

Review Article

The effect of platelet-rich plasma in the treatment of external humeral epicondylitis and an analysis of the influencing factors

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Abstract: Objective: To observe the clinical effect of platelet-rich plasma in the treatment of external humeral epicondylitis and the influencing factors. From May 2017 to January 2019, 156 patients with external humeral epicondylitis and who were admitted to our hospital were selected as research participants. Among them, 80 patients who were treated with glucocorticoid were assigned to the control group (CG), and 100 patients who were treated with platelet-rich plasma were assigned to the research group (RG). In both groups, the patients received rehabilitation training at the time of the treatment. Before and after the treatment, the serum interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) levels in the two groups were measured using an enzyme-linked immunosorbent assay (ELISA). Before and after the treatment, the limb symptoms and quality of life were observed in the two groups. A logistic regression analysis was used to analyze the risk factors affecting the treatment effects on the patients. The clinical efficacy in the RG was significantly better than it was in the CG, and there were no adverse reactions in either group. After the treatment, the symptoms in both groups were improved. The pain visual analog scores (VAS) and the forearm-shoulder-hand dysfunction scores (DASH) in the RG were significantly lower than they were in the CG, but the Mayo elbow joint function scores (MEPS) and the quality of life scores were significantly higher than they were in the CG. After the treatment, the levels of IL-6 and TNF- α in the RG were significantly lower than they were in the CG. A multivariate logistic regression analysis showed that the risk of ineffective treatment for patients treated with low levels of IL-6, low levels of TNF- α , or platelet-rich plasma was reduced before the treatment. Platelet-rich plasma can promote limb recovery and improve the quality of life in patients with external humeral epicondylitis.

Keywords: Platelet-rich plasma, external humeral epicondylitis, glucocorticoids, risk factors

Introduction

External humeral epicondylitis, also known as tennis elbow, is a tendon disease that mainly affects middle-aged people, causing pain to the lateral elbow of the patient [1, 2]. According to epidemiological statistics, men's wrestling, baseball, and tennis are risk activities for the disease, and the incidence rate of females is 1.29 times that of males [3, 4]. The most frequently involved muscle in patients with external humeral epicondylitis is the extensor carpi radialis brevis, the etiology of which is related to the repeated overuse of the extensor carpi radialis brevis and the related involved muscles [5]. Most of the screening for external humeral epicondylitis can be confirmed by the clinical symptoms, while the rest depends on X-rays for

the evaluation [6]. At present, the treatment methods for external humeral epicondylitis include oral non-steroidal anti-inflammatory drugs, glucocorticoid injections, platelet-rich plasma, etc. After these treatments, rehabilitation programs are often added to correct the biomechanical abnormalities caused by the disease [7]. Although the diagnosis of external humeral epicondylitis is relatively easy, the best treatment strategy for it is still uncertain [8]. We will study the treatment method, curative effect and influencing factors of external humeral epicondylitis. It is of great value for the selection of treatment strategies for this disease.

Platelet-rich plasma is an autologous therapy rich in fibrin and growth factors, and it has certain therapeutic effects on chronic wounds,

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arthritis, tendon diseases, etc. [9-11]. The key to treating external humeral epicondylitis lies in the platelet concentrate taken from patients' blood, as the concentrate can participate in promoting the repair process, including angiogenesis, collagen synthesis, and tensile strength [12]. Studies have shown that the necessity of surgical intervention will be greatly reduced when platelet-rich plasma is used for the injection therapy of patients with external humeral epicondylitis [13]. Glucocorticoid is the gold standard for the treatment of external humeral epicondylitis. It has the advantages of having a quick effect, and it can significantly relieve pain and improve grip strength [14, 15]. In the studies by Tang et al. [16], glucocorticoid therapy has the greatest short-term efficacy advantage, but platelet-rich plasma therapy has a long-term efficacy advantage, mainly reflected in the improvement of pain and elbow function.

At present, there are few published studies on the efficacy and influencing factors of platelet-rich plasma and glucocorticoid in the treatment of external humeral epicondylitis. We will evaluate their efficacy and analyze the influencing factors, hoping to provide a clinical reference for the treatment of external humeral epicondylitis.

Materials and methods

Baseline data

From August 2017 to December 2018, 180 patients with external humeral epicondylitis who were admitted to our hospital were selected. 100 patients who were treated with platelet-rich plasma were enrolled in the RG, including 22 males and 78 females, aged 25-60 years old. 80 patients who were treated with glucocorticoid were enrolled in the CG, including 19 males and 61 females, aged 27-63 years old. This study was approved by the ethics committee of the hospital. The subjects or their guardians signed informed consent forms. Inclusion criteria: (1) Patients who were diagnosed with external humeral epicondylitis [17]; (2) Patients who had no mental illness and who communicated normally; (3) Patients who had complete clinicopathological data; (4) Patients who had no malignant tumors or infectious or autoimmune diseases. Exclusion criteria: (1) Patients with bone frac-

tures, rheumatoid arthritis, knee osteoarthritis, or other orthopedic diseases; (2) Patients who were allergic to the drugs used in this study; (3) Patients who had taken drugs orally in the previous six months that might affect the indicators of this study; (4) Patients who had a history of surgery in the past six months. The inclusion criteria were applicable to the patients in both groups.

Treatment

In the RG, the patients were treated with platelet-rich plasma: 30 mL of contralateral cubital median venous blood of the patient was put in a test tube. Then, 3 mL of 2.5% sodium citrate (Mengya Biotechnology Co., Ltd., Shanghai, China, A31110-500 g) was added. After fully mixing it, the mixture was centrifuged at 1500×g and at 4°C for 10 min. The supernatant was taken and centrifuged again. 4 mL of plasma at the junction of upper and lower layers was taken as spare platelet-rich plasma. 3.6 mL platelet-rich plasma was used for the treatment, and the rest was used for whole blood cell analysis. Then, the pain point of the patient was found. After local strict disinfection, an amount of platelet-rich plasma was allocated according to the pain point range for the trigger point injection. After half an hour of observation, the patient was confirmed to have no adverse reactions, and the treatment was finished. The patients were treated once a month for a total of three times.

In the CG, the patients were treated with glucocorticoid: the patients were injected with prednisolone acetate injection (Huazhong Pharmaceutical Co., Ltd., Xiangyang, China, H 4202-21216) and lidocaine hydrochloride injection (Yubo Biotechnology Co., Ltd., Shanghai, China, CP-100342). The injection method and dosage were the same as those in the RG.

In the two groups, the patients received the same rehabilitation program after the treatment.

Therapeutic evaluation

The lateral epicondyle part of the humerus is completely free of pain, the affected limb moves smoothly, the patient has no pain when holding the object and the patients can work daily, which can be regarded as a cure. The original symptoms and physical signs are sig-

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Table 1. Baseline data of the patients in the two groups [n (%), mean \pm SD]

Factors	n	CG (n=80)	RG (n=100)	χ^2/t	P
Gender				0.077	0.781
Male	41	19 (23.75)	22 (22.00)		
Female	139	61 (76.25)	78 (78.00)		
Age/years old				0.040	0.841
<45	84	38 (47.50)	46 (46.00)		
\geq 45	96	42 (52.50)	54 (54.00)		
Average duration (months)	180	21.50 \pm 8.49	22.33 \pm 9.10	0.626	0.532
Healthy elbow				1.278	0.258
No	48	18 (22.50)	30 (30.00)		
Yes	132	62 (77.50)	70 (70.00)		
Labor degree				0.143	0.705
Light worker	68	29 (36.25)	39 (39.00)		
Heavy worker	112	51 (63.75)	61 (61.00)		
Diabetes history				0.823	0.364
No	143	66 (82.50)	77 (77.00)		
Yes	37	14 (17.50)	23 (23.00)		
Drinking history				1.258	0.262
No	125	59 (73.75)	66 (66.00)		
Yes	55	21 (26.25)	34 (34.00)		
Smoking history				3.047	0.081
No	133	54 (67.50)	79 (79.00)		
Yes	47	26 (32.50)	21 (21.00)		
Place of residence				0.098	0.755
Rural	43	20 (25.00)	23 (23.00)		
City	137	60 (75.00)	77 (77.00)		
VAS (points)	180	5.97 \pm 1.89	6.06 \pm 1.95	0.312	0.756
MEPS (points)	180	58.73 \pm 2.26	58.57 \pm 2.34	0.463	0.644
DASH (points)	180	45.23 \pm 2.65	45.51 \pm 2.57	0.716	0.475

Table 2. Clinical efficacy of the patients in the two groups [n (%)]

Grouping	n	Cure	Markedly effective	Effective	Ineffective	Total effective rate (%)
CG	80	43 (53.75)	15 (18.75)	3 (3.75)	19 (23.75)	76.25
RG	100	62 (62.00)	23 (23.00)	7 (7.00)	8 (8.00)	92.00
χ^2 value	-	-	-	-	-	8.647
P value	-	-	-	-	-	0.003

nificantly relieved, but they do not completely disappear, and the patient has some pain when holding an object, which can be regarded as markedly effective. If the patient's pain and tenderness are slightly relieved, it is considered effective. After the treatment, if the symptoms and signs do not improve or the improvement is very little, it is considered ineffective.

comparisons of the measurement data in the two groups were conducted using independent sample T-tests. The comparisons before and after the treatment within groups was conducted using paired T-tests. Logistics multivariate regression analysis was applied to analyze the risk factors affecting the curative effect of patients with external humeral epicondylitis.

Outcome measures

The clinical symptoms, VAS [18], MEPS [19], DASH [20], adverse reactions, quality of life scores (SF-36) [21] and the serum inflammatory factor IL-6, TNF- α levels were observed and compared between the two groups. Among them, the levels of the serum inflammatory factors IL-6 and TNF- α were determined using ELISA [22]. The operation was conducted in strict accordance with the instructions of the human IL-6 ELISA and the human TNF- α ELISA kits (Qiaoyu Biotechnology Co., Ltd., Shanghai, China, QN-PS0049, QN-PS0122).

Statistical analysis

SPSS 22.0 (Beijing Baiao Yijie Technology Co., Ltd., China) was used for the statistical analysis. The count data were expressed as the number/percentage (n/%) of cases. The comparison of the count data in the two groups was conducted using chi-square tests. When the theoretical frequency in the chi-square tests was less than 5, a continuity correction chi-square test was used. The measurement data were expressed as the mean \pm SEM. The comparisons of the measurement data in the two groups were conducted using independent sample T-tests. The comparisons before and after the treatment within groups was conducted using paired T-tests. Logistics multivariate regression analysis was applied to analyze the risk factors affecting the curative effect of patients with external humeral epicondylitis.

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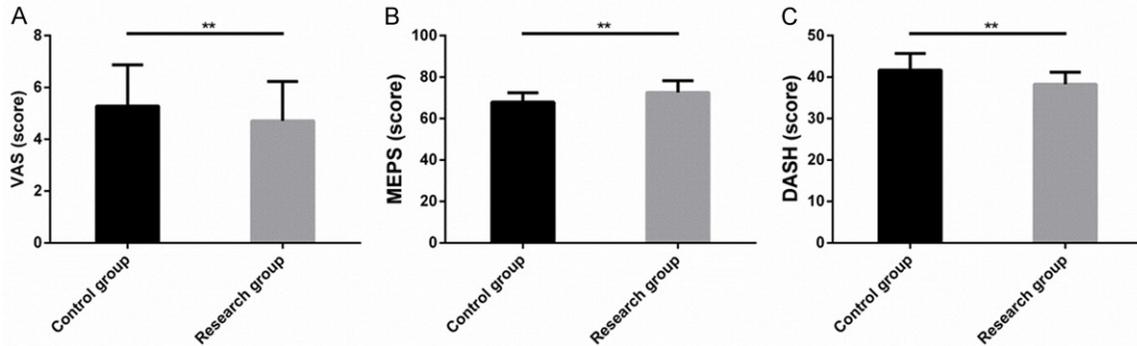


Figure 1. The VAS, MEPS, and DASH scores of the patients in the two groups. A. The VAS scores in the RG were significantly lower than they were in the CG. B. The MEPS scores in the RG were significantly higher than they were in the CG. C. The DASH scores in the RG were significantly lower than they were in the CG. Note: ** $P < 0.01$.

The differences were statistically significant when $P < 0.05$.

Results

Baseline data

There were no significant differences in terms of gender, age, average course of the disease, healthy elbow, labor degree, diabetes history, drinking history, smoking history, place of residence, VAS, MEPS, DASH, or other aspects between the two groups ($P > 0.05$). More details are shown in **Table 1**.

Clinical efficacy of the patients in the two groups

After the treatment, the total effective rate in the RG was 92.00%, and in the CG it was 76.25%. The total effective rate in the RG was significantly higher than that it was in the CG. The difference was statistically significant ($P < 0.05$). In addition, there was no fever, allergies, local bleeding, infection, or other adverse reactions in the two groups of patients after the treatment. More details are shown in **Table 2**.

VAS, MEPS, and DASH scores of patients in the two groups

The VAS and DASH scores in the RG were significantly lower than those in the CG, but the MEPS score was significantly higher than it was in the CG. The differences were statistically significant ($P < 0.05$). More details are shown in **Figure 1**.

Quality of life of the patients in the two groups

The quality of life scores in physiological function, physiological role, bodily pain, general health, life vigor, social function, emotional role, and mental health in the RG were significantly higher than those in the CG. The differences were statistically significant ($P < 0.05$). More details are shown in **Figure 2**.

Levels of the patients' inflammatory factors in the two groups

There was no significant difference in the levels of the inflammatory factors IL-6 and TNF- α of the patients between the two groups before the treatment ($P > 0.05$). After the treatment, the levels of IL-6 and TNF- α of the patients in the two groups were significantly reduced, and the levels of IL-6 and TNF- α in the RG were significantly lower than those in the CG. The differences were statistically significant ($P < 0.05$). More details are shown in **Figure 3**.

Risk factors influencing the efficacy of patients with external humeral epicondylitis

The differences in the clinical parameters and the related indexes between the effective and ineffective patients were compared. In this study, 153 patients were treated effectively and 27 were not. In addition, VAS, MEPS, DASH, and other scoring tools were not included in the analysis scope because they had a certain efficacy evaluation value. There was no significant difference in terms of gender, age, average course of disease, healthy elbow, labor

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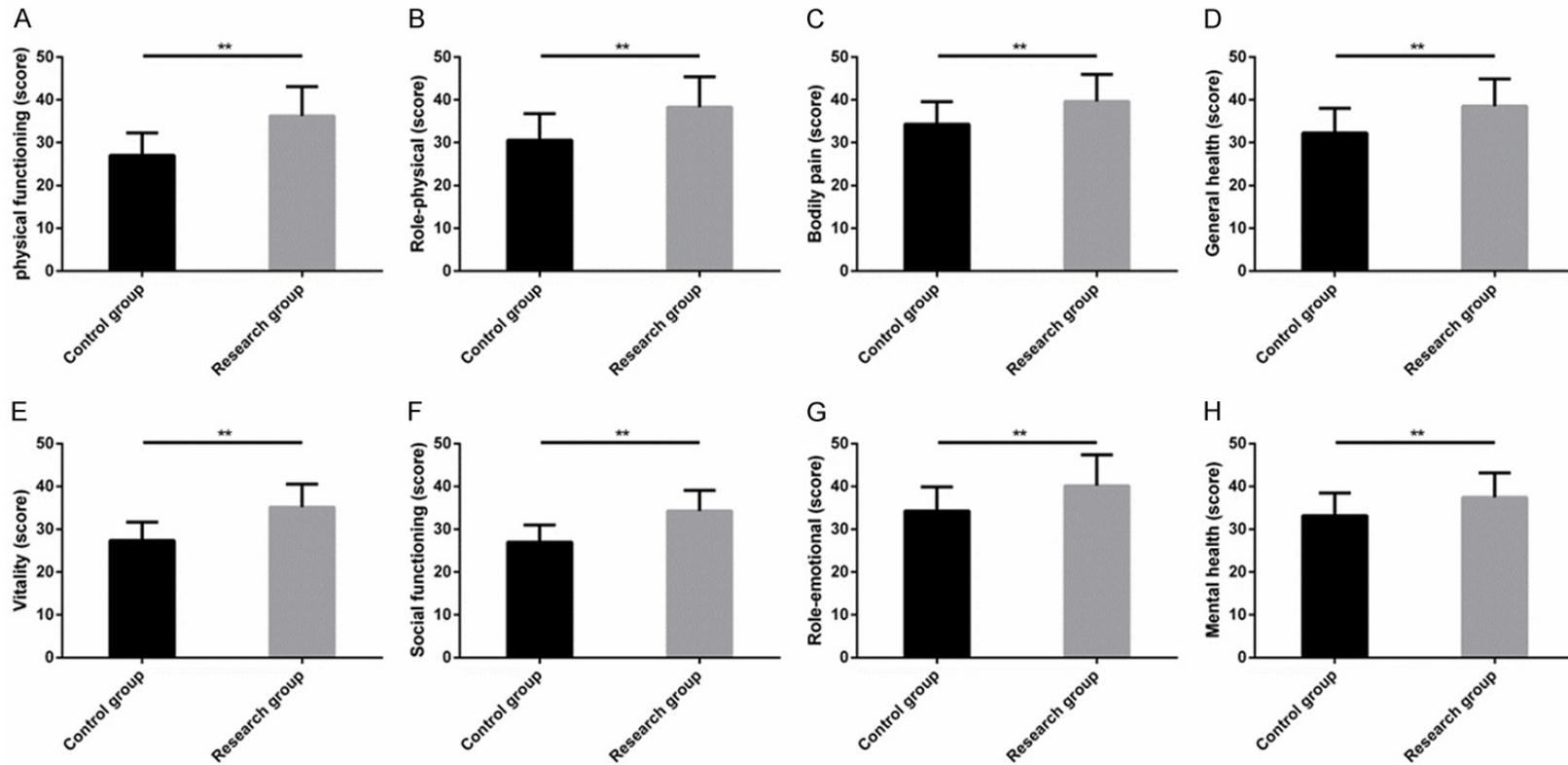


Figure 2. Quality of life of the patients in the two groups. A. The physiological function scores in RG were significantly higher than they were in the CG. B. The physiological role scores in RG were significantly higher than they were in the CG. C. The bodily pain scores in RG were significantly higher than they were in the CG. D. The general health scores in RG were significantly higher than they were in the CG. E. The life vigor scores in RG were significantly higher than they were in the CG. F. The social function scores in RG were significantly higher than they were in the CG. G. The emotional role score in RG were significantly higher than they were in the CG. H. The mental health scores in RG were significantly higher than they were in the CG. Note: ** $P < 0.01$.

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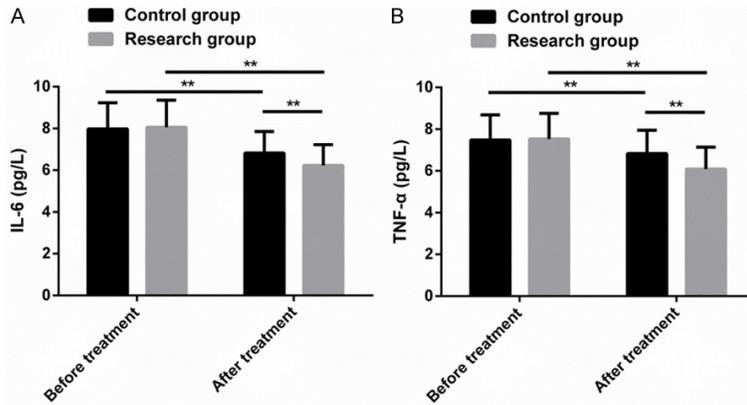


Figure 3. The levels of the inflammatory factors of the patients in the two groups. A. After the treatment, the IL-6 levels in RG were significantly reduced and lower than they were in the CG. B. After the treatment, the TNF- α levels in the RG were significantly reduced and lower than they were in the CG. Note: ** $P < 0.01$.

degree, diabetes history, drinking history, smoking history, or place of residence between the effective and ineffective patients ($P > 0.05$), but there was a statistical difference in the IL-6, TNF- α , and treatment methods ($P < 0.05$). A multivariate logistic regression analysis was carried out on the different factors. The results showed that IL-6 ($P = 0.023$), TNF- α ($P = 0.015$) and the treatment methods ($P = 0.006$) were independent risk factors affecting the efficacy of patients with external humeral epicondylitis. Patients with external humeral epicondylitis treated with high levels of IL-6, high levels of TNF- α and glucocorticoid had an increased risk of ineffective treatment. More details are shown in **Tables 3-5**.

Discussion

External humeral epicondylitis is a self-limiting disease, and it usually resolves within half a year to one year. However, the disease process can cause patients to suffer considerable pain, which has a negative impact on the patients' quality of life [23]. Therefore, we focused our study on the treatment of humeral lateral epicondylitis and the influencing factors of efficacy, aiming at improving the quality of life of patients and providing effective and definite therapeutic clinical treatment options for patients.

More and more scholars have reported on the treatment and curative effects of external humeral epicondylitis. For example, in the

studies of Yi et al. [24], deep friction massage and cortisone injections were found to have a long-term curative effect on improving the pain and disability of patients with external humeral epicondylitis who failed to respond to other treatment. In the reports by Gautam et al. [25], the therapeutic mechanism of platelet-rich plasma may lie in the bioremediation of lesions, and while glucocorticoid therapy may cause tendon degeneration, it can relieve the symptoms in a short period of time. In this study, the total effective rate in the RG was 92.00%, and the total effective

rate in the CG was 76.25%. The total effective rate in the RG was significantly higher. In the two groups, there was no fever, allergy, local bleeding, infection, or other adverse reactions, indicating that platelet-rich plasma is more effective in treating external humeral epicondylitis. In addition to the treatment methods in this study, there are also other surgical treatment methods. For example, in a comparative study on the therapeutic effects of platelet-rich plasma and percutaneous aponeurotomy on external humeral epicondylitis by Boden et al. [26], both treatment methods can significantly improve the pain and disability degree of patients, and the therapeutic effects have no significant difference, suggesting that percutaneous aponeurotomy may become an alternative treatment scheme for patients with platelet-rich plasma patients who failed to respond to treatment.

VAS, MEPS, and DASH are scoring systems for evaluating the degree of pain, elbow joint function and disability of patients with external humeral epicondylitis [27]. We also applied these scoring systems to further evaluate the curative effect of the patients. The results showed that the VAS and DASH scores in the RG were significantly lower than they were in the CG, and the MEPS scores were significantly higher than they were in the CG, indicating that the pain and disability degree of patients who were treated with platelet-rich plasma were significantly reduced, elbow joint function was significantly improved,

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Table 3. A univariate analysis of factors influencing the treatment efficacy of external humeral epicondylitis patients [n (%), mean \pm SD]

Factors	n	Effective group (n=153)	Ineffective group (n=27)	χ^2/t	P
Gender				0.848	0.357
Male	41	33 (21.57)	8 (29.63)		
Female	139	120 (78.43)	19 (70.37)		
Age/years old				1.183	0.277
<45	84	74 (48.37)	10 (37.04)		
\geq 45	96	79 (51.63)	17 (62.96)		
Average duration (months)	180	20.97 \pm 8.24	22.50 \pm 9.16	1.164	0.246
Healthy elbow				3.217	0.073
No	48	37 (24.18)	11 (40.74)		
Yes	132	116 (75.82)	16 (59.26)		
Labor degree				1.898	0.168
Light worker	68	61 (39.87)	7 (25.93)		
Heavy worker	112	92 (60.13)	20 (74.07)		
Diabetes history				3.725	0.054
No	143	124 (81.05)	19 (70.37)		
Yes	37	21 (18.95)	8 (29.63)		
Drinking history				0.629	0.428
No	125	108 (70.59)	17 (62.96)		
Yes	55	45 (29.41)	10 (37.04)		
Smoking history				0.859	0.354
No	133	115 (75.16)	18 (66.67)		
Yes	47	38 (24.84)	9 (33.33)		
Place of residence				0.072	0.269
Rural	43	36 (23.53)	7 (25.93)		
City	137	117 (76.47)	20 (74.07)		
IL-6 (pg/L)	180	6.02 \pm 1.27	8.15 \pm 1.42	10.476	<0.001
TNF- α (pg/L)	180	5.97 \pm 1.18	7.60 \pm 1.34	8.547	<0.001
Methods of treatment				8.647	0.003
Platelet-rich plasma therapy	100	92 (60.13)	8 (29.63)		
Glucocorticoid therapy	80	61 (39.87)	19 (70.37)		

Table 4. Assignment of the logistic multivariate regression analysis

Factors	Variables	Assignment
IL-6 (pg/L)	X1	Continuous variables
TNF- α (pg/L)	X2	Continuous variables
Methods of treatment	X3	Platelet-rich plasma therapy=0, Glucocorticoid therapy=1

Table 5. Multivariate logistic regression analysis of factors influencing the treatment efficacy of patients with external humeral epicondylitis

Variables	B	S.E	Wals	P	OR	95% CI
IL-6 (pg/L)	1.134	0.472	5.338	0.023	3.127	1.176-7.699
TNF- α (pg/L)	1.997	0.694	5.312	0.015	2.749	1.240-6.358
Methods of treatment	2.116	0.749	6.981	0.006	6.514	1.524-10.982

and the clinical symptom relief and recovery effects were better than those in the CG. SF-36

is a reliable, effective, and acceptable health questionnaire, which can be used to measure the health perception of the general population [28]. We also used this tool to evaluate the quality of life of the patients. The results indicated that the quality of life scores in all dimensions in the RG were

significantly higher than they were in the CG, suggesting that the quality of life of patients who were treated with platelet-rich plasma were greatly improved. We also measured the levels of the inflammatory factors in the patients' serum. The study demonstrated that the levels of IL-6 and TNF- α in the RG were significantly lower than they were in the CG after treatment, suggesting that platelet-rich plasma was more helpful in improving the inflammatory response of the patient's body. The mechanism of platelet-rich plasma to reduce the pain of the body may be related to its significant inhibition of the secretion of the inflammatory factors. Finally, we also analyzed the risk factors that affected the curative effect of patients with external humeral epicondylitis. The results demonstrated that IL-6, TNF- α , and the treatment methods were independent risk factors that affected the therapeutic effect of patients with external humeral epicondylitis, indicating that the risk of ineffective treatment for patients treated with low levels of IL-6, low levels of TNF- α , or platelet-rich plasma was reduced before the treatment. In the multifactorial analysis results of Knutsen et al. [29] on the failure of non-surgical treatment in patients with external humeral epicondylitis, orthopedic surgery history, the duration of symptoms for at least one year and bone tunnel syndrome were also risk factors for the failure of non-surgical treatment in patients with external humeral epicondylitis.

To sum up, platelet-rich plasma can promote limb ability and improve the quality of life in patients with external humeral epicondylitis, as well as help to inhibit inflammatory response and reduce the risk of treatment failure, which is the innovation of this study. However, there is still room for improvement in this study. For example, we can supplement the basic experiments of the therapeutic mechanism of the two therapeutic methods and explore the risk factors affecting the curative effect of patients from the molecular level. Furthermore, we can also increase the pathological research related to inflammation of external humeral epicondylitis. In the future, we will gradually improve the research from the above perspectives.

Disclosure of conflict of interest

None.

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