Integrative Medicine Research 12 (2023) 100973

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Original Article

Clinical effectiveness of decoction form of herbal medicine in primary care treatment of allergic rhinitis: A retrospective cohort study

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ARTICLE INFO

Keywords:
Allergic rhinitis
Retrospective cohort study
Herbal medicine
Propensity score matching

ABSTRACT

Background: The decoction form of herbal medicine (D-HM) is mainly prescribed to patients with allergic rhinitis (AR) in Korean Medicine (KM) clinics in the Republic of Korea; however, it is difficult to conduct clinical trials of D-HM due to regulatory issues. This study investigated the clinical safety and effectiveness of D-HM combination therapy for the treatment of AR by analyzing the AR outpatient data from 17 KM clinics.

Methods: This retrospective cohort study included patients who visited KM clinics for AR treatment from January 1, 2021, to March 31, 2022. Cases were collated using structured case report forms and divided into the D-HM with KM usual care group (D-HM group) and the KM usual care group (UC group). Since D-HM therapy could not be randomly assigned to the study population, we used optimal propensity score (PS) matching to investigate the effectiveness and safety of D-HM combination therapy in the treatment of AR.

Results: Data from 228 patients were collected. After PS matching, 144 patients were finally analyzed. The total nasal symptom score (TNSS) and mini-rhinoconjunctivitis quality of life questionnaire (mini-RQLQ) were significantly improved in the D-HM group compared with those in the UC group (TNSS: p=0.02; mini-RQLQ: p=0.04). Four patients in the D-HM group experienced minor adverse events that were mild and resolved within 15 days.

Conclusions: D-HM combination therapy may be beneficial in the management of symptoms and rhinitis-associated quality of life and potentially useful in clinical practice. However, randomized placebo-controlled clinical trials are required to confirm their effectiveness.

Study registration: This study has been registered at Clinical Research Information Service (KCT0007242).

1. Introduction

Allergic rhinitis (AR), chronic nasal inflammatory disease, affects 10–30% of the global population[1,2] and has a negative impact on daily function and performance.[3] Herbal medicines (HMs), such as Socheongryongtang, Okbyeongpoongsan, Bojoong-ikkitang, and Hyeong-gaeyeongyotang, have been used for ameliorating symptoms, enhancing the quality of life, and strengthening the body constitution in patients with AR.[4–7] According to the Allergic Rhinitis Clinical Practice Guideline of Korean Medicine, HM is a well-tolerated treatment option for AR to alleviate symptoms and prevent recurrence.[7]

The traditional use of HM is usually in the form of decoction, powder, pills, or tablets, with decoction being the most popular of all oral dosage forms administered in the Republic of Korea.[8] Decoction is a method of extraction by boiling herbal or plant material to dissolve their chemicals, and it can be tailored to the patient's condition defined according to traditional Chinese medicine (TCM) syndrome differentiation and treatment principles.[9] Although the decoction form of HM (D-HM) can be customized for more personalized treatment, it lacks productization and sufficient research data availability. It is necessary for HMs to be manufactured in facilities that are certified for good manufacturing practices (GMP) in order to conduct clinical trials.[10] However, the patient-specific

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https://doi.org/10.1016/j.imr.2023.100973
Received 18 November 2022; Received in revised form 6 July 2023; Accepted 11 July 2023
Available online 13 July 2023

nature of customized D-HM prescribed in Korean Medicine (KM) clinics poses a challenge for conducting randomized controlled trials (RCTs), as it is difficult to produce these formulations in GMP-certified facilities. Therefore, evaluating the therapeutic efficacy of customized D-HM through RCTs is not feasible in the Republic of Korea.

Based on a survey among Korean traditional medicine doctors,[11] it was found that D-HM is the most commonly used and preferred treatment method compared with other HM formulations. Although previous studies have demonstrated the effectiveness of HM prescriptions and they are widely used treatment options, the Korean government does not accord equal recognition to D-HM prescriptions due to differences in their formulation.

Although D-HM is currently used to treat AR in Korean clinical practice, no rigorous empirical studies attesting to its effects have been reported owing to regulatory issues. As a first step in clinical appraisal, it is necessary to review the safety and effectiveness of D-HM. The current study aimed to assess the safety and effectiveness of D-HM for the treatment of AR through a retrospective cohort study. The purpose of this study is to assess the clinical effectiveness and safety of D-HM combination therapy in the treatment of AR with KM usual care.

2. Methods

2.1. Study design and ethical considerations

This study aimed to evaluate the safety and clinical effectiveness of D-HM in patients with AR through the retrospective cases analysis of 17 KM clinic units located in the Republic of Korea (Supplementary Fig. 1) by collating the patient records of patients who visited the KM clinics for AR treatment (International Classification of Disease-10 [ICD-10], vasomotor, and allergic rhinitis [J30]) from January 1, 2021, to March 31, 2022.

KM doctors who received training on the use of standardized case report forms and used it in their clinical practice were involved in this study. The 17 KM clinics obtained informed consent from their patients during their initial visit for the purpose of utilizing their medical data in the research. The study protocol was exempted from ethical review by the Institutional Review Board of the Korea Institute of Oriental Medicine on January 20, 2022 (IRB No, I-2201/001-001), and registered in the National Clinical Trial Registry, Clinical Research Information Service (KCT0007242, https://trialsearch.who.int/?TrialID=KCT0007242). This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Supplementary Table 1).

2.2. Inclusion and exclusion criteria

The inclusion criteria were: 1) subjects who were diagnosed with AR at the KM clinics and 2) those who had all data records, such as demographic information, outcome evaluation [Total Nasal Symptom Score (TNSS), Mini-Rhinoconjunctivitis Quality of Life Questionnaire (mini-RQLQ), EuroQol-5Dimension-5Level (EQ-5D-5L)], and treatment data available at the end of treatment.

The exclusion criteria were: 1) subjects who did not consent to the collection of medical records, 2) subjects who did not have medical records after the first visit, 3) subjects who had medical records since the first visit but could not be evaluated for the changes before and after treatment due to the absence of evaluation records, and 4) subjects who had taken extract or powder forms of HM and/or oral over the counter (OTC) and ethical (ETC) drugs were excluded from data collection.

2.3. Variables

- Demographic information: anonymized identification number and initial, age, sex, height, and weight.
- Allergic medical history: accompanied by other allergic diseases (such as atopic dermatitis, asthma, and food allergies), family history of allergies, allergy testing, date of onset, International Classification of Diseases codes, and basis for diagnosis.
- Symptom evaluation: TNSS, mini-RQLQ, EQ-5D-5L, evaluation of KM treatment satisfaction questionnaire.
- D-HM prescription records.
- Major adjunctive therapies administered along with D-HM, such as acupuncture, laser/infrared therapy, and intranasal ointment.
- Costs incurred by the patient for D-HM and/or adjunctive therapies.
- Adverse event (AE) data.

This study was conducted as an observational study, in which the clinical data for the treatment of AR at a KM clinic was collected and analyzed without imposing artificial constraints on treatment duration, method, or frequency. The duration of treatment, method, and frequency were determined at the discretion of the physician and patient and could vary depending on multiple factors, such as the severity of the condition, treatment protocol, and physician-patient relationship. Such inter-group differences, such as sex, age, family history of allergies, TNSS, mini-RQLQ, EQ-5D-5L baseline values, and duration of treatment, were adjusted as covariates.

2.4. Interventions

D-HM was prescribed at the physician's discretion according to the patient's condition, and traditionally prepared by decocting medicinal herbs with water. The D-HMs prescribed in this study are shown in Supplementary Fig 2. KM usual care included acupuncture, intranasal treatment, infrared therapy, moxibustion, cupping therapy, and Chuna manual therapy. Supplementary Table 2 provides a detailed overview of the D-HM and KM usual care treatment.

2.5. Outcomes

The primary outcome was the TNSS. TNSS comprises four nasal symptoms (nasal congestion, rhinorrhea, nasal itching, and sneezing) evaluated using a four-point scale ranging from 0 (no symptoms) to 3 (severe).[12] The Mini-RQLQ, EQ-5D-5L, and KM treatment satisfaction questionnaire were also examined. The Mini-RQLQ is a rhinoconjunctivitis-related, quality of life instrument comprising 14 questions in five domains (activity limitation, practical problems, nose symptoms, eye symptoms, and non-nose/eye symptoms) evaluated using a seven-point scale ranging from 0 (not troubled) to 6 (extremely troubled).[13] The EQ-5D-5L questionnaire is a brief questionnaire comprising five questions that documents the patient's overall health status using a five-point scale.[14] KM Treatment Satisfaction questionnaire included "Overall satisfaction," "Safety," "Helpful," "Recommendation," and "Retreatment" items evaluated using a five-point scale ranging from 1 (strongly disagree) to 5 (strongly agree).[15] The TNSS, mini-RQLQ, and EQ-5D-5L scores were assessed before and after KM treatment, and the KM Treatment Satisfaction questionnaire was assessed after treatment.

2.6. Other measures

To ensure the safety of the study, any potential AE occurring during KM treatment were examined.

2.7. Statistical analysis

We used optimal propensity score (PS) matching to adjust the differences between the groups to reduce selection bias.[16] Each patient receiving HM therapy was matched to a non-receiver with a similar PS. Potential confounding variables were controlled by matching the covariates of the two groups according to PSs calculated using generalized linear mixed effect model analysis. PS was based on the following covariates: sex, age, family history of allergies, duration of treatment, and

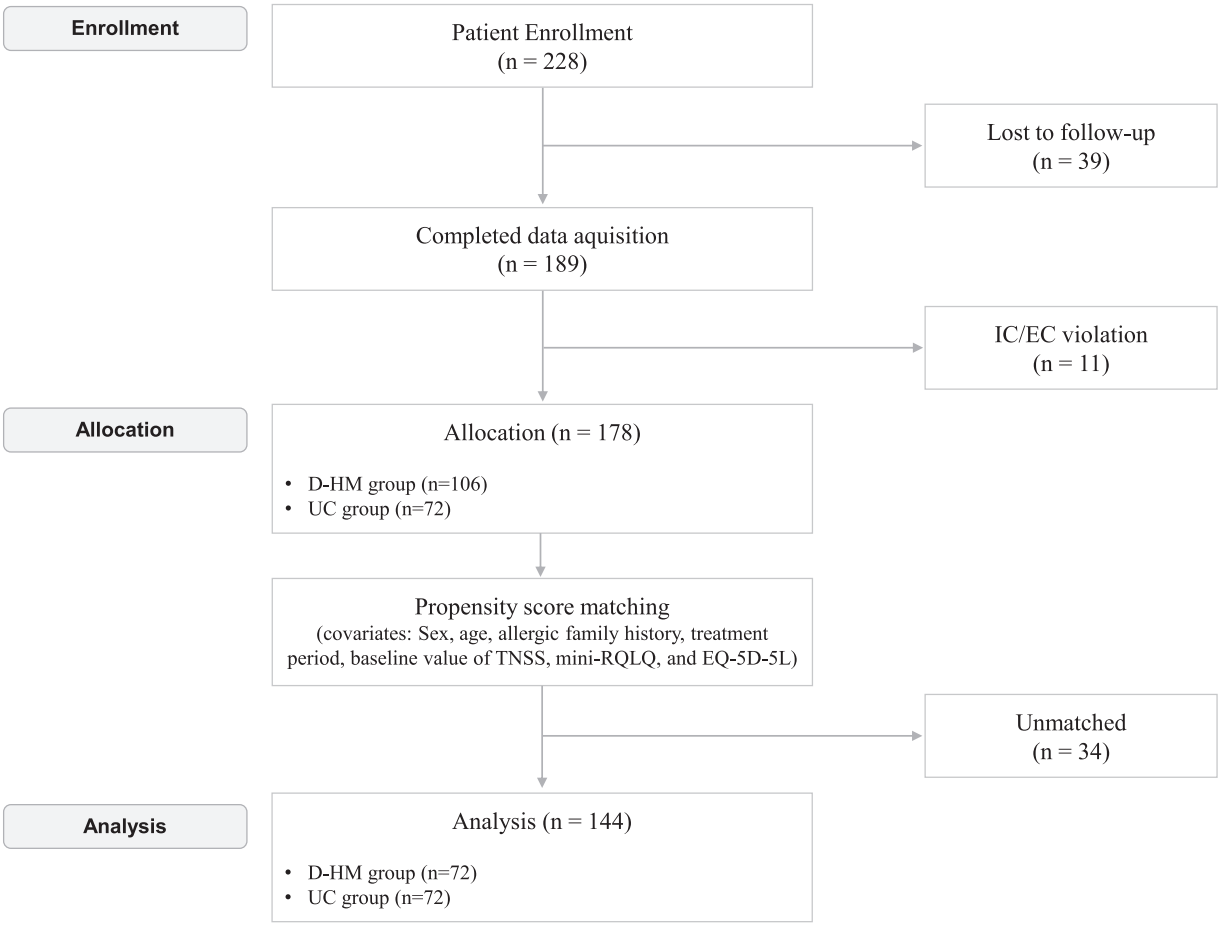

Fig. 1. Study flow diagram.

TNSS, mini-RQLQ, and EQ-5D-5L baseline values. The primary rationale for the selection of covariates was due to the imbalance observed in the baseline values. Upon examining supplementary table 3, it became evident that there were notable differences in certain variables such as age, family history of allergies, baseline TNSS values, and mini-RQLQ values among the groups. Thus, it was deemed necessary to perform PS matching to address the discrepancies between the groups. Height and weight imbalances between the groups were not included as covariates because it was determined that they were primarily influenced by age variation among the included patients. Therefore, controlling for age using PS matching was expected to naturally rectify the imbalance in height and weight. Given that males and females may respond differently to drug treatment, we included sex as a covariate. Additionally, the EQ-5D-5L value was included due to concerns that imbalances in baseline values could affect the interpretation of results after PS matching.

After PS matching, the demographic characteristics and effectiveness outcomes between the two groups were compared using a paired two-sample t-test, McNemar's Chi-squared test, and McNemar-Bowker test that take into account the matched nature of the sample. All statistical analyses were performed using R (version 4.0.5, "R & R" of the Statistics Department of the University of Auckland, Auckland, New Zealand), with a significance level of 0.05 and two-sided tests.

3. Results

3.1. Demographic characteristics

A total of 228 patients with AR visited the 17 KM clinics from January 1, 2021, to March 31, 2022. After excluding 50 patients based on the inclusion/exclusion criteria, 178 AR patients were finally included. Among the 178 patients, 106 were treated with D-HM and KM usual care (D-HM group), and 72 were treated only with KM usual care (UC group). KM usual care includes acupuncture, intranasal treatment, infrared therapy, moxibustion, cupping therapy, and Chuna manual therapy.

Statistically significant differences were observed between the two groups in terms of age, family history of allergies, and baseline mini-RQLQ scores (Supplementary Table 3).

A total of 144 patients (72 each in the D-HM and UC groups) were matched after PS matching, with the two matched groups showing no statistically significant differences. The sample selection procedure is depicted in Fig. 1, and the matched patient characteristics are summarized in Table 1.

3.2. Changes in the nasal symptom scores

As the D-HM and UC therapy progressed, the mean TNSS from baseline exhibited significant improvements in both groups. The mean TNSS was 6.18 in the D-HM group (95% CI [5.58, 6.78]) and 6.18 in the UC group (95% CI [5.60, 6.76]) at the baseline. At the end of treatment, the TNSS was significantly improved in the D-HM group (3.08, 95% CI [2.63, 3.53]) than that in the UC group (3.81, 95% CI [3.31, 4.31]) (p=0.02). Among the TNSS subgroups, rhinorrhea symptoms improved significantly in the D-HM group compared with those in the UC group (p=0.01) (Fig. 2).

3.3. Changes in the mini-RQLQ scores

In the D-HM group, the mean mini-RQLQ score was 31.31 (95% CI [27.49, 35.13]) at baseline, which reduced to 14.31 (95% CI [12.02,

Table 1
Demographic characteristics of the matched patients.

Group Item	D-HM group (N=72)	UC group (N=72)	p-value
Sex			0.75[a]
Male	33 (45.8%)	31 (43.1%)	
Female	39 (54.2%)	41 (56.9%)	
Age (year)	28.6 [24.0, 33.2]	31.8 [26.8, 36.8]	0.32[b]
Age group			0.58[c]
0–10	20 (27.8%)	19 (26.4%)	
11–20	10 (13.9%)	8 (11.1%)	
21–30	13 (18.1%)	6 (8.3%)	
31–40	9 (12.5%)	15 (20.8%)	
41–50	8 (11.1%)	11 (15.3%)	
51–60	6 (8.3%)	5 (6.9%)	
> 60	6 (8.3%)	8 (11.1%)	
Height (cm)	153.1 [148.1, 158.1]	153.7 [148.9, 158.5]	0.86[b]
Weight (kg)	53.7 [48.9, 58.5]	52.0 [47.6, 56.4]	0.56[b]
BMI (kg/m^2)	21.7 [20.7, 22.7]	21.0 [20.0, 22.0]	0.29[b]
Accompanied by other allergic disease (Y/N)			
Asthma	1 (1.4%) / 71 (98.6%)	5 (6.9%) / 67 (93.1%)	0.10[a]
Atopic dermatitis	8 (11.1%) / 64 (88.9%)	9 (12.5%) / 63 (87.5%)	0.81[a]
Allergic conjunctivitis	19 (26.4%) / 53 (73.6%)	20 (27.8%) / 52 (72.2%)	0.85[a]
Food allergy	6 (8.3%) / 66 (91.7%)	3 (4.2%) / 69 (95.8%)	0.18[a]
Others	5 (6.9%) / 67 (93.1%)	3 (4.2%) / 69 (95.8%)	0.48[a]
Allergic family history (Y/N)	47 (65.3%) / 25 (34.7%)	51 (70.8%) / 21 (29.2%)	0.52[a]
TNSS	6.18 [5.58, 6.78]	6.18 [5.60, 6.76]	1.00[b]
Mini-RQLQ	31.31 [27.49, 35.13]	29.83 [26.66, 33.00]	0.56[b]
EQ-5D-5L	0.84 [0.82, 0.87]	0.85 [0.83, 0.88]	0.80[b]
Duration of treatment (day)	67.2 [54.0, 80.4]	63.0 [50.3, 75.7]	0.64[b]

The results are reported as mean [95% confidence interval] for continuous variables or frequencies (percentage) for categorical variables.
The D-HM group received D-HM in addition to the KM usual care, whereas the UC group received only the KM usual care, which included acupuncture, intranasal therapy, moxibustion, and other related treatments.
[a]: McNemar's Chi-squared test,
[b]: paired two-sample t-test,
[c]: McNemar-Bowker test.*Abbreviations:* BMI, Body mass index; EQ-5D-5L, EuroQol-5Dimension-5Level; mini-RQLQ, Mini-Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, Total Nasal Symptom Score.

16.60]) at the endpoint. In the UC group, the mean mini-RQLQ score was 29.83 (95% CI [26.66, 33.00]) at baseline, which reduced to 18.43 (95% CI [15.40, 21.46]) at the endpoint. The D-HM group showed improved rhinitis-associated quality of life compared with that in the UC group (p=0.04). In the mini-RQLQ subgroup, activities and nose symptoms were significantly improved in the D-HM group compared with those in the UC group (p=0.01, p=0.03, respectively) (Fig. 2).

3.4. Changes in the EQ-5D-5L scores

The EQ-5D-5L score of the D-HM group at baseline was 0.84 (95% CI [0.81, 0.87]), which improved by 0.07 (95% CI [0.05, 0.09]) to 0.91 (95% CI [0.89, 0.93]) at the endpoint. The EQ-5D-5L score of the UC group at baseline was 0.85, 95% CI [0.82, 0.88], which improved by 0.05 (95% CI [0.03, 0.07]) to 0.90 (95% CI [0.88, 0.92]) at the endpoint. There was a small, non-significant difference in the EQ-5D-5L scores between the D-HM and UC groups (p=0.22).

3.5. KM treatment satisfaction questionnaire

In the patient satisfaction questionnaire evaluated after treatment, the D-HM group was found to be more satisfied than the UC group, and the "Overall satisfaction" and "Safety" item were statistically significant (p=0.00 and p=0.01, respectively) (Table 2).

3.6. Adverse events

Among the 106 patients in the D-HM group, AEs were assessed in 98 patients (AEs were not mentioned in eight cases). Four AEs were reported among these patients. The AEs observed in the D-HM group, which included skin irritation, insomnia, mouth dryness, and dyspepsia, were mild and resolved within 15 days. In the UC group, AEs were assessed in 69 out of the 72 patients (AEs were not mentioned in three cases). No AEs were observed in this group. There was no significant difference between the two groups (p=0.14).

4. Discussion

The therapeutic effect of HMs on the treatment of AR has already been confirmed in well-designed RCTs.[17–21] D-HM, wherein herbs can be added or excluded to customize treatment for each patient, is used most frequently in the Republic of Korea.[11] Changes in the dosage form may be regarded as different pharmacological actions through absorption-distribution-metabolism-excretion processes,[9,22] thereby necessitating evaluation of the therapeutic effects of D-HM.

In the present study, 228 AR patients' data collected from 17 KM clinics were divided into D-HM and UC groups to evaluate the clinical effectiveness of D-HM with KM usual care compared to that of KM usual care only.

In the present study, D-HM combination therapy reduced the TNSSs and rhinorrhea score compared to that of KM usual care. It also improved mini-RQLQ scores and its subgroup "activities" and "nose symptoms" score. The EQ-5D-5L scores in the D-HM group were not significantly different from those in the UC group. It is assumed that D-HM is effective in improving nasal symptoms and the related quality of life in AR. In particular, the mini-RQLQ was shown to be effective, but there were no differences in EQ-5D-5L. This means that D-HMs mainly improve nasal symptoms and related quality of life, and AR patients

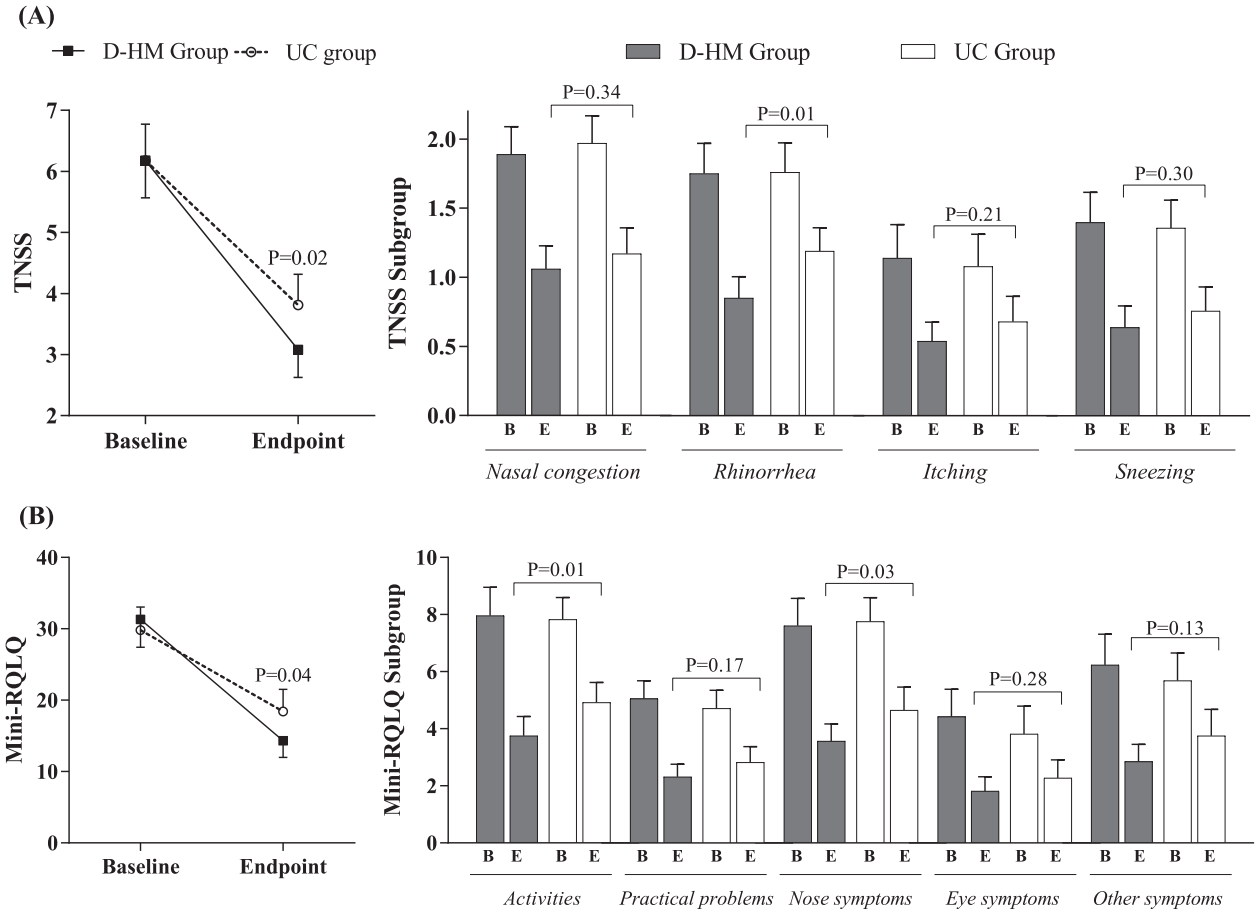

Fig. 2. Treatment differences between the groups. (A) TNSS; (B) Mini-RQLQ.
The results are expressed as the mean and 95% confidence interval (error bar). Paired two-sample *t*-tests were used for statistical analyses.
Abbreviations: B, baseline; E, endpoint; mini-RQLQ, mini-rhinoconjunctivitis quality of life questionnaire; TNSS, total nasal symptom score.

Table 2
Evaluation of KM Treatment Satisfaction questionnaire.

		D-HM Group	UC Group	p-value‡
Overall satisfaction	Strongly disagree	0 (0.0%)	0 (0.0%)	0.00
	Disagree	1 (1.4%)	0 (0.0%)	
	Neutral	3 (4.2%)	11 (15.3%)	
	Agree	36 (50.0%)	34 (47.2%)	
	Strongly agree	32 (44.4%)	27 (37.5%)	
Safety	Strongly disagree	0 (0.0%)	0 (0.0%)	0.01
	Disagree	0 (0.0%)	0 (0.0%)	
	Neutral	0 (0.0%)	3 (4.2%)	
	Agree	31 (43.1%)	30 (41.7%)	
	Strongly agree	41 (56.9%)	39 (54.2%)	
Helpful	Strongly disagree	0 (0.0%)	0 (0.0%)	0.28
	Disagree	2 (2.8%)	3 (4.2%)	
	Neutral	3 (4.2%)	11 (15.3%)	
	Agree	34 (47.2%)	34 (47.2%)	
	Strongly agree	33 (45.8%)	24 (33.3%)	
Recommendation	Strongly disagree	0 (0.0%)	0 (0.0%)	0.59
	Disagree	1 (1.4%)	2 (2.8%)	
	Neutral	8 (11.1%)	11 (15.3%)	
	Agree	40 (55.6%)	36 (50.0%)	
	Strongly agree	23 (31.9%)	23 (31.9%)	
Retreatment	Strongly disagree	0 (0.0%)	0 (0.0%)	0.36
	Disagree	1 (1.4%)	1 (1.4%)	
	Neutral	5 (6.9%)	8 (11.1%)	
	Agree	32 (44.4%)	36 (50.0%)	
	Strongly agree	34 (47.2%)	27 (37.5%)	

The results are reported as frequencies (percentage).
‡ p-value calculated using the McNemar-Bowker test.

are rarely correlated with the EQ-5D-5L items, such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Numerous HMs used to help in the recovery of nasal mucous membranes in AR have been reported to have anti-allergic and anti-inflammatory effects.[23,24] Based on these results, it is highly advisable to use D-HMs to improve the nasal symptoms and related quality of life.

The current study has several limitations. First, we aimed to determine the therapeutic effect of D-HM alone; however, KM clinics and hospitals prescribe treatments, such as acupuncture, moxibustion, and intranasal therapies, in addition to D-HM; thus, the results indicate the combined effect of D-HM and other therapies and not necessarily the effect of D-HM alone. Moreover, KM doctors provided symptomatic treatment with D-HM, and the results present the overall effects of D-HM combination therapy, which does not imply the effectiveness of a particular HM prescription. Future studies are needed to investigate the effects of D-HM alone by conducting well-designed prospective cohort studies.

Second, the diagnosis of AR was confirmed by an allergy test; however, the diagnosis of AR relied on the judgment of the doctor based on the history of present illness, nasal endoscopic findings, past and family allergic history, and history of allergy testing. The clinical diagnosis of AR can be established through patient history and a physical examination that aligns with an allergic cause and encompasses AR-associated symptoms, including rhinorrhea, sneezing, itching of the nose/palate/eyes, or nasal congestion triggered by exposure to allergens. Clinicians may consider performing specific immunoglobulin E (IgE) (skin or blood) allergy testing in cases where patients with a clinical diagnosis of AR do not respond to empirical treatment, when the diagnosis is uncertain, or when identifying the specific allergen is necessary to guide therapy.[25] However, in primary care settings, allergy testing is not obligatory for diagnosing AR. In this study, data were collected from KM clinics, which serve as primary care facilities. The diagnosis of AR in the study participants relied on the clinical judgment of the physicians and took into account various factors, such as previous allergic test results, family history of allergies, clinical symptoms, and nasal endoscopy. Allergy tests, including multiple allergen simultaneous test, ImmunoCAP, and serum IgE tests, were not administered. Therefore, the accuracy of the AR diagnosis in this study may be subject to some degree of uncertainty or misclassification. Third, the treatment effect was evaluated using only subjective questionnaires, such as TNSS and mini-RQLQ, which cannot be evaluated using objective measurements as objective measurements cannot be adapted to all 17 KM clinics.

In the Republic of Korea, unlike other KM usual care, D-HM can be relatively expensive, leading some patients to hesitate in selecting this option. In the present study, the mean expenditure per patient in the D-HM group was found to be 630,202.9±393,295.1 Korean Won, whereas in the UC group, it amounted to 127,542.3±140,222.3 Korean Won. Furthermore, out of the 72 patients who did not receive D-HM treatment, 59 were recommended D-HM treatment according to the doctor's judgment. However, the majority of these patients (n=53) rejected the treatment due to perceived cost barriers. Other reasons for rejection included inconvenience (n=8) and perceived ineffectiveness (n=3). The cost factor may introduce a bias in the choice of treatment and subsequently impact the interpretation of the study's findings.

This study has the strength of reducing regional and inter-institutional variation by analyzing data collected from 17 KM clinics across the Republic of Korea. Retrospective cohort studies have limitations due to the absence of the "balancing principle" inherent in RCTs, which can lead to various sources of biases and confounding factors. As a result, the comparison of outcomes between the treatment and control groups may not be as robust. PS adjustment offers a solution to this problem by enabling the balancing of the distribution of biases and confounding factors between groups, thereby allowing for greater comparability between the two groups. The PS matching method was applied to overcome the limitations of observational studies.

Based on its effectiveness with regard to improvements in TNSSs and the mini-RQLQ scores in patients with AR and the complete absence of serious AEs, the present study suggests that D-HM combination therapy may be a beneficial and safe option for the treatment of AR. This is an alternative study that reflects the reality of clinical research fields in the Republic of Korea, where clinical trials of D-HMs cannot be conducted. Considering the popular use of D-HM for patients with AR,[11] future studies will need investigate the effects of D-HM by conducting well-designed prospective cohort studies.

Conflict of interest

The authors have no conflicts of interests to declare.

Funding

This study was supported by a grant from the Guideline Center for Korean Medicine, National Institute for Korean Medicine Development (HI16C0275).

Ethical statement

The study protocol was exempted from ethical review by the Institutional Review Board of the Korea Institute of Oriental Medicine on January 20, 2022 (IRB No.: I-2201/001-001), and registered in the National Clinical Trial Registry, Clinical Research Information Service (KCT0007242) (available URL: https://trialsearch.who.int/?TrialID=KCT0007242). Written informed consent was obtained from all participants.

Data availability

The datasets generated in the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Mi Ju Son: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Sungha Kim:** Conceptualization, Methodology, Writing – review & editing. **Young-Eun Kim:** Data curation. **Bo-Young Kim:** Data curation. **Chang-Sub Yeum:** Investigation. **Jong Cheol Lee:** Investigation. **Jae Hoon Cha:** Investigation. **Soonsik Kang:** Investigation. **Ching Hao Chang:** Investigation. **Seokho Son:** Investigation.

Acknowledgments

The authors thank all KM doctors and clinics for providing patient data listed below.

- Jeong Sin Choi from KEUM O Korean Medicine Clinic.
- Seongmin Kim from EOGGAEDONGMU Korean Medicine Clinic.
- Jisun Kang from Haneol Korean Medicine Clinic.
- Yoon Suh Choi from I-lean Korean Medicine Clinic.
- Jae Hyung Ahn from Dasun Korean Medicine Clinic.
- Gilhee Yi from Siwon Korean Medicine Clinic.
- Daeyoung Kim from Sunghye Korean Medicine Clinic.
- Woong Ki Min from Jami Korean Medicine Clinic.
- Jeong-ill Roh from Roh Jeong ill Korean Medicine Clinic.
- Seong-an Kang from Kwangjaedang Korean Medicine Clinic.
- Yongkwang Seo from Dreamforest Korean Medicine Clinic.
- Sung Eun Bae from MadiMadi Korean Medicine Clinic.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.100973.

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