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Original Article

Effects of herbal medicines (*Eunkyosan/Yin qiao san* and *Samsoeum/Shen su yin*) for treating the common cold: A randomized, placebo-controlled, multicenter clinical trial

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ABSTRACT

Background: *Eunkyosan* (EKS) and *Samsoeum* (SSE), which are called *Yin qiao san* and *Shen su yin* in Chinese, are commonly used herbal medicines for the common cold in East Asian countries. This study aimed to evaluate the effectiveness and safety of EKS and SSE for treating the common cold.

Methods: A randomized, patient-assessor-blind, placebo-controlled, parallel, and multicenter clinical trial was conducted. Adult participants who had one or more cold within 48 h before screening, were randomly allocated to EKS, SSE, or placebo groups. The recruitment goal was planned to be 375 participants. They took an EKS, SSE, or placebo, thrice daily for up to 8 days. The primary outcome was the change in the total score of the Wisconsin Upper Respiratory Symptom Scale-21-Korean version (WURSS-21-K) on day 6 compared to the baseline. The secondary outcomes included visual analog scale (VAS) scores and the duration of symptoms was assessed throughout the trial.

Results: A total of 128 participants were enrolled and 44, 42, and 42 were allocated to the EKS, SSE, and placebo groups, respectively. This study was prematurely terminated due to the COVID-19 pandemic, and we were unable to recruit all the planned participants (n = 375). EKS showed significant clinical effectiveness over the placebo group in the treatment of the common cold, as assessed by the total, symptom, and quality of life scores of WURSS-21-K and VAS, whereas SSE showed significant improvement over the placebo group in terms of WURSS-21-K symptom score. No severe adverse events were reported.

Conclusions: Although EKS and SSE demonstrated statistically significant clinical effectiveness and safety in patients with the common cold, we failed to recruit our pre-planned number of participants. Future definitive full-scale studies are needed to confirm these results.

Trial registration: ClinicalTrials. gov, registration number: NCT04073511. Registered on 29 August 2019.

1. Introduction

The common cold is a syndrome defined as a mild disease of the upper respiratory tract involving symptoms such as cough, sputum, sneezes, nasal congestion, and throat pain.[1] It is a self-limiting disease that can be cured naturally; however, is also the most frequently contracted disease that places a heavy burden on society in terms of economic loss and personal pain. Management of respiratory diseases is considered ever more important during this era of the coronavirus disease (COVID-19) crisis.

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Eunkyosan (EKS), which is called *Yin qiao san* in Chinese, is a Lonicera and Forsythia herbal formula. It is a prescription recorded in *Onbyeongjobyeon* (*Wen Bing Tiao Bian* in Chinese; also known as *Systematized Identification of Warm Pathogen Diseases*) by Wu Ju-Tong and is used for "wind-heat cold" with symptoms of chills, fever without sweating, head and throat pain, and cough. EKS is the most popular Traditional Chinese Medicine prescription for patients with upper respiratory tract infections/common colds in Taiwan[2] and clinical studies on the effectiveness of EKS in the common cold have been performed in other countries.[3–7]

Samsoeum (SSE), which is called *Shen su yin* in Chinese, is a prescription recorded in *Donguibogam* (*Principles and Practices of Eastern Medicine*) by Heo Jun, and is used to treat symptoms of headache, fever, and cough from "wind-cold".[8] SSE is a prescription of Korean Medicine for the common cold covered under the national insurance system. The number of patients visiting Korean Medicine clinics with the common cold (Korean Standard Classification of Diseases: J00, Acute nasopharyngitis [common cold]) between the years 2010 to 2016 was 350,000 to 450,000, and approximately 22~27 % of these patients were given prescriptions for SSE.[9] This confirmed that SSE is a treatment of high clinical utility.

EKS is used quite frequently for the common cold in Korea as a non-reimbursed prescription and SSE is also actively prescribed for the common cold as a reimbursed prescription. However, no clinical trials have investigated the effectiveness and safety of both prescriptions for the common cold in Korea.

In 1999, Barrett conducted a randomized, placebo-controlled study on the upper respiratory tract infection[10] and felt the need for an assessment tool that included the quality of life factor. He developed and validated a new assessment tool composed of a total of 44 questions, the Wisconsin Upper Respiratory Symptom Scale (WURSS),[11] by the year 2000 to overcome the limitations of the previous assessment tool for common cold treatment. Subsequently, 21 questions of high importance were selected to develop and validate a shorter version of WURSS, a WURSS-21.[12] A Korean version[13] of the WURSS-21 (WURSS-21-K) is available, whose reliability and validity have been established, and which this study used to assess the efficacy of the treatments.

Herein, we conducted a multicenter clinical trial to investigate the therapeutic efficacy using the WURSS-21-K and the safety of EKS and SSE in common cold patients.

2. Methods

2.1. Objective

This study aimed to assess the effectiveness and safety of EKS and SSE for the common cold in comparison to those of placebo for 8 days in patients diagnosed with acute nasopharyngitis (common cold).

2.2. Registration

The study was registered on ClinicalTrials.gov (Registration number: NCT 04073511) on August 29, 2019. The protocol was published in advance.[14]

2.3. Design and procedures

The study was a randomized, patient-assessor-blind, controlled, parallel, and multicenter trial.

The study participants were recruited from the following four sites: the Pusan National University Korean Medicine Hospital, Kyung Hee University Korean Medicine, Daejeon University Korean Medicine Hospital, and Semyung University Korean Medicine Hospital. The participants signed the consent form after being informed about the research and went through electrocardiography, laboratory test, and screening for common cold-like illnesses before being enrolled in the trial.

The selected participants were randomized to either the EKS, SSE, or placebo group. Each group was given the drug three times per day as long as the symptoms persisted for up to a maximum of 8 days. Symptoms were measured after 3 (phone call), 6 (phone call), and 8 days (visit) from the baseline. WURSS-21-K surveys and visual analog scale (VAS) associated with common cold symptoms were collected from the participants through diaries.

Adverse events were assessed after 3 (phone call), 6 (phone call), 8 (visit), and 15 days (phone call) from the baseline.

2.4. Participants

2.4.1. Inclusion criteria

1) Men and women aged between 19 and 60 years on the screening date.
2) Occurrence of cold symptoms within 48 h before screening.
3) Those who had symptoms of runny nose and sore throat and one or more additional related symptoms (nasal congestion, sneezing, cough, sore throat, headache, chest tightness, and fatigue).
4) Those who voluntarily decided to participate after hearing a detailed explanation of this clinical trial and fully understanding it, and giving written informed consent to abide by the precautions.
5) Those who could be followed up during the clinical trial period.
6) Those who were not included in the exclusion criteria.

2.4.2. Exclusion criteria

1) Those with sinusitis (when the maxillary and frontal sinuses are opaque during examination through transillumination), allergic rhinitis, pneumonia, influenza (when coughing or sore throat with a sudden fever above 38 °C), bronchitis, otitis media, tonsillitis (paranasal sinus [PNS] view, chest radiographic test if an accurate test is needed).
2) Those who have a chronic respiratory disease (chronic obstructive pulmonary disease, interstitial lung disease) or asthma.
3) Those who have taken or should take or are taking antibiotics, antivirals, steroids, nasal decongestants, antihistamines, or other medications expected to alleviate cold symptoms, or those who have taken food that is expected to relieve cold symptoms within 1 week of the start of the study.
4) Those who are undergoing treatment for liver cancer or cirrhosis, chronic renal failure, and congestive heart failure.
5) Those who have systemic diseases or autoimmune diseases although they do not affect cold symptoms.
6) Those who have severe mental illnesses such as depression or anxiety disorders, or those who are currently taking psychoneurological drugs such as antidepressants.
7) Drug or alcohol addicts.
8) Those with alanine transaminase (ALT) or aspartate transaminase (AST) levels exceeding three times the upper limit of normal of the research institution.
9) Those with creatinine levels exceeding twice the upper limit of normal of the research institution.
10) Weak person (less than body mass index [BMI] of 18.5, clinically judged by a Korean medical doctor through physical examination).
11) Those deemed inappropriate to take the investigational drug due to a weak stomach (clinically determined by a Korean medical doctor through physical examination).
12) Those with high blood pressure (at screening, systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥ 100 mg on vital signs measured in a sitting position after resting for 5 min or more) or elderly.
13) Those with a cardiac or renal disorder (clinically determined by a Korean medical doctor through physical examination, electrocardiogram [ECG], and serum biochemistry).
14) Those with histories of hives, rashes, or itching while taking medicine.

15) Those who had participated in another clinical trial within 1 month before the start of this trial (30 days before the screening visit) or plan to participate in other clinical trials during the trial.
16) Pregnant women or women who might be pregnant.
17) Those who did not agree to contraception in the case of women of childbearing age.
18) Those who were being held in group facilities, such as social welfare facilities.
19) Those who were deemed inappropriate to participate in the trial by the investigator's judgment.
20) Those with hypersensitivity to the investigational drug (main ingredient and its components).
21) Those with genetic problems, such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.
22) Those with hypokalemia.
23) Those who had difficulty in daily life due to sweats (excessive sweating, general weakness).
24) Those who had difficulty in daily life due to anorexia, nausea, or vomiting.
25) Those who were suspected of having pneumonia and were judged to need antibiotic treatment or those who were being treated by a doctor (those receiving other medications).

2.5. Randomization, allocation, and blinding

The randomization table was generated by a statistician using SAS 9.0 (SAS Institute Inc). The three groups were stratified only by the institutions, and 125 participants were randomized per group at a ratio of 1:1:1. The generated randomization table was delivered to the person in charge at the sponsor, Hanpoong Pharm & Foods Co., Ltd, who packaged the drugs in the order of randomization. The packaged drugs were sent directly to the sub-investigators (clinical trial pharmacists) at each institution. Sub-investigators stored the received drugs at the clinical pharmacy before providing them to each participant based on the respective randomization numbers given. The already assigned randomization number could not be reassigned even after the given participant dropped out in the middle of the trial.

To maintain the double blindness of patients and assessors, the investigational medicinal products were packaged in the same packaging.

To confirm the maintenance of blinding, a blinding test was performed by asking the participants to select the drug they thought they were administered (EKS, SSE, placebo, or do not know) at the third visit.

2.6. Intervention

The investigational medicinal products used during the clinical study were packaged and supplied by Hanpoong Pharm & Foods Co., Ltd. EKS and SSE are both already on the market and have been manufactured following the Korean Ministry of Food and Drug Safety (K-MFDS) guidelines. The placebo drugs were also manufactured by the same pharmaceutical company with the best effort to resemble the taste, smell, and appearance of the Korean Medicine granules.

In this trial, 24 sachets of the drugs were packaged as 8 days doses.

The amount of each drug administered to the participants followed the 1-day dose defined in the approved label (EKS: 1-day dose; three times, each 2.3 g per sachet, SSE: 1-day dose; three times, each 3.37 g per sachet, placebo: 1-day dose; three times, each 3.0 g per sachet).

The composition of drugs is presented in Table 1.

2.7. Outcome

2.7.1. Primary outcome

The primary outcome was the change in the total WURSS-21-K scores (symptoms score + quality of life score) at day 6 compared to the baseline scores. WURSS-21-K, the Korean version of WURSS-21, included 10 questions on disease symptoms, nine on functional quality of life, one on the overall severity of the disease, and one on overall changes in condition. It was recorded on a seven-point Likert scale (score of 0–7). The final question asked for the overall change in the condition and the possible responses include "Very much better-Somewhat better-A little better-Same-A little worse-Somewhat worse-Very much worse." Since the final question was unrelated to the rest of the questions, the total score was calculated as the sum of the first 20 questions. The total score was used to evaluate the severity of the symptoms and 140 points indicated the highest severity. When necessary, the sub-total scores for symptom-associated items and quality-of-life-associated items were used.

Table 1
Composition of investigational medicinal products.

	Appearances	Ingredients	Amount (g)
Eunkyosan	Brown colored granule	Lonicerae Flos	0.410
		Forsythiae Fructus	0.410
		Platycodonis Radix	0.240
		Menthae Herba	0.240
		Glycyrrhizae Radix et Rhizoma	0.240
		Glycine Semen Preparatum	0.200
		Arctii Semen	0.200
		Lophatheri Herba	0.160
		Schizonepetae Spica	0.160
		Antelopis Cornu	0.010
Samsoeum	Brown colored powder	Puerariae Radix	0.560
		Platycodonis Radix	0.400
		Angelicae Decursivae Radix	0.360
		Zizyphi Fructus	0.340
		Menthae Herba	0.310
		Ginseng Radix	0.300
		Citri Unshius Pericarpium	0.300
		Aurantii Fructus Immaturus	0.290
		Glycyrrhizae Radix et Rhizoma	0.250
		Perillae Folium	0.200
		Poria Sclorotium	0.030
		Zingiberis Rhizoma Crudus	0.030
Placebo	Brown colored granule	Corn starch	1.500
		Lactose carb	1.476
		Caramel pigment	0.014
		Ginseng-flavored powder	0.010

The questions were provided to the participants in a form of a daily diary. The efficacy was assessed by comparing the baseline score before intervention and the last obtained score after intervention in each group. The average score on the last day of measurement for each group was also compared to evaluate the effectiveness.

2.7.2. Secondary outcomes

The changes in the symptom and quality of life scores of the WURSS-21-K on day 6 from baseline were secondary outcomes. The duration of the cold symptoms and change in the VAS at day 6 from baseline were also evaluated. The duration of symptoms was determined by checking whether symptoms remained from the first onset date through participant reports of diary, phone calls, and visits. The VAS used was the EuroQol-visual analog scales (EQ-VAS), which indicates how participants rate their overall health condition on a scale from 100 (best health imaginable) to 0 (worst health imaginable).

2.8. Safety assessments

The adverse events and vital signs of the participants were assessed for safety. Moreover, laboratory tests were also performed. The laboratory test items were as follows: Glucose, White Blood Cells, Red Blood Cells, Hemoglobin (Hb), Hematocrit (Hct), Blood Urea Nitrogen (BUN), Creatinine, AST, ALT, Sodium, Potassium, and Chloride. Urine Human Chorionic Gonadotropin (hCG) test was performed when there was uncertainty about pregnancy.

2.9. Statistical analysis

All statistical analyses were conducted using SAS 9.0 (SAS Institute Inc) and statistical significance was defined as a p-value< 0.05. The intention-to-treat (ITT) analysis included all participants with at least one primary or secondary effectiveness data endpoint obtained after the first visit. The last observation carried forward analysis method was used for the ITT group analysis. Additionally, a Per-Protocol (PP) analysis was performed for participants that did not consecutively miss 3 days of investigational drugs and had taken 80 % or more of the given drugs.

As for the baseline verification among groups, the continuous variable was analyzed using the analysis of variance (ANOVA), and categorical variable using Chi-square or Fisher's exact test. The continuous variables were shown in average and standard deviation and categorical variables were presented as frequency and percentage.

The analysis of covariance (ANCOVA) with baseline as covariance was performed to assess the effectiveness, and post-hoc analysis was performed using the Bonferroni test. A paired-t-test was used to verify differences from the baseline at each time point for each group. To verify the duration of cold symptoms among the three groups, ANOVA was performed, and post-hoc analysis was performed using the Duncan test.

The validity of the blinding test was assessed using the Chi-square test.

2.10. Sample size

We implemented a superiority trial to determine the differences in changes in the WURSS-21-K score measured at 6 days compared to those at the baseline in the three groups (EKS, SSE, Placebo) (two-tailed test). Regarding the other clinical trials that used the WURSS-21-K to evaluate the effectiveness of Korean medicine,[15] the clinical difference between the experimental and placebo groups was set to 10 and the standard deviation to 30. The null hypothesis was as follows:

Null hypothesis: There was no difference among the three groups for the changes in the WURSS-21-K score measured at 6 days compared to that at the baseline.

The sample size in each group was determined following the equation:

$$n = \frac{2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \sigma^2}{\left(\mu_t - \mu_c\right)^2} \approx 112$$

Considering the 10 % drop-out rate, a sample size of a total of 375 participants was required, 125 in each group.

3. Results

3.1. Participants' flow

Due to the COVID-19 outbreak, the study was terminated prematurely. A total of 128 participants were enrolled between October 11, 2019, and February 19, 2021. A total of 44, 42, and 42 participants were allocated to the EKS, SSE, and placebo groups, respectively. In the EKS group, six participants dropped out owing to inadequate medication compliance, taking prohibited medicines, loss of test drugs, violation of visit day, or withdrawal of consent. In the SSE group, six participants dropped out owing to inadequate medication compliance, taking prohibited medicines, loss of test drug, violation of visit day, or violation of inclusion criteria. In the placebo group, four participants dropped out due to inadequate medication compliance, taking prohibited medicines, or loss of test drug (Fig. 1).

3.2. Baseline characteristics

There were no significant differences between the three groups (EKS, SSE, placebo) in age, sex, weight, height, BMI, the ratio of smoking and drinking alcohol, and baseline WURSS-21-K scores (Table 2).

3.3. Primary outcome

The total WURSS-21-K scores in the EKS group decreased significantly more compared with those of the placebo group; The adjusted mean difference with 95 % confidence interval (CI) between EKS and placebo group was −14.91 (−26.48, −3.33). However, the adjusted mean difference with 95 % CI of WURSS-21-K between the SSE and the placebo group was −11.03 (−22.71, 0.64), which did not show a statistical significance (Table 3).

3.4. Secondary outcomes

The EKS and SSE groups showed a significant decrease in the symptom score of the WURSS-21-K on the sixth day compared with that of the placebo group (Table 3). The adjusted mean differences with 95 % CI of WURSS-21-K symptom score from the placebo group were –8.10 (−14.26, −1.94) and −6.72 (−12.93, −0.51) for EKS and SSE respectively.

The mean change in the quality of life score of the WURSS-21-K in the EKS group showed a significant decrease compared with that of the placebo group; however, the score in the SSE group did not significantly decrease (Table 3). The adjusted mean differences with 95 % CI of WURSS-21-K life score from the placebo group were –7.14 (−12.92, −1.37) and −4.69 (−10.51, 1.13) for EKS and SSE, respectively.

The mean change in VAS score in the EKS group increased significantly more compared with that of the placebo group; however, the score in the SSE group did not significantly increase (Table 3). The adjusted mean differences with 95 % CI of VAS score from the placebo group were 9.88 (1.83, 17.93) and 7.83 (−0.30, 15.96) for the EKS and SSE group, respectively.

The duration of the cold symptoms was 6.46±1.74 days, 7.67±2.06 days, and 7.05±2.15 days in the EKS, SSE, and placebo groups, respectively, and there was no significant difference between the groups (p = 0.115) (Table 4).

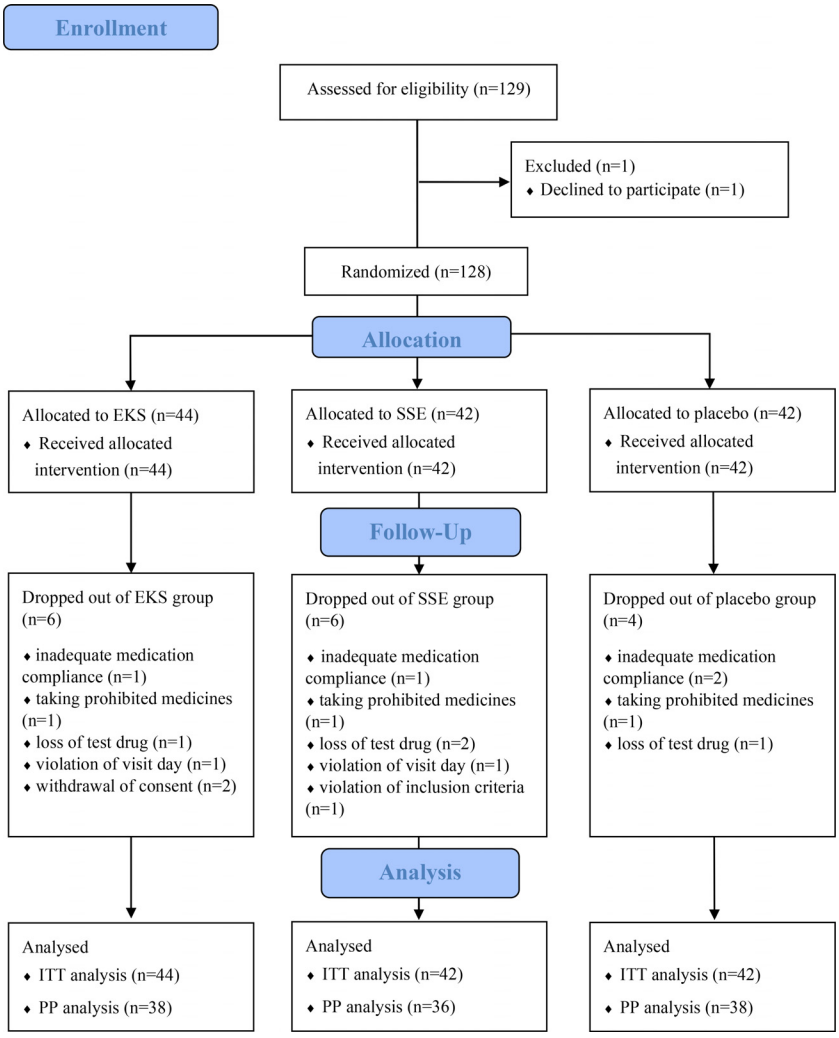

Fig. 1. CONSORT flow diagram of the study. EKS, *Eunkyosan*; SSE, *Samsoeum*; ITT, Intention-To-Treat; PP, Per-Protocol.

3.5. Safety assessments

There were no severe adverse events. No significant abnormalities were observed in the vital signs and laboratory test. In addition, there were no significant differences between groups in laboratory tests (Table 5).

3.6. Blinding test

As a result of the questionnaire, 14 out of 41 participants (34.1 %) in the EKS group, seven out of 41 participants (17.1 %) in the SSE group, and 15 out of 41 participants (36.6 %) in the placebo group matched the expected and administered drug (Table 6).

In the EKS group, five participants (12.2 %) predicted that the drug they were taking was SSE, two (4.9 %) predicted that it was a placebo, and 20 (48.8 %) selected "do not know." In the SSE group, seven participants (17.1 %) predicted that the drug they were taking was EKS, three (7.3 %) predicted that it was a placebo, and 24 (58.5 %) selected "do not know." In the placebo group, four participants (9.8 %) predicted that the drug they were taking was EKS, four (9.8 %) predicted that it was SSE, and 18 (43.9 %) selected "do not know."

4. Discussion

This study aimed to recruit 375 participants to assess the effectiveness of both EKS and SSE in a single trial. However, as it became difficult for common cold patients to access medical institutions owing to the COVID-19 outbreak, the study was terminated prematurely after recruiting 128 participants. Nevertheless, significant results were obtained for EKS and SSE, allowing for the verification of their clinical effectiveness and safety.

The changes in the total score of WURSS-21-K, the primary outcome of this study, showed significant improvement in the common cold after EKS administration over placebo treatment. In addition, the changes in the symptom and quality of life scores of the WURSS-21-K and those in the VAS indicated significant improvements in the EKS group compared with those of the placebo group.

In the SSE group, although the changes in the symptom scores of the WURSS-21-K improved, those in the total and quality of life scores of the WURSS-21-K were insignificant compared with those in the placebo group. In addition, the changes in the VAS did not show significant improvement in the SSE group over the placebo group.

The duration of the cold symptoms did not differ significantly between the treatment (EKS or SSE) and placebo groups. Since the common cold is a self-limiting disease, the drugs do not seem to have any effect on shortening its duration.

During the study, no severe adverse events were reported. Moreover, there were no significant abnormalities in the laboratory test for safety evaluation. There was no difference in the laboratory test among the treatment (EKS or SSE) and placebo groups. There was a statistically significant increase in BUN after drug administration in the EKS group ($p = 0.035$). However, this change was within the normal range.

Because the drugs used in this study have different doses, there may be a bias for blinding. To compensate for this, we conducted a ques-

Table 2
Characteristics of participants at the baseline.

Characteristics	EKS (n = 44)	SSE (n = 42)	Placebo (n = 42)	p-value
Age, years	31.09±7.66	32.33±10.48	33.14±9.21	0.580[a]
Sex				0.813[b]
Male, no. (%)	8 (18.2)	9 (21.4)	10 (23.8)	
Female, no. (%)	36 (81.8)	33 (78.6)	32 (76.2)	
Weight, kg	63.83±14.61	60.16±10.50	66.15±13.58	0.109[a]
Height, cm	164.462±7.54	164.00±7.37	164.60±7.60	0.928[a]
BMI, kg/m^2	23.49±4.47	22.31±4.47	24.26±3.61	0.065[a]
Smoking, no. (%)	0 (0.0)	0 (0.0)	1 (2.4)	0.656[c]
Drinking alcohol, no.(%)	8 (18.2)	11 (26.2)	15 (35.7)	0.184[b]
WURSS-21-K				
Runny nose	4.45±1.68	3.79±2.01	4.38±1.55	0.160[a]
Plugged nose	4.57±1.77	3.50±2.11	4.45±2.09	0.028[a]
Sneezing	3.45±2.08	3.10±1.92	3.69±2.18	0.415[a]
Sore throat	4.27±1.90	3.81±1.64	4.19±1.99	0.470[a]
Scratchy throat	4.02±1.86	3.43±1.77	4.00±2.34	0.305[a]
Cough	3.55±2.05	3.05±2.02	3.12±2.28	0.499[a]
Hoarseness	2.64±2.21	2.55±1.98	2.67±2.19	0.965[a]
Head congestion	4.30±2.11	4.05±2.06	4.48±2.09	0.640[a]
Chest congestion	3.00±2.19	2.86±2.15	3.31±2.20	0.624[a]
Felling tired	4.73±2.02	4.90±1.69	5.14±1.87	0.587[a]
Total score	56.28±30.47	54.74±30.98	66.48±31.64	0.173[a]
Symptom score	30.63±14.85	29.64±15.40	34.57±16.09	0.305[a]
QoL score	25.65±17.53	25.10±16.71	31.90±16.98	0.131[a]
VAS	55.14±18.28	57.98±17.82	53.81±19.59	0.577[a]

Values are presented as means±standard variation or number (%). BMI, body mass index; WURSS-21-K, Wisconsin Upper Respiratory Symptom Scale-21-Korean version; QoL, Quality of life; EKS, *Eunkyosan*; SSE, *Samsoeum*.
[a] p-values are derived from ANOVA.
[b] p-values are derived from the Chi-square test.
[c] p-values are derived from Fisher's exact test.

Table 3
Changes in outcome measures.

Variable	EKS (n = 44)	SSE (n = 42)	Placebo (n = 42)	p-value[b]
WURSS-21-K Total Score				
6 days later	13.86±22.43	17.05±24.29	33.33±30.02	
p-value[a]	<0.001*	<0.001*	<0.001*	
Adjusted mean change	−44.00 (−50.58, −37.42)[c]	−40.12 (−46.80, −33.45)[c,d]	−29.09 (−35.81, −22.38)[d]	0.007†
WURSS-21-K Symptom Score				
6 days later	8.23±11.94	9.19±11.79	18.02±15.92	
p-value[a]	<0.001*	<0.001*	<0.001*	
Adjusted mean change	−22.95 (−26.47, −19.44)[c]	−21.57 (−25.14, −18.01)[c]	−14.85 (−18.43, −11.28)[d]	0.004†
WURSS-21-K QoL Score				
6 days later	5.63±10.87	7.86±12.83	15.31±14.56	
p-value[a]	<0.001*	<0.001*	<0.001*	
Adjusted mean change	−21.14 (−24.42, −17.86)[c]	−18.69 (−22.01, −15.37)[c,d]	−14.00 (−17.35, −10.65)[d]	0.012†
VAS				
6 days later	78.07±16.60	77.43±16.10	67.52±20.46	
p-value[a]	<0.001*	<0.001*	<0.001*	
Adjusted mean change	22.68 (18.07, 27.29)[c]	20.63 (15.94, 25.31)[c,d]	12.80 (8.12, 17.47)[d]	0.009†

Values are presented as means±standard variation or mean (95 % CI). WURSS-21-K, Wisconsin Upper Respiratory Symptom Scale-21-Korean version; QoL, Quality of life; VAS, Visual Analog Scale; EKS, *Eunkyosan*; SSE, *Samsoeum*.
[a]p-value is derived from the paired t-test to compare within each group (*$p < 0.05$).
[b]p-value is derived from ANCOVA to compare mean change among the groups adjusted for baseline score (post-hoc Bonferroni test.
†$p < 0.05$).
[c,d]Same letter within the same line means no statistically significant difference.

Table 4
Duration of cold symptoms.

Variable	EKS (n = 44)	SSE (n = 42)	Placebo (n = 42)	p-value[a]
Visit 3	6.46±1.74	7.67±2.06	7.05±2.15	0.115

Values are presented as means±standard. EKS, *Eunkyosan*; SSE, *Samsoeum*.
[a] p-value is derived from ANOVA.

tionnaire asking participants which drug they thought they were taking. Consequently, there was an insignificant concordance between the administered drug and participants' predictions (p = 0.107). Therefore, blinding was maintained throughout.

This study is meaningful in that it evaluated cold symptoms and quality of life using a validated measurement, WURSS-21-K,[13,16] and showed that EKS and SSE are more effective than placebo.

A recent systematic review[17] analyzed four clinical studies that explored the effectiveness of EKS for the common cold. Although some included studies in review[3–5] reported that EKS was effective for the com-

Table 5
Safety assessment.

Variable	Obseved Value				Change from baseline						
	EKS (n = 44)	SSE (n = 42)	Placebo (n = 42)	p value**	EKS (n = 44)	p value*	SSE (n = 42)	p value*	Placebo (n = 42)	p value*	p value**
WBC											
visit 1	6.82±1.96	6.21±1.57	6.44±1.85	0.286							
visit 3	6.83±1.87	6.15±1.52	6.19±1.79	0.125	0.01±1.24	0.943	−0.06±1.49	0.809	−0.26±1.30	0.211	0.635
Glucose											
visit 1	93.91±16.00	95.29±22.34	96.17±15.77	0.846							
visit 3	95.16±14.44	95.81±13.59	94.45±20.30	0.930	1.25±18.85	0.662	0.52±23.14	0.884	−1.71±17.75	0.535	0.776
RBC											
visit 1	4.51±0.46	4.42±0.49	4.41±0.48	0.556							
visit 3	4.52±0.50	4.45±0.45	4.42±0.46	0.625	0.01±0.24	0.827	0.03±0.19	0.282	0.01±0.14	0.539	0.844
Hb											
visit 1	13.50±1.55	13.24±1.84	13.06±1.73	0.478							
visit 3	13.56±1.67	13.34±1.76	13.04±1.64	0.367	0.05±0.71	0.613	0.10±0.54	0.235	−0.02±0.42	0.796	0.641
Hct											
visit 1	40.25±4.17	39.50±4.86	38.95±4.51	0.414							
visit 3	40.23±4.74	39.51±4.66	39.05±4.32	0.485	−0.01±2.10	0.966	0.01±1.77	0.979	0.10±1.25	0.615	0.952
BUN											
visit 1	11.44±3.16	10.45±2.42	11.61±2.83	0.127							
visit 3	12.27±2.76	11.13±2.54	11.66±3.02	0.166	0.83±2.52	0.035	0.69±2.43	0.074	0.05±2.83	0.914	0.338
Creatinine											
visit 1	0.72±0.17	0.70±0.13	0.73±0.14	0.709							
visit 3	0.72±0.18	0.71±0.15	0.71±0.12	0.939	0.00±0.06	0.596	0.01±0.07	0.413	−0.02±0.07	0.142	0.183
AST											
visit 1	19.70±5.54	19.93±6.22	20.98±8.24	0.651							
visit 3	20.05±6.28	19.55±4.71	22.93±17.69	0.482†	0.34±5.33	0.673	−0.38±3.60	0.497	1.95±11.90	0.294	0.373
ALT											
visit 1	16.23±9.32	16.95±10.94	20.38±21.80	0.397							
visit 3	16.95±11.41	16.21±8.50	20.38±21.78	0.517†	0.73±8.06	0.553	−0.74±5.00	0.344	0.00±10.19	1.000	0.700
Na											
visit 1	138.91±1.79	138.69±2.10	139.07±1.69	0.645							
visit 3	138.80±1.58	138.98±1.70	138.81±1.60	0.851	−0.11±1.66	0.652	0.29±1.74	0.294	−0.26±1.91	0.380	0.345
K											
visit 1	4.25±0.38	4.25±0.31	4.25±0.31	0.995							
visit 3	4.32±0.43	4.23±0.32	4.30±0.33	0.519	0.07±0.34	0.193	−0.02±0.33	0.748	0.05±0.32	0.291	0.457
Cl											
visit 1	103.50±2.10	103.69±1.76	104.21±2.09	0.233							
visit 3	104.05±2.49	103.98±1.98	104.14±2.27	0.944	0.55±2.69	0.185	0.29±1.94	0.346	−0.07±2.22	0.836	0.466

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Cl: chloride, Hb: hemoglobin, Hct: hematocrit, K: potassium, Na: sodium, RBC: red blood cell, WBC: white blood cell.
*P values were compared within each group from baseline. (paired test).
**P values were compared between groups. (ANOVA, post hoc : Duncan test).
†Welch ANOVA.

Table 6
Blinding test results.

Variable*	EKS (n = 41)	SSE (n = 41)	Placebo (n = 41)	Sum (n = 123)	p-value [a]
Discordance	27 (65.9 %)	34 (82.9 %)	26 (63.4 %)	87 (70.7 %)	0.107
Concordance	14 (34.1 %)	7 (17.1 %)	15 (36.6 %)	36 (29.3 %)	

*Concordance between the administered drug and the subject's predictions.
[a]p-value is derived from the Chi-square test.

mon cold, they compared it with conventional medicine, not a placebo and all of included studies[3–5,7] did not use outcome measurements that were validated for reliability and validity, so the review concluded that the quality of the studies was relatively low.

Currently, the indications for EKS in Korea are limited to "sore throat, thirst, cough and headache caused by a common cold;" however, this study confirms that it can improve the overall symptoms of a common cold using a validated measurement. Therefore, the range of indications of EKS can be expanded to "general cold symptoms." Furthermore, if economic feasibility is evaluated through further studies, it could be included in a Korean Medicine prescription for common cold covered under national insurance.

As a result of analyzing traditional medicine prescribed for the common cold from 2010 to 2016 through the Health Insurance Review and Assessment Service database, SSE was frequently prescribed to treat adult patients with colds in Korea.[18] The anti-inflammatory and anti-allergic effects of SSE were confirmed in several experimental studies.[19–21] SSE was effective in cough with nasal obstruction in an observational study of patients who had cold sequelae in qi-deficiency type[22] and the SSE group showed a better treatment rate than the control group using the ambroxol-hydrochloride in the treatment of postinfectious cough.[23] The SSE group also showed clinical efficacy and fewer adverse reactions to treat coughs following cold compared with those in the control group given carbetapentane plus an ambroxol-hydrochloride treatment.[24] However, no clinical studies have assessed the common cold treated with SSE compared to placebo. In this study, it was confirmed that SSE had a significant effect on the improvement of cold symptoms compared with that of the placebo. However, there was no statistically significant difference in the total and quality of life scores of the WURSS-21-K and VAS scores compared to those of the placebo group. This was probably because SSE is traditionally used for weak or elderly individuals[25] rather than young adults who were mainly recruited in this study.

As this was conducted as a multicenter study, it would have been possible to reduce participant bias.

Despite these strengths, there are a few limitations of this study. First, the trial was terminated prematurely. The study protocol had been significant in that no large-scale clinical trials were using a placebo on the efficacy of EKS or SSE for the common cold before. However, owing to the COVID-19 crisis, it was difficult to recruit clinical trial participants. Although EKS and exhibited a significant effect compared to that of placebo in this study, Leandro[26] concluded that it should be highly cautious in evaluating the results of this study as clinically positive because the planned number of participants could not be recruited and enrolled. In further studies, a countermeasure for a situation must be prepared to recruit the planned sample size of participants.

Second, although it was possible to confirm that our study was blinded through the blinding test, there is a possibility that the EKS and SSE were differentiated if participants had experience taking EKS or SSE drugs because commercially available drugs were used as an intervention in this trial.

Third, considering that diagnosis and treatment are made through pattern identification in East Asian traditional medicine,[27] it would have been better if the design of this study was also taken into consideration for the administration of drugs according to the pattern type. In this study, pattern identification was not performed owing to a lack of validated measurements of pattern identification. The Questionnaire for Common Cold Pattern Identification was developed as a diagnosis of pattern identification for the common cold; however, there was a limitation in that reliability and validity were not proved.[28] According to a study comparing tongue characteristics,[29] which is an important factor in the diagnosis of pattern type, the common cold patient group showed a difference in that the tongue color was red, the tongue coating was thick, and the color of the tongue coating was white compared to those of the healthy control group. However, it was not possible to confirm whether there was a difference in the tongue characteristics by pattern type on the common cold. Thus, the development of a verified and reliable measurement of pattern identification is necessary.

Finally, since this study was conducted on adults, it is difficult to apply the study results to children. Generally, children have more common cold experiences than adults who generally experience 1–3 per year and have more prolonged symptoms than adults.[30] If children do not get timely and appropriate treatment for cough, it can lead to serious infections.[31] However, cold and cough medicines could lead to death in children under 5 years of age[32] and the US Food and Drug Administration recommended that cold and cough medicines for children under 2 years should be avoided.[31,32] Therefore, the treatment for colds and coughs in children should be safe as well as effective. Since EKS and SSE are used in the common cold of children[33–35] and a valid and reliable measurement for children 4–10 years of age[36] has been developed, studies in children could be considered.

In conclusion, EKS and SSE may have clinical effectiveness and safety in the common cold. However, in spite of statistically significant effectiveness and safety of EKS and SSE for the common cold patients, we have failed the planned number of participants. Therefore, future full-scaled clinical trial should be needed.

Conflict of interests

The authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Kwan-Il Kim: Writing – original draft, Writing – review & editing. **Minna Hong:** Investigation, Writing – original draft, Writing – review & editing. **Yang-Chun Park:** Conceptualization, Investigation. **Beom-Joon Lee:** Conceptualization, Investigation. **Kitae Kim:** Conceptualization, Methodology, Investigation. **Byoung Kab Kang:** Conceptualization, Methodology, Formal analysis, Data curation, Investigation. **Jun-Yong Choi:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Ethical statement

This clinical trial was approved by the Institutional Review Board of Pusan National University Korean Medicine Hospital (PNUKHIRB-

2019001), the Institutional Review Board of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2019-01-003-002), the Institutional Review Board of Daejeon University Korean Medicine Hospital (DJDSKH-19-DR-03), and the Institutional Review Board of Semyung University Korean Medicine Hospital (SMJOH-2019-02-01).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Deviation from the protocol

This study was prematurely terminated due to the COVID-19 pandemic, and we were unable to recruit all the planned participants (n = 375).

Supplementary materials

Supplement 1. CONSORT checklist

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.101005.

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