Original Article

보중익기탕의 아토피 피부염 치료 효과 분석: 체계적 문헌 고찰

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Bojungikgi-Tang for atopic dermatitis: A systematic review of randomized controlled trial

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Abstract

This systematic review aimed to assess the clinical evidence supporting the use of an herbal drug, Bojungikgi-Tang (BIT) for the treatment of atopic dermatitis (AD). Eleven databases, including PubMed, EMBASE, and the CENTRAL, were searched from their inception to December 2019. All randomized controlled trials that reported on the effects of BIT on AD, without language restrictions, were included. The methodological quality of and risk of bias in the trials were assessed using the Cochrane Collaboration tool. We identified 2,674 studies, of which two met the inclusion criteria. The overall risk of bias in the included trials was relatively low or unclear. There were statistically significant improvements in the oozing and crust score (p=0.04) and total equivalent amount (TEA) of topical agents (p=0.02) in the BIT group in comparison to those in the placebo group. The evidence suggests that BIT can significantly reduce the oozing and crust symptoms and TEA of topical agents compared with placebo. However, the limited number of trials and the small effect size make it difficult to draw firm conclusions. Trial registration number: CRD42018105173

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Received 2021-11-19, revised 2021-12-15, accepted 2021-12-16, available online 2021-12-18
doi:10.22674/KHMI-10-1-1

Keywords: atopic dermatitis, Bojungikgi-Tang, Bu-Zhong-Yi-Qi-Tang, eczema, herbal medicine, systematic review

Introduction

Atopic dermatitis (AD) is a chronic relapsing skin disease, which can have a negative effect on the quality of life of patients.[1)] AD is a complex and heterogeneous disease whose pathophysiology has not been clearly explained; thus, its treatment focuses on symptomatic management, involving the long-term use of topical corticosteroids and topical calcineurin inhibitors.[1,2)] However, these treatments have been associated with adverse events (AEs) and the development of drug tolerance.[3)] Therefore, continuous efforts for the development of new therapeutics are needed.[4)]

Bojungikgi-Tang (Bu-Zhong-Yi-Qi-Tang, Hochu-ekki-to, BIT), an herbal drug, has anti-allergic and immunomodulatory properties,[5,6)] and is an emerging therapeutic candidate for AD. BIT has shown to improve AD symptoms and regulate serum immunoglobulin E levels in AD patients.[7,8)] However, no critical evaluations, such as systematic reviews or meta-analyses, of the potential benefits and dangers of BIT on AD were evident. Therefore, in the present study, we aimed to conduct a systematic review of randomized controlled trials (RCTs) to assess the evidence on the effectiveness of BIT in treating AD.

Methods

1. Protocol registration

This study's protocol, which has been published previously,[9)] was registered with PROSPERO under the number CRD42018105173 (available URL: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=105173), and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

2. Data sources

The following databases were searched from their inception to December 2019: PubMed, EMBASE, Cochrane Library, AMED, and CINAHL. We also searched four Korean (OASIS, KoreaMed, KISS, and NDSL), one Chinese (CNKI), and one Japanese (CiNii) databases.

Atopic dermatitis and BIT related terms were used as a search terms. Search strategy was provided in the protocol.[9] Two reviewers reviewed and screened titles and abstracts to identify eligible trials according to the inclusion criteria. Disagreements were resolved by discussion, and if required, by the arbiter.

3. Study selection and extraction

The following criteria were used to identify studies for inclusion in the review:
Type of study: RCTs or quasi-RCTs that reported the effects of BIT on AD.
Type of participant: Studies that evaluated patients with a diagnosis of AD.
Type of intervention: Both BIT and modified BIT, regardless of herbal formulations.
Type of comparison: Both active control and placebo were acceptable.
Types of outcome measures: Trials that reported at least one of the following outcome measures: Symptom severity assessment tools such as the SCORing atopic dermatitis index and eczema area severity index , total effectiveness rate, percentage of trial participants with the sum of “recovery” and “significant improvement”, AEs, quality of life assessment tools, and dosage of topical agents.

4. Risk of bias assessment

The risk of bias was assessed in seven domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases according to the Cochrane tool. Each domain was scored as follows: high risk, low risk, and unclear risk of bias. Any disagreements between the authors were resolved through discussion.

5. Data analysis

We used RevMan 5.3 (Cochrane Informatics and Knowledge Management Department; available at http://tech.cochrane.org/revman/download) to conduct the statistical analysis. Dichotomous data were expressed as risk ratio (RR) with 95% confidence interval (CI), whereas continuous data were presented as mean difference (MD) with 95% CIs. Other forms of data were converted into either RRs or MDs.

Results

1. Study selection and study characteristics

Our search generated a total of 2,674 potentially relevant studies, from which 827 duplicated and 1,648 irrelevant studies were excluded after titles and abstracts were screened. Subsequently, 199 full-text articles were reviewed, and two met our eligibility criteria (Fig. 1). However, the two selected studies[10,11] only reported one trial. Thus, we considered these two studies as one trial. The key data from the eligible RCT are summarized in Table 1.

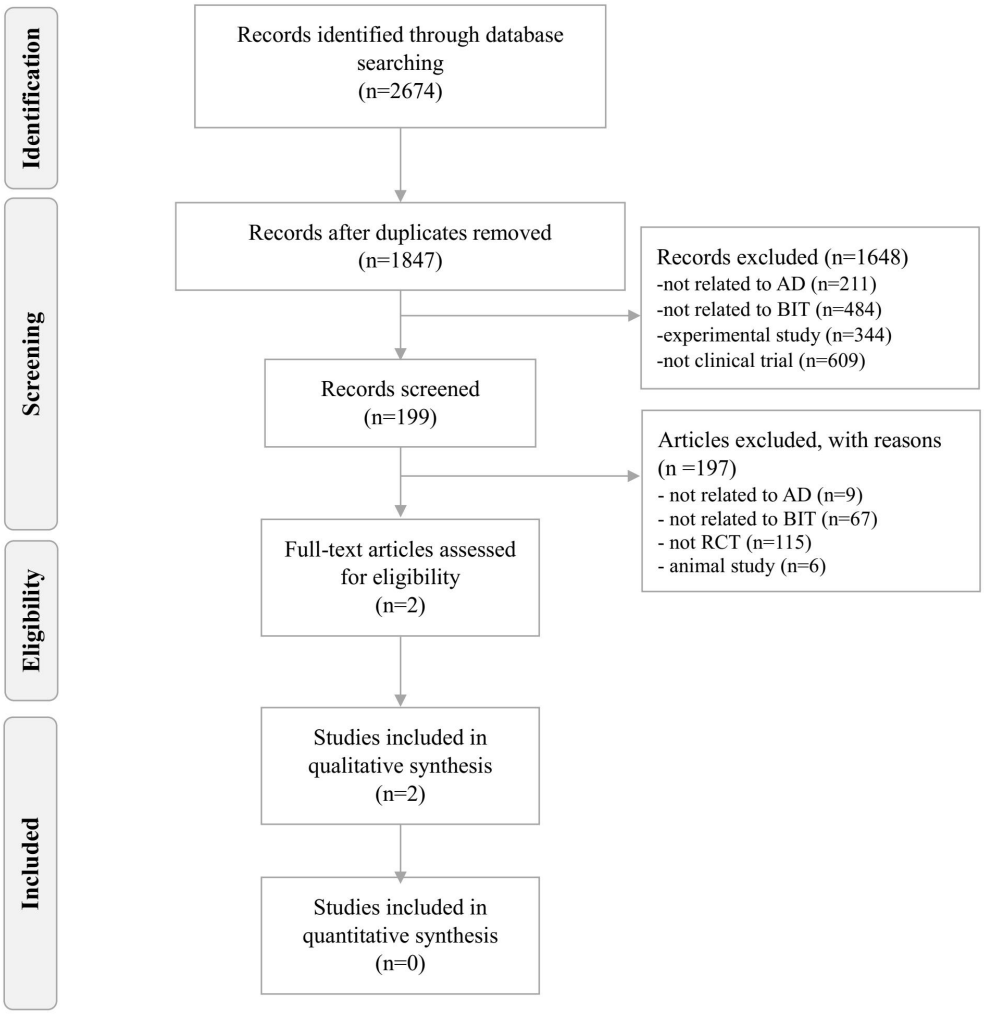

Fig 1. PRISMA Flow diagram

Table 1. Characteristics of the included randomized controlled trial

Kobayashi et al[10,11]	
Study Design	Block randomized, double blinded, multicenter trial
Participants	Qi deficiency type AD patients aged 20-40 years old who fulfilled the diagnostic criteria of the Japanese Dermatological Association for AD. Number of participants (enrolled/completed/without "oozing and crust") Hochu-ekki-to: 43/37/17 Placebo: 48/40/15
Intervention	BIT (Hochu-ekki-to) 3.75g twice a day for 24 weeks
Control	Placebo 3.75g twice a day for 24 weeks
Outcomes	1) Skin severity score, MD -1.70 [-5.62, 2.22], p=0.40 2) Erythema and acute papule score, MD -0.50 [-1.69, 0.69], p=0.41 3) Oozing and crust score, MD -0.70 [-1.36, -0.04], p=0.04 4) Chronic papule, nodule and lichenification score, MD -0.20 [-1.32, 0.92], p=0.73 5) Rash area, MD -0.60 [-2.03, 0.83], p=0.41 6) Total equivalent amount of topical agents used per day, MD -24.62 [-45.91, -3.33], p=0.02 7) Prominent efficacy rate, RR 3.78 [0.84, 17.07], p=0.08 8) Aggravated rate, RR 0.15 [0.02, 1.17], p=0.07 9) Serum IgE, LDH, eosinophil count, not significant (Data not shown)
Subgroup Analysis (without "oozing and crust")	1) Eruption score, MD 32.00 [9.15, 54.85], p=0.006 2) Decreased rate of the amount of topical agents, MD 71.00 [27.93, 114.07], p=0.001
Note	Treatment rationale: Met qi deficiency criteria by questionnaire Adverse effects: *BIT*: nausea (2), diarrhea (2), stomach discomfort (2), enlarged feeling of abdomen, epigastralgia, anorexia, loose stools, right hypochondrium pain, malaise, dizziness, headache, light-headed feeling, rhinitis, acne pustulosa, feverish thirstiness, dental caries, eosinophilia (3), ALT elevation, IgE elevation, BUN decline, serum K elevation. *Placebo*: ovarian disorder (2), diarrhea, epigastric discomfort, anorexia, malaise, hives, insomnia, feverish limbs, eosinophilia (4), LDH elevation (2), AST elevation (2), γ-GTP elevation, serum total protein decline, hemoglobin decline. Intention to treat: Full analysis set Author conclusion: Hochu-ekki-to is a useful adjunct to conventional treatments for AD patients with Kikyo constitution. Use of Hochu-ekki-to significantly reduces the dose of topical steroids and/or tacrolimus used for AD treatment without aggravating AD.

Risk of bias

Item	Author's judgement	Description
Random sequence generation (selection bias)	Low risk of bias	Described as conducting block randomization handled by an independent investigator
Allocation concealment (selection bias)	Low risk of bias	Stated that random code was concealed
Blinding of participants and personnel (performance bias)	Low risk of bias	Described as double blinding
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Not stated
Incomplete outcome data (attrition bias)	High risk of bias	Missing data imputation method was not described
Selective reporting (reporting bias)	Unclear risk of bias	Protocol not available
Other bias	Unclear risk of bias	Sample size calculation method was not stated

Abbreviations: AD, atopic dermatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; BIT, Bojungikgi-Tang; γ-GTP, gamma glutamyl transferase; IgE, immunoglobulin E; LDH, lactate dehydrogenase; MD, mean difference; RR, risk ratio

2. Risk of bias within included studies

The included RCT[10,11] had a low risk of bias in terms of its random sequence generation, allocation concealment, and blinding of participants. But it also had an unclear risk of bias for its blinding of outcome assessment, selective reporting, and other biases. Because the missing data imputation method was not described, the RCT had a high risk of bias with respect to incomplete outcome data (Table 1).

3. Outcomes

The study tested skin severity score and subgroup scores including erythema and papule score, oozing and crust score, chronic papule, nodule and lichenification score, rash area, total equivalent amount (TEA) of topical agents used per day, prominent efficacy rate, aggravated rate, and immunological factors. Among these outcomes, there was a statistically significant improvement in oozing and crust score (p=0.04) and TEA of topical agents (p=0.02) in the BIT group when compared to those in the placebo group.

4. Adverse events

Any serious AEs were not reported. AEs in the trial reported the Table 1. Most of AEs in BIT group are gastrointestinal symptoms, same in placebo group. It seemed to be unrelated to BIT compared to placebo.

Discussion

Despite our extensive efforts to collect all RCTs without any language limitations, only one trial[10,11] qualified for our review. Relatively high-quality evidence was obtained from this well-conducted trial; it reported the effects of BIT on AD, wherein BIT potentially improved oozing and crust symptoms and TEA of treatment compared to the placebo control group. However, the small effect size and trial number made it difficult to draw precise conclusions.

The main feature of the included trial was that it utilized the concept of pattern identification (PI). In East Asian countries, herbal drugs are often prescribed according to PI, a unique traditional Chinese medicine (TCM) diagnostic tool; it is based on a comprehensive analysis of signs and symptoms. The clinical indications of BIT are fatigue, anorexia, and night sweats, all qi-deficiency-type PI symptoms. By applying a unique TCM diagnostic concept using the qi-deficiency questionnaire, the trial aimed to enroll

AD patients suitable for the indication of BIT.

The limitation of this study was the lack of control of the concomitant treatment dose, which meant that the patients without improvement were more likely to use a higher dose of the concomitant treatment, thus minimizing the differences between the treatment and control groups. In fact, the placebo group used more amount of topical treatment than the BIT group, implying that had the concomitant treatment dose been controlled, the differences in the primary and secondary outcomes could have been greater.

In conclusion, BIT could potentially improve oozing and crust symptoms as well as the TEA of concomitant treatment among patients with qi-deficiency type AD. However, the evidence is too weak to suggest that BIT is an effective therapy for AD. Further investigation of the effects and safety of BIT in patients with AD through rigorously designed randomized trials should be conducted.

Acknowledgements

This study was funded by the Korea Institute of Oriental Medicine (KSN2021210). The funder has no role in the study design, data collection and analysis, preparation of the manuscript, or decision to publish.

The study's review protocol was published in the Medicine® Journal (Medicine® 2019;98(1):e13938, doi: 10.1097/md.0000000000013938).

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