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감기 임상시험 가이드라인 제정을 위한 최신 임상시험 연구 분석

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Analysis of Recent Clinical Studies to Establish Korean Herbal Medicine Clinical Trial Guidelines for the Common Cold

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ABSTRACT

Objectives: The aim of this study was to help develop a guideline for the common cold. We searched recent clinical studies of the common cold in Western medicine and reviewed their objectives, inclusion and exclusion criteria, primary outcome, secondary outcome, and assessment tools to establish evidenced-based guideline.

Methods: We searched electronic databases (Cochrane Library, MEDLINE, EMBASE) to identify eligible randomized controlled trials (RCTs) about the common cold for the last 10 years. We included 29 RCTs and showed their research summary via their objectives, participants, interventions, control, treatment duration, and results. We also analyzed the definition of the common cold presented in the article, inclusion and exclusion criteria, primary and secondary outcomes, and assessment tools.

Results: We reported the aforementioned areas in detail. At first, the definition of the common cold was confused across the articles. Second, herbal medication clinical trials for the common cold have been extensively studied recently. Third, the eligibility criteria frequently included the Jackson Symptom score. Fourth, validated assessment tools (i.e., the Wisconsin Upper Respiratory Symptom Survey-21) have only been used in a few recent studies.

Conclusions: Our research will be helpful to establish Korean herbal medicine clinical trial guidelines for the common cold.

Key words: common cold, randomized controlled trial, review

Ⅰ. 서 론

감기는 경증의 바이러스에 의한 상기도 감염 증후군으로 콧물, 코막힘, 재채기, 기침 등의 증상을 동반하는 증후군이다[1]. 감기를 일으키는 바이러스는 총 200여종에 달하며 이 중 rhinovirus 30-50%, corona virus 10%, respiratory syncytial virus(RSV)가 5%의 원인을 차지하여 rhinovirus와 corona virus가 흔한 원인 바이러스로 알려지고 있다[1,2]. 감기는 경증의 질환이고, 자체 한정기간을 지니지만 일상적인 삶이나 사회적 활동에 지장을 초래하며 막대한 사회적 비용을 야기하고 있다[3]. 감기의 원

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인이 매우 다양하여 특정 바이러스에 대한 치료는 효율성이 없는 것으로 밝혀져 있으며[2], 기존에 사용되던 항생제, 항히스타민제 모두 뚜렷한 효과가 없고[4] 오히려 부작용이 보고되고 있어[5], 증상을 치료하는 대증 치료에 관심이 모아지고 있다. 이에 서양에서는 양약 관련 임상시험보다 단일 본초나 대체요법에 대한 임상시험 연구를 최근 들어 진행하여 왔고 그에 대한 체계적 리뷰도 연구되었으나 아직까지 명확한 효과를 보이는 약물은 없는 실정이다[4,6]. 이에 여러 나라에서 한약에 대한 관심이 증대되고 있는 추세이다[7,8].

한약제제와 관련된 임상시험은 최대한 표준화된 방법으로 정교하게 이루어져야 하며, 이와 관련하여 Consolidated Standards of Reporting Trials (CONSORT)는 한약제제에 대해서 지침을 따로 개정하여 발표하기도 하였다[9]. 국내에서도 잘 설계된 임상시험의 중요성을 절감하여 한약제제에 대한 가이드라인을 일부 구축하였으나 감기와 관련된 한약제제 임상시험 가이드라인은 아직 제정되지 않은 상태이다. 감기 치료에서의 한방적 접근이 필요하고 이를 위한 임상시험 요구가 증대되는 상황으로, 한약제제의 안정성과 유효성을 객관적으로 체계적으로 밝히기 위해 임상시험을 준비하는 연구자들에게 도움이 되도록 감기 치료 및 예방에 대한 한방제제 임상시험 가이드라인 제정이 필요한 시점이라 판단하였다. 이에 경희대학교한방병원 한의약임상시험센터에서는 국내 한방호흡기내과 교수진을 전문가 자문위로 구성하고 한의약임상시험센터 협의체와 공동으로 가이드라인을 제정하고자 계획하였다.

가이드라인 제정을 위한 기초 단계로 여러 선행논문과 유수 외국 참고서적 및 가이드라인을 검색한 결과 외국에서 발간된 신뢰성 있는 가이드라인은 없는 상황이며, 중국에서 발간된 변증관련 가이드라인이나 진료지침을 참고로 할 수 있었다[10]. 그러나 감기에 대한 한약제제 임상시험에 필요한 필수 정보를 제공하는 참고할만한 기존 자료는 없다고 판단하여, 최신의 임상시험 연구 논문을 분석하여 가이드라인에 필요한 여러 사항에 대해 정리할 필요성이 대두되었다. 선행연구를 보더라도 감기는 임상적 증상으로 이루어진 증후군인 관계로 증상 포함 범위가 다양하였고, 이에 따라 선정 제외기준도 불명확한 상황이었다. 앞서 감기에 대한 임상시험의 중요성을 파악하고 2003-2007년까지 임상연구를 고찰한 논문이 있었으나[11], 시일이 지나 최신의 연구경향을 반영하지 못한다는 점에서 가이드라인 관련하여 정보를 얻기에 한계가 있었다. 이에 최근 10년간 감기에 대한 세계적인 임상시험 경향을 살펴보고, 감기에 대한 정의 및 선정, 제외기준, 평가도구 등을 분석하여, 향후 국내에서 시행될 감기 치료 및 예방에 대한 임상시험의 가이드라인 제정에 도움이 되고자 본 연구를 시행하였다.

Ⅱ. 연구방법 및 절차

1. 검색방법 및 연구대상 선정

PubMed, EMBASE, the Cochrane Central Register of Controlled Trials(CENTRAL) 검색을 통해 감기에 대한 임상시험 논문을 선정하였다. 'common cold', 'upper respiratory tract infection', 'rhinovirus', 'corona virus'를 검색어로 하여 title & abstract 범주에서 기간은 10년 이내, 대상은 Human, 언어는 English로 제한하여 검색을 시행하였다.

검색 결과 총 676편의 논문이 검색되었고, 중복으로 208편의 논문을 제외한 총 468편의 논문 중에서 제목 초록을 검토하여 실시한 1차 스크리닝 결과, 무작위 대조군 임상시험이 아닌 경우, 영어가 아닌 경우, 실험 논문 등의 이유에 해당되는 343편의 논문이 제외되었다. 2차 스크리닝은 125편 논문 중에서 title에 'common cold'가 포함된 논문으로 이루어졌다. 감기는 상기도 감염에 포함되는 증후군이나 기존에 용어가 혼재되는 경향이 있어서 이로 인해 감기에 대한 정의 및 증상에 대한 범주가 모호하였으므로, 이에 감기를 명확하게 제목에 포

함하여 진행된 임상시험을 간추려 1차적으로 감기에 대한 정의 및 선정, 제외기준, 평가도구 등에 대한 분석을 해보는 것이 중요할 것으로 판단되었기 때문이다. 위의 과정을 거쳐 총 37편의 논문이 간추려졌으며, 전문을 검토하여 전문이 없는 경우(n=3), RCT가 아닌 경우(n=5)의 이유로 8편이 제외하여 총 29편[12-40]을 선정하였다.

2. 연구내용

최근 10년 동안 감기 환자를 대상으로 진행된 무작위 대조군 임상시험을 대상으로 연구개요와 관련하여 연구목적, 연구대상자 수, 중재군 및 대조군, 치료기간, 연구결과 순으로 살펴보았다. 논문에서 제시한 감기의 정의를 살펴보고, 각 논문의 선정기준, 제외기준, 논문에서 사용한 1차 평가변수, 2차 평가변수 및 평가도구를 분석하여 고찰하였다.

Ⅲ. 결 과

1. 연구개요

2006년부터 2014년에 걸쳐 총 29개의 논문이 선정되었다. 2006년 4편, 2007년 5편, 2008년 1편, 2009년 1편, 2010년 4편, 2011년 3편, 2012년 4편, 2013년 4편, 2014년 1편으로 최근 10년간 감기와 관련된 무작위 대조군 임상시험이 꾸준히 진행되어 온 것을 확인하였다. 연구개요는 연구목적을 분류하여 연도순으로 나열하여 제시하였다(Table 1).

1) 연구목적

중재의 감기 치료에 대한 효능을 살펴본 논문이 21편, 감기 예방에 대한 효능을 살펴본 논문이 8편이었다.

2) 연구대상자 수

모집된 연구 대상자 수는 치료에 대한 효능을 보는 임상시험은 최소 35명에서 최대 719명까지였고, 예방에 대한 효능을 보는 임상시험에서는 최소 80명에서 최대 755명 이였다.

3) 중재군 및 대조군

치료에 대한 효능은 총 21편 중 비강 내 스프레이 제제 5편(23%), 한약복합제제 4편(19%), 아연 3편(14%), 양약 3편(14%), Echinacea 1편(5%) Pelargonium Sidoides 1편(5%) 그 외, 폴리페놀 음료, 고온다습한 공기, autologous blood therapy, 의사-환자 유대관계 각 1편(5%) 씩 이루어졌다.

예방에 대한 효능은 총 8편 중 프로바이오틱 박테리아 2편(25%), 아연 2편(25%), Echinacea 1편(12.5%), 비타민 C 1편(12.5%), 과일 야채 혼합주스 1편(12.5%), 초유단백질 1편(12.5%)이 진행되었다.

4) 중재기간

치료에 대한 효능 연구의 중재 기간은 7일 이내가 6편(29%), 7일 이상 10일 이내가 7편(33%), 10일 이상 14일 이내가 4편(19%), 14일 이상 21일 이내 4편(19%)이었다.

예방에 대한 연구 3개월이 3편(37.5%), 4개월 1편(12.5%), 7개월 1편(12.5%), 8개월(run-in-period 2개월) 1편(12.5%), 관찰기간 1년(중재투여기간 불명확) 1편(12.5%), 5년 1편(12.5%)이었다.

5) 연구결과

총 29편 중 효능이 있다고 보고한 논문은 17편(59%), 제한적으로 효능이 있었던 논문이 3편(10%), 효능이 없었던 논문이 9편(31%)이었다. 제한적으로 효능이 있다고 판단한 논문은 일차평가변수에 대한 효능은 없었으나, 관련된 이차평가변수에 대한 효능이 있는 것으로 서술된 논문이다. 효과가 없다고 판단한 Okabayashi 논문은 대조군으로 양약을 사용하고 제목에서 비우월성(non-superiority)이라는 용어를 사용하여 중재군과 대조군의 약효가 같거나 열등하다는 것을 보이려 한 것으로 보였으나 실제 논문 서술을 토대로 샘플사이즈를 구하는 방식이나 전반적인 연구 설계를 살펴볼 때 비우월성과 관련된 디자인이나 가설을 명확히 제시하지 않은 것으로 보여 효과가 없음으로 판단하였다(Table 1).

Table 1. Characteristics of the Studies Included in the Review

Author (years)	Objective	Participants enrolled	Participants analyzed	Intervention group	Control group	Treatment duration (study duration)	Results
Eby GA (2006)	Treatment	47	33	zinc	placebo	7 days	ineffective
Hull D (2007)	Treatment	441	269	low pH gel nasal spray (for non-specific virus-hostile environment)	placebo	maximum 7 days	effective
Kurugol Z (2007)	Treatment	129	120	zinc sulphate	placebo	maximum 7 days	ineffective
Latte J (2007)	Treatment	216	212	oral pseudoephedrine	placebo	3 days	ineffective
Lizogob VG (2007)	Treatment	207	103*	Pelargonium sidoides	placebo	maximum 10 days	effective
Mizoguchi H (2007)	Treatment	545	432	syrup (paracetamol, dextromethorphan, hydro bromide, doxylamine succinate, ephedrine sulfate)	placebo	21 days	effective
Eccles R (2008)	Treatment	66	61	xylometazoline (Otrivin) nasal decongestant	placebo	10 days	effective
Prasad AS (2008)	Treatment	50	50	zinc acetate lozenges	placebo	5 days	effective
Hensler S (2009)	Treatment	139	114	autologous blood therapy (gluteal intramuscular injection of venous blood)	placebo	7 days	ineffective
Barrett B (2010)	Treatment	719	713	echinacea(blinded)/ echinacea(open)	no pill /placebo (blinded)	14 days	ineffective
Eccles R (2010)	Treatment	35	32	iota-carrageenan nasal spray	placebo	4 days	effective
Pach D (2010)	Treatment	157	155	inhaling hot dry air (in sauna)	dry air at room temperature	3 days	effective
Schütz K (2010)	Treatment	100	98	polyphenol-rich beverage	placebo	10 days	ineffective
Byun JS (2011)	Treatment	480	473	*so-cheong-ryong-tang yeon-gyo-pae-dok-san*	placebo	maximum 8 days	limited effective

Rakel D (2011)	Treatment	719	713	"standard" interaction "enhanced" interaction	no patient -practitioner interaction	maximum 7 days	effective
Yakoot M (2011)	Treatment	62	61	natural multiherbal formula (Immumax) containing echinacea, garlic powder, nigella sativa oil, and panax ginseng +vitamin C, elemental zinc	placebo	maximum 14 days	effective
Chang J (2012)	Treatment	360	346	shi-cha capsule /shi-cha capsule+placebo	placebo	3 days	effective
Fazekas T (2012)	Treatment	213	153	iota-carrageenan nasal spray	placebo	7 days	ineffective
Ludwig M (2013)	Treatment	211	203	carrageenan nasal spray	placebo	maximum 21 days	effective
Picon PD (2013)	Treatment	146	138	paracetamol, chlorphenamine and phenylephrine	placebo	10 days	effective
Okabayashi S (2014)	Treatment	410	340	kakkonto (Japanese herbal medicine)	western-style multiple cold medicine (PabronGold-A)	4 days	ineffective
de Vress M (2006)	Prevention	479	454	vitamin+mineral +probiotic bacteria	vitamin +mineral	unclear (01 Jan-May, 01 Dec-02 June, 12 months)	limited effective
Kurugol Z (2006)	Prevention	200	194	zinc sulphate	placebo	7 months	effective
Sasazuki S (2006)	Prevention	439	244	500 mg of vitamin C	50mg of vitamin C	5 years (4 years after protocol amendment)	ineffective
Roll S (2010)	Prevention	543	529	juice powder (fruit+vegetables)	placebo	8 months, (including a 2-month run-in period)	effective
Jawad M (2012)	Prevention	755	717	echinacea purpurea	placebo	4 months	effective

Rerksuppaphol S (2012)	prevention	80	80 (dropout: 4)	probiotic (lactobacillus acidophilus and bifidobacterium bifidum	placebo	3 months	effective
Rerksuppaphol S (2013)	Prevention	100	100 (dropout: 5)	chelated zinc	placebo	3 months	limited effective
Vitetta L (2013)	Prevention	126	105	lactoferrin/whey protein Ig-rich faction (Lf/IgF)	placebo	3 months	effective

2. 감기 정의

총 29편 논문 중에서 감기에 대한 정의가 제시되지 않고 유병률이나 역학만을 제시한 논문은 16편에 해당하였다. 13편에서 정의된 감기는 '바이러스에 의한 상기도 감염이다'가 거의 대부분이었으며, 1편은 '전통적으로 급성상기도감염으로 통칭되던 감기는 유병률이 매우 높은 질환으로 바이러스에 의해 발병된다.' 라고 정의되었다. 가장 최신 논문인 2014년에 발표된 Okabayashi 논문에서는 '바이러스에 의해 발생되는 경증의 상기도 질환'으로 정의되었다(Table 2).

Table 2. Definition about Common Cold in the Included Studies

Treatment		
No	Author (year)	Definition
1	Eby GA (2006)	not presented
2	Hull D (2007)	Upper Respiratory Tract Infections (URTIs) of viral aetiology, commonly described as "Common Cold" and "Flu", remain the most common of human illnesses.
3	Kurugol Z (2007)	not presented
4	Latte J (2007)	not presented
5	Lizogob VG (2007)	The common cold is a viral infection with symptoms such as sneezing, sore throat, and running nose.
6	Mizoguchi H (2007)	The common cold is a symptom complex resulting from viral infection of the upper respiratory tract.
7	Eccles R (2008)	not presented
8	Prasad AS (2008)	not presented
9	Hensler S (2009)	not presented
10	Barrett B (2010)	Acute viral respiratory infection (common cold) is humanity's most frequent illness. Etiologic agents include rhinovirus, coronavirus, influenza, parainfluenza, respiratory syncytial virus, adenovirus, enterovirus, and metapneumovirus. While influenza caused illness is the most serious and is often categorized separately, symptoms are usually indistinguishable from those produced by other viruses.

11	Eccles R (2010)	Common cold is the most prevalent contagious viral disease in humans. It is caused by a variety of viral pathogens with human rhinoviruses (HRV) being the most abundant ones. Affecting the upper respiratory system, symptoms like blocked nose, cough and sneezing are most common.
12	Pach D (2010)	Common cold, mainly caused by rhinoviruses or coronaviruses, is a frequent problem all over the world.
13	Schütz K (2010)	Acute upper respiratory tract viral infection, also referred to as the common cold, is the most frequent infectious disease in human beings.
14	Byun JS (2011)	The common cold is caused by various types of viruses, especially rhinovirus which has more than 100 different serotypes.
15	Rakel D (2011)	not presented
16	Yakoot M (2011)	not presented
17	Chang J (2012)	not presented
18	Fazekas T (2012)	Acute viral infection of the upper respiratory tract, also referred to as common cold.
19	Ludwig M (2013)	Common colds are caused by respiratory viruses such as rhinovirus, coronavirus, parainfluenza, influenza, respiratory syncytial virus, adenovirus, enterovirus, or metapneumovirus.
20	Picon PD (2013)	Acute respiratory infections are highly prevalent in the population, with the common cold, flu-like syndromes, t racheobronchitis, sinusitis, laryngitis and pneumonias being particularly important.
21	Okabayashi S (2014)	The term "common cold" refers to virus-induced, relatively mild upper respiratory tract illnesses.
	Prevention	
No	Author (year)	Definition
1	de Vress M (2006)	not presented
2	Kurugol Z (2006)	not presented
3	Sasazuki S (2006)	not presented
4	Roll S (2010)	The common cold is viral infectious disease of the upper respiratory tract, caused by a variety of viruses, with rhinoviruses and corona viruses as the most common.
5	Jawad M (2012)	not presented
6	Rerksuppaphol S (2012)	not presented
7	Rerksuppaphol S (2013)	not presented
8	Vitetta L (2013)	Acute respiratory tract illnesses and acute upper respiratory tract infections (URTIs), traditionally referred to as common colds, are the most prevalent diseases experienced by the community.

3. 선정, 제외 기준

1) 감기 치료

감기에 대한 중재의 치료 효과를 보는 논문 21편 중 2편[14,29]이 소아를 대상으로 진행되었다.

선정기준에 연구에 포함되는 감기 증상 및 정도를 제시하였고, 감기의 지속기간을 고려하여 모집 당시 시점부터 증상이 지속된 기간의 제한을 두었다. 24시간 이내가 3편[17,19,23], 24-48시간 2편[14,16], 36시간 이내 4편[18,21,26,27], 48시간 이내 7편[15,22,25,28,29,30,32], 그 외 72시간 1편[31], 7일이 1편[20]이었다.

감기 증상을 정의하는데 있어 출처 없이 증상 기준을 제시한 논문이 10편[12,13,15,17-19,24,25,27,28]에 해당하였고, Jackson 증상 지표를 이용한 논문이 9편[16,20-22,26,29,30-32]이였다. 1편[23]은 prasad가 진행한 연구를 근거로 하였으며 1편[14]은 아연을 중재로 하는 선행연구 15편을 근거로 하여 불분명한 출처를 제시하였다.

제외기준은 대부분 감기와 혼동될 수 있는 질환이 배제되었는데, 알레르기성 비염, 부비동염, 편도염, 인두염, 후두염, 유양돌기염, 중이염 등과 호흡기 질환(천식, 만성폐쇄성폐질환) 등이 이에 해당되었다. 이 외에도 연구 결과에 영향을 줄 수 있다고 판단되는 기타 전신 질환 등이 연구자의 판단에 의해 제외기준에 포함되어 있었다. 감기 증상에 영향을 줄 수 있는 약물 복용력이 있거나(항히스타민제, 항생제, 기타 대증요법 등), 여타 임상 시험 진행에서도 제외 기준에 포함되는 임신 여부, 기타 임상시험 참여 여부, 낮은 인지 능력 등이 제외기준에 포함되었다(Appendix).

2) 감기 예방

감기에 대한 중재의 예방 효과를 보는 논문 8편 중 3편이 소아[34,38,39]를 대상으로 진행되었다. 아토피성 위염 환자를 대상으로 진행한 연구 한 편[35]을 제외하고 모두 건강한 소아 또는 성인을 대상으로 진행되었다. 알레르기 성향이 있거나 기타 연구에 영향을 줄 수 있는 전신질환, 낮은 인지 능력 등이 제외기준에 포함되었다(Appendix).

4. 1차, 2차 평가변수 및 평가도구

1) 1차 평가변수

감기 치료에 대한 연구 21편 중, 1차 평가변수는 감기 증상 지속기간이 7편, 감기 증상 총 점수 또는 점수변화량이 7편, Wisconsin Upper Respiratory Symptom Survey(WURSS-21) 3편, 비기도저항(nasal airway resistance, NAR)이 2편, 증상이 악화된 연구시험대상자 수 1편, 감기 증상의 중증도를 합하여 그린 곡선 하 면적(area under the curve, AUC) 1편이었다. WURSS-21은 감기 증상의 중증도 및 삶의 질을 함께 측정가능하게 만든 평가도구로 신뢰도와 타당도가 검증된 평가도구이다. 이 중 2편은 동일한 임상시험에서 발표된 논문으로, 1차 변수에서 중복으로 체크되었다. 감기 예방에 대한 연구 8편의 1차 평가변수는 한편을 제외하고는 모두 감기의 발병 횟수였다. 한 편은 이상반응이 1차 평가변수, 감기 발병 횟수가 2차 변수였다(Table 3).

2) 2차 평가변수

(1) 감기 치료 연구

감기 증상과 관련된 변수로, 증상의 중증도 점수 변화, 전신증상과 국소증상을 나눠서 부분의 합 또는 부분의 증상 중증도 변화 등이 2차 평가변수에 포함되었다. 시각적 상사 척도(visual analogue scale, VAS) 역시 2차 평가변수에 포함되었다. 1차 평가변수에서 증상점수의 합 또는 증상점수 변화를 선정한 연구는 2차 평가변수에 증상의 지속기간을 포함하였다. 실험실적 분석을 보면, 아연 중재 연구 1편에서는 혈청에서 zinc, soluble interleukin-1 receptor antagonist(sIL-1ra), soluble tumor necrosis factor receptor(sTNF-R), the plasma adhesion molecules, soluble vascular endothelial cell adhesion molecule(sVCAM)-1, soluble ICAM(sICAM)-1을 살펴보았다. Echinacea 연구에서는 nasal wash에서 interlukin-8(IL-8), 중성구 수(neutrophil count)를 2차 평가변수로 분석하였다. 콧물에서 바이러스 검출 여부 등도 포함되었다. 이 외에는 이상반응이 2차 평가변수에 포함되었고, 감기로 인한 삶의 질 측면에서는 EuroQol-5D(EQ-5D), SF-8, SF-36 평가도구가 총 2편에서 사용되었다. 이 외 치료에 대한 만족도, 전반적 몸 상태, (콧물을 닦기 위한) 휴지 사용 횟수, 수면 장애 정도, 병용약물을 허용한 연구 중에는 병용약물 투약횟수 등이 2차 평가변수에 포함되었다(Table 3).

(2) 감기 예방 연구

감기 증상 지속지간 및 중증도, 삶의 질(SF-12)을 살펴본 연구 1 편, international physical activity questionnaire(IPAQ), perceived stress scale-10 항

목을 함께 살펴본 연구 1편, 면역학적 지표를 살펴본 연구 1편(CD45+(lymphocytes), CD45+, CD19+(B-lymphocytes), CD45+, CD3+(T lymphocytes), CD45+, CD3+, CD4+(TH cells), CD45+, CD3+, CD8+(TS plus TC cells), CD 45+, CD 56+(natural killer cells)) 등이 있었다(Table 3).

3) 평가도구

감기 증상과 관련해서는 신뢰도와 타당도가 검증된 WURSS-21을 이용한 연구가 총 3편[21,25,26]이였다. 그 외는 연구진들이 제시하였던 증상 도구를 대부분 감기 일지(cold diary)를 이용하여 측정하였다.

Table 3. Primary and Secondary Outcomes

		Treatment	
No	Author (year)	Primary outcome	Secondary outcome
1	Eby GA (2006)	• duration of cold	• the change of severity score
2	Hull D (2007)	• time to resolution of symptom	• time to alleviation of symptoms and no rhinorrhoea • time to alleviation of symptoms • time to response of number to bothersome cold question
3	Kurugol Z (2007)	• time to resolution of cold symptom	• none
4	Latte J (2007)	• mean nasal airway resistance (NAR)	• tNVol and tCSA • subjective symptom score (100- mm visual analogue scale, VAS) • symptoms of nasal congestion, nasal runniness, and sneezing between the two visits.
5	Lizogob VG (2007)	• sum of symptom intensity • differences of the cold intensity score from day 1-5	• change of cold intensity score • ability to work, activity level, general well-being • EQ-5D • treatment outcome according to an integrative medicine outcomes scale, and satisfaction with treatment according to the integrative medicine patient satisfaction scale
6	Mizoguchi H (2007)	• the symptom relief composite scores 3 hours post-dosing	• the overall relief assessment upon arising on day 2 • the day-2 symptom relief composite scores • day-2 sleep satisfaction • hour-3 relief assessments for the individual symptoms • day-2 relief assessments for the individual symptoms

7	Eccles R (2008)	• nasal airway resistance (NAR)	• VAS • total and individual common cold symptoms
8	Prasad AS (2008)	• average duration of cold symptoms	• plasma levels of - zinc - soluble interleukin-1 receptor antagonist (sIL-1ra), soluble tumor necrosis factor receptor (sTNF-R) - the plasma adhesion molecules, soluble vascular endothelial cell adhesion molecule (sVCAM)-1, soluble ICAM (sICAM)-1.
9	Hensler S (2009)	• illness duration	• none
10	Barrett B (2010)	• Wisconsin Upper Respiratory Symptom Survey (WURSS-21)	• short form (SF-8) scale • SF-36 • Cohen's Perceived Stress Scale (PSS-4) • Ryff Personal Relationships (PR-9) scale • the Life Orientation Test (LOT-6) • IL-8, Neutrophil count (in nasal wash)
11	Eccles R (2010)	• mean total symptom score for study days 2-4	• total symptom score on separate study days 1/2/3/4/5 • the mean total systemic symptom score (headache, muscle ache, chilliness) for study days 2-4 • total systemic symptom score on separate study days 1/2/3/4/5 • local symptom score (sore throat, blocked nose, runny nose, cough, sneezing) • mean of study days 2-4
12	Pach D (2010)	• the area under the curve (AUC) which summarised symptom severity over time	• symptom severity scores • use of medication for the common cold on days 1-7 • general ill feeling • adverse events
13	Schütz K (2010)	• total score of the cold symptoms	• disturbance of daily activities • sleep disorders • additional concurrent medication • the number of tissues used
14	Byun JS (2011)	• WURSS-21-K	• the duration of illness
15	Rakel D (2011)	• WURSS-21	• evaluation of perceived stress (PSS-4) • general quality of life (physical and mental subscales of the (SF-8)) • the feeling thermometer and optimism (LOT)
16	Yakoot M (2011)	• total symptom severity scores	• none

17	Chang J (2012)	• symptom duration	• main symptom duration • minor symptom duration • the changes in main symptom score, minor symptom score • cumulative symptom score 4 days after the treatment • adverse events
18	Fazekas T (2012)	• mean of total symptom scores	• total symptom score on different study days • total systemic and total local symptom scores
19	Ludwig M (2013)	• duration of disease	• presence of cold viruses in nasal fluid samples • severity of common cold symptoms on separate study days • number of days without symptoms during the observation period • use of co-medication additional to the study treatment between days 8-21, the number of cleared or newly acquired • viral infections during the observation period
20	Picon PD (2013)	• the sum of the scores of 10 common cold symptoms	• overall symptom duration • time to return to usual activities • use of rescue medication
21	Okabayashi S (2014)	• the aggravation of cold, nasal, throat or bronchial symptoms	• aggravation of cold symptoms within seven days after study entry and the severity of the main cold symptoms during the first five and seven days
		Prevention	
No	Author (year)	Primary outcome	Secondary outcome
1	de Vress M (2006)	• incidence of cold, duration, severity of cold symptoms	• flow cytometry - CD45+ (lymphocytes), - CD45+,CD19+ (B-lymphocytes) - CD45+, CD3+ (T lymphocytes), - CD45+, CD3+, CD4+ (TH cells) - CD45+, CD3+, CD8+ (TS plus TC cells), - CD 45+, CD 56+ (natural killer cells) • virus infection • fecal lactobacilli, bifidobacteria
2	Kurugol Z (2006)	• the number of colds	• the duration and the severity of cold symptoms
3	Sasazuki S (2006)	• incidence of common cold	• none

4	Roll S (2010)	• the number of days with at least moderate (i.e. moderate or severe) common cold symptoms	• days with any common cold symptoms • common cold-related days unable to work • days with common cold-related medication use • health related quality of life (SF-12)
5	Jawad M (2012)	• adverse events	• the number of cold episodes
6	Rerksuppaphol S (2012)	• occurrence of any symptom of cold	• occurrence of vomiting • diarrhea • use of antibiotics • school absence due to any cause • school absence due to cold • duration of all symptoms
7	Rerksuppaphol S (2013)	• occurrence of any symptom of cold	• occurrence of vomiting • diarrhea • use of antibiotics • school absence due to any cause • school absence due to cold • duration of all symptoms
8	Vitetta L (2013)	• cold events	• International Physical Activity Questionnaire (IPAQ), • 3 day dietary recall questionnaire • Perceived Stress Scale-10 item

Ⅳ. 고 찰

감기는 여러 바이러스에 의한 경증의 상기도 감염 증후군으로 정의되며 독감, 편도염, 급성 기관지염, 급성 비부비동염, 후두염 등과 구별되는 증상이다[41]. 전통적으로 급성상기도감염과 동일하게 정의되기도 했으나 최근에는 상기도감염은 감기, 후두염, 인두염/편도염, 급성 비염, 급성 부비동염, 급성 중이염을 포함하는 개념으로 정의되었고[42], 감기는 상기도 감염에 포함되는 경증의 자체 한정적 기간을 가지는 증후군으로 정의되는 추세이다.

미국의 경우, 아이들은 일년에 약 5-7번 정도의 감기에 걸리며 성인은 2-3번의 감기에 걸리는 것으로 보고되고 있다. 감기로 인해 매해 2500만 명이 의사를 찾으며, 2000만 번 정도의 직장 결근과 2200만 번 정도의 학교 결석의 원인이 되고 있다[2]. 한국의 2014년 건강보험심사지표에 따르면 감기관련 상병은 외래 진료일수의 11.8%(101,546천 일), 외래요양급여비용의 6.03%(1조3840억원)를 차지한다고 보고되었다[42].

이처럼 감기는 경증의 증후군이지만, 사회생활과 일상생활에 지장을 초래하며 경제적 손실도 큰 증후군으로, 감기 치료에 대한 관심이 높아지고 있는 실정이다. 특히 감기를 일으키는 바이러스가 200종이 넘어 원인을 규명하여 치료하는 방법 자체가 실효성을 거두지 못하고 항생제에 대한 리뷰논문을 통해서도 치료에 대한 근거가 없어지면서[5], 감기 관련한 많은 임상시험이 증상을 회복시키는 대증치료에 초점을 맞추고 있다.

이를 기반으로 감기에 대한 한약제제의 치료 또는 예방에 대한 효능에 대한 연구의 필요성이 제기되고 있으며, 이를 객관적으로 규명할 수 있는

임상시험 가이드라인이 시급한 실정이다. 감기에 대한 한약제제 가이드라인을 만들기 위한 기초자료 조사로서 우선 최근 10년간 시행된 감기 관련 임상시험을 분석하여, 감기의 범위 및 선정 제외기준, 1차 · 2차 평가변수, 평가 도구 등에 대한 고찰을 시행하였다.

우선, 감기에 대한 정의를 살펴보니 '바이러스에 의한 상기도 감염'으로 정의한 논문이 일반적이었다. '경증'이나 '자체 한정기간을 가지는' 등의 용어는 1편 외에는 정의에 포함되어 있지 않았으며 감기의 범위를 다른 편도염이나 부비동염과 한정짓는 문구도 거의 사용되지 않았다. 다만 선정 제외기준에서 보면 제외기준에 감기와 유사한 질환을 구분하고자 한 연구가 2-3편 있어 감기관련 최신의 정의를 반영한 논문도 다소 있었다. 향후 진행되는 임상시험에서는 최신의 정의를 따라 '경증의, 자체 한정기간을 가지는 바이러스에 의한 상기도 감염 증후군'으로 정의하는 것이 타당할 것으로 판단되며, 기타 세균성으로 일어나는 편도염, 부비동염, 중이염, 후두염, 인두염 등과 구별 짓는 것이 필요할 것으로 보인다.

연구개요를 보면 우선 감기 치료에 대한 효과를 밝히고자 한 논문이 21편, 예방에 대한 논문이 8편으로 이루어졌다. 2003-2007년 임상연구를 분석한 논문과 비교한 결과[11], 기존에는 echinacea에 관한 임상연구만 있었던 반면, 최근에는 한약복합제제(소청룡탕 및 연교패독산, Shi-cha 캡슐, Immuonomax (echinacea+마늘+인삼+sativa oil+비타민+아연), Kakkonto(갈근탕))에 대한 연구가 2011년부터 2014년 사이에 발표되어 감기 치료에 대한 한약복합제제에 대한 연구가 활발해지는 것을 확인할 수 있었다. 치료에 대한 효능연구에서 중재군의 투여기간은 7일 이내 혹은 7일에서 10일 이내가 62%에 해당되어, 감기 이환기간을 고려하여 일주일 내외의 투여기간을 이용하는 것을 확인하였다. 연구결과는 유의한 효과가 있었던 논문이 59%였으며, 한약제제에 대한 논문 4편에서 보면 2편에서는 유의한 효과를 보고하였고, 1편은 제한적 효과를 1편은 대조군과 유의한 차이를 발견하지 못하였다.

선정기준에서 감기에 대한 중증도 기준은 Jackson이 임상연구를 위해 발표한 증상 범주를 가장 빈용하고 있었다[43,44]. 많은 연구들이 이 증상 범주를 기준으로 그대로 차용하거나 한두 문항을 수정하여 연구를 진행하여 왔다. 2003-2007년의 임상연구를 고찰한 논문과 비교할 때 Jackson 증상 범주를 기존보다 많이 차용하고 있음을 알 수 있었는데, 이는 객관적이고 신뢰성 있는 기준을 세우고자 하는 연구자들의 고민이 반영된 것으로 판단된다. Jackson의 증상도구는 비록 타당도 연구가 진행되지는 않았으나, 많은 연구자들이 사용하고 있는 도구로 증상은 4가지 증상(콧물, 코막힘, 재채기, 인후통) 또는 8가지 증상(콧물, 코막힘, 재채기, 기침, 인후통, 두통, 근육통, 오한)으로 구성된 것을 가장 많이 사용하였다. 최신 임상연구를 분석해 볼 때, 선정기준에서 Jackson의 증상도구로 중증도를 판단하거나 일정 점수 이상을 선정기준으로 취하는 것은 적절하다고 판단된다.

감기와 관련된 평가도구 중 신뢰도와 타당도가 입증된 도구는 WURSS-21[45]였다. WURSS-21은 감기증상을 측정하는 문항에 삶의 질을 측정하는 문항을 추가한 평가도구로, 이미 한국어로 번안하여 신뢰도와 타당도 연구가 진행되었으므로[46], 감기 임상시험에서 평가도구로 WURSS-21를 사용하는 것을 일차적으로 권고할 수 있을 것으로 판단된다. 최근에는 문항을 간소화한 WURSS-11도 개발되어 발표되었으므로[47], 이를 번안하여 국내에서 적용해 보는 것도 고려해야 한다. WURSS-21에는 Jackson의 증상 도구 중 4가지 증상은 모두 포함되며, 8가지 증상도구 중에서는 두통, 오한, 근육통이 제외되어 있다. 보다 간소화된 WURSS-11 평가도구에도 Jackson 증상도구 4가지 증상은 포함되며, 8가지 증상도구 중에서는 동일하게 두통, 오한, 근육통이 제외되었다. 평가도구에서 WURSS-21을 사용하는 것은 가능하지만, 한의학적 변증형을 포함한

임상시험을 진행할 경우에, 변증 진단에 중요하게 사용되는 증후에 대한 포함 여부에 대해서는 고민이 필요할 것으로 판단된다.

V. 결 론

최근 10년간 PubMed, EMBASE, CENTRAL에 발표된 감기 치료 및 예방에 대한 효능에 대한 임상시험 논문을 분석하여 다음의 결론을 얻었다.

1. 감기에 대한 정의는 최신지견이 반영되지 않고 기존에 사용되던 정의가 혼재되어 있었다.
2. 감기에 대한 치료 효과 연구에서 최근 3-4년간 한약제제를 중재로 사용된 연구가 새로 시행되었다. 기타 단미 한약재 2편 및 대체요법과 관련한 임상시험이 주를 이루었으며, 양약 관련된 임상시험의 수는 감소하는 추세를 보였다.
3. 선정기준에 Jackson의 증상도구가 감기 증상을 채택하고 중증도를 결정하는 도구로 다수 사용되었다.
4. 신뢰도와 타당도를 획득한 WURSS-21 평가도구가 최근에 개발되어 연구에 사용되었으나, 활용빈도수는 높지 않았다.

감기와 관련된 임상시험에서 신뢰도와 타당도가 확보된 평가도구는 WURSS-21이였으며, 한국에서도 번안되어 신뢰도와 타당도가 입증되었으므로, 감기에 대한 한약제제 임상시험을 진행할 때 일차적으로 고려할 수 있는 평가도구로 판단되었다. 감기라는 임상 증후군은 실험실적 지표 등을 평가변수로 두기 어려운 관계로 환자가 기입하는 주관적 증상에 의존해야 하므로, 신뢰도와 타당도가 검증된 평가도구의 사용이 더욱 중요할 것이다. 그 외에 본 연구의 자료를 바탕으로 감기의 명확한 정의, 그에 따른 선정 제외기준, 중재기간, 연구 설계 등의 국내 감기 임상시험 가이드라인 제정에 기본이 되는 정보를 제공할 수 있을 것으로 판단된다.

향후 한국 및 중국을 포함하여 감기와 관련된 한약제제에 대한 임상시험을 분석 및 고찰하여 최근 진행되고 있는 한약제제에 대한 임상시험을 구체적으로 살펴보고 기존에 발표된 한의학적 변증 가이드라인을 포함하여 한의학적 변증에 대한 분석도 필요할 것으로 판단되며, 이는 가이드라인 제정을 함에 있어 추후 보고하고자 한다.

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참고문헌

1. Heikkinen T, Järvinen A. The common cold. *Lancet* 2003;361(9351):51.
2. Turner RB. Epidemiology, pathogenesis, and treatment of the common cold. *Ann Allergy Asthma Immunol* 1997;78(6):531-9.
3. Benson V, Marrano MA. Current estimates from the National Health Interview Survey, 1995. *Vital Health Stat 10* 1998;199:1-428.
4. Fashner J, Ericson K, Werner S. Treatment of the common cold in children and adults. *Am Fam Physician* 2012 Jul 15;86(2):153-9.
5. Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1998;316:906-10.
6. Pratter MR. Cough and the common cold:

ACCP evidence-based clinical practice guidelines. *Chest* 2006 Jan;129(1 Suppl):72S-4S.
7. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998;280(18):1569-75.
8. Roxas M, Jurenka J. Colds and influenza: a review of diagnosis and conventional, botanical, and nutritional considerations. *Altern Med Rev* 2007;12:25-48.
9. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C; CONSORT Group. Recommendations for reporting randomized controlled trials of herbal interventions: Explanation and elaboration. *J Clin Epidemiol* 2006;59(11):1134-49.
10. Jiao Y, Liu J, Jiang L, Liu Q, Li X, Zhang S, et al. Guidelines on common cold for traditional Chinese medicine based on pattern differentiation. *J Tradit Chin Med* 2013;33(4):417-22.
11. 양수영, 변준섭, 황지호, 안정조, 홍권의, 강위창, 등. 감기 임상연구의 최신 동향 및 평가도구에 관한 연구. 대한한의학회지 2008;29(2):165-81.
12. Eby GA, Halcomb WW. Ineffectiveness of zinc gluconate nasal spray and zinc orotate lozenges in common-cold treatment: a double-blind, placebo-controlled clinical trial. *Altern Ther Health Med* 2006;12(1):34-8.
13. Hull D, Rennie P, Noronha A, Poore C, Harrington N, Fearnley V, et al. Effects of creating a non-specific, virus-hostile environment in the nasopharynx on symptoms and duration of common cold. *Acta Otorhinolaryngol Ital* 2007; 27(2):73-7.
14. Kurugöl Z, Bayram N, Atik T. Effect of zinc sulfate on common cold in children: randomized, double blind study. *Pediatr Int* 2007;49(6) :842-7.
15. Latte J, Taverner D. Clinical trial of 3 days of treatment with oral pseudoephedrine for the common cold in the southern hemisphere. *Am J Rhinol* 2007;21(4):452-5.
16. Lizogub VG, Riley DS, Heger M. Efficacy of a pelargonium sidoides preparation in patients with the common cold: a randomized, double blind, placebo-controlled clinical trial. *Explore (NY)* 2007;3(6):573-84.
17. Mizoguchi H, Wilson A, Jerdack GR, Hull JD, Goodale M, Grender JM, et al. Efficacy of a single evening dose of syrup containing paracetamol, dextromethorphan hydrobromide, doxylamine succinate and ephedrine sulfate in subjects with multiple common cold symptoms. *Int J Clin Pharmacol Ther* 2007;45(4):230-6.
18. Eccles R, Eriksson M, Garreffa S, Chen SC. The nasal decongestant effect of xylometazoline in the common cold. *Am J Rhinol* 2008;22(5):491-6.
19. Prasad AS, Beck FW, Bao B, Snell D, Fitzgerald JT. Duration and severity of symptoms and levels of plasma interleukin-1 receptor antagonist, soluble tumor necrosis factor receptor, and adhesion molecules in patients with common cold treated with zinc acetate. *J Infect Dis* 2008;197(6):795-802.
20. Hensler S, Guendling PW, Schmidt M, Jork K. Autologous blood therapy for common cold--a randomized, double-blind, placebo-controlled trial. *Complement Ther Med* 2009;17(5-6):257-61.
21. Barrett B, Brown R, Rakel D, Mundt M, Bone K, Barlow S, et al. Echinacea for treating the common cold: a randomized trial. *Ann Intern Med* 2010 ;153(12):769-77.
22. Eccles R, Meier C, Jawad M, Weinmüllner R,

Grassauer A, Prieschl-Grassauer E. Efficacy and safety of an antiviral Iota-Carrageenan nasal spray: a randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold. *Respir Res* 2010;11:108.

23. Pach D, Knöchel B, Lüdtke R, Wruck K, Willich SN, Witt CM. Visiting a sauna: does inhaling hot dry air reduce common cold symptoms? A randomised controlled trial. *Med J Aust* 2010;193(11-12):730-4.
24. Schütz K, Sass M, de With A, Graubaum HJ, Grünwald J. Immune-modulating efficacy of a polyphenol-rich beverage on symptoms associated with the common cold: a double-blind, randomised, placebo-controlled, multi-centric clinical study. *Br J Nutr* 2010;104(8):1156-64.
25. Byun JS, Yang SY, Jeong IC, Hong KE, Kang W, Yeo Y, et al. Effects of So-cheong-ryong-tang and Yeon-gyo-pae-dok-san on the common cold: randomized, double blind, placebo controlled trial. *J Ethnopharmacol* 2011;133(2):642-6.
26. Rakel D, Barrett B, Zhang Z, Hoeft T, Chewning B, Marchand L, et al. Perception of empathy in the therapeutic encounter: effects on the common cold. *Patient Educ Couns* 2011;85(3):390-7.
27. Yakoot M, Salem A. Efficacy and safety of a multiherbal formula with vitamin C and zinc (Immumax) in the management of the common cold. *Int J Gen Med* 2011;4:45-51. Treatment of common cold patients with the shi-cha capsule: a multicenter, double-blind, randomized, placebo-controlled, dose-escalation trial.
28. Chang J, Dong SJ, She B, Zhang RM, Meng MB, Xu YL, et al. Treatment of common cold patients with the shi-cha capsule: a multicenter, double-blind, randomized, placebo-controlled, dose-escalation trial. *Evid Based Complement Alternat Med* 2012;2012:254571.
29. Fazekas T, Eickhoff P, Pruckner N, Vollnhofer G, Fischmeister G, Diakos C, et al. Lessons learned from a double-blind randomised placebo-controlled study with a iota-carrageenan nasal spray as medical device in children with acute symptoms of common cold. *BMC Complement Altern Med* 2012;12:147.
30. Ludwig M, Enzenhofer E, Schneider S, Rauch M, Bodenteich A, Neumann K, P et al. Efficacy of a carrageenan nasal spray in patients with common cold: a randomized controlled trial. *Respir Res* 2013;14:124.
31. Picon PD, Costa MB, da Veiga Picon R, Fendt LC, Suksteris ML, Saccilotto IC, et al. Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial. *BMC Infect Dis* 2013;13:556
32. Okabayashi S, Goto M, Kawamura T, Watanabe H, Kimura A, Uruma R, et al. Non-superiority of Kakkonto, a Japanese herbal medicine, to a representative multiple cold medicine with respect to anti-aggravation effects on the common cold: a randomized controlled trial. *Intern Med* 2014;53(9):949-56.
33. de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al. Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial. *Vaccine* 2006;24(44-46):6670-4.
34. Kurugöl Z, Akilli M, Bayram N, Koturoglu G. The prophylactic and therapeutic effectiveness

of zinc sulphate on common cold in children. *Acta Paediatr* 2006;95(10):1175-81.
35. Sasazuki S, Sasaki S, Tsubono Y, Okubo S, Hayashi M, Tsugane S. Effect of vitamin C on common cold: randomized controlled trial. *Eur J Clin Nutr* 2006;60(1):9-17.
36. Roll S, Nocon M, Willich SN. Attenuation of common cold symptoms by encapsulated juice powder concentrate. *Eur J Integr Med* 2010;2(4):213.
37. Jawad M, Schoop R, Suter A, Klein P, Eccles R. Safety and Efficacy Profile of Echinacea purpurea to Prevent Common Cold Episodes: A Randomized, Double-Blind, Placebo-Controlled Trial. *Evid Based Complement Alternat Med* 2012;2012:841315.
38. Rerksuppaphol S, Rerksuppaphol L. Randomized controlled trial of probiotics to reduce common cold in schoolchildren. *Pediatr Int* 2012 Oct;54(5):682-7.
39. Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of chelated zinc for prevention of the common cold in Thai school children. *Paediatr Int Child Health* 2013 Aug;33(3):145-50.
40. Vitetta L, Coulson S, Beck SL, Gramotnev H, Du S, Lewis S. The clinical efficacy of a bovine lactoferrin/whey protein Ig-rich fraction (Lf/IgF) for the common cold: a double blind randomized study. *Complement Ther Med* 2013 Jun;21(3):164-71.
41. National Institute for Health and Clinical Excellence (NICE 69). Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. 2008. (Clinical guideline 69)
42. 건강보험심사평가원, 2014년 건강보험통계지표.
43. Jackson GG, Dowling HF, Spiesman I, Boand AV. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. *AMA Arch Intern Med* 1958 Feb;101(2):267-78.
44. Jackson GG, Dowling HF, Muldoon RL. Acute respiratory diseases of viral etiology. VII. Present concepts of the common cold. *Am J Public Health Nations Health* 1962;52:940-5.
45. Barrett B, Brown RL, Mundt MP, Thomas GR, Barlow SK, Highstrom AD, et al. Validation of a short form Wisconsin Upper Respiratory Symptom Survey (WURSS-21). *Health Qual Life Outcomes* 2009;7:76.
46. Yang SY, Kang W, Yeo Y, Park YC. Reliability and validity of Wisconsin Upper Respiratory Symptom Survey, Korean version. *J Epidemiol* 2011;21(5):313-8.
47. Obasi CN, Brown RL, Barrett BP. Item reduction of the Wisconsin Upper Respiratory Symptom Survey (WURSS-21) leads to the WURSS-11. *Qual Life Res* 2014;23(4):1293-8.

【Appendix】

		Treatment	
		Inclusion	Exclusion
1	Eby GA (2006)	• patients with 2 or more signs and symptoms of common colds (with at least 1 nasal symptom)	• not presented
2	Hull D (2007)	• healthy males and females between the ages of 18 and 65 years	• were experiencing any of the symptoms of a Common Cold at the time of recruitment • females who were pregnant, trying to become pregnant, or nursing history of hypersensitivity to zinc or any component of the nasal test formulations • currently suffering from a chronic medical condition requiring medication • taking any medication, with the exception of birth control pills and hormone replacement products, on a regular basis (3 or more times per week) • frequent infections in the nose, lung or ear, problems related to upper or lower respiratory tract (e.g. nose bleeds, breathing difficulties or throat sensitivity) • history of frequent headaches /migrain • having been exposed to any investigational drug within 1 month prior to the start of the study, or if the subject planed to participate in any other investigational drug study while in this trial • was currently suffering, or was prone to experiencing, the symptoms of respiratory allergy (rhinitis) • was currently using decongestants, oral antihistamines or oral zinc products, or had experienced problems using nasal sprays
3	Kurugol Z (2007)	• Children who developed symptoms of common cold within the first 24-48h • Had two or more of the following 10 symptoms. 10 symptoms: cough, nasal drainage, nasal congestion, headache, hoarseness, muscle ache, scratchy throat, sneezing, sore throat, and fever (axillary temperature 〉37 ℃)	• patients with common cold symptoms for 〉48h • immunodeficiency disorder, chronic disease, recent acute respiratory disease (diagnosed by a physician in the previous 2 weeks), zinc allergy, allergic disease or non-allergic rhinitis • patients with a positive culture for group A Streptococcus and a positive cell culture for influenza A or B viruses • children who received antibiotics, antihistamines, decongestants, steroids or other zinc preparations during the course of the study

4	Latte J (2007)	• male and female subjects aged 18-65 years old in good general health • currently suffering an episode of the common cold of no more than 48 hours duration before visit 1	• women were pregnant or lactating or not using an appropriate form of contraception • history of perennial allergic rhinitis or any unstable medical condition
5	Lizogob VG (2007)	• male and female patients aged 18 to 55 years • provision of written informed consent • presence of either two major cold symptoms (nasal discharge, sore throat) and at least one minor cold symptom (nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, and fever), or presence of one major and at least three minor cold symptoms • duration of cold symptoms for 24 to 48 hours	• presence of any other acute ear, nose, and throat and respiratory tract disease than the common cold (eg, tonsillitis, sinusitis, allergic rhinitis, otitis, bronchitis) • positive rapid test for group A beta-hemolytic streptococcus • recurrent tonsillitis, sinusitis or otitis of greater than or equal to three episodes or recurrent bronchitis of greater than or equal to six episodes • during the 12 months prior to enrollment in the trial • any chronic ear, nose, and throat and respiratory tract disease (eg, allergic rhinitis, bronchitis, bronchial asthma, obstructive pulmonary disease, cystic fibrosis • treatment with antibiotics, glucocorticostroids or antihistamines during the four weeks prior to enrollment in the trial, • treatment with cold medications that might impair the trial results (eg, decongestants, local anesthetics), cough or pain relief medications and/or any other treatment for the common cold during the seven days prior to enrollment in the trial Known or suspected hypersensitivity to the investigational product • previous or existing severe cardiovascular disease or unstable diabetes mellitus, severe renal or hepatic dysfunction (serum creatinine, serum AST, ALT, or alkaline phosphatase more than three times the upper limit of normal) at any time during the 12 months prior to enrollment in the trial • evidence of any malignant disease during the five years prior to enrollment in the trial • pregnancy or breast-feeding • participation in another clinical trial in the same time period or within three months prior to inclusion in the trial

6	Mizoguchi H (2007)	• common cold symptoms for at least 1 day and not longer than 5 days prior • symptoms within the last 24 hours of enrollment must have included moderate or severe nasal congestion, moderate or severe runny nose, at least mild cough, at least mild pain from one or more of the following pain sore throat, sore chest, headache or body aches/pains and sleep disturbance	• allergic to any of the study medications • were experiencing acute symptoms of respiratory allergies • history of chronic aches/pains, chronic fatigue or mood disorders, or chronic respiratory illness, or had a significant coexisting illness or medical condition that would compromise their ability to swallow, absorb, metabolize or excrete the study medication • any medications/supplements within the previous 24 hours that were indicated for cold symptoms, pain relief or that could produce drowsiness or promote alertness Taken any antihistamines within the previous 72 hours • taken any sedatives within the previous weeks • taken any antidepressants within the previous 3 weeks
7	Eccles R (2008)	• ≥18 years of age, with recent onset of • nasal congestion associated with common cold • minimum nasal congestion score of 2 (moderate) according to a 4-point scale (0 not present; 1 mild; 2 moderate; and 3 severe • had cold symptoms of 36 hours duration before study entry • presented with a minimum of two common cold symptoms (runny nose, blocked nose, sore throat, and/or cough) on entry to the study • were male patients or a nonpregnant, nonlactating female patient • were willing and able to undergo measurement of total nasal airway • resistance (NAR) using active posterior rhinomanometry and score symptoms	• inability to abstain from smoking for 1 hour before and for the duration of each visit • NAR of 0.2 Pa/cm3 per second at screening visit 1 • history of perennial allergic rhinitis, unless recruited out of season • clinically significant abnormalities (e.g., polyps and deviated septum) • history of transsphenoidal hypophysectomy or rhinitis medicamentosa • bacterial sinusitis infection during the past 2 weeks before study entry; use of drugs (antibiotics, adrenergics, glucocorticosteroids, antidepressants, or monoamine oxidase inhibitors); use of any medication that may affect sleep as judged by the investigator • known hypersensitivity to xylometazoline or any of the excipients of Otrivin nasal spray • alcohol intake • uncontrolled arterial hypertension
8	Prasad AS (2008)	• cold symptoms for 24 h or less • 〉18 years of age • at least two out of 10 common cold symptoms (cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever)	• pregnant • had any known immune deficiency disorder or chronic illness • symptoms of the common cold for 〉24h • had previously used zinc lozenges to treat the common cold

9	Hensler S (2009)	• patients (18-75 years of age) • symptoms of common cold (cough, rhinitis, sore throat, fever etc.) which lasted not longer than 7 days and resulted in at least four points on a modified Jackson-Score	• illness duration before treatment longer than 7 days • severe forms of respiratory infections (exacerbation of chronic obstructive pulmonary disease by infection, exacerbation of asthma by infection, streptococcal tonsillitis, peritonsillar infection, pneumonia, mastoiditis, etc.) • other diseases with similar symptoms (e.g. allergic rhinitis) • immunosuppressing diseases (e.g. AIDS) or medication (e.g. Cyclosporin), dementia or coagulopathy
10	Barrett B (2010)	• "Yes" to either. "Do you think that you have a cold?" or "Do you think you are coming down with a cold?" • using Jackson's criteria, participants had to report at least one of four cold symptoms: A) nasal discharge; B) nasal obstruction; C) sneezing; and/or D) sore throat. • symptoms had to start within 36 hours before enrollment • participants needed a Jackson score of 2 or higher, summing symptom scores, with 0=absent, 1=mild, 2=moderate, 3=severe	• use of antibiotics, antivirals, nasal steroids, decongestants, antihistamines, combination cold formulas, echinacea, zinc or vitamin C • to avoid confounding from allergy or asthma symptoms, we excluded anyone with a history of allergic rhinitis who reported sneezing or itching of the nose or eyes and anyone with a history of asthma who reported current cough, wheezing or shortness of breath • people with autoimmune and immune deficiency disease were excluded by self-report, as were pregnant women
11	Eccles R (2010)	• by Jackson score, subjects had symptom scores of 1 or greater for sore throat, runny or blocked nose and a total symptom score of 9 or less for the sum of severity scores comprising headache, muscle ache, chilliness, sore throat, runny nose, blocked nose, cough, and sneezing	• unwilling to sign the consent form • known hypersensitivity or allergy to any component of the study medication • clinically significant cardiovascular, endocrine, neurological, respiratory, or gastrointestinal disease history • any other current disease that was considered by the investigator as an exclusion criteria, e.g. current allergic rhinitis, chronic obstructive pulmonary disease (COPD) • history of alcohol/substance abuse Prescription medication/concomitant therapy other than for contraception, e.g. systemic steroids, intranasal medicines, antibiotics • incidence of common cold or flu like symptoms for more than 48h • current smoking • relationship to any study personnel, administration of any investigational drug, participation in any other clinical trial within 4 weeks of entry into our study

12	Pach D (2010)	• between 18 and 60 years of age • at least two out of 10 common cold symptoms cough, headache, hoarseness, muscle ache, nasal drainage (nasal drip), nasal congestion, scratchy throat, sore throat, sneezing and fever (〉38.5 ℃) for 24 hours or less	• had any of these cold symptoms for more than 24 hours • circulatory problems • severe chronic illness • systolic blood pressure below 100 mmHg or above 160 mmHg • pregnancy
13	Schütz K (2010)	• aged between 20 and 65 years scoring in total at least 5 points on the severity of five cold symptoms (maximum 15 points) • having present at least one cold-related local finding	• active allergic rhinitis or asthma • fever (body temperature 39.8 ℃) clinically relevant laboratory value deviations indicating severe organ or system disease • bacterial tonsillitis • pyorrhoea on the back of the throat cancer or AIDS (HIV positive) pregnancy or nursing • alcohol • medication or drug dependence, participation in a clinical study within the previous 30 days • intake of immune suppressants, immune stimulants, • analgesics/anti-rheumatics, anti-inflammatories, antitussives, expectorants influenza remedies, mouth and throat therapeutics • inability to comply due to language difficulties
14	Byun JS (2011)	• diagnosed with the common cold by research physicians. • due to the onset of cold symptoms in less than 48 h, such as (i) runny nose, sore throat, and one of the 8 symptoms (plugged nose, sneezing, scratchy throat, cough, hoarseness, headache, body aches, and fever) or (ii) either runny nose or sore throat and at least three of the 8 symptoms	• age under 18 years or over 60 years pregnant or lactating • with allergic rhinitis, asthma, COPD, sinusitis (recurrent over 2 times per year) • anatomical nasal obstruction or deformity • otitis, exudative pharyngitis, other chronic illness
15	Rakel D (2011)	• “yes” to one of two questions • “Do you think you have a cold?” or “Do you think you are coming down with a cold?” The person then had to answer “yes” to at least one of the following four symptoms (nasal discharge, nasal obstruction, sneezing sore throat) • symptoms no more than 36 hours prior to enrollment	• pregnancy • use of antibiotics, decongestants, antihistamines, echinacea, zinc, vitamin C or a combination cold formula • history of allergies or asthma with current symptoms of allergic rhinitis, cough, shortness of breath, sneezing, nose or eye itching

16	Yakoot M (2011)	• cold symptoms for 36 hours or less • two of the following 10 symptoms: cough, headache, hoarseness, muscle aches, nasal discharge, nasal congestion, scratchy throat, sore throat, sneezing, or an oral temperature 37.7 ℃	• pregnancy • immune deficiency, cancer, severe liver /renal dysfunction, or critical illness • symptoms of the common cold for more than 36 hours
17	Chang J (2012)	• 18 to 65 years of age • diagnosis of common cold by a respiratory expert according to relevant criteria and the syndrome criteria of wind-cold type in TCM • patient within 48 hours of onset of common cold-like illness • patient must be able to understand and give written informed consent and report adverse events and concomitant medication for the duration of the study	• patient has suffered from acute viral pharyngitis or laryngitis, acute herpetic pharyngitis or laryngitis, acute conjunctivitis, as well as acute tonsillitis • patient has taken any medication for relief of symptoms prior to study initiation • patient who has fever (>38.5 ℃) • patient who is on analgesic or anti-inflammatory regimen requiring treatment with analgesics, nonsteroidal anti-inflammatory drugs, or steroids • patient is pregnant, nursing, or a woman of childbearing potential not practicing adequate contraception. Women, who are uncertain if they are pregnant, may participate in the study, if they undergo a pregnancy test, which shows a negative result • patient has comorbid condition, uncontrolled metabolic condition or psychiatric condition that might make tolerance or evaluation of the symptoms difficult
18	Fazecas T (2012)	• previously healthy, immunocompetent children and adolescents between 1 and 18 years of age with symptoms of acute rhinitis prevailing for less than 48 hours, and a total symptom score (TSS) ≤9	• suspected bacterial infections, recent use of antimicrobial drugs, and intranasal treatment at first presentation
19	Ludwig M (2013)	• adults (18 years and older) • early symptoms of the common cold (onset less than 48 hours before inclusion) • mild to moderate intensity (Total Symptoms Score [TSS], of 2 to 9)	• hypersensitivity or allergy to any component of the test product • concomitant disease or infection that could interfere with participation in the study • other reasons for nasal obstruction and other past or present conditions and treatments that could influence symptom scores

20	Picon PD (2013)	• aged 18 to 60 years • duration of symptoms no longer than 72 hours • the common cold was defined by the presence of at least two of the following 10 symptoms: sneezing, rhinorrhoea, nasal congestion, headache, myalgia, throat discomfort, sore throat, dysphonia, cough and fever.	• pregnancy or breast feeding • known hypersensitivity to any component of the study formulation • use of alcohol or illicit drugs • use of monoamine oxidase (MAO) inhibitors or barbiturates • perennial or seasonal allergic rhinitis confirmed at screening • any current acute disease or uncontrolled exacerbation of chronic disease • clinical evidence of immunosuppression • vaccination against influenza up to 1 week before inclusion • need for antiviral therapy to treat influenza A or B infection • need for antibacterial therapy to treat acute respiratory infection • use of medication to treat conditions acquired before inclusion for a time shorter than two time intervals of administration of these drugs • participation in another clinical trial less than 1 year before
21	Okabayashi S (2014)	• 18 to 65 years of age with throat discomfort and some feeling of chills without sweating • history of colds during the preceding three years • who visited a participating facility within 48 hours after the beginning of cold symptoms	• patients who were moderately or severely afflicted • had a fever of 37.5 ℃ or more • had already taken medicine for the cold • had a serious underlying disease
		Prevention	
		Inclusion	Exclusion
1	de Vress M (2006)	• healthy adults	• not vaccinated against influenza within the last 12 month • without known congenital or acquired immune defects or allergies
2	Kurugol Z (2006)	• children were required to be in overall good health and to be 2 to 10 years of age	• history of sensitivity to or an idiosyncratic experience with zinc • parents were unwilling or unable to comply with clinical study procedures

3	Sasazuki S (2006)	• men and women aged 40-69 years living in four municipalities of the Yokote Public Health Center District • subjects with a diagnosis of chronic atrophic gastritis (defined as pepsinogen (PG) Io70 ng/ml and PG I/PG II ratio o3.0) • no history of gastric cancer, gastric surgery, liver cancer, cirrhosis, or other cancers within the previous 5 years • no abnormal liver function (aspartate aminotransferase 4100 IU/l, alanine aminotransferase 4100 IU/l, or alkaline phosphatase 4800 IU/l) • no use of diet supplements containing b-carotene or vitamin C no expectation of moving outside the study area within 1 year	• early stage the subjects who either did not comply or showed side effects
4	Roll S (2010)	• 18-65 years of age • able and willing to take the active or placebo capsules over the entire study period • healthcare professionals with direct patient contact (physicians, nurses, physiotherapists, etc.) • written informed consent	• acute influenza or common cold present at the time of enrolment known or suspected hypersensitivity or allergy to one of the ingredients of Juice Plus • any alarming symptoms such as significant unintentional weight loss, fever, or any other sign indicating serious or chronic disease including suspected or confirmed malignancy, or other significant cardiovascular, gastrointestinal, pulmonary, renal, pancreatic or liver disease • alcohol addiction or drug abuse pregnancy or lactation • language limitations regarding interviews and questionnaires
5	Jawad M (2012)	• adults (≥18 years old) of good physical condition, that experienced ≥2 colds per year	• ineffective contraception • participation in another study • women that were pregnant or breast feeding • current cold infection • currently taking antimicrobial or antiviral medication • alcohol or drug abuse • psychiatric disorders, epilepsy, attempted suicide • planned surgical intervention • serious chronic disease that could influence absorption, metabolism, or elimination of the medication • known AIDS or other autoimmune diseases • diabetes type 1 • corticosteroid-treated asthma • medicinally treated atopy or allergy • known allergy to plants of the composite family (Asteraceae).

6	Rerksuppaphol S (2012)	• healthy children aged 8-13 years, in grades 3-6	• history of chronic illnesses, such as chronic cough or chronic respiratory disease, asthma, chronic gastrointestinal conditions • behavioral or psychiatric problems or other neurological conditions, immune deficiency • diabetes mellitus • malignancy • chronic renal diseases • congenital heart diseases • chronic liver disease
7	Rerksuppaphol S (2013)	• healthy children aged 8-13 years who were in grades 3-6	• history of chronic illnesses, such as chronic cough or chronic respiratory disease, asthma, chronic gastrointestinal conditions • behavioral or psychiatric problems or other neurological conditions, immune deficiency • diabetes mellitus • malignancy • chronic renal diseases • congenital heart diseases • chronic liver disease • children who were taking vitamin or mineral supplements or had a history of any drug allergy
8	Vitetta L (2013)	• 18 years or older • frequently experience two or more cold-associated symptoms that lasted ≥2 days in the previous 6 months • general good health • female participants agreeing to continue adopting birth control measures for the duration of the trial.	• current or recent (within the last month0 use of all natural supplements including vitamins and minerals, herbal preparations and probiotics • pregnancy or lactating • unwilling to adhere to the study protocol • history of alcohol or substance abuse • history of serious or unstable cardiac, renal, hypertensive, pulmonary, endocrine, immunologic, neurologic or neuropsychiatric disorders