Efficacy of needle-knife combined with etanercept treatment regarding disease activity and hip joint function in ankylosing spondylitis patients with hip joint involvement

A randomized controlled study

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Abstract

This study aimed to assess the efficacy of needle-knife (NK) combined with etanercept (NKCE) in attenuating pain, inflammation, disease activity, and improving hip joint function in ankylosing spondylitis (AS) patients with hip joint involvement.

Totally, 90 patients with active AS involving unilateral hip joint were enrolled and randomly assigned in 1:1:1 ratio to receive NKCE, NK or conventional drugs (control). The ESR, CRP, hip joint pain Visual Analogue Scale (VAS) score, bath ankylosing spondylitis disease activity index (BASDAI), bath ankylosing spondylitis functional index (BASFI), modified Harris hip score (mHHS), and range of motion (ROM) of affected hip joint were assessed at baseline (W0), after 1-week treatment (W1) and after 24-week treatment (W24).

ESR and CRP were decreased in NKCE group compared with NK and control groups, while was not attenuated in NK group compared with control group. Regrading pain and disease activity, NKCE group presented a reduction in hip pain VAS score and BASDAI compared with NK and control groups, and NK group showed a decrease in hip pain VAS score and BASDAI compared with control group. Besides, BASFI was lowered in NKCE and NK groups compared with control group, but similar between NKCE and NK groups. mHHS and hip ROM were raised in NKCE and NK groups compared with control group, but similar between NKCE and NK groups.

NKCE decreases hip pain, inflammation, disease activity and improves hip joint function in AS patients with hip joint involvement.

Abbreviations: AS = Ankylosing spondylitis, BASDAI = bath ankylosing spondylitis disease activity index, BASFI = bath ankylosing spondylitis functional index, CRP = C-reactive protein (CRP), ESR = erythrocyte sedimentation rate, KOA = knee osteoarthritis, mHHS = modified Harris hip score, NK = Needle-knife, NKCE = NK combined with etanercept, THA = Total hip arthroplasty, VAS = Visual Analogue Scale, W1 = 1-week, W24 = 24-week.

Keywords: ankylosing spondylitis, etanercept, hip joint function, inflammation, needle-knife

1. Introduction

Ankylosing spondylitis (AS), an inflammatory rheumatic disease, mainly affects axial skeleton, which is prevalent in young people.[1] As a common condition of AS, hip joint involvement occurs in 24% to 36% of AS patients, resulting in severe deformities, greater functional impairment, decline in quality of life and poor prognosis compared to no hip joint involvement due to the central function of hip joint, which brings in great burdens to patients and society.[2,3] Total hip arthroplasty (THA) is the standard operation for end-stage hip involvement.[4] However, due to limited life-span of hip prostheses, the need of revision surgery in AS patients underwent THA leads to higher mortality.[5] Therefore, more treatment options in reducing pain, improving hip joint function and decreasing subsequent need for THA in AS patients with hip joint involvement are needed.

Needle-knife (NK), also called as acupotomy, mini-scalpel acupuncture or miniscalpel-needle, is a needle with a flat knife attached on the tip, which has been exhibited to be efficacious in treating orthopaedic diseases such as knee osteoarthritis (KOA) and osteonecrosis.[6–9] For example, one study exhibits that NK treatment reduces pain and improves physical function of the knee joint in patients with KOA.[8] In treatment of osteonecrosis,
NK treatment restores hip joint function in patients with osteonecrosis.\textsuperscript{19} While, no study has been done to evaluate the effect of NK treatment in AS patients with hip joint involvement. Etanercept, the most commonly used tumor necrosis factor inhibitor, has demonstrated an impressive role in pain relief, clinical symptoms improvement and inflammation reduction in AS patients by accumulating studies.\textsuperscript{2,10–12} Additionally, a few studies display that etanercept is effective in decreasing inflammation and disease activity in AS patients with hip joint involvement as well.\textsuperscript{13,14} However, it is not clear whether the addition of etanercept to NK treatment has synergistic effect in treating AS patients with hip joint involvement. Thus, the aim of this study was to assess the efficacy of NK combined with etanercept (NKCE) in attenuating pain, inflammation, disease activity and improving hip joint function in AS patients with hip joint involvement.

2. Methods

2.1. Patients

Between June 2016 and May 2018, 90 patients with AS involving unilateral hip joint were recruited from Quanzhou Orthopedic-Traumatological Hospital of Fujian Traditional Chinese Medicine University in this randomized, controlled study. The inclusion criteria were as follows:

1. confirmed diagnosis of AS according to the modified New York criteria for AS (1984);\textsuperscript{15}
2. aged 16 to 50 years;
3. had obvious symptoms on hip joint: X-ray showed that there was hip joint space, the anastomosis between femoral head and acetabulum was good, and there was no fibrous or bony ankylosis; magnetic resonance imaging (MRI) showed synovial hyperplasia, hypertrophy and effusion of hip joint.

The exclusion criteria were:

1. intolerant or allergic to drugs used in the study;
2. concurrent with cardiovascular and cerebrovascular diseases, hematopoietic system diseases, other serious primary diseases or psychiatric disease;
3. presenting with tuberculosis, viral hepatitis, local infection, or other infectious diseases;
4. liver or kidney dysfunction or coagulation dysfunction,
5. complicated with intervertebral disc disease, peripheral arthropathy, other seronegative spondyloarthopathy, or other rheumatic diseases;
6. pregnant or lactating women.

2.2. Ethics statement

This study was approved by the Institutional Review Boards of Quanzhou Orthopedic-Traumatological Hospital of Fujian Traditional Chinese Medicine University and adhered to the standards set by the International Conference on Harmonization and Good Clinical Practice. It was performed in accordance with the principles expressed in the Declaration of Helsinki. All patients provided written informed consents.

2.3. Randomization and grouping

After confirmation of patient eligibility, patients were randomly assigned in a 1:1:1 ratio to NKCE group (N=30), NK group (N=30), or control group (N=30) using blocked randomization method with a block size of 6. Assignment procedures were performed by an independent nurse according to the random allocation list created by use of SAS 9.0 (SAS Institute, Inc, Cary, NC).

2.4. Interventions

In the NKCE group, patients were treated with NK combined with intra-articular injection of etanercept at the first week, which was performed only once. Afterward, they were administered with conventional drugs until 24 weeks. The needle-knife treatment was performed as follows: the patient was prostrated on the operating bed with a pillow under abdomen. First, the middle point of the line between the posterior iliac spine and the superior iliac spine was positioned, then moved 2.0 cm to the side and 2.0 cm downward. After touching the space between the sacroiliac joint with hand, the metal wire of the band loop was fixed locally with adhesive tape. According to the pelvic plain film, the severely damaged point of the sacroiliac joint was selected. The puncture point was then positioned by C-arm X-ray machine. After accurate positioning, the puncture point was marked with a special maker pen. After routine disinfection with iodine and alcohol, aseptic hole-towel was spread. With 2% lidocaine anesthesia, the No. 3 needle-knife was inserted through the skin, subcutaneous tissue, posterior sacroiliac ligament and into the sacroiliac joint space at an oblique angle of 70°. After the C-arm cross-location was performed (confirming that the needle-knife was in the sacroiliac joint cavity), acupotomy lysis by needle-knife was performed in the upper, middle, and lower layers of the space, then the needle-knife was pulled out and fixed locally with sterile gauze. After needle-knife treatment (only once), etanercept was administered for once by intra-articular injection at a dose of 50 mg. The conventional drugs were given as follows: Sulfasalazine: started at 0.25 g, then increased by 0.25 g per week up to 0.75 g orally, three times a day, for a total of 24 weeks. For those with aggravated pain, Diclofenac Sodium of 50 mg and Omeprazole of 20 mg were administered to be taken orally three times a day, which were discontinued until the pain was tolerable or after 3 months.

In the NK group, patients were given needle-knife treatment (for once) at the first week on the basis of 24-week treatment of conventional drugs. The procedures of needle-knife treatment and the management of conventional drugs were as same as that in the NKCE group.

In the control group, patients were only treated with conventional drugs for 24 weeks, which were administered as same as in the NK group.

2.5. Assessments

For efficacy evaluation, pain Visual Analogue Scale (VAS) score of hip joint, ROM of affected hip joint (range of flexion and extension, range of abduction and adduction, range of rotation at extension, and range of rotation at flexion of 90°), modified Harris hip score (mHHS), bath anklosing spondylitis functional index (BASFI) and bath anklosing spondylitis disease activity index (BASDAI) were assessed at baseline (W0), after 1-week treatment (W1), and after 24-week treatment (W24), respectively. Besides, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also detected at the same time points as above.
2.6. Samples size calculation

The required sample size for this study was estimated based on predictions: at W24, pain VAS score on hip joint was 1.0 ± 0.5 (mean ± standard deviation [SD]) in NKCE group, 3.0 ± 1.5 NK group, and 5.5 ± 2.75 in control group. Using a two-sided t test, a two-sided 5% level of significance (α), and 80% power to detect a significant difference between NKCE group and control group, required 6 patients in each group; to detect a significant difference between NKCE group and NK group, required 9 patients in each group; to detect a significant difference between NK group and control group, required 22 patients in each group. In order to ensure a power of 80%, the sample size of at least 22 in each group was required, meanwhile, assuming a 25% attrition rate, finally, the sample size was inflated to 90 with 30 patients in each group.

2.7. Statistical analysis

SPSS 24.0 software (IBM, Chicago, IL) was used for statistical data processing, and GraphPad Prism 7.02 software (GraphPad Software Inc, San Diego, CA) was applied to construct graphs. Data were displayed as mean and SD or count (percentage). Comparison among groups was determined by Chi-square test or one-way analysis of variance (ANOVA) followed by post hoc test (Bonferroni correction). P < .05 indicated a significant difference.

3. Results

3.1. Baseline characteristics of AS patients

No difference of age (P = .690), gender (P = .770), disease duration (P = .730), ESR (P = .886), CRP (P = .536), hip pain VAS score (P = .731), hip ROM (all P > .05), mHHS (P = .695), BASDAI (P = .522), BASFI (P = .745) or HLA-B27 positive (P = .872) was observed among NKCE group, NK group and control group. In details: The mean age of AS patients was 20.33 ± 4.56 years in NKCE group, 20.10 ± 4.15 years in NK group and 21.01 ± 4.08 years in control group. Furthermore, there were 2 (6.7%) females and 28 (93.3%) males in NKCE group, 1 (3.3%) female and 29 (96.7%) males in NK group, 1 (3.3%) female, and 29 (96.7%) males in control group. Regarding inflammation markers, the mean ESR was 62.25 ± 32.82, 59.12 ± 29.24, and 62.73 ± 30.54 mm/h in NKCE, NK and control groups, respectively; and the mean CRP was 48.31 ± 15.21, 50.02 ± 13.01, and 45.69 ± 16.76 mg/L in NKCE, NK, and control groups, respectively. Additionally, the mean hip pain VAS score was 7.08 ± 2.01, 6.82 ± 1.54, and 7.19 ± 1.98 in NKCE, NK and control groups respectively; and the mean BASDAI was 5.21 ± 0.97, 5.36 ± 1.08, and 5.53 ± 1.19 in NKCE, NK and control groups respectively. Other detailed characteristics of AS patients were listed in Table 1.

3.2. Comparison of ESR and CRP

After 1-week treatment, three-group comparison analysis showed differences of mean ESR (P < .001) and CRP (P < .001) among NKCE, NK, and control groups (Table 2). The followed two-group comparison analysis exhibited that mean ESR and CRP were lower in NKCE group compared to NK and control groups (all P < .05). While, there was no difference of mean ESR or mean CRP between NK and control groups (all P > .05). After 24-week treatment, differences of ESR (P = .005) and CRP (P = .021) were observed among NKCE, NK, and control groups according to three-group comparison analysis. The subsequent two-group analysis displayed that mean ESR was reduced in NKCE group compared to NK (P < .05) and control (P < .05) groups, and mean CRP (P < .05) was decreased in NKCE group compared to control group. No difference of mean ESR or mean CRP was observed between NK and control groups (all P > .05). These data exhibited that the NKCE decreased inflammation effectively.

3.3. Comparison of hip pain VAS score, mHHS, BASDAI, and BASFI

After 1-week treatment, mean hip pain VAS score (P < .001), mHHS (P < .001), BASDAI (P < .001), and BASFI (P < .001) decreased in NKCE group compared to NK and control groups (all P < .05). These data exhibited that the NKCE decreased inflammation effectively.

| Table 1 | Baseline characteristics of patients. |
|---------|--------------------------------------|
| Items   | NKCE group (N = 30) | NK group (N = 30) | Control group (N = 30) | P       |
| Age, years, M ± SD | 20.33 ± 4.56 | 20.10 ± 4.15 | 21.01 ± 4.08 | .690 |
| Gender, no. (%) | | | | .770 |
| Female | 2 (6.7) | 1 (3.3) | 1 (3.3) | |
| Male | 28 (93.3) | 29 (96.7) | 29 (96.7) | |
| Disease duration, years, M ± SD | 2.87 ± 1.67 | 2.61 ± 1.43 | 2.90 ± 1.58 | .730 |
| ESR, mm/h, M ± SD | 62.25 ± 32.82 | 59.12 ± 29.24 | 62.73 ± 30.54 | .886 |
| CRP, mg/L, M ± SD | 48.31 ± 15.21 | 50.02 ± 13.01 | 45.69 ± 16.76 | .536 |
| Hip pain VAS score, M ± SD | 7.08 ± 2.01 | 6.82 ± 1.54 | 7.19 ± 1.98 | .731 |
| Hip ROM, degree, M ± SD | | | | |
| Range of flexion and extension | 73.23 ± 11.27 | 75.81 ± 9.84 | 74.01 ± 10.18 | .620 |
| Range of abduction and adduction | 37.91 ± 5.64 | 38.01 ± 5.21 | 39.97 ± 7.46 | .361 |
| Range of rotation at extension | 31.73 ± 8.19 | 30.86 ± 7.96 | 29.07 ± 8.97 | .401 |
| Range of rotation at flexion of 90° | 36.33 ± 4.58 | 35.67 ± 4.12 | 36.49 ± 6.01 | .778 |
| mHHS, M ± SD | 60.12 ± 10.28 | 62.26 ± 9.32 | 61.02 ± 8.67 | .695 |
| BASDAI, M ± SD | 5.21 ± 0.97 | 5.36 ± 1.08 | 5.53 ± 1.19 | .522 |
| BASFI, M ± SD | 5.42 ± 1.37 | 5.64 ± 1.58 | 5.71 ± 1.61 | .745 |
| HLA-B27 positive, no. (%) | 27 (90.0) | 28 (93.3) | 27 (90.0) | .872 |

Difference among groups was determined by one-way ANOVA or Chi-square test. BASDAI = bath ankylosing spondylitis disease activity index, BASFI = bath ankylosing spondylitis functional index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, mHHS = modified Harris hip score, M ± SD = mean ± standard deviation, NK = needle-knife, NKCE = needle-knife combined with transept at.
were different among NKCE, NK, and control groups according to the three-group comparison analysis (Table 3). The followed two-group comparison analyses disclosed that mean hip pain VAS score, BASDAI and BASFI were lower in NKCE and NK groups compared to control group (all \( P < .05 \)), while mean mHHS was higher in NKCE (\( P < .05 \)) and NK (\( P < .05 \)) groups compared to control group. After 24-week treatment, three-group comparison analysis showed that there were differences of mean hip pain VAS score (\( P < .001 \)), mHHS (\( P < .001 \), BASDAI (\( P < .001 \), and BASFI (\( P < .001 \) among NKCE, NK, and control groups. Furthermore, the subsequent two-group comparison analyses displayed that the mean hip pain VAS score and BASDAI were decreased in NKCE group compared to NK and control groups (all \( P < .05 \)), while mean mHHS was increased in NKCE (\( P < .05 \)) and NK (\( P < .05 \)) groups compared to control group. Additionally, mean BASFI was reduced in NKCE (\( P < .05 \)) and NK (\( P < .05 \)) groups compared to control group. These data showed that NK treatment reduced pain and disease activity as well as improved hip joint function, and NKCE treatment further decreased pain and disease activity, but not enhanced hip joint function.

### 3.4. Comparison of hip ROM indexes

After 1-week treatment, three-group comparison analysis exhibited that NKCE, NK, and control groups were with different mean range of flexion and extension (\( P < .001 \)), range of abduction and adduction (\( P < .001 \), range of rotation at extension (\( P < .001 \)), range of rotation at flexion of 90° (\( P < .001 \)) (Table 4). The followed two-group comparison analysis disclosed that mean range of flexion and extension, range of abduction and adduction, range of rotation at extension, range of rotation at flexion of 90° were higher in NKCE and NK groups than that in control group (all \( P < .05 \)). While, there was no difference of mean hip ROM indexes between NKCE and NK groups (all \( P > .05 \)). After 24-week treatment, three-group comparison analysis showed that NKCE, NK, and control groups presented with different mean range of flexion and extension (\( P < .001 \)), range of abduction and adduction (\( P < .001 \), range of rotation at extension (\( P < .005 \)) and range of rotation at flexion of 90° (\( P = .004 \)). The subsequent two-group comparison analysis displayed that mean range of flexion and extension, range of abduction and adduction were elevated in NKCE and NK groups compared to control group (all \( P < .05 \)).
After 24-week treatment (W24) NK treatment showed better outcomes than NK treatment for hip joint involvement. This result might be explained by:

1. The middle point of the line between the posterior iliac spine and 2.0cm downward was the place of femoral neck.
2. Since the 2.0cm downward was the position of femoral neck and fibrous capsule of hip joint, the needle depth was 2.0cm to point the femoral neck.
3. We confirmed this position with C-Arm X-Ray Machine, and the result showed that 2.0cm to the side of the middle point of the line between the posterior iliac spine and the superior iliac spine and 2.0cm downward was the place of femoral neck.

Inflammation plays an important role in the development and pathogenesis of AS with hip involvement. Synovitis inflammation within hip joint leads to bone erosion and joint space, resulting in degeneration of hip joint in AS. Etanercept, a TNF receptor inhibitor, binds to TNF-a, which competitively blocks the interaction of TNF-a with cell surface and subsequent TNF-a-mediated immune response and inflammation. One study discloses that etanercept reduces BASDAI, ESR, and CRP in AS patients with concurrent hip joint lesions. Another study also shows that there was a decrease in BASDAI after etanercept treatment in AS patients with hip synovitis. These studies suggest that etanercept is efficacious in resolution of inflammation and reduction of disease activity in AS patients with hip joint involvement. While, whether etanercept has synergistic effect with NK in the treatment of AS with hip joint involvement has not been reported. Our study characterized that the NKCE treatment showed better outcomes than NK treatment for inflammation, hip pain and disease activity in AS patients with hip joint involvement. This result might be explained by:

1. Etanercept suppressed TNF-a-triggered immune response and inflammation in AS patients through inhibiting the interaction of TNF-a with cell surface, which decreased synovitis inflammation within hip joint.

**Table 4**

Comparison of hip ROM indexes among groups at different time points.

| Items                                      | NKCE group (N = 30) | NK group (N = 30) | Control group (N = 30) | P     |
|--------------------------------------------|---------------------|-------------------|------------------------|-------|
| **Baseline (W0)**                          |                     |                   |                        |       |
| Range of flexion and extension, degree, M±SD| 73.23±11.27         | 75.81±9.84        | 74.01±10.18            | .620  |
| Range of abduction and adduction, degree, M±SD| 37.91±5.64         | 38.01±5.21        | 39.97±7.46             | .351  |
| Range of rotation at extension, degree, M±SD| 31.73±8.19         | 30.86±7.96        | 29.07±6.97             | .401  |
| Range of rotation at flexion of 90°, degree, M±SD| 36.33±4.58         | 35.67±4.12        | 36.45±5.01             | .778  |
| **After 1-week treatment (W1)**            |                     |                   |                        |       |
| Range of flexion and extension, degree, M±SD| 109.24±10.04*      | 108.32±9.41*      | 80.29±8.71             | <.001 |
| Range of abduction and adduction, degree, M±SD| 58.20±8.51*        | 56.51±9.32*       | 40.08±13.49            | <.001 |
| Range of rotation at extension, degree, M±SD| 58.24±10.51*       | 56.46±9.94*       | 40.51±8.18             | <.001 |
| Range of rotation at flexion of 90°, degree, M±SD| 60.19±7.43*        | 58.61±9.34*       | 42.09±11.81            | <.001 |
| **After 24-week treatment (W24)**          |                     |                   |                        |       |
| Range of flexion and extension, degree, M±SD| 110.32±9.25*       | 109.81±10.13*     | 87.91±10.72            | <.001 |
| Range of abduction and adduction, degree, M±SD| 59.34±9.15*        | 55.37±8.28*       | 45.27±11.35            | <.001 |
| Range of rotation at extension, degree, M±SD| 59.41±9.34         | 55.36±11.08       | 50.24±10.97            | .005  |
| Range of rotation at flexion of 90°, degree, M±SD| 61.28±11.73*       | 57.42±9.16        | 52.37±9.33             | .004  |

Comparison was determined by one-way ANOVA followed by post hoc test (Bonferroni correction) or paired t test (Bonferroni correction).

M±SD = mean ± standard deviation, NK = needle-knife, NKCE = needle-knife combined with etanercept, ROM = range of motion.

* Compared with control group, P < .05.
2. NKCE further suppressed immune response and inflammation mediated by TNF-α in hip joints through inhibiting the binding of TNF-α with cell surface, subsequently decreasing pain and disease activity in AS patients with hip joint involvement.[20,23]

Furthermore, our study disclosed that no difference of hip ROM was observed between NKCE and NK. The possible reason was as follows: The restoration of hip joint function was mainly contributed by NK treatment in AS patients with hip joint involvement, while the single dose of etanercept had a slight improvement in hip joint function. Thus, there was no difference of hip joint function recovery between NK and NKCE.

Our study evaluated that the efficacy of NKCE in AS patients with hip joint involvement for the first time. However, there were some limitations in this study:

1. The detailed mechanism of NK in improving hip joint function in AS patients with hip joint involvement is needed to be further investigated.
2. Because there was a lack of published articles for references, the smallest sample size was calculated by predictions based on clinical practice. While the sample size was relatively small, thus, a multicenter study with larger samples is necessary for further verification.
3. The long-term efficacy of NKCE in AS patients with hip joint involvement should be studied further.

In conclusion, NK attenuates pain and disease activity, restores hip joint function in AS patients with hip joint involvement, and the addition of etanercept to NK further improves clinical outcomes except hip joint function.

Author contributions

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