa, joint space narrowing, bursitis and the adhesion of the joint capsule and the surrounding articulation could be observed; hyperplastic synovial tissues were cleared and adhesion was released after the exploration. Be alert not to damage nerves and tissues with normal structures.

Medication: Patients in B group underwent intra-articular injection of medicine under the guidance of B-scan ultrasonography. Blind ana-

Table 1. Comparison of general data in each subject

Group	Group A	Group B	*P* value	Group C	*P* value
Number of cases	30	30	0.425	15	0.317
Gender			0.527		0.716
Male	13	15		8	
Female	17	15		7	
Age (years)	49.5±5.4	50.8±4.2	0.556	49.2±4.9	0.476
Duration of disease (months)	9.2±1.2	9.8±1.1	0.327		
Stage of disease			0.326		
Stage I	12	14			
Stage II	18	16			

Table 2. Correlation analysis of each cytokine with VAS pain score and Constant shoulder score

Cytokine	VAS pain score		Constant shoulder score	
	R	P	R	P
IL-1	0.852	0.013	-0.885	0.034
IL-6	0.933	0.001	-0.911	0.001
TGF-β	0.881	0.014	-0.907	0.001
TNF-α	0.856	0.015	-0.832	0.028
VEGF	0.894	0.001	-0.896	0.021

Note: VAS, Visual Analogue Scale; IL-6, interleukins-6; IL-1, interleukins-1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

tomical orientation puncture was widely adopted in the previous medical therapy, which could result in damages to blood vessels, nerves, tissues or an unsuccessful puncture. In this paper, B-scan-guided puncture was adopted, which could outstandingly improve the success rate. Puncture under the guidance of B-scan ultrasonography was taken 2 cm below the shoulder. After local anesthesia around puncture site, the puncture needle was placed into joint cavity under B-scan ultrasonography. Then, the injection mixture containing 2% Lidocaine 5 mL with a dose of Triamcinolone Acetonide 25 mg and Sodium Hyaluronate Injection 25 mg (2.5 mL) was given.

Other treatment: Both groups were given Diclofenac Sodium Extended Release Tablets 75 mg per day for 7 days and were both under the guidance of the same rehabilitation physician to carry out regular joint activities.

Efficacy assessment

Visual analogue scale (VAS) pain score: A 10 cm horizontal line on a piece of paper with 0 on one end and 10 on the other was drawn; patients were asked to mark the level of their pain on this line based on their own perception. The higher the score was, the more severe the pain would be. The tests were performed before treatment and one month after treatment respectively.

Constant shoulder score: Pains, daily activities, active range of motion and muscle strength (4 subscale scores) were included, which were made up of 100 scores. The higher the score was, the better the shoulder function would be. The tests were taken before treatment and one month after treatment.

Joint fluid examination: Two to three milliliter fluid from the joint cavity was extracted under the guidance of B-scan ultrasonography in two groups of patients before treatment and one month after treatment. Due to the invasive operation, informed consents were fully obtained from patients before operation. The concentrations of IL-6, TGF-β, VEGF, IL-1 and TNF-α in the articular cavity were measured by ELISA kit provided by Neobioscience Technology Company. The tests were performed before treatment and one month after treatment respectively.

Safety assessment

If poor efficacy, unrelieved pain and unimproved joint function presented, other treatments would be taken and this case would be assigned as an invalid case.

Statistical analysis

All statistical analyses were performed with SPSS17.0 software and the measurement data were expressed as mean ± standard deviation, while the Student's t-test was used for compari-

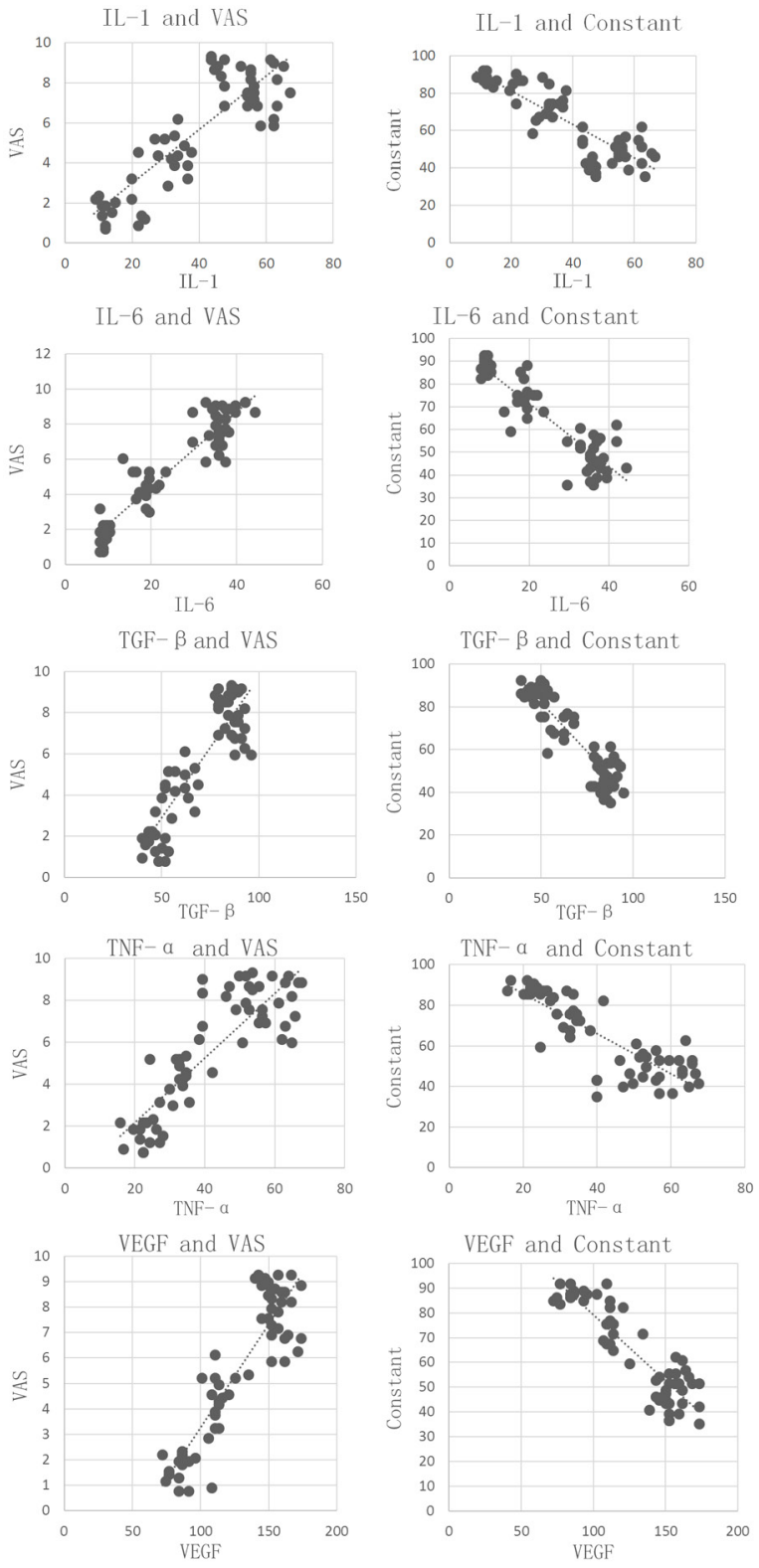

Figure 1. Correlation analysis of each cytokine with VAS pain score and Constant shoulder score. VAS, Visual Analogue Scale; IL-6, interleukins-6; IL-1, interleukins-1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

sons between independent samples from groups. The paired t test was adopted before and after treatment within-group and Chi-square test was used in the quantitative data. The relationship of each cytokine with VAS pain score and Constant shoulder score was analyzed by Pearson correlation analysis. *P* values were judged significant if they were less than 0.05.

Results

Patients' baseline characteristics

No apparent differences were found in A group and B group in general information such as age, sex, duration of disease, severity of disease (P> 0.05). In comparison with two groups, there was no significant difference in age and sex in group C (P>0.05). See **Table 1**.

Correlation analysis of each cytokine with VAS pain score and Constant shoulder score

Data like VAS pain score, Constant shoulder score and corresponding cytokines of 60 patients with frozen shoulder before and after treatment were collected and analyzed by Pearson correlation analysis. The results suggested that each cytokine concentration was positively correlated with VAS pain score, that is to say, the higher the concentration was, the higher VAS pain score got; while Constant shoulder score was negatively associated, which meant the higher the concentration was, the lower Constant shoulder score got. The results showed an association between the

Table 3. Analysis of therapeutic effect

Group	Group A	Group B
Before treatment		
VAS pain score	7.9±1.025	7.99±1.076
Constant shoulder score	46.4±7.548	49.3±6.829
One month after treatment		
VAS pain score	1.67±0.673	4.51±0.848
Constant shoulder score	87.4±2.898	73.7±7.575

Note: VAS, Visual Analogue Scale.

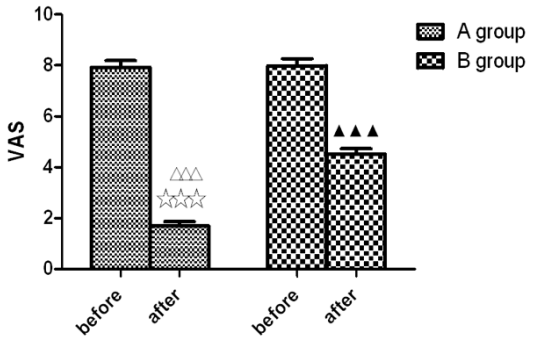

Figure 2. Changes of VAS pain score. The VAS pain score of group A at one month after treatment was obviously lower than that before treatment, and there was a statistically significant difference (☆☆☆P<0.001); The VAS pain score of group B at one month after treatment was much lower than that before treatment (▲▲▲P<0.001); The VAS pain score of group A at one month after treatment was apparently much lower than that of group B, and the difference was statistically significant (△△△P<0.001). VAS, Visual Analogue Scale.

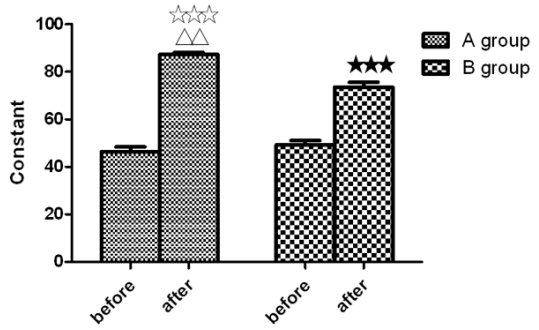

Figure 3. Changes of Constant shoulder score. The Constant shoulder score of group A at one month after treatment was noticeably higher than that before treatment, and there was a statistically significant difference (☆☆☆P<0.001); The Constant shoulder score in group B at one month after treatment was markedly higher than that before treatment (★★★P<0.001); In comparison with group B, the Constant shoulder score of group A at one month after treatment was distinctly much higher, and the difference was statistically significant as well (△△P<0.01).

concentrations of cytokines and the development of the disease. See **Table 2** and **Figure 1**.

Efficacy of treatment

The results showed that there was no prominent difference in VAS pain score and Constant shoulder score between the two groups before treatment (P=0.753, P=0.814). One month after treatment, the VAS pain scores of A group and B group both decreased while Constant shoulder scores increased noticeably (all P<0.05), which indicated that both treatments had an effect on the frozen shoulder. However, compared with those in B group, the VAS pain scores were more apparently decreased and Constant shoulder scores were more markedly increased in A group. The difference was statistically significant (both P<0.05), demonstrating that the therapeutic effect of A group was more favorable. See **Table 3**, **Figures 2** and **3**.

The concentration changes of fibrogenic cytokines and inflammatory factors

In comparison with non-frozen shoulder patients in C group, the expressions of IL-6, TGF-β, VEGF, IL-1 and TNF-α in the articular cavity fluid of patients with frozen shoulder in A group and B group were significantly increased (all P<0.05); there was no marked difference between A group and B group. The expressions of cytokines in both groups were distinctly declined at one month after treatment (all P<0.05). Compared with those in B group, the decrease in A group was much greater and the difference was statistically significant (all P<0.05). See **Table 4**, **Figures 4** and **5**.

Invalid cases

One patient in A group was invalid cases because of unfinished postoperative articular cavity fluid collection for personal reasons; two patients in B group were converted to surgeries because of ineffective medication injections and then were counted as the invalid cases. Without any prominent postoperative adverse events or adverse drug reactions, the remainders were valid cases.

Discussion

Primary frozen shoulder, with unclear pathogenesis, is one of the common diseases of joint pain and joint movement disorders. Some stud-

Table 4. Changes in each cytokine

Group	Group A	Group B	P	Group C
Before treatment (ng/mL)				
IL-1	55.50±7.68	53.2±6.6	0.736	4.79±0.88
IL-6	36.88±3.48	35.93±2.98	0.532	6.393±0.765
TNF-α	55.07±9.01	55.78±7.54	0.387	11.99±1.754
TNF-β	86.48±5.03	85.40±4.77	0.875	33.46±5.551
VEGF	154.56±9.18	156.83±8.88	0.462	54.86±6.437
One month after treatment (ng/mL)				
IL-1	15.08±5.07	31.90±4.05	<0.001	
IL-6	9.09±0.74	18.86±2.50	<0.01	
TNF-α	22.99±3.66	33.47±3.95	<0.05	
TNF-β	46.37±4.09	59.11±6.24	<0.05	
VEGF	87.37±11.16	113.61±7.91	<0.001	

Note: VAS, Visual Analogue Scale; IL-6, interleukins-6; IL-1, interleukins-1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

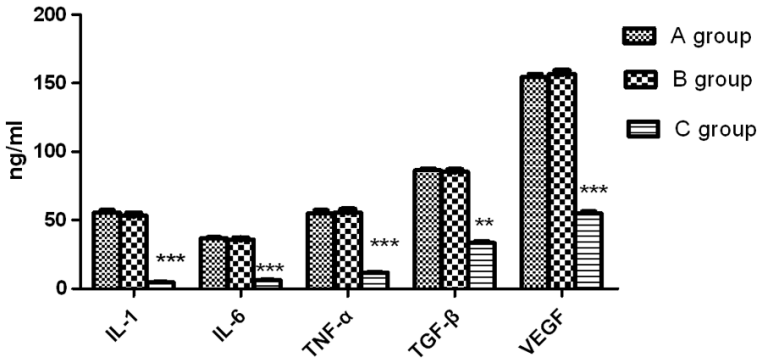

Figure 4. Comparison of each cytokine in study subjects of three groups. The concentration of each cytokine in the articular cavity fluid of patients with frozen shoulder in group A and group B was remarkably higher than that of non-frozen shoulder patients in group C, and there was no apparent difference between group A and group B (**P<0.01, ***P<0.001). IL-6, interleukins-6; IL-1, interleukins-1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

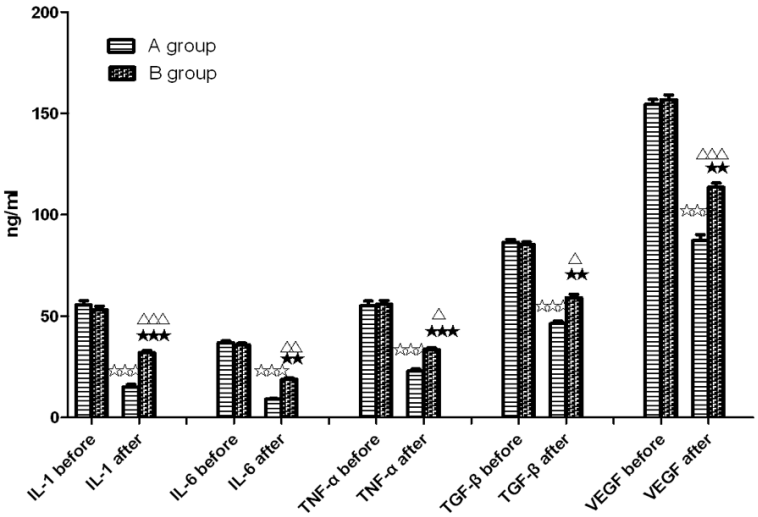

Figure 5. Comparison of each cytokine before and after treatment in group A and group B. The concentration of each cytokine in group A was evidently lower than that before treatment (☆☆☆P<0.001); The concentration of each cytokine in group B was remarkably lower than that before treatment (★★P<0.01, ★★★P<0.001); The concentration of each cytokine in group A after treatment was outstandingly lower than that of group B, and the difference was statistically significant (△P<0.05, △△P<0.01, △△△P<0.001). IL-6, interleukins-6; IL-1, interleukins-1; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

ies suggest that frozen shoulder has the following characteristics: (1) Joint capsule is apparently thickened and synovial membrane shows evidence of congestion and thickening [10, 11]; the presence of fibroblasts and chronic inflammatory cells are observed in the tissues of shoulder joint capsule [6]. (2) Normally, joint cavity volume is 15-18 mL, but compared with the normal ones, joint cavity volume decreases significantly in patients with frozen shoulder which is often less than 10

mL, mostly less than 5 mL. (3) Among all kinds of limited shoulder activities, the most common one is the lateral rotation function limitation [12]. Treatments for primary frozen shoulder are numerous, mainly including maneuver release, injection of medicine and minimally invasive surgery [13]. Before minimally invasive surgery, patients with frozen shoulder tended to choose medication for joint pain since the primary frozen shoulder is a self-limited disease. However, the efficacy in most patients was unsatisfied because medication did not completely relieve the symptoms of functional limitation and maneuver release hardly alleviated the patients' pain or caused a lot of complications as well. The minimally invasive surgery, with quicker postoperative recovery, less pain and trauma, fills the surgically gap for patients with the frozen shoulder. Compared with maneuver release, it is a more radical and thorough method. Our study mainly focuses on the therapeutic effect of arthroscopy for frozen shoulder. Based on the results presented, we can easily speculate that the therapeutic effect of shoulder arthroscopic release is shown to be pronouncedly superior to injection of medicine in relief of pain and recovery of shoulder function, which proves that shoulder arthroscopy for frozen shoulder is an effective and feasible way.

Some scholars have suggested that inflammation and fibrosis may be the main reason for joint pain and joint movement disorders in patients with frozen shoulder [10, 14]. Lots of imaging data and the pathological data also have confirmed that inflammation and fibrosis are observed in tissues of rotator cuff in patients with frozen shoulder, resulting in contracture and thickening of joint capsule [15]. Therefore, this article explores whether increased inflammatory factors and fibrogenic cytokines in the joint fluid can lead to the development of frozen shoulder. TGF-β plays a major regulatory role in many diseases related to fibrosis, such as hepatic fibrosis, renal fibrosis, pulmonary fibrosis [16, 17]. Hence, TGF-β, representing fibrogenic cytokines, is selected. Secreted by a variety of human cells, TGF-β is found in various tissues of human body. During the formation of fibrosis, TGF-β can not only promote the synthesis of extracellular matrix by fibroblasts, but also promote the transformation of epithelial cells into fibroblasts [18]. Interleukin is a cellular target inflammatory factor secreted by a variety of cells. In this paper, two common cytokines, IL-1 and IL-6, were selected. IL-1 is secreted by activated monocyte-macrophages, and an excess of IL-1 in the tissues suggests localized inflammation. Studies have demonstrated that IL-1 can stimulate the secretion of TGF-β by target cells in chronic inflammation, and thereby promotes fibrosis [19]. Secreted mainly by monocyte-macrophages, IL-6 is also a fibroblast growth factor that acts on the nucleus via the STAT3 pathway. Thus, it promotes the synthesis and secretion of type I collagen. It has been suggested that dense fibers in frozen shoulder are caused by the deposition of type I and type II collagen [20]. Additionally, TNF-α and VEGF, two common inflammatory cytokines, were also selected in this article. TNF-α is derived from a variety of inflammatory cells, and plays an essential role in fibrosis as well. In chronic inflammation, it can inhibit macrophages from engulfing collagen fibers and thereby promotes fibrosis [21]. VEGF, which can specifically promote the proliferation of vascular endothelial cells to form new blood vessels, is mainly secreted by T cells and macrophages. Some studies have proven that new blood vessels are observed in the capsule of shoulder joint in patients with frozen shoulder, which can cause severe congestion in the joint capsule, resulting in the local formation of chronic inflammation [22]. One of the major insights to emerge from our study is that the expressions of these cytokines are positively correlated with the VAS pain scores of patients and negatively correlated with the Constant shoulder scores, indicating that these cytokines are indeed associated to the development of frozen shoulder. In addition, in comparison with non-frozen shoulder patients, the expressions of these cytokines in the articular cavity fluid of patients with frozen shoulder were markedly increased but decreased noticeably after treatment, illustrating that the treatment for frozen shoulder may be achieved through the reduction of these fibrogenic cytokines and inflammatory factors thereby relieving fibrosis and inflammation of the shoulder joint. In contrast with medical treatments, the reduction of cytokines and the therapeutic effect are more outstanding in patients with surgical treatments under shoulder arthroscopy.

Taken together, we confirm that the favorable effect of shoulder arthroscopic release on frozen shoulder may be achieved by further reduc-

ing the concentrations of IL-6, TGF-β, VEGF, IL-1 and TNF-α in articular cavity. Nevertheless, our results only imply one possible mechanism for the treatment of frozen shoulder. Due to the limitation of time, this paper does not investigate other mechanisms. Further work may be needed to definitely determine whether other potential mechanisms exist or not.

Disclosure of conflict of interest

None.

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