대한한의학 방제학회지 제30권 제2호
Herbal Formula Science
2022;30(2):95~100
pISSN 1229-1218, eISSN 2288-5641
https://doi.org/10.14374/HFS.2022.30.2.95
Official Journal of The Korean Medicine Society For The Herbal Formula Study
Available at http://www.formulastudy.com HFS

Review Article / 종설

류마티스 관절염 치료제와 병용한 독활기생탕의 효과 및 안전성: 체계적 문헌고찰 및 메타분석 프로토콜

채수연[1], 정찬영[2], 김주희[3], 김은정[4], 서병관[5], 황민섭[6], 박성식[1], 김경호[2], 윤종화[6], 성원석[4*]

[1]동국대학교 분당한방병원 사상체질과, [2]동국대학교 일산한방병원 침구의학과, [3]상지대학교 한의과대학, [4]동국대학교 분당한방병원 침구의학과, [5]경희대학교 한의과대학, [6]동국대학교 한의과대학

The Effectiveness and Safety of Dokwhalkisaeng-tang Combined with the Medication on Rheumatoid Arthritis: A Study Protocol for Systematic Review and Meta-analysis

Soo-Yeon Chae[1], Chan-Yung Jung[2], Joo-Hee Kim[3], Eun-Jung Kim[4], Byung-Kwan Seo[5], Min-Seop Hwang[6], Seong-Sik Park[1], Kyung-Ho Kim[2], Jong-hwa Yoon[6], Won-Suk Sung[4*]

[1]Department of Sasang Constitutional Medicine, Dongguk University Bundang Oriental Hospital
[2]Department of Acupuncture & Moxibustion, Dongguk University Ilsan Oriental Hospital
[3]College of Korean Medicine, Sangji University
[4]Department of Acupuncture & Moxibustion, Dongguk University Bundang Oriental Hospital
[5]College of Korean Medicine, Kyung Hee University
[6]College of Korean Medicine, Dongguk University

ABSTRACT

Objectives : Recent studies reported that Dokwhalkisaeng-tang (DHJST) could relieve the clinical rheumatoid arthritis (RA) symptoms and the level of RA-related blood test. However, evidence-based review on effectiveness and safety of DHJST with medication on RA was not yet provided.

Methods : Searching randomized controlled trials on the use of DHJST for RA will be performed using multiple electronic databases, manual search, and contact to author. Studies will be selected according to the pre-defined criteria and collected data on study participants, interventions, control groups, outcome measurements, the results, adverse events, and risk of bias will be summarized. Primary outcome will be the disease activity score (including effective rate, swollen joint count, tender joint count, and morning stiffness), and the secondary outcomes will be RA-related blood test and adverse events. We will use Review Manager software to perform a meta-analysis, Cochrane Collaboration "risk of bias" tool for assessing the risk of bias, and Grades of Recommendation, Assessment, Development and Evaluation for the determination of quality of evidence.

Results : We are going to investigate the effectiveness and safety of DHJST with medication for RA.

Conclusion : This study will provide reliable evidence on whether DHJST combined with medicine is more effective on RA than medicine monotherapy.

Key words : rheumatoid arthritis, Dokwhalkisaeng-tang, randomized controlled trials, systematic review, meta-analysis.

Ⅰ. Introduction

Rheumatoid arthritis (RA) is a common chronic autoimmune disease with a global prevalence estimate of 0.46%,[1] that contributes to progressive disability, systemic complications, higher mortality, and societal burden.[2-4] The etiology is still unclear, but it is believed that multiple genetic and environmental factors lead to hyperresponsive condition of immune cells against the self-antigens, leading to inflammation and joint damage.[5] Typical presentations of RA include symmetrical pain and swelling on multiple joints, accompanied by morning stiffness lasting more than 30 minutes. Elevated levels of rheumatoid factor (RF) and acute phase reactant response including increased C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are also included in the diagnosis criteria.[6]

Current treatments for RA have a purpose to treat symptoms by alleviating pain, reduce inflammation, and delay the disease progression through suppressing immune players and inflammatory mediators. The representative treatment for RA is medication including glucocorticoids (GCs), nonsteroidal-anti-inflammatory drugs (NSAIDs), and disease modifying antirheumatic drugs (DMARDs).[7,8] However, these medications are not yet curative or preventative.[9] Some studies have reported that conventional medication induced several adverse effects leading to discontinuation.[9] The adverse effects of methotrexate, the predominant treatment for RA, varies from the most common gastrointestinal disorders, which 20-70% of patients suffer, to severe problems such as hepatitis, pulmonary damage and myosuppression,[9] and is also ineffective in a proportion of patients. Accordingly, natural products and other complementary and alternative medicine approaches are gaining interest.[10]

Dokwhalkisaeng-tang (Duhuojisheng-tang, DHJST), traditionally used for treatment of RA, is composed of multiple herbs including Dokwhal (Duhuo, *Radix Angelicae Pubescentis*), Danggui (Danggui, *Radix Angelicae Sinensis*), Sangkisaeng (Sangjisheng, *Herba Taxilli*), Jakyak (Baishao, *Radix Paeoniae Alba*). A randomized controlled trial (RCT) study showed that DHJST significantly mitigated the clinical symptoms of RA and the level of CRP, ESR, and RF comparing to the control group.[11] Animal experiments showed that DHJST inhibited inflammation and increased joint lymphatic function by promoting lymphangiogenesis and lymphatic drainage function.[12] Coumarins, the principle ingredient isolated from *Radix Angelicae*

*Corresponding author : Won-Suk Sung. Department of Acupuncture & Moxibustion, Dongguk University Bundang Oriental Hospital, 268 Buljeong-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13601, Republic of Korea.
Tel : +82-31-710-3725, Fax : +82-31-710-3780, E-mail : 1984sws@hanmail.net
•Received : May 11, 2022 / Revised : May 16, 2022 / Accepted : May 16, 2022

Pubescentis demonstrated significant anti-inflammatory and analgesic activities by inhibiting the production of inflammatory cytokines.[13] Total glucosides of paeony from the roots of *Paeonia lactiflora Pallas* is known to alleviate unanticipated hepatic adverse effects during conventional treatment of RA.[14]

Although there are several studies reporting the effectiveness of DHJST on RA, evidence-based review on effectiveness and safety of DHJST with medication was not yet provided. In this study, we are going to investigate the effectiveness and safety of DHJST with medication for RA.

Ⅱ. Methods

A. Study design

A systematic review (SR) will be conducted according to the Preferred Reporting Items for Systemic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement.[15]

B. Ethics

Since there will be no requirement of patients or personal information collection, ethical statement is not required.

C. Study registration

The protocol was registered in INPLASY (Registration number: 202220105).

D. Eligibility criteria

1. Participants

Patients who were diagnosed as RA, regardless of age and gender, will be included. Patients with osteoarthritis will be excluded.

2. Types of interventions

DHJST with various conventional medication including DMARDs, GCs, and NSAIDs for RA will be included.

3. Type of studies

This study will include RCTs that compared the effects of DHJST with medication on RA with control group containing conventional medication treatments. RCTs which did not provide the randomization method or conducted randomization incorrectly, and uncontrolled clinical trials (e.g., observational studies, pilot studies, case studies, and SR) will be excluded.

4. Outcome measures

Primary outcome will be the disease activity score including effective rate, swollen joint count, tender joint count, and morning stiffness. Blood test about RA including ESR, CRP and RF, and adverse events will be considered as secondary outcomes.

5. Language

There will be no limitation according to language.

E. Information sources and search strategy

MEDLINE, Cochrane Library, China National Knowledge Infrastructure (CNKI), CiNii, J-STAGE, KoreaMed, Korean Medical Database, Korean Studies Information Service System (KISS), National Digital Science Li-brary (NDSL), Korea Institute of Science and Technology Information (KISTI), and Oriental Medicine Advanced Searching Integrated System (OASIS) will be used to search for related studies published from initial time of each database to June 2022. A combination of following terms will be used to conduct a search, in each database's language (Arthritis, Rheumatoid OR Rheumatoid Arthritis) AND (Duhuojisheng decoction OR Duhuojisheng tang) AND Comparison (name of DMARDs OR GCs OR NSAIDs). More searches will be done from relevant gray literature sources, reports, and dissertations. Manual searches like textbooks on DHJST and its references and contacting authors via e-mail will be done if needed (Table 1).

F. Study selection

After the search is conducted, two researchers will independently screen through the records for inclusion. Duplicate studies will be excluded first and more

studies will be excluded according to the assessment of title, abstract, and full text. Then using pre-defined criteria, two reviewers will read the full texts of the potentially eligible articles for the assessment of inclusion, with any conflicts resolved through discussion. If the two reviewers fail to reach an agreement, the third reviewer will make a final decision.

G. Data management

Management software EndNote X20 will be used for the management of compiled data.

H. Data extraction

Two reviewers will take part in extracting the data in accordance to the pre-defined criteria. Data on study information including first author and publication year, patient characteristics, interventions and comparators, outcome measures, the results and information for assessment of study quality will be extracted. Any disagreement on data extraction will be solved by discussion until consensus is reached or by consulting a third reviewer.

I. Data synthesis and analysis

We will combine the changes from baseline to completion of the intervention by using the Review Manager software for Windows to perform a meta-analysis (Version 5.3; Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2014). We will calculate the mean difference and 95% confidence intervals (CIs) in same outcome measures, and the standardized mean difference and 95% CI in different outcome measures to estimate the effect with a random-effects or a fixed-effect model. The heterogeneity assessment will be calculated by Chi-squared and I-squared and be interpreted as follows; unimportant heterogeneity, 0%-40%; moderate heterogeneity, 30%-60%; substantial heterogeneity, 50%-90%; and considerable heterogeneity, 75%-100%. If possible, the subgroup analysis will be conducted based on the main intervention in control group. Narrative synthesis will be conducted if quantitative synthesis is not possible, using the available data. Funnel-plot will be used regarding the publication bias when there are more than 10 identified studies in the meta-analysis. In rating the quality of evidence for each outcome, Grading of Recommendations Assessment, Development and Evaluation (GRADE) method will be used.[16]

J. Risk of bias assessment

Risk of bias will be assessed by two reviewers independently using the Cochrane "risk of bias" tool.[17] The tool is composed of seven domains: sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other biases. The risk of bias will be rated as "low risk," "high risk," or "unclear risk" for each domain.

III. Discussion

Conventional medications for RA have been helpful but there are limitations and adverse effects to consider. Thus, an effort to find a safer, more effective method of treating RA is on process. DHJST has been clinically verified by previous researches, and has a potential to show better performance combined with medicine than medicine alone. This study will provide evidence-based review for patients, clinicians, policy makers, and researchers.

Acknowledgements

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health and Welfare through the Korean Health Industry Development Institute (KHIDI) (grant No. HF21C0077). Funder only provided the financial support and did not involve in this article including the review, editing, or the submission for publication.

References

1. Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. Rheumatol Int. 2021;41(5):863-77.
2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011; 365(23):2205-19.
3. Dadoun S, Zeboulon-Ktorza N, Combescure C, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. Joint Bone Spine. 2013;80(1):29-33.
4. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. Annals of the Rheumatic Diseases. 2014;73:1316-22.
5. Deane KD, Demoruelle MK, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2017;31(1):3-18.
6. Wasserman AM. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2011; 84(11):1245-52.
7. Singh JA, Saag KG, Bridges SL Jr, et.al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2016;68(1):1-25.
8. Abbasi M, Mousavi MJ, Jamalzehi S, et al. Strategies toward rheumatoid arthritis therapy; the old and the new. J Cell Physiol. 2019;234(7): 10018-10031.
9. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review. Eur J Med Chem. 2018;158: 502-16.
10. Moudgil KD, Berman BM. Traditional Chinese medicine: potential for clinical treatment of rheumatoid arthritis. Expert Rev Clin Immunol. 2014;10(7):819-22.
11. Yue J, Rong H. Clinical effect of DuhuoJisheng decoction in the treatment of rheumatoid arthritis patients. Chinese Medical Guidelines. 2021;19(14): 134-5.
12. Chen Y, Li J, Li Q, et al. Du-Huo-Ji-Sheng-Tang Attenuates Inflammation of TNF-Tg Mice Related to Promoting Lymphatic Drainage Function. Evid Based Complement Alternat Med. 2016;2016:7067691.
13. Lu Y, Wu H, Yu X, et al. Traditional Chinese Medicine of *Angelicae Pubescentis Radix*: A Review of Phytochemistry, Pharmacology and Pharmacokinetics. Front Pharmacol. 2020;11:335.
14. Liu B, Meng X, Ma Y, et al. Clinical safety of total glucosides of paeony adjuvant therapy for rheumatoid arthritis treatment: a systematic review and meta-analysis. BMC Complement Med Ther. 2021;21(1):102.
15. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ.2008;336:924－6.
17. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142.

Table 1. Search Strategy for the MEDLINE via PubMed

No.	Search terms
#1	rheumatoid arthritis
#2	rheumatoid OR arthritis
#3	#1 and #2
#4	randomized controlled trial OR random*
#5	controlled clinical trial OR trial
#6	Duhuojisheng OR Duhuojisheng decoction OR Duhuojisheng tang
#7	Methotrexate OR leflunomide OR sulfasalazine OR hydroxychloroquine
#8	Prednisone OR prednisolone OR methylprednisolone
#9	Nimesulide OR meloxicam OR diclofenac
#10	#7 OR #8 OR #9
#11	#3 AND (#4 OR #5) AND #6 AND #10