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Original Article

Correlations of serum TNF-α, IL-1β and IL-1 with the pain degree in patients with instability in traumatic anterior shoulder joints

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Abstract: Objective: The objective of this study was to observe the expression levels of serum interleukin-1 (IL-1), IL-1β and tumor necrosis factor-alpha (TNF-α) in patients with instability in traumatic anterior shoulder points, and to study their correlations with the pain degree. Methods: In our hospital, a total of 40 patients with instability in traumatic anterior shoulder points who were hospitalized, scheduled to receive shoulder joint arthroscopic surgery, and met the inclusion criteria between January 2017 and October 2017 were selected in this study. After admission, the relevant examinations were completed, the venous blood was collected, and the VAS score was used to evaluate the pain degree. Correlation analyses were conducted to study the correlations of the levels of serum IL-1, IL-1β and TNF-α before treatment with VAS scores. Results: Compared with those before treatment, the levels of serum IL-1, IL-1β and TNF-α expression after treatment were significantly decreased ($P<0.05$). Compared with those before treatment, the levels of serum IL-1, IL-1β and TNF-α mRNA expression were significantly decreased ($P<0.05$). Compared with that before treatment, the VAS score was significantly decreased after treatment ($P<0.05$). Additionally, the VAS score was gradually decreased with the extension of time ($P<0.05$). The variation trend of the expression levels of inflammatory cytokines before and after treatment was consistent with that of the VAS score. The serum IL-1, IL-1β and TNF-α levels were positively correlated with the VAS score. Conclusion: Inflammatory response occurs in serum of patients with instability in traumatic anterior shoulder joints. The expression levels of IL-1, IL-1β and TNF-α are positively correlated with the pain degree of shoulder joint.

Keywords: Instability, traumatic anterior shoulder joints, inflammation, inflammatory cytokines, pain, correlation

Introduction

Shoulder joint instability is the common cause of clinical shoulder joint pain, which refers to the condition that the head of humerus is beyond the normal physiological range of the scapula glenoid when shoulder joints are active, leading to the abnormal movement of shoulder joints [1]. The most common type of shoulder joint instability is the instability in traumatic anterior shoulder joints due to the injury in anterior shoulder joints caused by trauma when shoulder joints are in the external rotation position [2, 3]. Instability in traumatic anterior shoulder joints can cause severe pain in shoulder joints, limitations of shoulder joint function and traumatic arthritis, which seriously affect the lifelong treatment of patients. In current studies it is considered that one of the important pathological reactions of the instability in traumatic anterior shoulder joints is subacromial bursitis, which is closely related to shoulder joint pain and is one of the important causes of shoulder joint pain [4-6]. The objective of this study was to investigate the correlations of the expression levels of serum tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and IL-1 in patients with instability and pain in traumatic anterior shoulder joints, and to further clarify the correlations of inflammatory cytokines with pain.

Materials and methods

General materials

40 patients with instability in traumatic anterior shoulder joints who were scheduled to receive

Table 1. Primer sequences

Name	Primer sequence
IL-1	Forward primer: 5'GCTCTACTCCACCTTCACC3'
	Reverse primer: 5'CTCTGTCACCATTGCTCTT3'
IL-1β	Forward primer: 5'ATGGCAGAAGTACCTAAGCTC3'
	Reverse primer: 5'TTAGGAAGACACAAATTGCATGGTGAACTCAGT3'
TNF-α	Forward primer: 5'ATGAGCACTGAAAGCATGATC3'
	Reverse primer: 5'TCACAGGGCAATGATCCCAAAGTAGACCTGCCC3'
GADPH	Forward primer: 5'ACGGCAAGTTCAACGGCACAG3'
	Reverse primer: 5'GAAGACGCCAGTAGACTCCACGAC3'

shoulder joint arthroscopic treatment in our hospital between January 2017 and July 2017 were included. After admission, the relevant examinations were completed, and the venous blood was collected.

Inclusion criteria

Inclusion criteria: patients who were diagnosed with instability in traumatic anterior shoulder joints and planned to undergo arthroscopic surgical treatment; patients aged 18-65 years; patients who signed the informed consent; and patients who received no other drugs and other relevant treatments within 3 weeks.

Exclusion criteria

Exclusion criteria: patients who were not conformed to above inclusion criteria; pregnant or lactating women; patients who were complicated with major underlying diseases, hypertension and heart disease; patients who were complicated with serious primary diseases, mental illness or other major disease history; and patients with history of shoulder joint fractures, bone tumors, bone tuberculosis or other related diseases.

Experimental reagents

IL-1 enzyme-linked immunosorbent assay (ELISA) kit, IL-1β ELISA kit, TNF-α ELISA kit, AceQ quantitative polymerase chain reaction (qPCR) SYBR Green Master Mix kit (Vazyme, Nanjing), HiScript II Q Reverse Transcription (RT) Sperfect for qPCR [+genomic deoxyribonucleic acid (gDNA) wiper] kit (Vazyme, Nanjing), and fluorescence qPCR instrument (ABI 7500, USA).

Research methods

After the enrolled patients in the study were admitted to hospital, the relevant examinations were completed. The venous blood was collected before treatment. The expression levels of IL-1, IL-1β and TNF-α in serum were measured by ELISA, and then Visual Analog Scale (VAS) scoring was conducted. Patients were followed up for 1, 3 and 6 months after operation. Then the venous blood was collected. The expression levels of serum IL-1, IL-1β and TNF-α were measured by ELISA, and then followed by VAS scoring.

ELISA detection

1) Sampling: Each well was added with 100 μL standard or serum for detection, and placed at 37°C for 40 min for reaction. 2) Plate washing: The reaction plate was fully washed with a washing solution for 4-6 times. 3) Each well was added with 50 μL distilled water and 50 μL primary antibody working solution from the kit (except blank group), respectively, and then the plate was fully mixed and placed at 37°C for 20 min for reaction. 4) Plate washing: The reaction plate was fully washed with a washing solution for 4-6 times. 5) Each well was added with 100 μL enzyme-labeled antibody working solution in the kit, and placed at 37°C for reaction for 10 min in the darkness. 6) Plate washing: The plate was fully washed with a washing solution for 4-6 times. 7) Each well was added with 100 μL substrate working solution from the kit, and then placed at 37°C for reaction for 15 min in the darkness. 8) Each well was added with 100 μL termination solution in the kit and mixed well. 9) The optical density (OD) value at 450 nm was measured.

qPCR detection

The total RNA was extracted from blood cells using the RNA extraction kit. The total RNA extracted by RT kit was reversely transcribed into complementary DNA (cDNA), and the volume of reaction system was 20 μL. The conditions for reaction: at 51°C for 2 min, at 96°C for 10 min, pre-denaturation at 96°C for 10 min, denaturation at 96°C for 10 s and annealing at 60°C for 30 s, and 40 cycles in total. GADPH was used as an internal reference, and the relative expression levels of IL-1, IL-1β and TNF-α messenger RNA (mRNA) were measured. The detailed sequences of primers are shown in **Table 1**.

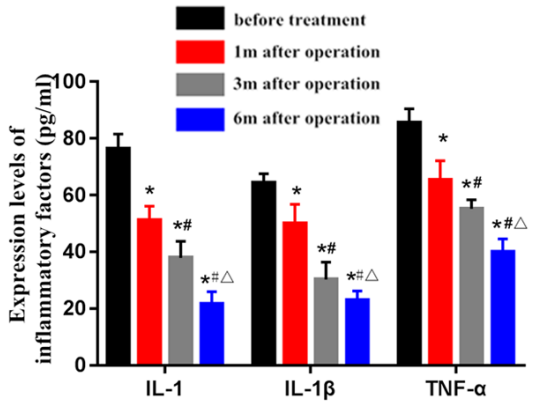

Figure 1. Detection of the IL-1, IL-1β and TNF-α expression levels by ELISA. Statistical analysis showed that the expression levels of IL-1, IL-1β and TNF-α expression levels at 1 month, 3 months and 6 months after operation were significantly lower than those before treatment, and the differences were statistically significant, **P<0.05*. The expression levels of IL-1, IL-1β and TNF-α at 3 months and 6 months after operation were significantly lower than those at 1 month after operation, and the differences were statistically significant, *#P<0.05*. The expression levels of IL-1, IL-1β and TNF-α at 6 months after operation were significantly lower than those at 3 months after operation, and the differences were statistically significant, Δ*P*<0.05.

VAS scoring

VAS scoring was used to assess the pain degree in the shoulder joints of the included patients. In the VAS scoring, a 10 cm-long ruler was used. 0-10 points represented painless degree to severe pain degree. Patients were asked to select the appropriate pain score based on their own pain degree. Specific grading criteria: 0 point for painless, 1-3 points for mild pain, 4-6 points for moderate pain, and 7-10 points for severe pain.

Statistical analysis

In this study, Statistical Product and Service Solutions (SPSS) 20.0 software was used to conduct the statistical analysis. Data satisfying the normal distribution and homogeneity of variance were analyzed using the *t*-test, those satisfying the normal distribution but not satisfying heterogeneity of variance were analyzed using the corrected *t*-test, and those not satisfying the normal distribution and homogeneity of variance were detected using the non-parametric test. The ranked data were examined via the rank-sum test, and the enumeration data were detected using the chi-square test. Correlation analysis was conducted using the Person correlation analysis. *P*< 0.05 was considered as statistically significant.

Results

Detection of the expression levels of IL-1, IL-1β and TNF-α by ELISA

Before treatment, the expression level of IL-1 in serum of patients with instability in traumatic anterior shoulder joints was 76.34±5.16 pg/ml, that of IL-1β was 64.37±3.21 pg/ml, and that of TNF-α was 85.49±4.99 pg/ml. At 1 month after operation, the expression level of IL-1 was 54.38±4.46 pg/ml, that of IL-1β was (58.23±5.49) pg/ml, and that of TNF-α was 64.55±4.87 pg/ml. At 3 months after operation, the expression level of IL-1 was 38.74±7.31 pg/ml, that of IL-1β was 32.87±7.62 pg/ml, and that of TNF-α was 55.19±3.21 pg/ml. At 6 months after operation, the expression level of IL-1 was 21.56±4.39 pg/ml, that of IL-1β was 22.98±3.21 pg/ml, and that of TNF-α was 39.87±4.69 pg/ml. Statistical analysis showed that the expression levels of IL-1, IL-1β and TNF-α at 1, 3 and 6 months after operation were significantly lower than those before treatment, which were statistically significant (*P*<0.05). The expression levels of IL-1, IL-1β and TNF-α at 3 months and 6 months after operation were significantly lower than those at 1 month after operation, which were statistically significant (*P*<0.05). The expression levels of IL-1, IL-1β and TNF-α at 6 months after operation were significantly lower than those at 3 months after operation, which were statistically significant (*P*<0.05) (**Figure 1**).

Detection of the relative expression levels of IL-1, IL-1β and TNF-α mRNAs via qPCR

Before treatment, the expression level of IL-1 mRNA in serum of patients with instability in traumatic anterior shoulder joints was 0.81±0.05, that of IL-1β mRNA was 0.76±0.03, and that of TNF-α mRNA was 0.89±0.04. At 1 month after operation, the expression level of IL-1 mRNA was 0.62±0.04, that of IL-1β mRNA was 0.59±0.06, and that of TNF-α mRNA was 0.75±0.06. At 3 months after operation, the expression level of IL-1 mRNA was 0.46±0.05,

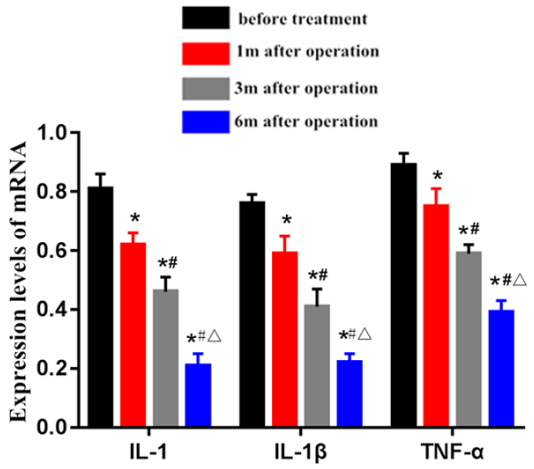

Figure 2. Expression levels of mRNA of inflammatory cytokines in each group. Statistical analysis showed that the IL-1, IL-1β and TNF-α mRNA expression levels at 1, 3 and 6 months after operation were significantly lower than those before treatment, which were statistically significant, *$P<0.05$. The IL-1, IL-1β and TNF-α mRNA expression levels at 3 and 6 months after operation were significantly lower than those at 1 month after operation, and the differences were statistically significant, #$P<0.05$. The IL-1, IL-1β and TNF-α mRNA expression levels at 6 months after operation were significantly lower than those at 3 months after operation, which were statistically significant, Δ$P<0.05$.

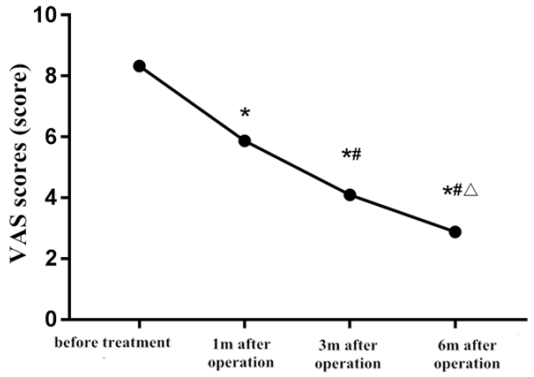

Figure 3. VAS scores. VAS scores at 1, 3 and 6 months after operation were significantly lower than that before treatment, which were statistically significant, *$P<0.05$. VAS scores at 3 months and 6 months postoperatively were significantly lower than that at 1 month postoperatively, which were statistically significant, #$P<0.05$. VAS score at 6 months after operation was significantly lower than that at 3 months after operation, which was statistically significant, Δ$P<0.05$.

that of IL-1β mRNA was 0.41±0.06, and that of TNF-α mRNA was 0.59±0.03. At 6 months

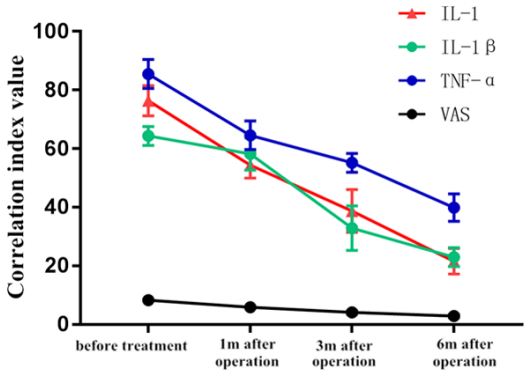

Figure 4. Variation trends of inflammatory cytokines and VAS scores before and after treatment. The inflammatory cytokine expression levels of IL-1, IL-1β and TNF-α as well as VAS scores before and after treatment showed decreasing trends, suggesting that the variation trend of the inflammatory cytokines expression levels including IL-1, IL-1β and TNF-α was the same as that of VAS scores.

after operation, the expression level of IL-1 mRNA was 0.23±0.04, that of IL-1β mRNA was 0.24±0.03, and that of TNF-α mRNA was 0.38±0.04. Statistical analysis showed that the expression levels of IL-1, IL-1β and TNF-α mRNA at 1, 3 and 6 months after operation were significantly lower than those before treatment, which were statistically significant ($P<0.05$). The expression levels of IL-1, IL-1β and TNF-α mRNA at 3 and 6 months after operation were significantly lower than those at 1 month after operation, and the differences were statistically significant ($P<0.05$). The expression levels of IL-1, IL-1β and TNF-α mRNA at 6 months after operation were significantly lower than those at 3 months after operation, which were statistically significant ($P<0.05$) (**Figure 2**).

VAS scores

VAS score before treatment was 8.33±0.34, that at 1 month after operation was 5.87±0.26, that at 3 months after operation was 4.10±0.53, and that at 6 months after operation was 2.88±0.48. VAS scores at 1, 3 and 6 months after operation were significantly lower than that before treatment, which were statistically significant ($P<0.05$). VAS scores at 3 months and 6 months postoperatively were significantly lower than that at 1 month postoperatively, which were statistically significant ($P<0.05$). VAS score at 6 months after

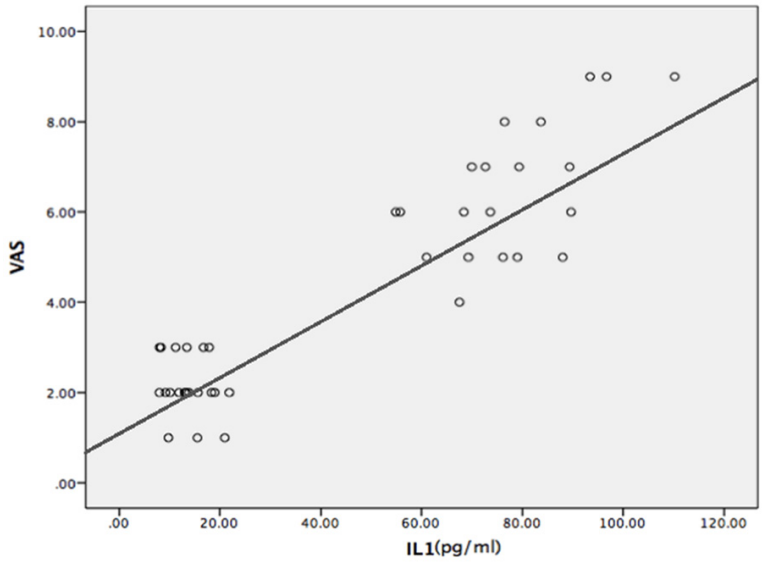

Figure 5. Correlation between IL-1 and VAS. The correlation analysis indicating a positive correlation between the VAS score and IL-1, r=0.916, P<0.05.

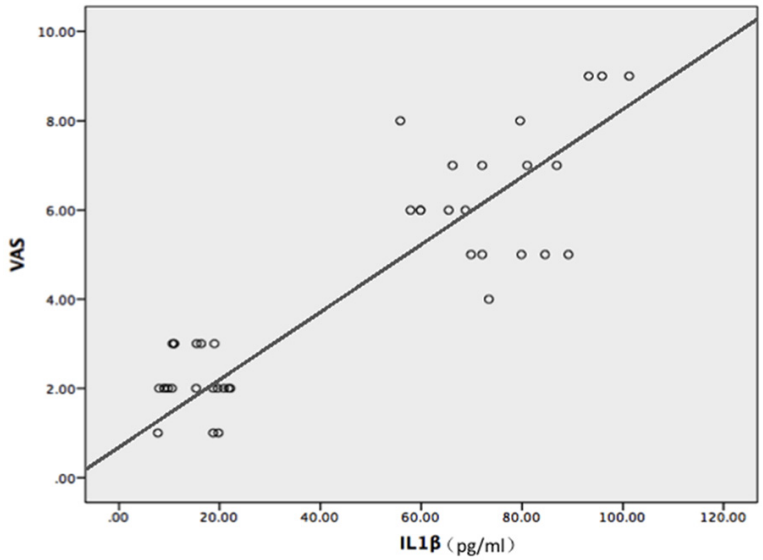

Figure 6. Correlation between IL-1β and VAS. The correlation analysis indicating a positive correlation between the VAS score and IL-1β, r=0.889, P<0.05.

operation was significantly lower than that at 3 months after operation, which was statistically significant (*P*<0.05) (**Figure 3**).

Comparisons of the variation trends of inflammatory cytokines and VAS scores before and after treatment

The inflammatory cytokine expression levels of IL-1, IL-1β and TNF-α as well as VAS scores before and after treatment showed decreasing trends, suggesting that the variation trend of the expression levels of inflammatory cytokines including IL-1, IL-1β and TNF-α was the same as that of VAS scores (**Figure 4**).

Correlation analysis of the VAS score with the expression levels of IL-1, IL-1β and TNF-α

Based on calculation results, the correlation analysis indicated a positive correlation between the VAS score and IL-1 (r=0.916, P<0.05, **Figure 5**). The correlation analysis indicated a positive correlation between the VAS score and IL-1β (r=0.889, p<0.05, **Figure 6**). The correlation analysis indicated a positive correlation between the VAS score and TNF-α (r=0.905, P<0.05, **Figure 7**).

Discussion

One of the major causes of shoulder joint pain is the instability in traumatic anterior shoulder joints, which is often accompanied with rotator cuff injury caused by excessive movement of shoulder joints. This results in shoulder joint pain and limited shoulder joint mobility [7]. A recent study [8] has confirmed that trauma leads to rotator cuff injury and further causes instability in traumatic anterior shoulder joints in patients, and inflammation does exist in bursa mucosa tissues of those patients. After the treatment with epoxygenase inhibitors and dexamethasone, the expression levels of inflammatory cytokines in bursa mucosa tissues can be decreased significantly. In addition, conservative treatments for patients with instability in traumatic anterior shoulder joints, such as local injection of corticosteroids in combination with local anesthetics in the intracapsular subacro-

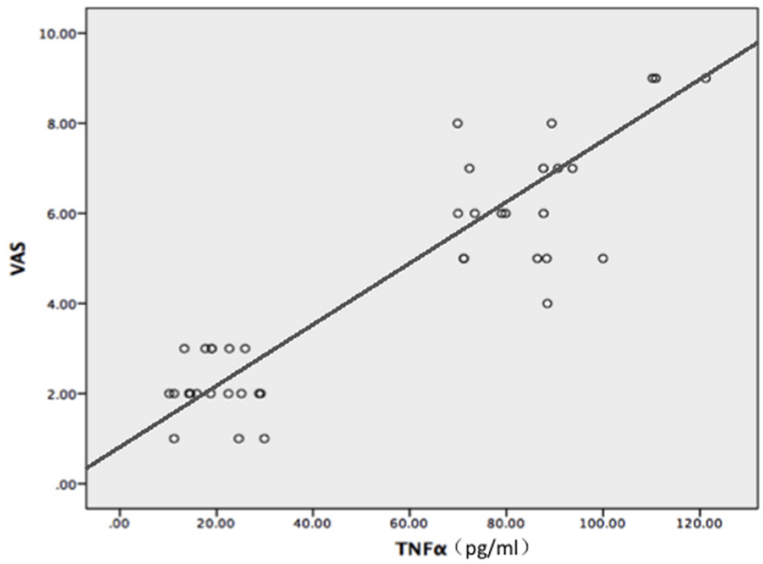

Figure 7. Correlation between TNF-α and VAS. The correlation analysis indicating a positive correlation between the VAS score and TNF-α, r=0.905, P<0.05.

mial bursa, can significantly alleviate pain and improve shoulder joint mobility, suggesting that inflammation exists in the intracapsular subacromial bursa of patients with instability in traumatic anterior shoulder joints. Therefore, pain degree and shoulder joint mobility can be improved by suppressing inflammation using corticosteroids [9, 10]. The results further confirmed that the expression levels of inflammatory cytokine in serum of patients with instability in traumatic anterior shoulder joints are relatively high, indicating that there is a certain degree of serum inflammatory response. After treatment, the expression levels of inflammatory cytokine in serum were gradually decreased with the extension of time, indicating that inflammation gradually subsided. Inflammatory cytokines play important pro-inflammatory roles in mediating radicular inflammation in inflammatory responses [11, 12]. IL-1, IL-1β and TNF-α, as important members of the inflammatory cytokine family, have strong pro-inflammatory effects and are agonists and catalysts for inflammatory responses. They are key initiators for activating inflammatory responses and may mediate and aggravate inflammation [13, 14]. These inflammatory factors can stimulate pain receptors, resulting in the occurrence of radicular pain and reflecting changes in pain [15]. IL-1 can upregulate the production of urokinase-type plasminogen activators, reduce the generation of plasminogen activator inhibitor 1, lead to unbalance of plasminogen activator system, promote the synthesis of prostaglandin E2 and aggravate the degree of inflammation as well as the pain degree [16]. A study has confirmed that IL-1 induces the release of large amounts of phospholipase A2 and prostaglandin E2, and mediates and exacerbates inflammation [17]. Therefore, IL-1 is considered as a pain-inducing factor. IL-1β, as a strong inducer of adhesion molecules, can promote the gathering of a variety of adhesion molecules in vascular endothelial cells, reflects the corresponding ligands combined with leukocytes, and is conducive to leukocyte adhesion to the vascular endothelium and mediate inflammatory exudation [18]. A study has revealed that, in the rat pain model, pain inhibitors significantly reduce the expression level of IL-1β in tissues and inhibit pain, indicating that IL-1β is also an important factor resulting in pain [19]. As an important pro-inflammatory factor, TNF-α, widely expressed in injured tissues at high levels, is considered as one of the important factors that cause pain [20, 21]. The study results revealed that patients with instability in traumatic anterior shoulder joints had a higher VAS score, and the VAS score gradually decreased with the extension of time after treatment, suggesting that the patient' pain degree is gradually improved, and the variation trend of the VAS score is the same as that of the expression levels of inflammatory cytokines. A correlation analysis of the VAS score with the levels of inflammatory cytokines was further conducted, which showed that the higher the expression levels of inflammatory cytokines were, the higher the VAS score would be, and the latter was decreased with the decrease in the former. In other words, the expression levels of inflammatory cytokines including IL-1, IL-1β and TNF-α were positively correlated with pain.

The sample size in our study was relatively small, and the research results may be biased. Further research needs to expand the sample

size to obtain more reliable research data and improve the quality of clinical nursing.

In conclusion, the high expressions of inflammatory cytokines including IL-1, IL-1β and TNF-α in bursa mucosa tissues of patients with instability in traumatic anterior shoulder joints is one of the possible causes of shoulder joint pain in patients.

Disclosure of conflict of interest

None.

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