Exploring the efficacy and safety of topical Jaungo application in patients with atopic dermatitis: A pilot randomized, double-blind, placebo-controlled study

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ABSTRACT

Background: Atopic dermatitis (AD) is a chronic relapsing eczematous skin disease with an increasing prevalence. In Korea, Jaungo is a traditional medicinal ointment, which is commonly used for treating skin wounds.

Objective: Thus, we aim to explore the basic clinical efficacy and safety data for Jaungo in patients with AD.

Methods: This study was a pilot randomized, double-blind, placebo-controlled, single-center trial with three groups. The participants in treatment group 1 applied Jaungo to the lesion twice a day for 3 weeks. Those in treatment group 2 applied Jaungo and placebo ointments to the lesion once a day for 3 weeks. Those in the placebo group applied placebo ointments to the lesion twice a day for 3 weeks. The Eczema Area and Severity Index and SCORing Atopic Dermatitis scores, transepidermal water loss value, and Dermatology Life Quality Index score were assessed. The outcomes used to evaluate safety were the Draize score, blood test results, and expert opinion.

Results: In total, 28 patients (82.4%) completed the study. During the study, significant decline of EASI scores in treatment group 2 and placebo group was observed (p < 0.05). And there was significant decline of SCORAD scores in treatment group 1 and placebo group (p < 0.05). Patients in all groups showed decreased TEWL and DLQI scores with no significant difference. There was significant decline of IL-17 in all groups (p < 0.05). No serious adverse event was observed.

Conclusion: This is the first study that has explored the potential therapeutic effect of Jaungo as a complementary therapy for AD. However, further large study with adjusting placebo ingredients is needed to confirm the effectiveness of Jaungo in patients with chronic-phase AD.

1. Introduction

Atopic dermatitis (AD) is a chronic disease in which inflammatory and allergic reactions are induced in patients with a genetic predisposition. The worldwide prevalence of this disease is approximately 5–20%, and it is gradually increasing in industrialized countries. AD is accompanied by severe pruritus and symptoms of eczema. In the acute phase, severe pruritus, erythema, papules, and exudation appear prominently and secondary infection is likely to occur. In the chronic phase, symptoms such as lichenification, excoriation, dryness, and hyperpigmentation appear characteristically.

In modern medicine, AD is commonly treated with antihistamines, topical or oral steroids, and immunomodulators. Among them, steroids are recommended as the most effective treatment medication for acute-
phase AD, which can adjust skin inflammation over a wide range. However, in the case of chronic AD, these may cause side effects, such as atrophy of the skin, vasodilation, and bacterial and fungal infections caused by long-term use. Therefore, in the international community, there is an increasing demand for new remedies based on various crude drugs systematically and medically verified for patients with chronic-phase AD.

Jaungo is an external herbal medicine which is derived from Wai-Ke-Zheng-Zong, a classical medical book, with lard added to the ingredient. It is currently composed of two herbs and three carrier oils: Lithospermi radix and Angelica gigantis radix and sesame seed oil, bees wax, and swine oil. Recently, non-clinical studies have shown anti-allergic and anti-inflammatory effects of Jaungo by applying it to AD mouse models for 2 weeks. In Korea, Jaungo has been approved by the Korea Food and Drug Administration (KFDA) and manufactured as a drug for the treatment of xerosis cutis, frostbite, miliaria, anal fissures, and rhus dermatitis since 2013. However, AD is not included in these allowed indications, and there have been only few randomized controlled clinical trials on Jaungo for the treatment of AD.

Thus, based on these points, we designed this randomized, double-blind, placebo-controlled clinical study. The aim of this study was to investigate the efficacy, safety, and dose response of topical Jaungo application in patients with mild-to-moderate AD with excoriation, lichenification, and dryness.

### 2. Methods

#### 2.1. Study design

This randomized, double-blind, placebo-controlled, single-center, phase IIa clinical trial was conducted at Kyung Hee University Korean Medicine Hospital in Seoul, Korea (ClinicalTrials.gov, NCT02900131). This study assessed the safety, efficacy, and dose response of Jaungo for the treatment of mild-to-moderate AD. The study aimed to enroll 34 patients with AD. Participants who met the eligibility criteria were selected and randomly divided into three parallel groups: treatment group 1 (application of Jaungo twice a day for 3 weeks), treatment group 2 (application of Jaungo and placebo ointments once a day for 3 weeks), and placebo group (application of placebo ointments twice a day for 3 weeks). The study flow chart is shown in Fig. 1. The study was conducted in accordance with the Good Clinical Practice guidelines and adhered to the Declaration of Helsinki principles. This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (KHNC-OH-IRB 2013-0014). Written informed consent was obtained from each subject before study enrollment.

#### 2.2. Patients

We enrolled patients (age, 5–65 years) diagnosed with mild-to-moderate AD, mainly focusing on chronic symptoms such as excoriation, lichenification, and dryness. The inclusion criteria comprised the following: (1) diagnosis of AD according to the criteria of Hanifin and Rajka; (2) mild-to-moderate AD symptoms based on the objective SCORing AD (SCORAD) score of ≤ 40 points; and (3) scores of excoriation, lichenification, and dryness in the SCORAD of at least 1 point each or a sum of ≥ 3 points.

The exclusion criteria were as follows: (1) oozing from the lesion, (2) usage of oral steroids, immunosuppressants, and antibiotics within 4 weeks prior to this trial, (3) usage of topical steroids, immunosuppressants, and antibiotics or light therapy within 2 weeks prior to this trial, (4) severe burn or wide wound, (5) allergic reactions to Jaungo or its components, (6) active skin diseases other than AD, (7) renal or liver dysfunction (sCr level of > 2.0 mg/dL; ALT, AST, and ALP levels of ≥ 2.5 × normal limits), (8) other uncontrolled chronic diseases, (9) pregnancy or breastfeeding, and (10) judgment by experts that the potential subject’s participation is inappropriate.

Recruitment was conducted via bulletin board advertisements and the online homepages of Kyung Hee University Korean Medicine Hospital, Kyung Hee University Hospital at Gangdong and Kyung Hee University in Seoul, Korea.

#### 2.3. Randomization and masking

Thirty-four patients were randomly assigned (1:1:1) to treatment

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>n=34</td>
</tr>
<tr>
<td>Allocation</td>
<td>n=38</td>
</tr>
<tr>
<td>Analysis</td>
<td>n=38</td>
</tr>
</tbody>
</table>

**Fig. 1. Study Flow Diagram.**
group 1, treatment group 2, and placebo group. A total of 11 or 12 patients were planned for inclusion in each group using block randomization distribution with a block size of 3 or 6. This was conducted on visit 2 at the clinical trial center. The assigned random number was generated via Django Web Framework (https://www.djangoproject.com), which was developed by an independent expert. Further, the experimental and placebo ointments were prepared in identical containers and labeled with random numbers and the phrases, “for morning use” or “for evening use,” which were used for deciding the experimental or placebo ointments. Each patient received a couple of sets, which consisted of two containers of Jaongo or placebo, one labeled with “for morning use” and the other “for evening use.” The participants, principal investigators, outcomes assessors, statistician, and other staff were blinded to the treatment assignment during the study.

2.4. Procedures

After the enrollment, the participants received Jaongo or placebo ointment used for 3 weeks twice a day. The Jaongo ointment (Hanpoong Pharm and Foods, Co., Ltd., Wanju, Korea) was manufactured in accordance with the Korea Good Manufacturing Practice standards. The placebo ointment was prepared with the same formulation in red color and with a herbal fragrance, similar to that of Jaongo, without the addition of the other active agent. The substances, contents, and preparative methods of the placebo ointment were approved by the KFDA. The participants applied the study ointment to the site designated by the investigator and received instructions for the specific amount of ointment to apply depending on their AD lesions. The amount of ointment was decided on the basis of the range of AD lesions in the individual, as much as 1 finger unit dose based on one palm of the subject. All subjects were instructed to apply the study ointment in a fixed amount at fixed sites twice a day.

The subjects were not permitted to apply topical and oral corticosteroids, immunosuppressants, and antibiotics during the study period. With the exception of antihistamines, all other concomitant drugs and procedures indicated for the treatment of AD were also prohibited. However, after discussion with the investigators, the patients were allowed to self-administer antihistamines orally for controlling pruritus. The patients were also allowed to use emollients, lotions, and ointments that do not contain GCs during the study. All efficacy assessments were conducted on visit 2 (after enrollment) and visit 3 (3 weeks after applying the study drug). The full protocols are provided at Trials.

2.5. Outcomes

The primary efficacy endpoint was the change in the Eczema Area and Severity Index (EASI) score before and 3 weeks after application of the experimental medications. The EASI is a widely used outcome measure, which is considered as an evaluation index in the study of AD; its validity and reliability have been confirmed, since it can evaluate symptoms from each region.11 The secondary efficacy endpoints included: SCORAD score, transepidermal water loss (TEWL) value, Dermatology Life Quality Index (DLQI) score, total IgE level, eosinophil count, and interleukin (IL)-17, IL-22, and interferon (IFN)-γ levels. All these parameters were measured before and 3 weeks after application of the experimental medications to evaluate the change from each baseline. The values of the TEWL were measured in a constant temperature and humidity room (20 ± 2°C, 40–60%), using TM300 (Germany, Courage khazaka electronic GmbH) according to the guidelines.12 We assessed the TEWL values thrice at the most severe lesion site and used the average values.

Prior to the subjects’ registration in the study, blood tests, including those for CBC D/C, AST/ALT, BUN/Cr, and ESR, were conducted, and the vital signs were assessed to evaluate the condition of the subjects. These parameters were also measured 3 weeks after application of the study ointments. Additionally, subjective dermal tolerability and the Draize score were assessed after completion of the study to evaluate the extent of erythema, dryness, and edema of the skin induced by the test drug application at 0 to 4 points. Adverse events were also monitored from baseline to week 3.

2.6. Statistical analyses

The IBM SPSS software 13.0 (IBM Inc., Armonk, NY, USA) was used to manage and analyze the data. All analyses of the study outcomes were performed for two populations: (1) an intention-to-treat population consisting of all randomized participants who had at least one measurable outcome to report following treatment (missing data were replaced with the last observation values) and (2) a per-protocol population including only participants without major protocol deviations. In all tests, a p-value < 0.05 was considered statistically significant. The baseline characteristics of the three groups, including sex, age, duration of AD, body surface area with AD involvement, EASI score, and SCORAD score, were compared using ANOVA (parametric statistics) or Kruskal-Wallis test (nonparametric statistics). We also compared the efficacy of the Jaongo and placebo ointments based on the change in the primary outcome or EASI score from visit 2 to visit 3 (after 3 weeks). The mean differences in the EASI score from baseline to the end of treatment were compared using ANOVA or Kruskal-Wallis test among the three groups. A paired t-test (parametric statistics) or Wilcoxon signed rank test (nonparametric statistics) was used to compare the mean change within the groups. The secondary outcomes, which included the SCORAD score, TEWL value, DLQI score, total IgE level, eosinophil count, and IL-17, IL-22, and IFN-γ levels, were also utilized to compare the efficacy of the Jaongo and placebo ointments as in the primary outcome/EASI score. To evaluate safety, the Draize score and adverse events were presented in a descriptive manner.

2.7. Role of the funding source

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health and Welfare through the Korea Health Industry Development Institute (HI12C1889 and HI13C0530). The funder had no role in the study design, data collection, analysis and interpretation of data, writing of the report, or the decision to submit the manuscript for publication.

3. Results

3.1. Patients

From September 19, 2016 to March 16, 2017, a total of 38 patients were screened; four patients were ineligible for the study; thus, 34 patients with AD were included in this study. Six patients discontinued the use of the ointments for the following reasons: AE (n = 3), lack of efficacy (n = 1), and failure to comply (n = 2); a total of 28 patients completed the study (Fig. 1). The characteristics of the study population are summarized in Table 1. No statistically significant differences were noted among the three groups based on age, sex, body mass index, disease duration, body surface area with AD involvement, EASI score, and total SCORAD score.

3.2. Efficacy evaluation

3.2.1. Clinical effects

The mean change in the EASI score decreased in all groups; however, significant changes only occurred in treatment group 2 (p = 0.018) and placebo group (p = 0.028) from baseline. There was no significant difference among the three groups (Table 2, Fig. 2).

We also analyzed the changes in the EASI subsection scores:
Table 1
Demographic and clinical characteristics of the participants at baseline.

<table>
<thead>
<tr>
<th></th>
<th>Treatment group 1 (n = 11)</th>
<th>Treatment group 2 (n = 11)</th>
<th>Placebo group (n = 12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.91 ± 53.49</td>
<td>20.82 ± 64.71</td>
<td>21.67 ± 241.15</td>
<td>0.886</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 3 (27.27%)</td>
<td>3 (27.27%)</td>
<td>4 (33.33%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body mass index</td>
<td>21.70 ± 20.02</td>
<td>22.68 ± 17.35</td>
<td>0.711</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>16.00 ± 62.20</td>
<td>11.70 ± 33.57</td>
<td>14.67 ± 91.70</td>
<td>0.287</td>
</tr>
<tr>
<td>Body surface area with atopic dermatitis involvement</td>
<td>11.55 ± 58.47</td>
<td>10.10 ± 79.38</td>
<td>7.92 ± 34.492</td>
<td>0.572</td>
</tr>
<tr>
<td>EASI score</td>
<td>6.68 ± 31.18</td>
<td>5.00 ± 17.97</td>
<td>4.68 ± 15.05</td>
<td>0.872</td>
</tr>
<tr>
<td>Total SCORAD score</td>
<td>42.56 ± 98.27</td>
<td>36.87 ± 77.72</td>
<td>39.75 ± 136.27</td>
<td>0.537</td>
</tr>
</tbody>
</table>

Values are expressed as numbers (percentages) or means ± standard deviations. EASI: Eczema Area and Severity Index; ITT: intention-to-treat population; PP: per-protocol population.

3.2.4. Effects on the DLQI score
The mean change in the DLQI score decreased in all groups; however, a significant change was only observed in treatment group 2 (p = 0.042) (Fig. 3).

3.3. Use of other medications
During the clinical trial, only one subject took other drugs: antihistamine, which was taken every day twice for 3 days for itching of the skin; this subject belonged to the control group. No subject used topical GCs, immunosuppressants, antibiotics, or phototherapy.

3.4. Safety and tolerability
A total of four subjects (14.3%) had adverse events after application of the experimental medications. The adverse events were pruritus (n = 4) and wheal formation (n = 1). These occurred in one case in treatment group 1, in one case in treatment group 2, and in two cases in the placebo group. Of these, only two cases were directly associated with the experimental medications and these were a mild level of adverse events of which symptoms were alleviated after discontinuation of the medications.

All subjects had 0 points in the subjective dermal tolerability and the Draize score assessment, except for one subject in treatment group 2 with a minimal reaction from the medications: erythema/dryness, 1 point and edema, 1 point. He dropped out from this study because of poor compliance.

There were no significant changes in the blood test results: CBC D/C, AST/ALT, BUN/Cr, and ESR. One subject had an AST level of 51 U/L and an ALT level of 85 U/L before application of the medication; however, the levels returned to normal levels after application.

4. Discussion
Jaungo is an oriental medicinal ointment that has been reported to have anti-inflammatory, analgesic, hemostasis, and disinfection effects by many experimental studies. Previous studies have demonstrated the anti-inflammatory and anti-allergic activities of Jaungo in in vitro and in vivo AD models. A recent RCT has reported that topical application of Jaungo reduces the degree of skin tissue damage caused by radiation therapy with no adverse effects. In Korea, Jaungo is the only herbal topical medication approved by the KFDA, and it is frequently used for the treatment of pruritus, lichenification, and papules of chronic AD in clinical practice.

In our study, both the excoriation and lichenification scores in the EASI decreased significantly in treatment group 1. However, only the lichenification score in the EASI decreased in treatment group 2 and placebo group. These results indicate that Jaungo had the effect of wound healing corresponding with the previous findings; Ferulic acid,
Fig. 2. The Changes of EASI and SCORAD scores.
(A) Changes in the EASI score; (B) Changes in the EASI excoriation score;
(C) Changes in the EASI lichenification score; (D) Changes in the SCORAD score
EASI: Eczema Area and Severity Index; SCORAD: SCORing Atopic Dermatitis
*p < 0.05 vs. baseline (week 0), analyzed using the paired t-test or Wilcoxon signed rank test.

Table 3
Changes in the SCORAD score.

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Treatment group 1</th>
<th>Treatment group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT</strong> Baseline</td>
<td>39.92 ± 11.53</td>
<td>42.26 ± 9.91</td>
<td>37.40 ± 8.55</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>30.10 ± 13.12</td>
<td>30.32 ± 15.52</td>
<td>29.74 ± 12.84</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−9.82 ± 8.55</td>
<td>−11.05 ± 11.90</td>
<td>−7.66 ± 11.62</td>
<td>0.691</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002*</td>
<td>0.008*</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td><strong>PP</strong> Baseline</td>
<td>40.20 ± 12.71</td>
<td>41.39 ± 9.99</td>
<td>34.84 ± 8.57</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−11.78 ± 7.98</td>
<td>−13.14 ± 11.83</td>
<td>−10.54 ± 12.59</td>
<td>0.974</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.008</td>
<td>0.069</td>
<td></td>
</tr>
</tbody>
</table>

SCORAD: SCORing Atopic Dermatitis; ITT: intention-to-treat population; PP: per-protocol population.
Data are presented as means ± standard deviations.
p < 0.05: group differences, analyzed using the Kruskal-Wallis test.
*p < 0.05 vs. baseline (week 0), analyzed using the paired t-test or Wilcoxon signed rank test.
the primary bioactive constituent of *Angelica sinensis*, has been shown to promote wound healing in a diabetic rat model and Deoxyshikonin, the constituent of *Lithospermum radix*, to heal skin wounds in damaged tissues, such as cuts, abrasions, frostbite, and burns.17-19

In addition, to provide laboratory evidence of the efficacy of Jaungo, we determined the serum IgE level, eosinophil count, and cytokine (IFN-γ, IL-17, and IL-22) level, which were previously shown to be correlated with the chronic phase of AD. The IL-17 levels significantly decreased in all groups. This significant change suggests that sesame oil, lard, and swine oil, which were present in all of the experimental medications, may also be effective in diseases involving hyperkeratosis, such as psoriasis, among chronic skin diseases. IL-17, a cytokine secreted by TH17, has been shown to promote the Th2 immune type in chronic inflammatory diseases, such as AD, psoriasis, and autoimmune diseases, thereby contributing to the chronicity of the inflammatory process.23-25 It has been also reported that IL-17 is critical for the pathogenesis of psoriasis and acts on keratinocytes to stimulate the production of β-defensins; antimicrobial peptides; and chemokines, such as IL-8, CCL20, and CCL2.21

We also analyzed the change in the dryness score, including the SCORAD score (eTable 2). The mean change in the dryness score significantly improved in all groups. However, in the analysis of the TEWL values, there was no significant difference among all groups. These results indicate that the moisturizing effect of the Jaungo and placebo ointments may have been caused by the stimulating tactile receptors when applying topical agents, affecting the reactivity of the autonomic nervous system and improving blood circulation,26 rather than by the restoration of the skin barrier function.

On the basis of the above-mentioned results, Jaungo is considered to be effective for the treatment of AD, especially for chronic phase symptoms such as excoriation, lichenification, and dryness. However, there was no significant difference in the three groups, and no drug dose response, which was another objective of our study, was observed because the placebo ointment had an unexpected effect on AD.

Our placebo ointment, which did not include *Lithospermum radix* and *Angelica gigas radix*, was mainly composed of sesame seed oil, bees wax, and swine oil, which have been known for their following effects on the skin. First, sesame seed oil has antibacterial, anti-inflammatory, antioxidant, regeneration-promoting, and moisturizing effects.23,24 Second, bees wax, which is a wax from honeycombs, contains vitamin A that softens skin and is effective in conditioning dry skin. Recently, bees wax is also used for infectious skin diseases owing to its antibacterial and anti-inflammatory effects.25 Third, swine oil is used to moisturize the skin when it is sore, itching, or tearing in Donguibogam: Principles and Practice of Eastern Medicine.

Despite their above-mentioned effects, we selected these oils for the placebo after consultation with theKFDA because of the following reasons: (1) no study has applied a topical herb-based placebo yet and (2) the study subjects could have used commercially available Jaungo. Thus, we had to manufacture the placebo medication to be as similar to Jaungo as possible.

Another limitation of this study was that it was a pilot study conducted in a single center; thus, the number of subjects in each group was small, which could potentially influence the generalizability of the study results. Furthermore, our study was conducted from September 19, 2016 to March 16, 2017; thus, other seasonal conditions might have affected the results.

Nevertheless, to our knowledge, this is the first pilot RCT study to explore the efficacy and safety of the herbal topical agent Jaungo among patients with chronic-stage AD with mild-to-moderate symptoms. Moreover, TEWL measurement and blood sampling of valid indicators were performed to establish a quantitative evaluation index of the study results in addition to subjective assessments of the changes in AD symptoms using EASI, SCORAD, and DLQI. Further, on the basis of the results of our study, it was confirmed that aggressive treatment with Jaungo alone without modern medicine, such as topical and oral steroids, immunosuppressants, and antibiotics, improved the symptoms of AD.

In conclusion, our findings suggest that Jaungo and its three carrier oils, i.e., sesame seed oil, bees wax, and swine oil, may have the potential therapeutic effect in patients with chronic-phase AD, especially on their dry skin. Moreover, Jaungo had an effect of wound healing, which was distinctive compared with that of the placebo medication.

Further investigations should be conducted in multiple centers to investigate the dose response effects of Jaungo in patients with chronic-phase AD by improving and adjusting placebo ingredients.

**Conflict of interest**

The authors state no conflict of interest.

**Acknowledgments**

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