Effect of Etanercept Combined with Synovectomy on Function and Serum Levels of Associated Factors in AS Patients with Coexisting Coxarthrosis

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Abstract: Objective To investigate the clinical effect and value of etanercept combined with arthroscopic synovectomy in the treatment of ankylosing spondylitis (AS) complicated with coxarthrosis. **Methods** 66 patients with AS complicated with coxarthrosis admitted in our hospital were taken as the study objects and were randomly divided into two groups with random number table: test group (n = 33) and control group (n = 33). The arthroscopic synovectomy was given to both groups. The control group was given basic anti-inflammatory and analgesic measures, promoting blood circulation and detumescent measures after surgery, and the test group was added with etanercept on the basis of the control group. Changes in scores of coxae function, serum transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) at different time after operation were compared between the two groups. **Results** There was no significant difference in Harris score between the test group and the control group before operation (P>0.05). The Harris score of the test group was higher than that of the control group 3 months after operation and 6 months after operation (P<0.05). There was no statistically significant difference in the determination of flexion angle and abduction angle of coxae between the test group and the control group before operation (P>0.05). The flexion angle and abduction angle of coxae of the test group were higher than that of the control group 6 months after operation (P<0.05). The difference of measured values of serum levels TGF-β1, TNF-α, IL-6, CRP and ESR in the test group and the control group had no statistical significance (P>0.05). The determination values of serum levels TGF-β1, TNF-α, IL-6, CRP and ESR in the test group were lower than those in the control group at 3 months after operation (P<0.05). **Conclusion** Etanercept combined with arthroscopic synovectomy for the treatment of AS complicated with coxarthrosis is beneficial to regulate the level of related cytokines and promote the recovery of postoperative joint function.

Key words: Etanercept; Arthroscopy; Synovectomy; Ankylosing spondylitis; Coxarthrosis
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Ankylosing spondylitis (AS) is a relatively common chronic progressive inflammation that invades the spine and affects the sacroiliac and peripheral joints to varying degrees [1]. Among them, coxarthrosis is the main cause of disability. In AS patients, coxarthrosis occurs earlier and progresses rapidly. If effective treatment measures are not taken in time, articular cartilage destruction and even deformity will occur [2] . At present, the more conservative treatment is drug therapy. Some patients with AS do not respond well to medical therapy, which may lead to hip pain and

claudication, and later on, bony ankylosis of the joints and associated deformity of skeletal structures may occur [3] . Minimally invasive synovectomy should be considered to prevent further damage to the articular cartilage and delay or avoid the occurrence of joint deformity when AS patients have symptoms such as coxae pain and dysfunction, or when MRI shows synovitis and joint effusion [4] . Studies have shown that [5] tumor necrosis factor - α (TNF-α) plays a key role in the pathogenesis and inflammation of joint inflammatory immunity in rheumatic diseases. TNF antagonists have good clinical efficacy and safety in the treatment of joint inflammation in active rheumatic diseases. Etanercept is a TNF antagonist. In order to investigate the clinical effect and value of etanercept combined with arthroscopic synovectomy for the treatment of AS complicated with coxarthrosis, 66 cases of AS complicated with coxarthrosis in our hospital were selected as study objects.

DATA AND METHODS

Data

66 patients with AS complicated with coxarthrosis admitted in our hospital were selected as study objects. They were randomly divided into the test group and the control group with random number table, with 33 cases in each group. The patients were admitted from January 2014 to December 2018. Inclusion criteria: (1) The diagnostic criteria of AS patients refer to the criteria in the "Guidelines for Diagnosis and Treatment of Ankylosing Spondylitis" [6] ; (2) The patients with different degrees of hip pain discomfort and limitation of motion were found to have massive effusion of coxae, synovial hyperplasia and ischemic changes of femoral head after MRI examination; (3) The positive result of human leukocyte antigen B27 (HLA-B27) and the elevated level of rheumatoid factor were found before operation; (4) All patients were treated with arthroscopic synovectomy in our hospital; (5) The study was conducted in accordance with the requirements of the Medical Ethics Committee, and informed consent was obtained from the study objects. Exclusion criteria: (1) Joint trauma; (2) Malignant tumor; (3) Bone tuberculosis; (4) Endocrine system diseases; (5) Severe cardiac and hepatic renal dysfunction.

In the test group, the patients' age was 14 - 45 years, with an average age of 26.8 ± 3.8 years; 19 cases were male and 14 cases were female; the body mass index (BMI) was 23.2 ± 2.2 kg/m 2; the sites of coxarthrosis: 15 cases on left side, 14 cases on right side and 4 cases on bilateral side. In the control group, the patients' age was 16 - 40 years, with an average age of 28.0 ± 4.6 years; 21 patients were male and 12 were female; the BMI of the patients was 23.0 ± 2.5 kg/m 2; the sites of coxarthrosis: 12 cases on the left side,16 cases on the right side and 5 cases on both sides. The difference of above baseline data between the two groups had no statistical significance (P>0.05).

Surgical methods

All patients were recumbent, thick pads wrapped around the perineal column against the base of the thigh, and both feet were placed on the foot support plate of the traction bed and bandaged. Under traction, anterolateral and posterolateral portals were routinely established and arthroscopic and surgical instruments were placed separately. Firstly, enter the central compartment to observe the lesion of femoral head, horseshoe fossa and acetabulum center area, clean up the hyperplastic congestion synovium, remove the free cartilage flap, remove the free cartilage joint, stop bleeding and clean the osteomalacia lesion, return the arthroscope to the peripheral cavity, remove the visible hyperplastic osteophyte with burr, thoroughly flush the articular cavity, and send the synovium tissue for pathological examination. After surgery, the wound was covered with a sterile dressing and the adhesive dressing was used the next day with no drainage from the wound. After recovery from anesthesia, the free posture can be restored and the coxae can be practiced in flexion, adduction, abduction and rotation to gradually increase the angle. Medication was continued according to the opinion of the Rheumatology Consultation.

Postoperative rehabilitation therapy

The control group was given basic

anti-inflammatory and analgesic measures, promoting blood circulation and detumescent measures after surgery and the test group was added with etanercept on the basis of the control group. Etanercept Injection (Pfizer Ireland Pharmaceuticals, specification: 0.47 ml:25 mg / nos., Batch No.:20130505), for intramuscular injection. 50mg weekly for 3 months.

Observed indicators

Harris scores were used for coxae function evaluation: mainly including pain, deformity, range of motion, need for assistance in walking, lacing shoes, wearing socks, sitting on chair, getting on the car, limping, walking distance, and stair climbing items, with a total score of 100 points. Higher scores indicated that the patients had better coxae function. The flexion angle and abduction angle of coxae were measured before and after treatment in the two groups.

Serum transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured by ELISA before and after treatment.

Collect 10ml venous blood from the elbow of the patient, centrifuge at 1000r/min for 10min, and take the supernatant to be tested. Take out the test strip in sealed bag, add 100μl sample or diluent/hole in blank hole, add 100μl sample/hole in test hole, seal the test strip hole with adhesive paper, incubate at 36 ℃ for 60-90min, wash with phosphate buffer for 5 times, add 100μl biotin antibody diluent in blank control hole, add 100μl biotin antibody detection solution in test hole, seal the test strip hole with adhesive paper, incubate at 36 ℃ for 30-60min, add 100μl enzyme-binding diluent in the blank control hole, add 100μl enzyme-binding detection solution in the detection hole, block the test strip hole with adhesive paper, wash with phosphate buffer for 5 times, add TMB color rendering base solution (brand: YSRIBIO, Fuzhou Innoreagents Biotechnology Co., Ltd.), incubate at 36 ℃ in the dark for 15min, add 100μl stop solution, and detect the OD450 value within 3min. The BioTekenzyme-labeled analyzer is purchased from BioTek Instruments, Inc. of USA.

Statistical treatment

SPSS 21.0 software was used for statistical analysis. Harris scores and other measurement data of the two groups were expressed by x±s. t was used for comparison between groups. χ 2 test was used for comparison between counting data groups. P<0.05 was considered statistically significant.

RESULTS

Variation of Harris score in the two groups

There was no statistically significant difference in Harris scores between the test group and the control group before operation (P>0.05). The Harris scores in the test group were higher than that in the control group 3 months after operation and 6 months after operation (P<0.05). See Table 1.

Evaluation of coxae mobility of patients before and after operation in the two groups

Before operation, there was no statistically significant difference in the measured results of flexion angle and abduction angle between the test group and the control group (P>0.05). 6 months after operation, the flexion angle and abduction angle of the test group were higher than that of the control group (P<0.05). See Table 2.

Table 1
Change of Harris Scores (x ± s, Points) of Patients in the Two Groups

Group	n	Before operation	3 months after operation	6 months after operation
Test group	33	64.15±8.04	83.64±5.90	85.41±6.04
Control group	33	65.54±7.83	80.26±5.76	82.15±5.87
t value		-0.711	2.355	2.223
P value		0.479	0.022	0.030

Table 2
Evaluation of Coxae Mobility of Patients before and after Operation in the Two Groups (x±s)

Group	n	Flexion angle (°)		Abduction angle (°)	
		Before operation	6 months after operation	Before operation	6 months after operation
Test group	33	68.64±6.20	88.17±5.24	10.34±2.23	15.51±2.48
Control group	33	67.00±5.94	85.25±6.05	10.58±2.46	14.20±2.61
t value		1.097	2.096	-0.415	2.090
P value		0.277	0.040	0.679	0.041

The comparison of laboratory indicators of patients before and after operation in the two groups

There was no statistically significant difference in the measured values of serum TGF-β1, TNF-α, IL-6, CRP and ESR between the test group and the control group before operation (P>0.05); the measured values of serum TGF-β1, TNF-α, IL-6, CRP and ESR in the test group were lower than those in the control group 3 months after operation (P<0.05); see Table 3.

Table 3
Comparison of Laboratory Indicators of Patients before and after Operation in the Two Groups (x±s)

Group	n	TGF-β1 (ng/mL)		TNF-α (pg/mL)		IL-6 (pg/mL)	
		Before operation	3 months after operation	Before operation	3 months after operation	Before operation	3 months after operation
Test group	33	48.56±6.77	33.20±5.15	144.8±20.6	111.0±15.7	42.84±5.70	24.16±3.39
Control group	33	46.80±7.14	36.64±6.28	140.1±24.3	120.7±18.4	41.05±6.00	26.84±4.41
t value		1.028	-2.433	0.848	-2.304	1.243	-2.768
P value		0.308	0.018	0.400	0.024	0.219	0.007

Group	n	CRP (mg/L)		ESR (mm/h)	
		Before operation	3 months after operation	Before operation	3 months after operation
Test group	33	25.77±5.59	6.41±2.04	47.51±6.94	22.30±2.46
Control group	33	26.30±6.28	7.80±2.11	45.83±7.33	24.68±3.01
t value		-0.362	-2.721	0.956	-3.517
P value		0.718	0.008	0.343	0.001

Comparison of adverse reactions between the two groups

During the treatment, the incidence rate of adverse reactions in the test group was 18.18% compared with 6.06% in the control group, and the difference had no statistical significance (P>0.05). See Table 4.

Table 4
Comparison of Adverse Reactions between the Two Groups

Group	n	Abnormal liver function	Leukocyte elevation	Acute upper respiratory tract infection	Adverse reactions (%)
Test group	33	2	2	2	6(18.18)
Control group	33	1	0	1	2(6.06)
χ 2 value					2.276
P value					0.131

DISCUSSION

AS is a non-specific connective tissue disorder involving the axial and sacroiliac joints of unknown etiology with a high degree of peripheral joint involvement. Coxarthrosis is most common [7]. Coxarthrosis is associated with early pain and progresses to limited coxae mobility, flexion contracture, and fibrous or skeletal stiffness, resulting in irreversible deformity and disability of the coxae [8]. The specific mechanism of AS coxarthrosis remains controversial. It is believed [9] that inflammatory synovial tissue promotes

inflammatory changes in the subchondral bone during early AS coxarthrosis, while eroding the articular cartilage surface, leading to joint degeneration and new bovine bone formation, ultimately leading to reversible deformity and joint stiffness. Therefore, for AS patients with coexisting coxarthrosis, early diagnosis and routine treatment should be obtained as early as possible to avoid severe hip injury. Early non-operative treatment does not provide effective relief of hip lesion, and synovial tissue hyperplasia and edema are common in affected joints, resulting in varying degrees of fluid accumulation, fibrous adhesions to the coxae, and even skeletal stiffness [10] . Synovectomy is one of the most common surgical methods in joint surgery. However, conventional open resection has the disadvantages of high blood loss, large trauma, and slow recovery. With the improvement of the knowledge of arthroscopy and the development of arthroscopic techniques, it has the advantages of small trauma, less bleeding, quick recovery and less complications in the diagnosis and treatment of hip diseases, providing a brand-new method [11]. It is important to find effective methods to treat patients with AS complicated with coxarthrosis, and to improve the range of motion and quality of life.[12]

Nonsteroidal anti-inflammatory drugs and methotrexate are commonly-used drugs for AS complicated with hip diseases. There are still problems such as large individual differences, many adverse reactions and poor long-term efficacy though they have certain therapeutic effect[13] . TNF antagonists have been widely used in the clinical treatment of AS and secondary diseases in recent years, which can effectively control the chronic inflammatory injury and reduce the abnormal immune response. Greater than 40% of patients achieved high rates of clinical remission. Previous studies have shown that [14] TNF-α is a cytokine that plays a key role in the development of rheumatic joint inflammation, with abnormally high levels inducing joint inflammation and aggravating cartilage destruction, which is inversely related to coxae function. Therefore, this study was performed in combination with etanercept for the treatment of AS coxae lesions after arthroscopic synovectomy.

TNF-α, IL-6, CRP and ESR are all markers of inflammatory activity. Cytokines play an important role in the occurrence and development of various inflammatory diseases. TNF-α plays a role in mediating the immunomodulation of inflammation and immune responses, and is a cytokine closely related to inflammation. TNF-α promotes the expression of IL-6, a multifunctional cytokine of downstream of TNF that is involved in the development of disease. IL-6 may play an important role in the joint and form a cytokine network that regulates the immune system [15] . TGF-β1 is a multipotential growth factor, and pathologic studies of synovial tissue of skeletal joints in patients with AS have shown that TGF-β1 is highly expressed at sites of new bone formation [16,20] . TGF-β1 is an important pathogenic factor that stimulates fibrosis and ankylosis and ossification of ligaments [17] . The results of this study showed that the measured values of the serum levels of TGF-β1, TNF-α, IL-6, CRP and ESR in the test group were lower than those in the control group 3 months after operation. This suggests that the patient's systemic inflammatory response is reduced after treatment with etanercept combined with arthroscopic synovectomy. The Harris scores, flexion angle and abduction angle of coxae in the test group were significantly higher than those in the control group. This suggests that etanercept combined with arthroscopic synovectomy for AS with coexisting coxae disease is effective in improving Harris scores, allowing for more normal flexion and abduction angles. The reason for the analysis was that etanercept is a soluble TNF-α receptor fusion-antibody fusion protein that acts primarily by binding to TNF-α in serum and blocking its further binding to receptors on the cell membrane, thereby acting and inhibiting the aberrant immune response and inflammatory processes mediated by the TNF-α receptor, serving as the fastest and most effective method of suppressing inflammation and reducing joint destruction. There was no significant difference in the incidence of adverse reactions in the test group during the course of treatment. The results indicate that the combination of etanercept

is associated with improved efficacy and a high safety profile.

In the present clinical study [18,19] , there were few studies on the use of etanercept combined with arthroscopic synovectomy for the treatment of AS complicated with coxarthrosis, and the evaluation indicators for improvement of patients before and after treatment were relatively single. In this study, patients with AS were treated with etanercept combined with arthroscopic synovectomy protocol, and the evaluation of coxae mobility and the detection of a variety of serum inflammatory markers were conducted with high illustration.

In conclusion, etanercept combined with arthroscopic synovectomy for the treatment of AS complicated with coxarthrosis is beneficial to regulate the level of related cytokines and promote the recovery of postoperative joint function.

REFERENCES

1. Raynal M, Bouderraoui F, Ouichka R, et al. Performance of 18 F-sodium fluoride positron emission tomography with computed tomography to assess inflammatory and structural sacroiliitis on magnetic resonance imaging and computed tomography, respectively, in axial spondyloarthritis. Arthritis research & therapy. 2019;21(1):1-11.
2. He C, He X, Tong W, et al. The effect of total hip replacement on employment in patients with ankylosing spondylitis. Clinical rheumatology. 2016;35(12):2975-2981.
3. Vander Cruyssen B, Muñoz-Gomariz E, Font P, et al. Hip involvement in ankylosing spondylitis: epidemiology and risk factors associated with hip replacement surgery. Rheumatology. 2010;49(1):73-81.
4. Lee B, Morrey B. Arthroscopic synovectomy of the elbow for rheumatoid arthritis: A prospective study. The Journal of bone and joint surgery British volume. 1997;79(5):770-772.
5. Braun J, Baraliakos X, Listing J, et al. Persistent clinical efficacy and safety of anti-tumour necrosis factor α therapy with infliximab in patients with ankylosing spondylitis over 5 years: evidence for different types of response. Annals of the rheumatic diseases. 2008;67(3):340-345.
6. Rachid B, El Zorkany B, Youseif E, Tikly M. Early diagnosis and treatment of ankylosing spondylitis in Africa and the Middle East. Clinical rheumatology. 2012;31(11):1633-1639.
7. Druce KL, Aikman L, Dilleen M, Burden A, Szczypa P, Basu N. Fatigue independently predicts different work disability dimensions in etanercept-treated rheumatoid arthritis and ankylosing spondylitis patients. Arthritis research & therapy. 2018;20(1):1-9.
8. Zhang G, Li J, Xia Z, Xu W. The gait deviations of ankylosing spondylitis with hip involvement. Clinical rheumatology. 2019;38(4):1163-1175.
9. Maatallah K, Mahmoud I, Belghali S, et al. Reparative radiological changes of hip joint after TNF inhibitors in ankylosing spondylitis. Caspian journal of internal medicine. 2018;9(3):303.
10. Laktašiü-Žerjaviü N, Periü P. Correspondence of vitamin D status with functional scores and disease activity among Croatian patients with ankylosing spondylitis: a preliminary study. Psychiatria Danubina. 2019;31(1):S105-S111.
11. Aytekin MN, Atalar H, Yanik B, Arikan M. Acceleration of coxarthrosis by an exostosis causing femoroacetabular impingement. Health. 2010;2(04):318.
12. Wang C, Zhang C, Liu D-L, et al. Simplified Chinese version of hip and knee replacement expectations surveys in patients with osteoarthritis and ankylosing spondylitis: cross-cultural adaptation, validation and reliability. BMC musculoskeletal disorders. 2018;19(1):1-10.
13. Zhao M, Zhang P, Fang L, Luo Z, Gu J, Lin Z. Possible predictors for relapse from etanercept discontinuation in ankylosing spondylitis patients in remission: a three years' following-up study. Clinical rheumatology. 2018;37(1):87-92.
14. Sargin G, Senturk T, Yavasoglu I. The relationship between blood eosinophil count and disease activity in ankylosing spondylitis patients treated with TNF-α inhibitors. Saudi Pharmaceutical Journal. 2018;26(7):943-946.
15. Sveaas S, Berg I, Provan S, et al. Circulating levels of inflammatory cytokines and cytokine receptors in patients with ankylosing spondylitis: a cross-sectional comparative study. Scandinavian journal of rheumatology. 2015;44(2):118-124.
16. Bonamichi-Santos R, Castells M. Diagnoses and management of drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: reactions to taxanes and monoclonal antibodies. Clinical reviews in allergy & immunology. 2018;54(3):375-385.
17. Tan X-C, Xue G-F, Guo H-Z. Bilateral total hip replacement for ankylosing spondylitis with hip joint lesion and acetabular pelvic deformity: a case report. Zhongguo gu shang= China journal of orthopaedics and traumatology. 2018;31(5):480-483.
18. Guo H-Z, Yang C-X, Tang Z-P, Wang C-X. The effects of total hip arthroplasty in treating hip bony fusion in young and middle-aged patients with ankylosing spondylitis. Journal of orthopaedic surgery and research. 2019;14(1):1-6.
19. Zhu X-B, Yuan L-L, Han G-S, Han J-Z, Zhou J-S. Short term effect of total hip arthroplasty through direct anterior approach for the treatment of ankylosing spondylitis with hip flexion deformity. Zhongguo gu shang= China journal of orthopaedics and traumatology. 2019;32(2):141-145.
20. Vermeulen, H., Gouse, M., Delport, M., Louw, M., & Miller, T. Consumer Acceptance of Sugar Derived from Genetically Modified Sugarcane in South Africa. AgBioForum, 2020; 22(1).