Systematic Review and Meta-Analysis

Medicine®

OPEN

Eunkyosan for the common cold

A PRISMA-compliment systematic review of randomised, controlled trials

Hesol Lee, KMD, MS[a], Bohyung Kang, KMD[a], Minna Hong, KMD, MS[b,c], Hye-Lim Lee, KMD, PhD[d], Jun-Yong Choi, KMD, PhD[b,c,*], Ju Ah Lee, KMD, PhD[e,*]

Abstract

Background: Eunkyosan (EKS), also known as the Yinqiaosan formula, is widely applied for the common cold in East Asia. Many clinical trials have reported the efficacy and safety of the EKS formula for the treatment of the common cold.

Objectives: This study aimed to assess the clinical evidence for and against the use of EKS formula as a treatment for the common cold.

Data sources: The following databases were searched from inception to the present: MEDINLE, EMBASE, CENTRAL, AMED CINAHL for English articles; OASIS, the Korean Traditional Knowledge Portal, the Korean Studies Information Service System, KoreaMed, the Korean Medical Database and DBPIA); and 3 Chinese databases, including CNKI (i.e., the China Academic Journal, the China Doctoral Dissertations and Master's Theses Full-text Database, the China Proceedings of Conference Full-Text Database and the Century Journal Project), Wanfang and VIP. In addition, we searched a Japanese database and conduct non-electronic searches of conference proceedings.

Study eligibility criteria: Prospective randomised controlled trials (RCTs) evaluating the effectiveness of EKS for the common cold were included in this review.

Participants: All types of common colds were eligible for inclusion. Participants who had both the common cold and other conditions were excluded. There were no restrictions based on other factors, such as age, sex, or symptom severity.

Interventions: Studies that evaluated any type of formulation (ie, decoction, tablet, pill, powder) of EKS were eligible for inclusion.

Study appraisal and synthesis methods: Differences between intervention and control groups were assessed. Mean differences with 95% confidence intervals (CIs) were used to measure the effects of treatment for continuous data.

Methods and analysis: Fourteen databases were searched in March 2018. We included RCTs examining EKS decoctions for any type of common cold. All RCTs of decoctions or modified decoctions were included. The methodological qualities of the RCTs were assessed using the Cochrane Collaboration tool for assessing risk of bias; confidence in the cumulative evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) instrument.

Results: A total of 315 potentially relevant studies were identified, and 4 RCTs met our inclusion criteria. Four RCTs tested the effects of EKS on the common cold, and all RCTs showed that EKS was superior regarding the treatment effect.

Limitations: All RCTs were conducted in China, and the generalisation of these results to other countries might be limited. Most trials did not use internationally recognised reliability and validity outcome measurements. Moreover, the result of the response rate can be distorted by the practitioner. Future trials in compliance with international standards in the evaluation of treatment effects may resolve this issue.

Conclusion: Our systemic review and meta-analysis provides suggestive evidence of the superiority of EKS over other therapies for treating the common cold. The level of evidence is low because of the high risk of bias.

Editor: Marcello Iriti.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Internal Medicine, College of Oriental Medicine, Gachon University, [b] Department of Internal Medicine, Korean Medicine Hospital of Pusan National University, [c] School of Korean Medicine, Pusan National University, [d] Department of Pediatrics, College of Korean Medicine, Daejeon University, [e] Hwapyeong Institute of Integrative Medicine.

[*] Correspondence: Ju Ah Lee, Hwapyeong Institute of Integrative Medicine, Republic of Korea (e-mail: motoong@gmail.com), Jun-Yong Choi, KMD, Korean Medicine Hospital of Pusan National University, Republic of Korea (e-mail: orientdoct@gmail.com).

How to cite this article: Lee H, Kang B, Hong M, Lee HL, Choi JY, Lee JA. A PRISMA-compliment systematic review of randomised, controlled trials. Medicine 2020;99:31(e21415).

Received: 4 November 2019 / Received in final form: 1 June 2020 / Accepted: 19 June 2020

http://dx.doi.org/10.1097/MD.0000000000021415

Implications of key findings: The results of this systematic review and meta-analysis provide suggestive evidence of the superiority of EKS alone or combined with conventional drugs.

Registration number: CRD42018087694.

Abbreviations: AE = adverse event, ChQoL = changes in the Chinese quality of life instrument, CM = conventional medicine, EKS = Eunkyosan, MD = mean difference, RCT = randomised controlled trial, RR = relative risk, SMD = standard mean difference, URTI = upper respiratory tract infection.

Keywords: common cold, eunkyosan, herbal medicine, randomised controlled trials, systematic review

1. Introduction

Upper respiratory tract infection (URTI) also known as the common cold, is a common and frequent respiratory disease mainly caused by viruses [1,2] and is typically diagnosed in physician offices[3] or emergency rooms.[4] Common cold symptoms include rhinitis, sore throat, rhinorrhoea, cough and malaise.[5,6] The average duration is approximately 7 days,[7] and most cases resolve within 10 days.[8]

In the USA, antibiotics are prescribed for more than 70% of URTI outpatients.[9] Additionally, in South Korea, the use of antibiotics for URTI is substantial, though the prescription rate of antibiotics for URTI decreased from 73.33% in 2002 to 43,73% in 2014.[10] Inappropriate antibiotic or overuse for URTI is a contributor to antibiotic resistance, a public health threat.[11,12] Therefore, it is necessary to prevent the overuse or abuse of antibiotics for URTI. For this purpose, the administration of medications other than antibiotics that have clinical evidence of safety and efficacy for URTI and active educational intervention of the appropriate use of antibiotics in URTI should be encouraged.

Eunkyosan (EKS) is commonly used in traditional Korean medicine and traditional Chinese medicine for URTI on its own or in combination with conventional medicine (CM). EKS was first introduced in *systematic differentiation of warm pathogen diseases (Wēn Bìng Tiáo Biàn)* by Wu Tang (1798) in China during the Qing Dynasty.[13] In clinical practice, it is spicy and cold and has detoxifying properties for turning off heat. Therefore, it is used for respiratory infections such as URTI, bronchitis and other inflammatory diseases.[13]

In contrast to its wide use in the clinical setting, the effects have been questioned because systematic reviews of randomised clinical trials of EKS have not been presented. The aim of this study was to explore the clinical efficacy and safety of EKS based on randomised controlled trials (RCTs).

2. Methods

2.1. Ethical issues

As this study did not collect any personal, sensitive or confidential information, ethical approval was not necessary.

2.2. Study registration

This study followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement for meta-analyses of healthcare interventions.[14] The protocol for this systematic review has been registered at PROSPERO 2018 under the number CRD42018087694.

2.3. Data sources

The following databases were searched from inception to the present: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), AMED, and CINAHL. We also searched 6 Korean medical databases (i.e., OASIS, the Korean Traditional Knowledge Portal, the Korean Studies Information Service System, KoreaMed, the Korean Medical Database and DBPIA) and 3 Chinese databases, including CNKI (i.e., the China Academic Journal, the China Doctoral Dissertations and Master's Theses Full-text Database, the China Proceedings of Conference Full-Text Database and the Century Journal Project), Wanfang and VIP. In addition, we searched a Japanese database and conduct non-electronic searches of conference proceedings. The search strategy applied for the MEDLINE database is presented in Supplement 1, http://links.lww.com/MD/E596. Similar search strategies were used for the other databases.

2.4. Types of studies

Prospective RCTs that evaluate the effectiveness of EKS for the common cold were included in this review. Both treatment with EKS alone and concurrent treatment with EKS and another therapy were considered acceptable if EKS was applied to the intervention group only and any other treatment was provided equally to both groups. Trials with any type of control intervention were included. No language restrictions were imposed. Hard copies of all articles were obtained and read in full.

2.5. Types of participants

All types of common colds were eligible for inclusion. Participants who had both the common cold and accompanying diseases were excluded. There were no restrictions based on other factors, such as age, sex, or symptom severity.

2.6. Types of interventions

Studies that evaluated any type of formulation (ie, decoction, tablet, pill, powder) of EKS were eligible for inclusion. The compositions of interventions were reviewed, and interventions involving herbal combinations that differ from original EKS from the perspective of traditional East Asian medicine were excluded from this review.

2.7. Data extraction and quality assessment

As mentioned above, hard copies of all articles were obtained and read in full. Two authors (HL and BK) performed the data extraction and quality assessment using a predefined data

extraction form. Risk of bias was assessed by another 2 authors (MH and HLL) using the Cochrane Handbook risk of bias assessment tool version 5.1.0, which considers random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.[15] The results of the assessments were categorised using scores of 'L', 'U', and 'H', with 'L' indicating a low risk of bias; 'U', an uncertain risk of bias; and 'H', a high risk of bias. Disagreements were resolved by discussion between all authors. When disagreements regarding selection could not be resolved through discussion, an arbiter (JAL) made the final decision.

2.8. Data collection

2.8.1. Outcome measures

2.8.1.1. Primary outcomes. Improved effectiveness including total treatment efficacy; that is, the number of patients whose common cold symptoms improved

2.8.1.2. Secondary outcomes. Change in symptoms (e.g., fever, cough, nasal symptoms, headache)

Changes in Chinese Quality of Life Instrument (ChQoL) scores

AEs

2.9. Assessment of bias in the included studies

We independently assessed the bias of the included studies according to the criteria in the Cochrane Handbook, version 5.1.0; these criteria include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias.

2.10. Data synthesis

Differences between intervention and control groups were assessed. Mean differences (MDs) with 95% confidence intervals (CIs) were used to measure the effects of treatment for continuous data. We converted other forms of data to MDs. For outcome variables on different scales, we used standard MDs (SMDs) with 95% CIs. For dichotomous data, we present treatment effects as relative risks (RRs) with 95% CIs; other binary data were converted to RR values.

All statistical analyses were conducted using Cochrane Collaboration's software program Review Manager (RevMan) version 5.3. (Copenhagen, The Nordic Cochrane Centre, the Cochrane Collaboration, 2012) for Windows. We contacted the corresponding authors of studies with missing information to acquire and verify data whenever possible. When appropriate, we pooled the data across studies to conduct a meta-analysis using fixed or random effects. We used GRADEpro software from Cochrane Systematic Reviews to create a summary of findings table.

2.11. Unit of analysis issues

For crossover trials, data from the first treatment period were used. For trials that assessed more than 1 control group, the primary analyses were combined data from each control group. Subgroup analyses of the control groups were performed. Each patient was counted only once in the analyses.

2.12. Addressing missing data

Intention-to-treat analyses including all randomised patients were performed. For patients with missing outcome data, the last observation carry-forward analysis was performed. When individual patient data were initially unavailable, we reviewed the original source or the published trial reports for these data.

2.13. Assessment of heterogeneity

Based on the data analysis, we used random- or fixed-effect models to conduct the meta-analysis. Chi-squared and I-squared tests were applied to evaluate heterogeneity among the included studies, whereby I^2 values >50 indicated high heterogeneity. When heterogeneity was observed, subgroup analyses were conducted to explore the possible causes.[16]

2.14. Assessment of reporting biases

Funnel plots were generated to detect reporting biases when a sufficient number of included studies (at least 10 trials) was available.[17] However, as funnel plot asymmetries are not equivalent to publication biases, we aimed to determine the possible reasons for any asymmetries in the included studies, such as small-study effects, poor methodological quality and true heterogeneity.[17,18]

3. Results

3.1. Study selection

The initial search identified 5536 records after duplicates (n = 621) were removed, of which 4915 full papers were identified for further examination. Records were screened, and studies were excluded on the basis of their titles and abstracts when they did not fulfil the inclusion criteria (n = 4600). After screening the full text of selected papers (n = 315), full-text articles were excluded, with the following reasons: not clinical (n = 13), not related to the common cold (n = 39), not related to EKS (n = 140), co-medication with CM (n = 35), EKS for the control group (n = 17), a thesis for a degree (n = 34), paediatric subjects (n = 32) and 1 study in 2 papers (n = 1). Ultimately, 4 studies met the inclusion criteria (Fig. 1).

3.2. Description of included trials

The main characteristics of the 4 included studies are presented in Table 1.[19–22] All of the included RCTs originated in China and were published between 2011 and 2013. The treatment periods were all 10 days, excepting follow-up days.

3.3. Risk of bias

The risk of bias was unclear across the several domains in the included trials (Fig. 2). Four trials were described as 'randomised', whereas only 1 trial reported the random sequence generation method.[22] One study mentioned allocation concealment,[22] and no studies reported blinding of the outcome assessment. Three studies used CM as the control.[19–21] All trials reported the patients' baseline characteristics. None of the trials published protocols; thus, the studies had an unclear risk of bias for selective reporting of outcomes. Another risk of bias is the participant's number difference in the comparison group between the comparison group total from men plus women participants.[20]

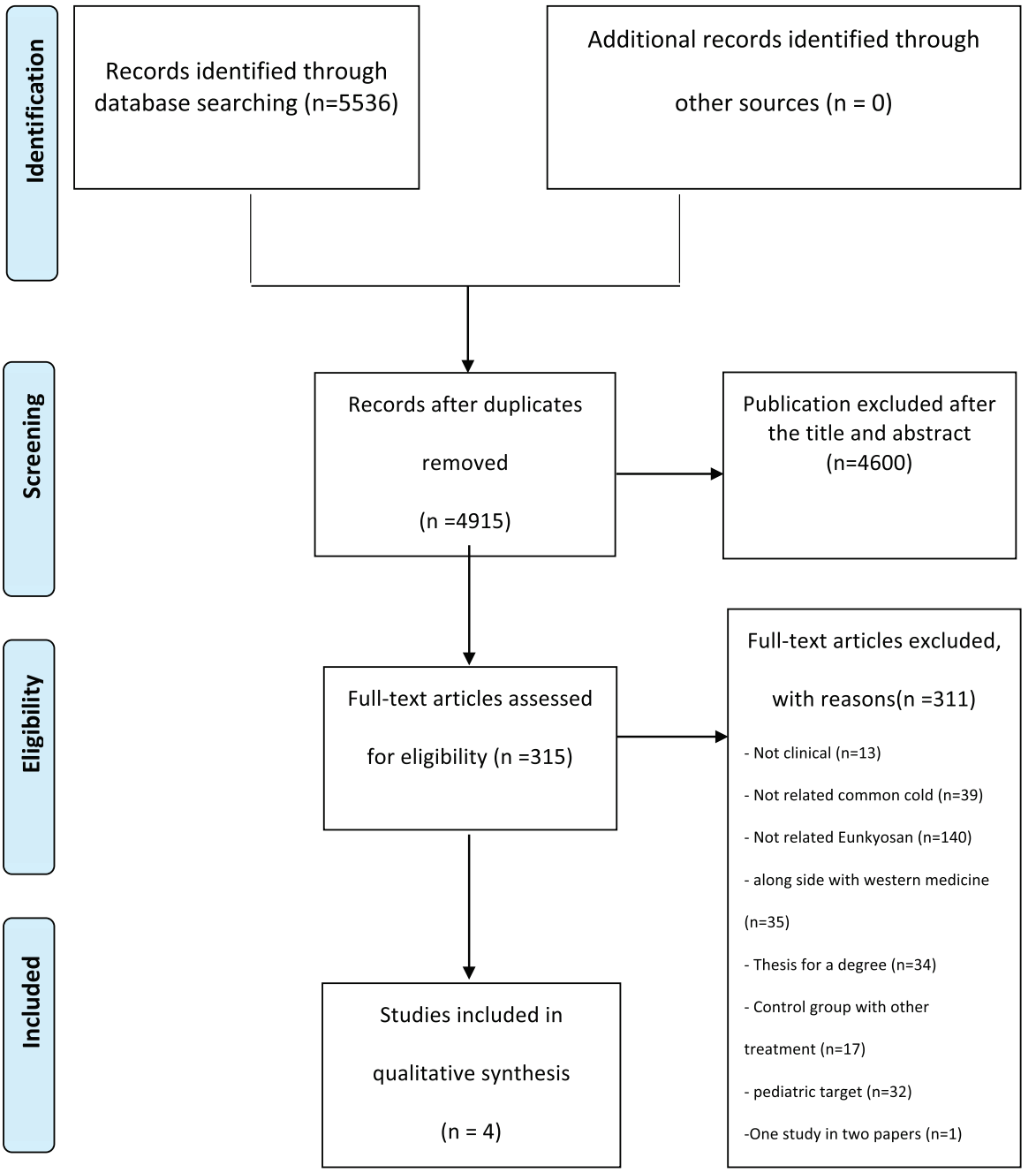

Figure 1. Flow chart of the trial selection process.

3.4. Outcome measurements
3.4.1. EKS alone vs CM

3.4.1.1. Response rate (total symptoms). Three RCTs examined the effects of EKS for treating the common cold compared to CM.[19–21] Two RCTs showed superior effects of EKS on the treatment effect.[19,20] The meta-analysis revealed favourable effects of EKS on the treatment effect (n = 308, RR: 1.22, 95% CI: 1.12 to 1.32, $P = .001$, $I^2 = 85\%$, Fig. 3A-1).

3.4.1.2. Time for remission (fever, hour). Two RCTs explored the effects of EKS for times for remission of fever compared to CM.[19,21] Two RCTs were included in the meta-analysis. Two RCTs demonstrated superior treatment effects of EKS. The meta-analysis result was favourable for the treatment effect of EKS (n = 116, SMD: −3.03, 95% CI: −8.85 to 2.79, $I^2 = 99\%$, Fig. 3A-2).

3.4.1.3. Time for remission (cough, hour). Two RCTs tested the effects of EKS for times for remission of nasal symptoms compared to CM,[19,21] and two RCTs were included in the meta-analysis. Superior treatment effects of EKS were reported in 1 RCT,[19] and the result of our meta-analysis was favorable for the treatment effect of EKS (n = 116, SMD: −0.62, 95% CI: −1.02 to −0.21, $I^2 = 97\%$, Fig. 3A-3).

Table 1

Eunkyosan for common cold.

Authors [year] Country	Study design	Sample size(I/C); mean±SD(years)	Intervention group	Control group	Start time	F/U	Outcome measurements	Results	Adverse events(n)
Hu [2012] China	RCT	60(30/30); (A) 69.76±9.96 (B) 70.12±9.68	(A) EKS (n.r *2#, 2 times daily, 3–5days)	(B) CM (ribavirin 150mg#3, 3 times daily, 3–5d)	Within 48 h	None	①Response rate ②Time for remission (fever, h) ③Time for remission (cough, h) ④Time for remission (nasal symptom, h)	①RR 1.40 (95%CI [1.05, 1.86]) (A) 27/29 (B) 18/27 P < 0.05 ②45.6±7.2vs106±12 ③103.2±12vs134±16.8 ④79.2±16.8vs96±21.6	n.r
Jiao [2013] China	RCT	192 (98/94); (A) 37.1 (B) 36	(A) EKS (100ml*3#, 3times daily, 2∼5days)	(B) CM (dexamethasone* n. r, paracetamol for high fever patients 1#6times daily, 3–7d)	n.r	2 weeks (A) None (B) 6 had symptoms of repeated colds	①Response rate	①96/98vs74/94	n.r
Wang [2011] China	RCT	60 (30/30); (A) 13-60 (B) 13-60	(A) EKS (400ml#1, once daily, 3days)	(B) CM (new contac 1#2, 2 times daily, 3d)	1–3 d	None	①Response rate ②Time for remission (fever, h) ③Time for remission (cough, h) ④Time for remission (nasal symptom, h) ⑤Time for remission (headache, h)	①30/30vs29/30 ②27.6±2.64vs27.84±2.4 ③50.88±0.72vs50.4±2.4 ④25.44±5.04vs26.64±3.12 ⑤42.72±3.36vs42.96±3.12	n.r
Wong [2012] China	RCT (Double blinded)	165 (82/83); (A) 44.3±10.4 (B) 44.3±11.5	(A) EKS (7g formulae#2, 2times daily, 1–10days	(B) Placebo (7g formula#2, 2times daily, 1–10 d)	n.r	3 wk	①Changes in the symptom scores ②Changes in the ChQoL scores	①2.3±1.0vs2.3±1.2 ②15.85±17.93vs16.05±15.17	(A) stomach-ache (4), thirsty (1), sweating (4), stomach gas (2), constipation (2), vomiting (2), insomnia (1) (B) stomach-ache (4), stomach gas (1), constipation (2), vomiting (2), frequent urine (1), yellow urine (2), productive phlegm (3), itchiness (1)

C = control, ChQoL = changes in the Chinese quality of life instrument, CM = conventional medicine, EKS = Eunkyosan or modified Eunkyosan, F/U = Follow up, I = Intervention, n.r = not report, SD = standard deviation.

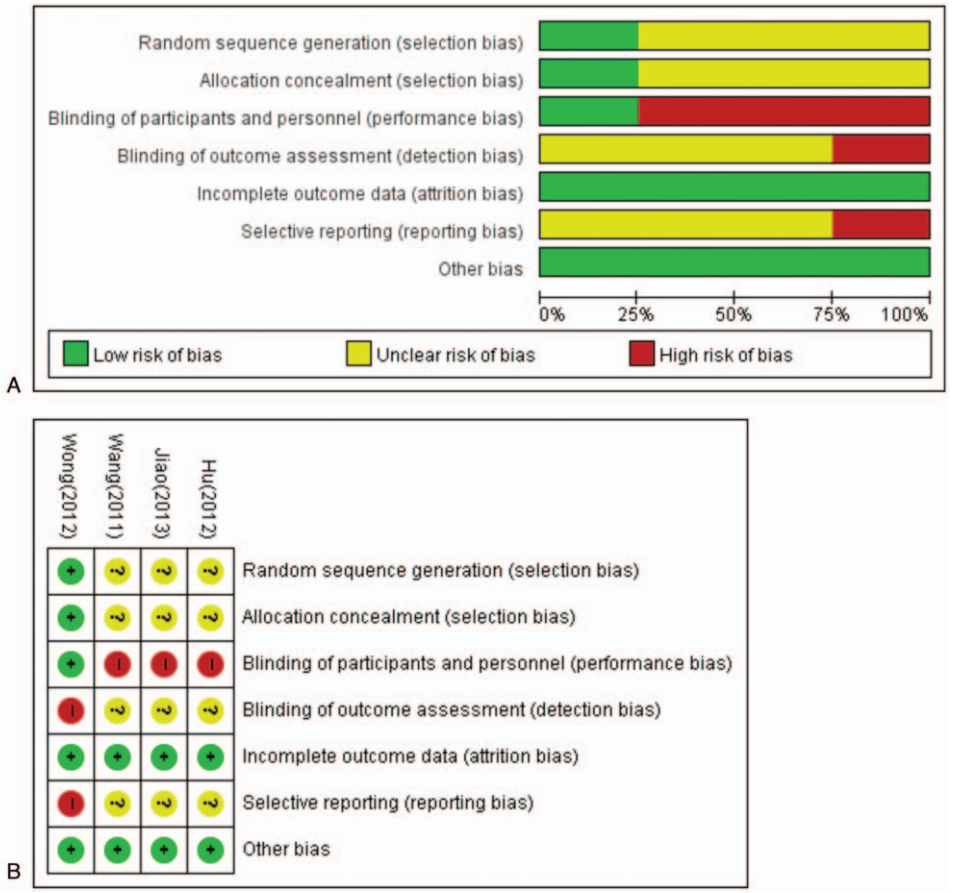

Figure 2. (A) Risk of bias graph: review authors' judgements about each item's risk of bias item presented as a percentage across all included studies. (B) Risk of bias summary: review authors' judgements about each item's risk of bias for each included study. +: low risk of bias; −: high risk of bias; ?: unclear.

3.4.1.4. Time for remission (nasal symptoms, hour). The effects of EKS for times for remission of nasal symptoms compared to CM were assessed in 2 RCTs.[19,21] Two RCTs were included in the meta-analysis, and 1 RCT showed superior treatment effects of EKS.[19] The meta-analysis result was not favorable for the treatment effect of EKS (n = 116, SMD: −0.59, 95% CI: −0.97 to −0.22, I^2 = 42%, Fig. 3A-4).

3.4.1.5. Time for remission (headache, hour). One RCT evaluated the effects of EKS for time for remission of nasal symptoms compared to CM,[21] and it was included in the meta-analysis. However, the meta-analysis result was not favourable for the treatment effect of EKS (n = 60, SMD: −0.07, 95% CI: −0.58 to −0.43, heterogeneity: not applicable, Fig. 3A-5).

3.5. EKS vs Placebo

3.5.1. Changes in the symptom scores. One RCT tested the effects of EKS for treating the common cold compared to placebo.[22] It was included in the meta-analysis, which showed no valid effect of EKS on changes in symptom scores (n = 165, MD: 0.00, 95% CI: −.0.34 to 0.34, Heterogeneity: Not applicable, Fig. 3B-1).

3.5.2. Changes in ChQoL scores. One RCT was included in the meta-analysis of changes in ChQoL scores[22] and showed no valid effect of EKS (n = 165, MD: −1.00, 95% CI: −3.15 to 1.15, Heterogeneity: Not applicable, Fig. 3B-2)

3.5.3. Adverse events (AEs). Only 1 study addressed AEs.[22] AEs reported for EKS were stomach-ache, thirst, sweating, stomach gas, constipation, vomiting, insomnia, frequent urine, yellow urine, productive phlegm, and itchiness. The AEs were regarded as mild symptoms.

3.5.4. Information related to EKS usage. Two studies reported the related TM pattern[21,22] as wind-heat syndrome, and they used the pattern as an inclusion criterion. All durations of the studies were within 10 days, excluding the follow-up duration. Four studies reported the kinds of EKS formulas, among which 2 studies reported the detailed composition of EKS.[20,21]

4. Discussion

The results of this systematic review and meta-analysis provide suggestive evidence of the superiority of EKS alone or combined with conventional drugs. In addition, the study results support the efficacy of EKS, which is widely used for the common cold in Asia, especially in Korea and China.[23,24] In contrast to its wide usage, evidence of the efficacy and safety of EKS has not been examined. Although some clinical study results have consistently shown that EKS is effective for the common cold, the study quality and quality of reporting were relatively low.[19–21] Studies of EKS have revealed that EKS is effective for treating the common cold, especially wind-heat syndrome, but those studies were conducted with a small sample size, and generalisation is

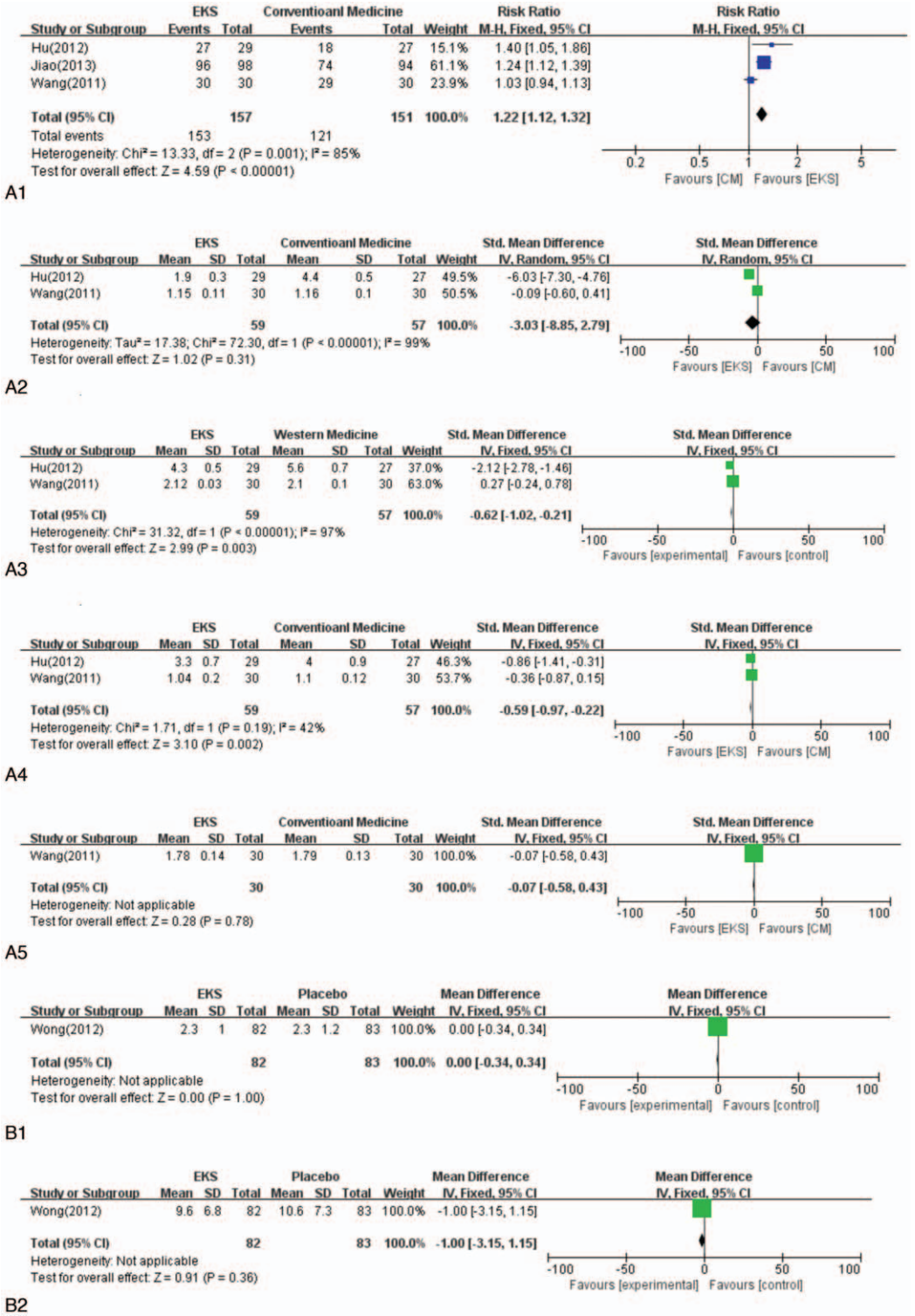

Figure 3. Forest plot of EKS versus conventional medicine for the following: response rate (total symptoms) (3A-1); time for remission of fever, hour (3A-2); time for remission of cough, hour (3A-3); time for remission of nasal symptoms, hour (3A-4); time for remission of headache, hour (3A-5). EKS versus placebo changes in symptom scores (3B-1); changes in ChQoL scores (3B-2). ChQoL = changes in the Chinese quality of life instrument, EKS = eunkyosan.

unclear. There is no report of the effect of EKS in a larger sample size. Its study quality and quality of reporting were relatively low. Therefore, the level of evidences was low or very low (Fig. 4).

The study objectives and designs were of 2 kinds: EKS compared with CM and with placebo. The results of the present study suggest that the use of EKS for the common cold is more effective than CM with regard to total symptom score, remission time of nasal symptoms and remission time of cough, but with no significant difference in remission time of fever, headache or comparison with placebo. The adverse effects were not

Summary of findings:

EKS compared to Conventional Medicine for common cold

Patient or population: common cold

Setting:

Intervention: EKS

Comparison: Conventional Medicine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Conventional Medicine	Risk with EKS				
Response Rate(total symptoms)	801 per 1,000	**978 per 1,000** (897 to 1,000)	**RR 1.22** (1.12 to 1.32)	308 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b]	
time for remission(fever, hour)	-	-	-	116 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]	
time for remission(cough, hour)	-	-	-	116 (2 RCTs)	⨁◯◯◯ VERY LOW [a,e]	
time for remission(nasal symptoms, hour)	-	-	-	116 (2 RCTs)	⨁◯◯◯ VERY LOW [a,f]	
time for remission(headache, hour)	-	-	-	60 (1 RCT)	⨁⨁◯◯ LOW [a]	

Figure 4. Summary of findings.

significantly different between the EKS treatment group and the placebo control group.

Relatively high heterogeneity was observed when comparing EKS with CM for the response rate (85%), time for remission of fever (99%), time for remission of cough (97%), and time for remission of nasal symptoms (42%). The reasons for the high heterogeneity are as follows: the risk of bias of each study was high, especially performance bias, and 3 studies that included EKS with CM did not have enough participants to explore actual effects.

In terms of TM theory, EKS is regarded to cure wind-heat syndrome. Wind-heat syndrome is a syndrome in which a contagion of external wind heat enters the skin, nose and mouth and causes the fluid in the lung to dry, resulting in the stagnant

Summary of findings:

EKS compared to Conventional Medicine for common cold

Patient or population: common cold

Setting:

Intervention: EKS

Comparison: Conventional Medicine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Conventional Medicine	Risk with EKS				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Do not follow random sequence generation method, not mentioned allocation concealment, blinding of the outcome assessment and none trials published protocols

b. high heterogeneities (I^2=85%)

c. high heterogeneities (I^2=99%)

d. SMD: -3.03, 95% CI: -8.85 to 2.79

e. high heterogeneities (I^2=97%)

f. high heterogeneities (I^2=42%)

Figure 4. (Continued)

fluid becoming sputum, heat trapped in the lung and coughing.[25] The clinical symptoms vary, and the main symptoms are chills and fever, cough, and sore throat.[26]

This review had several limitations. First, all the RCTs were conducted in China, and the generalisation of these results to other countries might be limited. Second, most of the trials did not use internationally recognised reliability and validity outcome measurements. The result of the response rate can be distorted by the practitioner. Future trials in compliance with international standards in the evaluation of treatment effects may resolve this issue. Another possibility is the lack of standardisation of herbal ingredients in each study. Indeed, 2 studies did not explain the exact composed herb formulas,[19,22] and in 1 study, the composition of the formula was different depending on the participant's symptoms.[20] In this situation, standardisation of natural products used in clinical trials is one of the most necessary factors for demonstrating good reproducibility of the research results for real clinical practice.

Summary of findings:

EKS compared to placebo for common cold

Patient or population: common cold

Setting:

Intervention: EKS

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with EKS**				
Changes in the symptom scores(overall)	The mean changes in the symptom scores(overall) was **0**	The mean changes in the symptom scores(overall) in the intervention group was 0 (0.34 lower to 0.34 higher)	-	165 (1 RCT)	⨁⨁◯◯ LOW [a,b]	
Changes in the ChQOL scores(overall)	The mean changes in the ChQOL scores(overall) was **0**	The mean changes in the ChQOL scores(overall) in the intervention group was 1 lower (3.15 lower to 1.15 higher)	-	165 (1 RCT)	⨁⨁◯◯ LOW [a,c]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

Figure 4. (Continued)

Summary of findings:

EKS compared to placebo for common cold

Patient or population: common cold

Setting:

Intervention: EKS

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with EKS				

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Does not blinding of the outcome assessment and not published protocols

b. MD:0.00, 95% CI: -.0.34 to 0.34

c. MD: -1.00, 95% CI: -3.15 to 1.15

Figure 4. (Continued).

Our results suggest that more studies should be conducted with a low risk of biases and heterogeneity to provide a clearer effect of EKS for the common cold.

Acknowledgments

This study was supported by the Traditional Korean Medicine R&D program funded by the Ministry of Health & Welfare through the Korea Health Industry Development Institute (KHIDI) (HB16C0006).

Author contributions

HL and JAL conceived of the study, developed the criteria, searched the literature, performed the data analysis and wrote the protocol. JAL and JYC conducted the preliminary search. BK and MH assisted in searching the Chinese literature and extracting the data. JAL and JYC revised the manuscript. All authors have read and approved the final manuscript.

References

[1] Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiol Rev 1994;16:351–73.
[2] Makela MJ, Puhakka T, Ruuskanen O, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol 1998;36:539–42.
[3] Woodwell DA, Cherry DK. National ambulatory medical care survey: 2002 summary. Adv Data 2004;346:1–44.
[4] McCaig LF, Burt CW. National hospital ambulatory medical care survey: 2002 emergency department summary. Adv Data 2004;340: 1–34.
[5] Arruda E, Pitkaranta A, Witek TJJr, et al. Frequency and natural history of rhinovirus infections in adults during autumn. J Clin Microbiol 1997;35:2864–8.
[6] Heikkinen T, Jarvinen A. The common cold. Lancet 2003;361:51–9.
[7] Marshall I. Zinc for the common cold. Cochrane Database Syst Rev 2000;2:CD001364.
[8] Scott J, Orzano AJ. Evaluation and treatment of the patient with acute undifferentiated respiratory tract infection. J Fam Pract 2001;50:1070–7.
[9] Lee GC, Reveles KR, Attridge RT, et al. Outpatient antibiotic prescribing in the United States: 2000 to. BMC Med 2014;12:96.
[10] Kim J-A, Park J, Kim B-Y, et al. The trend of acute respiratory tract infections and antibiotic prescription rates in outpatient settings using health insurance data. Korean J Clin Pharm 2017;27:186–94.
[11] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T 2015;40:277–83.
[12] Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Available from https://www.cdc.gov/drugresistance/Biggest-Threats.html.
[13] Tong WJ. Systematic Differentiation of Warm Pathogen Diseases (Warm disease). Beijing: China Medical Science Press; 1996.
[14] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.

[15] Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011): The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.; 2011.
[16] Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011): The Cochrane Collaboration. Available from www.cochrane-handbook.org; 2011.
[17] Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011): The Cochrane Collaboration, 2011. Available from www.cochrane-hand book.org.; 2011.
[18] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[19] Hu M. Clinical observation of Yinqiaosan in the treatment of viral upper respiratory tract infection in the elderly (Clinical Observation of Yinqiaosan in Treating Viral Upper Respiratory Tract Infection in the Elderly). J New Chin Med 2012;44:29–30.
[20] Jiao Z. Therapeutic effect of Yinqiaosan on acute upper respiratory tract infection (Observation on the therapeutic effect of Yinqiaosan on acute upper respiratory tract infection). Chin Foreign Med Treat 2013;32:115–6.
[21] Wang X. Yinqiaosan treatment of 30 cases of wind-heat cold (30 cases of wind-heat cold treated by Yinqiao Powder). J Med Forum 2011;32:171–2.
[22] Wong W, Lam CL, Fong DY. Treatment effectiveness of two Chinese herbal medicine formulae in upper respiratory tract infections–a randomized double-blind placebo-controlled trial. Fam Pract 2012;29: 643–52.
[23] Yu J-S, Ho C-H, Hsu Y-C, et al. Traditional Chinese medicine treatments for upper respiratory tract infections/common colds in Taiwan. Eur J Integr Med 2014;6:538–44.
[24] Sun-ju L, In-sik H, Hyun-suk O, et al. Effects of herbal treatment for in-patients with mild fever. J Korean Med 2011;32:122–30.
[25] Chao Y. General Treatise on the Causes and Symptoms of Diseases (On typhoid fever). Beijing: People's Health Publishing House; 1955.
[26] Zhang L, Yan J, Liu X, et al. Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: current status and future perspective. J Ethnopharmacol 2012;140:519–25.