

Clinical Efficacy and Safety of Yukgunja-tang for Gastroesophageal Reflux Disease: A Systematic Review and Meta-Analysis

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Objectives: The purpose of this meta-analysis was to evaluate the effects of Yukgunja-tang(YGJT, Rikkunshito, Liujunzi) on Gastroesophageal Reflux Disease(GERD).

Methods: Sixteen electronic databases were used to search for studies published through March 2019, and a randomized controlled study was conducted to study the effects of YGJT or modified YGJT on GERD. Study quality was assessed using the risk bias tool provided by Cochran, and data analysis was performed using Review Manager 5.3.0 software

Results: Two-hundred and forty articles were initially searched, and 13 studies that satisfied the study criteria were evaluated qualitatively; 11 of the 13 were included in the meta-analysis. In the two studies, the effects of YGJT and a placebo were compared. Meta-analysis showed that YGJT significantly improved FSSG (Frequency Scale for the Symptoms of GERD) scores, but not GSRS (Gastrointestinal Symptom Rating Scale) scores (FSSG: MD -2.40, 95% CI [-5.31, 0.51], $p=0.11$, GSRS: MD 0.05, 95% CI [-0.12, 0.22], $p=0.55$). Meta-analysis of nine studies comparing the efficacies of YGJT and conventional medicine showed that YGJT had a significant clinical effect (OR 5.72; 95% CI [3.41, 9.61]; $I^2 p<0.00001$).

Conclusion: This study suggests that YGJT effectively relieves the symptoms of GERD. Unfortunately, owing to the small sample sizes, limitations of several methodological qualities, we believe large-scale clinical studies with less bias will provide evidence of qualitative improvement.

Key Words : Gastroesophageal Reflux Disease, GERD, Yukgunja-tang, Systematic Review, Meta-analysis

Introduction

Gastroesophageal Reflux Disease (GERD) is commonly encountered in clinical practice¹. The prevalence of GERD in Korea increased from 3.4% in 1998 to 5-29.2% in 2005². The Montreal definition of GERD is a condition that develops when reflux of stomach contents causes troublesome

symptoms and/or complications³). Epidemiologic estimates of the prevalence of GERD are based primarily on the typical symptoms of heartburn and acid regurgitation¹. Empiric PPI therapy provides a reasonable means of confirming the presence of GERD when it is suspected in patients with typical symptoms¹. In Japan, the traditional medication Yukgunja-tang (YGJT, Rikkunshito, Liujunzi) has

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been approved for medicinal use, and is widely used to treat patients with upper gastrointestinal (GI) symptoms⁴).

Although YGJT is used for clinical treatment of GERD in China and Japan and related clinical studies are underway, only random studies on the effects of YGJT on functional dyspepsia⁵ and in animal models⁶ have been conducted in Korea. Therefore, the aim of this meta-analysis was to systematically review the efficacy and safety of YGJT when used to treat GERD.

Methods

1. Data Sources and Search Strategy

The following electronic databases were searched to identify relevant studies uploaded through March 2019: EMBASE, MEDLINE, the Cochrane Library (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, six Korean medical databases (Korea Med, the Korean Medical database, the Korean Studies Information Service System, the Korea Institute of Science and Technology Information, NDSL, and the Oriental Medicine Advanced Searching Integrated System), three Chinese medical databases (the Chinese Medical Database [CNKI], Chongqing VIP Chinese Science and Technology Periodical Database [VIP], and the WanFang Database), and two Japanese databases (J Global and J-Stage). The search terms used were as follows: (Liujunzi OR Rikkunshito OR Yukgunja tang OR Yukkunja tang) AND (gastroesophageal reflux disease OR reflux esophagitis OR nonerosive gastroesophageal reflux disease OR Barrett's esophagus OR Heartburn OR PPI-refractory OR Refractory OR Regurgitation OR Globus pharyngitis) in Korean, English,

Chinese, and Japanese. The databases used in this study were independently searched manually.

2. Selection

1) Types of Studies

All randomized controlled trials (RCTs) were included. Observational, cohort, case-control, case series, qualitative, laboratory studies, and uncontrolled trials were excluded.

2) Types of Participants

GERD was diagnosed using published diagnostic criteria. No restrictions were placed on race, age, or sex.

3) Types of Interventions

Studies that used YGJT or a modified YGJT were included. Modified YGJT prescribed according to traditional Korean medical syndrome definitions was deemed acceptable for the purposes of this study and was defined by practitioners as the addition of herbs to the herbs used to prepare YGJT that resulted in the same effects as YGJT.

4) Types of Comparisons

We included all types of control intervention, including placebo and conventional medication.

3. Outcome Measures

Outcomes were assessed using efficacies, Frequency Scale for the Symptoms of Gastroesophageal reflux disease (FSSG), or Gastrointestinal Symptom Rating Scale (GSRS) during or after intervention, recurrence rate, and adverse effects as a dichotomous and continuous outcome.

4. Data Extraction and Risk-of-Bias

Assessment

Two authors (SWP and SWL) performed the data extraction and collated information independently on participants, interventions, treatment durations, outcomes, and results. Any disagreement between the two authors was resolved by discussion. Risk of bias was assessed using the following seven criteria from Cochrane Collaboration's risk of bias tool.

5. Data Synthesis

The statistical analysis was conducted using Review Manager 5.3.0 software from the Cochrane Collaboration for Windows (The Nordic Cochrane Center, Copenhagen, Denmark). Differences between intervention and control groups were assessed. Dichotomous outcomes were analyzed using the odds ratio (OR) with 95% confidence intervals (CIs) for relative effect. For continuous outcomes, we used the mean difference (MD) with 95% confidence intervals (CIs) to measure effect. Heterogeneity was assessed using the chi-squared test and the I^2 test. A fixed effects model was used when studies were homogeneous, and a random effects model was used when there was heterogeneity ($I^2 > 50\%$) between studies.

Results

1. Description of the Included Trials

A total of 240 studies were originally identified by searching 16 databases using search terms and search strategies. Of these, 108 were excluded for duplication. The remaining 132 studies were reviewed with a focus on titles and abstracts, and 67 were primarily excluded. Subsequently, another 52 studies were excluded for the following

reasons: 25 articles could not find the full text, 15 were not randomized, 2 did not include a clinical trial, 6 did not discuss GERD, and 4 did not use YGJT. Finally, 13 studies were selected, and 11 were included in the meta-analysis. The flow chart of the selection process is provided in Figure 1.

Characteristic data from the 13 studies are summarized in Table 1. Four of the 13 were published in Japan and 9 were published in China between 2010 and 2018. Four studies were reported as GERD, five as RE, one as PPI-refractory GERD, two as PPI-refractory NERD, and one as PPI-refractory LPR (laryngopharyngeal reflux). Sample sizes ranged from 64 to 242, and patients' ages from 18 to 90 years. Seven studies reported disease durations from 1 month to 26 years, and disease durations were not mentioned in six studies.

Two studies compared YGJT with a placebo. One study compared YGJT plus PPI with double-dose PPI, and one compared the effects of YGJT and YGJT plus PPI. The remaining 9 studies compared the effects of YGJT with those of conventional medicines. Therapy durations ranged from 20 days to 8 weeks. Thirteen studies provided details of the herbal formulae of YGJT, and the constituents of the herbal formulae of YGJT are listed in Table 2.

2. Risk of Bias

All studies were described as 'randomized', but only seven studies reported the method of random sequence generation. Three studies described allocation concealments. Eleven studies had high risks of bias for participant and personnel blinding, and two studies had low risk. Only one trial used outcome assessment blinding. All included studies reported complete outcome data.

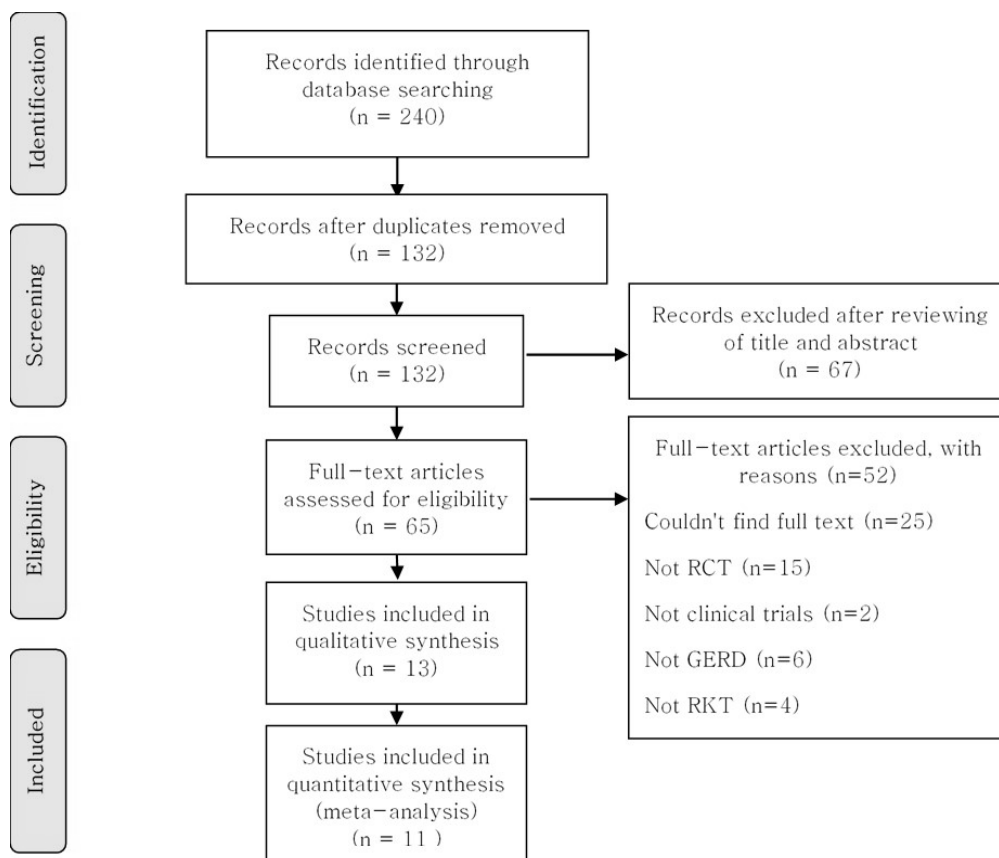


Fig. 1. Flow chart of trial selection process.

All studies had a low risk of selective reporting bias; four studies were published protocols and nine studies included all expected outcomes (Figure 2, 3).

3. Outcome Measurements

YGJT plus PPI versus double-dose PPI and YGJT versus YGJT plus PPI were excluded from the meta-analysis because these were conducted in one study each.

- 1) YGJT versus Placebo
- (1) Symptom Rating Scores

Two of the 13 studies compared the effects of YGJT versus a placebo. FSSG and GSRS scales were used to evaluate YGJT efficacy. Of the 348 patients, 178 received YGJT plus PPI and 170 received a placebo plus PPI. The FSSG scores of these two groups resulted in moderate heterogeneity ($I^2 = 58\%$), so a random effects model was adopted to produce the results (FSSG: MD -2.40, 95% CI [-5.31, 0.51], $P = 0.11$) (Figure 4). The fixed effects model was adopted for GSRS scores because $I^2 = 41\%$, (GSRS: MD 0.05, 95% CI [-0.12, 0.22], $P = 0.55$) (Figure 5). The FSSG score had statistically significant results in the

Table 1. Summary of randomized controlled trials on Yukgunja-tang (YGJT) for GERD

First Author (year)	Classification of GERD	Sample size: age (yrs) duration of disease	Preemptive treatment	Intervention group	Control group	F/U	Outcomes list	Adverse events
Sakata (2014)	PPI-refractory NERD	95(65-85) NR	PPI therapy for 4 wk	YGJT 7.5 g tid + PPI (n=52)	placebo 7.5g tid + PPI (n=43)	8w	(a)(b)	NR
Tomimaga.K (2014)	PPI-refractory NERD	242(≥20 years) NR	PPI therapy for 4wk	YGJT 7.5 g tid + PPI (n=126)	placebo 7.5 g tid + PPI (n=127)	2m	(a)(b)(c)	YGJT 17.4% control 10.2%
Tokashiki.R (2013)	PPI-refractory LPR	22(20-76) NR	PPI therapy for 2wk	YGJT 7.5 g tid (n=11)	YGJT 7.5 g tid + PPI (n=11)	4w	(b)(d)(k)	NS
Tomimaga.K (2012)	PPI-refractory GERD	114(25-90) NR	PPI therapy for 4wk	YGJT 7.5 g tid + PPI (n=57)	PPI double-dose (n=57)	4w	(a)	NS
Xu.C.F. (2014)	RE	64(24-60) NR		Xiangsha YGJT + Xuanfu Daizhe bid (n=32)	PPI + H2RA (n=32)	NR	(c)	NR
Du.X.Q. (2014)	GERD	86(22-61) 3-7m		Dahuangxiangsha YGJT 250ml bid (n=43)	D2RA + PPI (n=43)	4w	(f)(g)	NS
Wang.K.W. (2013)	GERD	77(22-53) 3m-3y		Dahuangxiangsha YGJT 200ml bid (n=39)	D2RA + PPI (n=38)	1m 2m	(g)(h)	NR
Li.J.Y. (2016)	RE	103(32-41) NR		YGJT qd (n=52)	PPI + 5-HT4RA (n=51)	8w	(f)(g)	NS
Huang.Y.J. (2017)	GERD(RE+NERD)	192(18-70) ≥1m	PPI therapy for 4wk	Chaishao YGJT + Wubei San qd (n=96)	PPI (n=96)	8w	(f)(g)(i)(j)	NR
Bai.H.T. (2013)	GERD	40(34-64) 1.8-5.1y		YGJT qd + Weisukeli 5g tid (n=20)	PPI + 5-HT4RA(n=20)	4w	(f)	NR
Jiang.Q.Y. (2013)	RE	96(19-65) 0.5-26y		YGJT + Simisanhe qd (n=48)	PPI + 5-HT4RA + Sucralfate (n=48)	8w 6m	(e)(g)(h)	control : 8
Zhao.J.M. (2010)	RE	160(21-64) 1-5y		YGJT 200ml qd (n=80)	PPI + Amoxicillin + 5-HT4RA	20d	(c)	NR
Yang.W (2018)	RE(after partial gastrectomy)	100(33-76) 3m-4y		Xiangsha YGJT qd (n=50)	PPI (n=50)	8w 1y	(c)(g)(h)	NR

GERD : Gastroesophageal reflux disease, NERD : Non-gastroesophageal reflux disease, LPR : Laryngopharyngeal reflux, RE : Reflux esophagitis, YGJT : Yukgunja-tang, PPI : Proton pump inhibitor, D2RA : D2 receptor antagonists, 5-HT4RA : 5-HT4 receptor agonists, H2RA : H2 receptor antagonists, FSSG : Frequency Scale for the Symptoms of GERD, GRSR : Gastrointestinal Symptom Rating Scale, SF-8 : Short-Form Health Survey-8, VAS : Visual Analog Scale, RDQ score : Reflux Diagnostic Questionnaire score, HADS score : Hospital Anxiety and Depression Scale, NR : Not reported, NS : Not significant, (a)FSSG, (b)GRSR, (c)SF-8, (d)Gastric emptying, (e)Efficacy under gastroscopy, (f)Symptoms score, (g)Clinical efficacy, (h)Recurrence rate, (i)RDQ score, (j)HADS score, (k)VAS

Table 2. Compositions of the YGJT formulae tested

Herb name	Sakata (2014)	Tominaga (2014)	Tokashiki (2013)	Tominaga (2012)	Xu,C.F (2014)	Du,X.Q (2014)	Wang,K.W (2013)	Li,J.Y. (2016)	Huang,Y.J (2017)	Bai,H.T (2013)	Jiang,Q.Y (2013)	Zhao,J.M (2010)	Yang,W (2018)
<i>Atractylodes lanceae rhizoma</i>	4.0	4.0	4.0	4.0	15.0	12.0	12.0	15.0	12.0	12.0	10.0	10.0	15.0
<i>Ginseng radix</i>	4.0	4.0	4.0	4.0									
<i>Pinelliae rhizoma</i>	4.0	4.0	4.0	4.0	16.0	10.0	9.0	10.0	7.0	15.0	10.0	12.0	10.0
<i>Poria</i>	4.0	4.0	4.0	4.0	25.0	10.0	15.0	12.0	10.0	10.0	10.0	10.0	15.0
<i>Ziziphi jujubae fructus</i>	2.0	2.0	2.0	2.0						1.0			
<i>Citri reticulatae pericarpium</i>	2.0	2.0	2.0	2.0	12.0	5.0	9.0	10.0	10.0	10.0	10.0	10.0	15.0
<i>Glycyrrhizae radix</i>	1.0	1.0	1.0	1.0	6.0	6.0	6.0	20.0	6.0	6.0	6.0	3.0	10.0
<i>Zingiberis rhizoma</i>	0.5	0.5	0.5	0.5	12.0					2.0			
<i>Codonopsis pilosulae radix</i>					15.0	12.0	15.0	15.0	12.0	12.0	15.0	15.0	15.0
<i>Helenii radix</i>					12.0	5.0	6.0						7.0
<i>Amonii Semen</i>					6.0	5.0	9.0						10.0
<i>Inule flos</i>					12.0								
<i>Haematitum</i>					25.0								
<i>Rhei rhizoma</i>						3.0	6.0						
<i>Perillae herba</i>							10.0						
<i>Massa medicata Fermentata</i>								10.0					
<i>Bupleuri radix</i>									12.0		9.0		10.0
<i>Paeoniae radix alba</i>									12.0		12.0		
<i>Sepiae os</i>									20.0				20.0
<i>Akebiae fructus</i>									15.0				
<i>Fritillariae thunbergii bulbos</i>									12.0				10.0
<i>Scutellariae radix</i>									12.0				
<i>Coptidiss rhizoma</i>									6.0				
<i>Perillae caulis</i>									10.0				
<i>Aurantii immaturus fructus</i>											10.0		10.0
<i>Cyperii rhizoma</i>													15.0
<i>Peucedani radix</i>												12.0	
<i>Magnoliae cortex</i>												12.0	
<i>Citrus reticulata blanco</i>												12.0	
<i>Weisu Keli</i>													5.0

YGJT : Yukgunja-tang

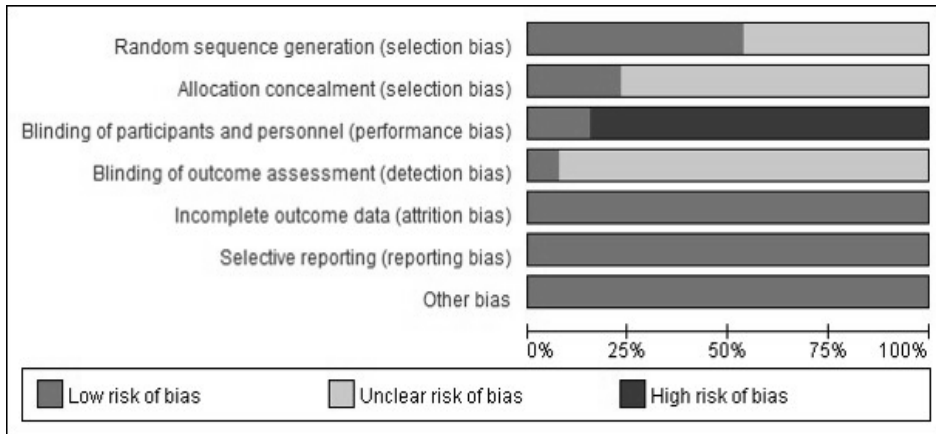


Fig. 2. Risk of bias graph

YGJT group, but the GSRs score did not show a statistically significant difference in the two studies.

2) YGJT versus Conventional Medicine

Nine¹¹⁻¹⁹⁾ studies on YGJT and conventional medicine included improvements in symptom scores and suggested effects of the treatment for each symptom; these comprised 918 patients (460 in the YGJT groups and 458 in the conventional medicine groups). In two studies, scores for each symptom were presented. Symptoms included heartburn, acid regurgitation, sternalgia, and reflux. Four studies reported efficacy under gastroscopy, but one study was excluded because its scoring criteria differed from those used in the three other studies^{12,15,17)}. In one study, reflux symptom scores were excluded from the meta-analysis.

PPIs (Proton pump inhibitors), PPIs+D₂RA (D₂ receptor antagonists), PPIs+5-HT₄RA (5-HT₄ receptor agonists), PPIs+5-HT₄RA + penicillin, PPIs + 5-HT₄RA + antiulcerant, and PPIs+H₂RA (H₂ receptor antagonists) were used in the studies; PPIs contained omeprazole, rabeprazole, lansoprazole,

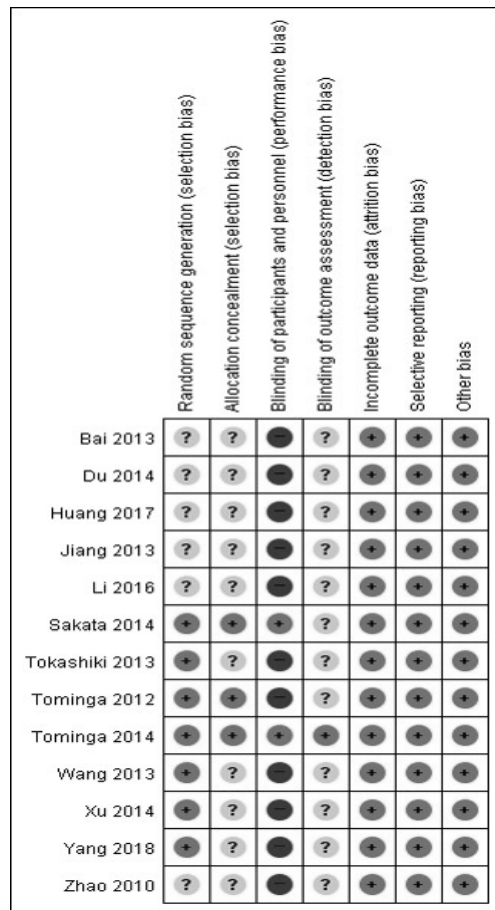


Fig. 3. Risk of bias summary

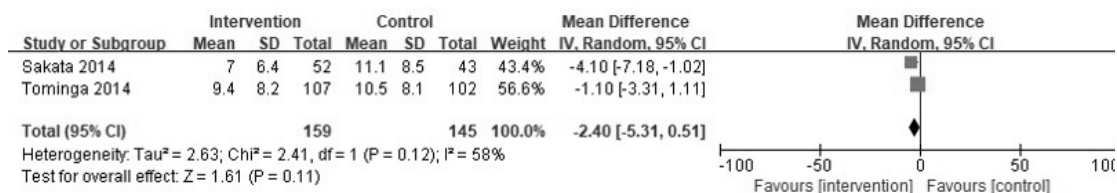


Fig. 4. Forest plot of FSSG scores (random effects model)

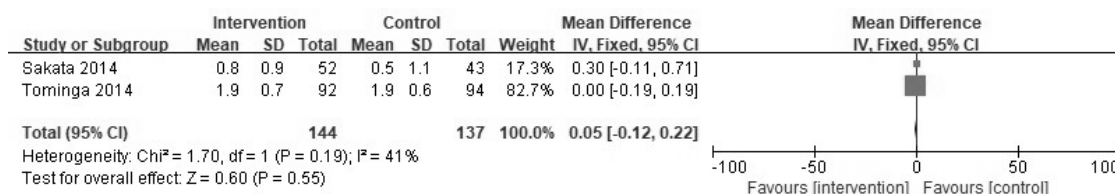


Fig. 5. Forest plot of GSRS scores (fixed effects model)

and esomeprazole; D₂RA contained domperidone; 5-HT₄RA contained mosapride and cisapride; H₂RA contained famotidine; penicillin contained amoxicillin; and antiulcerant contained sucralfate.

(1) Clinical Efficacy

In a comparative study of YGJT group versus conventional medicine group, subgroup analysis was conducted for statistical heterogeneity and response rate for these two groups, both separately and combined. Nine studies compared the effects of YGJT and conventional medicine, and a favorable effect was found for the response rate to YGJT by meta-analysis (OR 5.72; 95% CI [3.41, 9.61]; *P* < 0.00001). In two RCTs, YGJT had better effects on response rates than PPIs (OR 12.73; 95% CI [4.85, 33.38]; *P* < 0.00001), and in two other RCTs, YGJT had better response rates than PPIs plus D₂RA (OR 7.55; 95% CI [2.12, 26.90]; *P* = 0.002). In two RCTs that compared YGJT and PPIs plus 5-HT₄RA, YGJT had better response rates than 5-HT₄RA (OR 3.83;

95% CI [1.31, 11.17]; *P* = 0.01). YGJT with PPIs plus 5-HT₄RA plus penicillin, PPIs plus 5-HT₄RA plus antiulcerant, and PPIs plus H₂RA were found in only one study each, so we could not analyze their effects. (Figure 6).

(2) Efficacy under Gastroscopy

Three of the nine studies assessed the efficacies of YGJT and conventional medicine under gastroscopy in a total of 301 patients. The YGJT group contained 151 patients, and the conventional medicine group had 150 patients. Under gastroscopy, YGJT showed significantly better effects than conventional medicine (OR 6.34, 95% CI [2.32, 17.35], *P* = 0.0003) (Figure 7).

3) Recurrence Rate

Three of the 13 studies mentioned recurrence rate; recurrences occurred between one and ten months after treatment completion. Although the forest plot showed possible statistical heterogeneity (*I*² = 33%), the recurrence rate was significantly

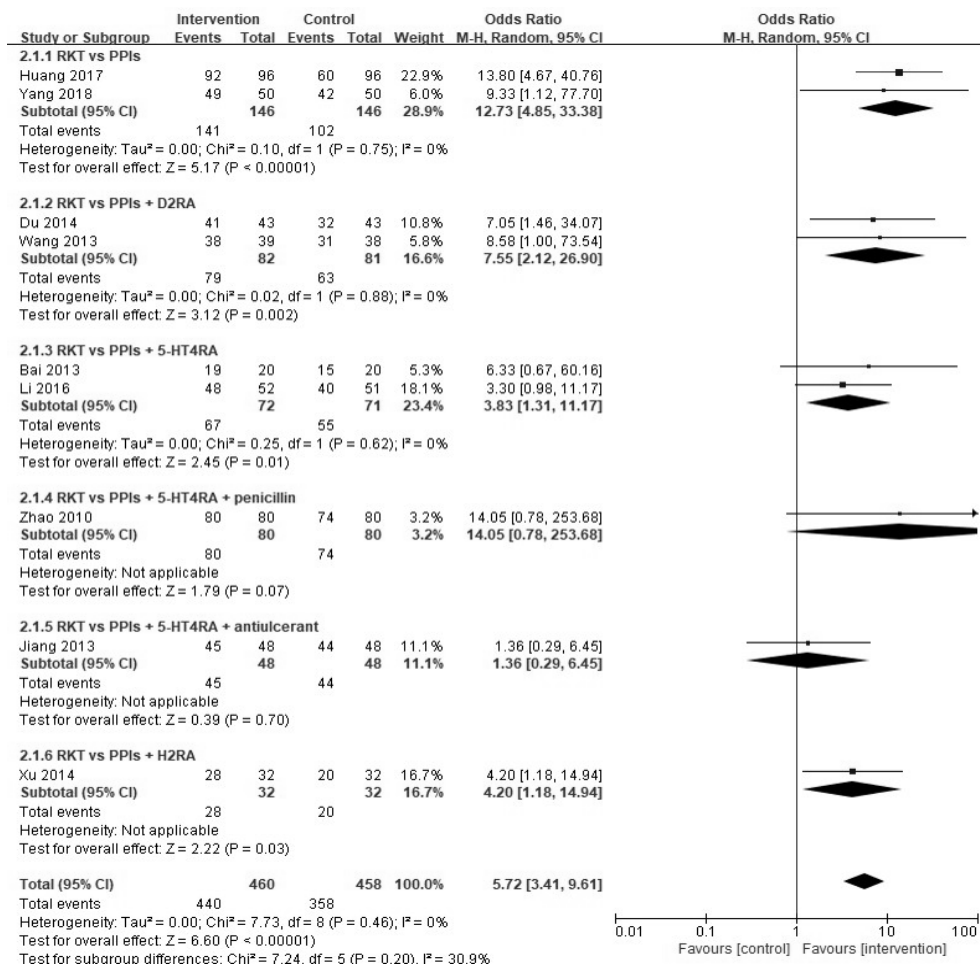


Fig. 6. Forest plot of clinical efficacy

decreased in the YGJT group compared to that of the conventional medicine group (OR 0.24, 95% CI [0.13, 0.45] and $P < 0.00001$) (Figure 8).

4) Adverse Effects

Six studies reported adverse effects during the treatment. Of these, four studies reported no significant adverse effects. In one study, nausea, mild cough, dizziness, and diarrhea were reported in both the YGJT group and the conventional medicine group. One study mentioned the number

of patients that experienced adverse effects, and eight patients administered conventional medicine reported headache or constipation. In all cases, symptoms disappeared after treatment cessation and did not affect outcomes.

Discussion

GERD is defined as a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications. Clinically troublesome

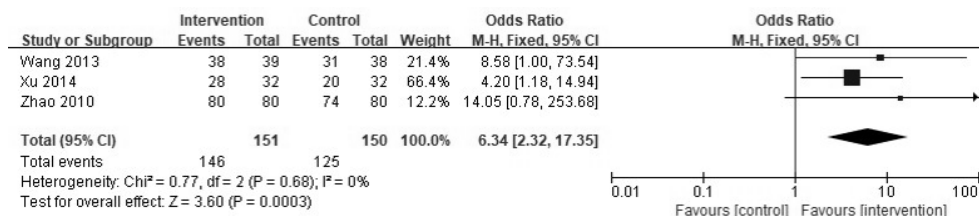


Fig. 7. Forest plot of efficacy under gastroscopy (fixed effects model)

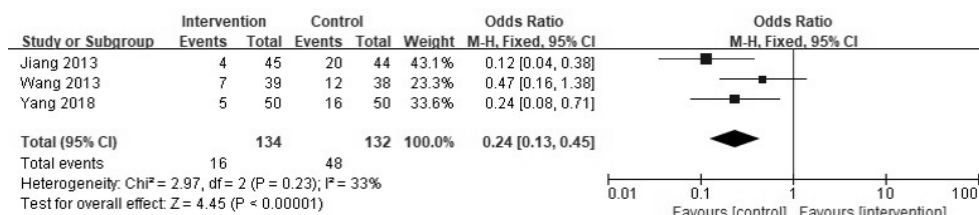


Fig. 8. Forest plot of recurrence rate (fixed effects model)

heartburn is seen in about 6% of the population, and regurgitation was reported in 16% of GERD patients. Heartburn, chest pain, and acid regurgitation are esophageal symptoms of GERD, and may be the presenting symptom on occasion¹⁾. GERD is diagnosed using the combinations of symptoms at presentation, endoscopy, ambulatory reflux monitoring, and response to anti-secretory therapy. PPIs are currently the mainstay treatment for GERD. According to treatment guidelines published by the American Journal of Gastroenterology in 2013, an 8-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis .

Recent studies have shown that YGJT promotes gastric emptying (by promoting the secretion of ghrelin), ameliorates upper gastrointestinal symptoms, and acts as a prokinetic agent in abnormalities of NO-mediated gastric functions such as delayed gastric emptying. In addition, YGJT enhances gastroesophageal clearance. Studies suggest that

gastric emptying and esophageal excretion may be enhanced by YGJT. These studies indicate that YGJT can relieve symptoms of GERD.

We selected 13 RCT studies from 16 published electronic databases through March 2019. Two studies compared YGJT plus PPI with a placebo plus PPI. One study compared YGJT with YGJT plus PPI, one study compared YGJT plus PPI with double-dose PPI, and nine studies compared YGJT with conventional medicine. Four of the 13 studies were conducted in Japan, and nine in China. YGJT versus YGJT plus PPI and YGJT plus PPI versus double-dose PPI were excluded from the meta-analysis, because these comparisons were conducted in only one study each. As a result, the meta-analysis was conducted on studies that compared YGJT plus PPI with placebo plus PPI and YGJT versus conventional medicine.

Two studies compared YGJT plus PPI and a placebo plus PPI. GSRS and FSSG scores were used in the Sakata study. In the Tominaga study

GSRS, FSSG, and SF-8 scores were used. Patients with PPI-refractory NERD were enrolled in two studies, and did not respond to standard doses of PPIs for more than 4 weeks. GSRS scores were not significant in either study in the meta-analysis. FSSG scores were reported to effectively decrease in the YGJT group by Sakata, but not by Tominaga. The meta-analysis of both studies showed that the YGJT group showed significantly improved FSSG scores.

The nine studies that compared YGJT with conventional medicine were included in the meta-analysis. The conventional medicines used were PPI, D₂RA, H₂RA, 5-HT₄RA, and 5-HT₄RA plus amoxicillin or sucralfate. Clinical efficacies were evaluated by scoring heartburn, throat symptoms, acid regurgitation, sternalgia, esophageal edema, and ulcer healing as determined by gastroscopy. In addition, YGJT had a statistically significant effect on heartburn, acid regurgitation, and sternalgia symptom scores. Clinical effects, gastroscopy determined efficacy, and recurrence rate were more effective in the YGJT group than in the conventional medicine group. In addition, recurrence rate was also significantly decreased in the YGJT group. YGJT was not found to be associated with any serious side effects. All reported side effects also disappeared after discontinuing medicines.

Although all RCT studies performed randomization, most did not provide details of the random sequence generation methods used. Furthermore, most studies did not perform allocation concealment or blinding of patients, practitioners, or assessors. These shortcomings might have resulted in selection, performance, or detection bias, and might have exaggerated therapeutic effects. These studies should be

revised, because bias could reduce the reliability of the research.

Several limitations of this systematic review should be considered. First, the RCTs included small sample sizes and low, questionable methodological qualities. Second, while domestic and foreign studies were originally extracted, no Korean or western countries studies were included, which means that generalizations of our results are limited by racial bias.

In conclusion, this meta-analysis shows that YGJT improves symptoms in GERD patients. In this study of systematic review(SR), there were few comparative studies of the placebo group and the YGJT group. Therefore, further study with a placebo group is needed. Recent studies on GERD have reported research on Banxiaxixin-tang, but research on acupuncture has been difficult to find. Clinical studies on acupuncture alone, or a combination of acupuncture and YGJT, should be performed. Although this study has focused on the analysis of the effects of YGJT on GERD, an acupuncture and YGJT combination treatment in GERD patients who have not responded to pharmacological treatments can be expected to be more effective.

Conclusions

The results of this systematic review and meta-analysis indicate that YGJT administration is effective at relieving symptoms in GERD patients. Unfortunately, owing to the small sample sizes, limitations of several methodological qualities, we believe large-scale clinical studies with less bias will provide evidence of qualitative improvement

References

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3): 308-28.
2. 한가진, 임정태, 김진성, 이준희. 위식도역류질환 한약제제 임상시험 가이드라인 개발을 위한 관련국내 가이드라인 분석 및 기존 한약임상시험과의 비교. *대한한방내과학회지*. 2016;37(1): 90-108.
3. Vakil N, Van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *The American journal of gastroenterology*. 2006;101(8):1900-20.
4. Sakata Y, Tominaga K, Kato M, Takeda H, Shimoyama Y, Takeuchi T, et al. Clinical characteristics of elderly patients with proton pump inhibitor-refractory non-erosive reflux disease from the G-PRIDE study who responded to rikkunshito. *BMC Gastroenterology*. 2014;14:116-.
5. Jeon S-H, Kim J-W. 기능성 소화불량에 대한 육군자탕 엑스과립의 사상체질별 치료효과: 위약대조, 이중 맹검, 무작위 시험. 2018;30.
6. 원종만, 윤상협. 六君子湯이 흰쥐의 胃 排出能에 미치는 영향. *대한한방내과학회지*. 2007;28(2): 242-49.
7. Higgins JPT AD. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: The Cochrane Collaboration. John Wiley & Sons 2008.
8. Tominaga K, Kato M, Takeda H, Shimoyama Y, Umegaki E, Iwakiri R, et al. A randomized, placebo-controlled, double-blind clinical trial of rikkunshito for patients with non-erosive reflux disease refractory to proton-pump inhibitor: the G-PRIDE study. *Journal of Gastroenterology*. 2014;49(10): 1392-405.
9. Tokashiki R, Okamoto I, Funato N, Suzuki M. Rikkunshito improves globus sensation in patients with proton-pump inhibitor-refractory laryngopharyngeal reflux. *World Journal of Gastroenterology*. 2013;19(31):5118-24.
10. Tominaga K, Iwakiri R, Fujimoto K, Fujiwara Y, Tanaka M, Shimoyama Y, et al. Rikkunshito improves symptoms in PPI-refractory GERD patients: a prospective, randomized, multicenter trial in Japan. *Journal of Gastroenterology*. 2012;47(3):284-92.
11. 蒋钦云, 滕飞燕. 中西医结合治疗反流性食管炎48例临床观察 *J Guiding Journal of Traditional Chinese Medicine and Pharmacology*. 2013; 19(5):54-5.
12. 赵建民. 中西医结合治疗反流性食管炎80例 *J Chinese Journal of Information on Traditional Chinese Medicine*. 2010;17(S1):46-7.
13. 杨玮. 中西医结合治疗胃部分切除术后反流性食管炎(RE)的作用分析. *J China Foreign Medical Treatment*. 2018;37(8):160-2.
14. 李建云. 六君子汤治疗反流性食管炎随机平行对照研究. *J 实用中医内科杂志*. 2016;30(4):32-4.
15. 徐春风, 刘子达. 加味香砂六君子汤合旋覆代赭汤治疗反流性食管炎. *J Journal of Changchun University of Traditional Chinese Medicine*. 2014;30(5):906-7.
16. 杜修桥, 张新贞. 大黄香砂六君子汤治疗胃食管反流病43例. *J Henan Traditional Chinese Medicine*. 2014;34(11):2222-23.
17. 王凯文, 郭海龙, 孙恒青. 大黄香砂六君子汤治疗胃食管反流病疗效观察. *J Chinese Journal of Information on Traditional Chinese Medicine*.

- 2013;20(10):68-9.
18. 黄亚娟, 蒋士生, 邓芳, 周立武, 胡锦涛, 王迪, et al. 柴芍六君子汤合乌贝散治疗难治性胃食管反流病96例临床观察. *J Hunan Journal of Traditional Chinese Medicine*. 2017;33(6):10-2.
 19. 白海涛, 吕小雪, 拓琚. 胃苏颗粒联合加味六君子汤治疗胃食管反流性咳嗽临床观察. *J CLINICAL MEDICINE*. 2013;33(7):117-8.
 20. Dai Y, Zhang Y, Li D, Ye J, Chen W, Hu L. Efficacy and safety of modified Banxia Xiexin decoction (Pinellia decoction for draining the heart) for gastroesophageal reflux disease in adults: a systematic review and meta-analysis. *Evidence-Based Complementary and Alternative Medicine*. 2017;2017:1-17.
 21. Takeda H, Muto S, Nakagawa K, Ohnishi S, Asaka M. Rikkunshito and ghrelin secretion. *J Current pharmaceutical design*. 2012;18(31):4827-38.
 22. Nahata M, Mizuhara Y, Sadakane C, Watanabe J, Fujitsuka N, Hattori T. Influence of food on the gastric motor effect of the Kampo medicine rikkunshito in rat. *J Neurogastroenterology Motility*. 2018;30(2):e13177.
 23. Kido T, Nakai Y, Kase Y, Sakakibara I, Nomura M, Takeda S, et al. Effects of Rikkunshi-to, a traditional Japanese medicine, on the delay of gastric emptying induced by NG-nitro-L-arginine. *Journal of pharmacological sciences*. 2005;0506030004-.
 24. Kawahara H, Kubota A, Hasegawa T, Okuyama H, Ueno T, Ida S, et al. Effects of rikkunshito on the clinical symptoms and esophageal acid exposure in children with symptomatic gastroesophageal reflux. *J Pediatric surgery international*. 2007;23(10):1001-5.

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