Efficacy of Ligustrazine Injection as Adjunctive Therapy for Angina Pectoris: A Systematic Review and Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: In the past decades, a large number of randomized controlled trials (RCTs) on the efficacy of ligustrazine injection combined with conventional antianginal drugs for angina pectoris have been reported. However, these RCTs have not been evaluated in accordance with PRISMA systematic review standards. The aim of this study was to evaluate the efficacy of ligustrazine injection as adjunctive therapy for angina pectoris.

Material/Methods: The databases PubMed, Medline, Cochrane Library, Embase, Sino-Med, Wanfang Databases, Chinese Scientific Journal Database, Google Scholar, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, and the Chinese Science Citation Database were searched for published RCTs. Meta-analysis was performed on the primary outcome measures, including the improvements of electrocardiography (ECG) and the reductions in angina symptoms. Sensitivity and subgroup analysis based on the M score (the refined Jadad scores) were also used to evaluate the effect of quality, sample size, and publication year of the included RCTs on the overall effect of ligustrazine injection.

Results: Eleven RCTs involving 870 patients with angina pectoris were selected in this study. Compared with conventional antianginal drugs alone, ligustrazine injection combined with antianginal drugs significantly increased the efficacy in symptom improvement (odds ratio [OR], 3.59; 95% confidence interval [CI]: 2.39 to 5.40) and in ECG improvement (OR, 3.42; 95% CI: 2.33 to 5.01). Sensitivity and subgroup analysis also confirmed that ligustrazine injection had better effect in the treatment of angina pectoris as adjunctive therapy.

Conclusions: The 11 eligible RCTs indicated that ligustrazine injection as adjunctive therapy was more effective than antianginal drugs alone. However, due to the low quality of included RCTs, more rigorously designed RCTs were still needed to verify the effects of ligustrazine injection as adjunctive therapy for angina pectoris.

MeSH Keywords: Angina Pectoris • Medicine, Chinese Traditional • Meta-Analysis as Topic

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/895362

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Background

Angina pectoris is triggered by decreased myocardial oxygen supply or increased myocardial oxygen demand [1]. An estimated 94.9 of every 100 000 urban residents die of coronary artery disease (CAD) in China and nearly 1 of every 6 deaths was due to CAD in the US in 2009 [2,3]. Chronic stable angina is the most prevalent manifestation of CAD, with an incidence of 500 000 new cases every year in the US [1]. Typical symptoms of angina pectoris are characterized by discomfort in various parts of the body, including the chest, jaw, shoulder, back, and arms. Angina pectoris elicited by exertion or emotional stress can be relieved by rest or nitroglycerin [4]. Conventional antianginal drugs (e.g., β-blockers, calcium antagonists, and nitrates) reduce angina attacks by lowering heart rate and blood pressure or enhancing coronary blood flow [5]. Despite the effectiveness of the antianginal drugs, episodes of angina pectoris may still persist or even worsen. In addition, most patients cannot tolerate the adverse effects of these antianginal drugs [6–8]. Therefore, a new treatment that has significant advantages in increasing the effects of conventional antianginal drugs is necessary. Recently, the benefits of traditional Chinese medicine (TCM) combined with the conventional antianginal drugs have attracted a growing and sustained interest from researchers and physicians.

Ligustrazine (2,3,5,6-tetramethylpyrazine, $C_8H_{12}N_2$, Figure 1A) is an active ingredient from the plant Szechwan Lovage Rhizome. This plant has been widely used to treat cardiovascular disease, angina pectoris, and headache for hundreds of years in China as herbal medicine [9,10]. Owing to the impressive effects of ligustrazine in scavenging cytotoxic oxygen free radicals, promoting blood flow, and antiplatelet aggregation, various dosage forms based on ligustrazine are developed in China, such as injection, tablets, and capsule [11]. Ligustrazine injection is the most popular form among them and it is commercially available as ligustrazine hydrochloride (Figure 1B) (40 mg/10 mL) and ligustrazine phosphate (Figure 1C) (50 mg/10 mL). Ligustrazine injection ranges from 40 mg to 80 mg was usually used in the method of intravenous drip (diluted with 250–500 mL of isotonic normal saline or glucose solution; one time, once daily) [12]. In order to provide better efficacy in treating angina pectoris, ligustrazine injection is usually used in combination with conventional antianginal drugs in China.

The clinical studies on ligustrazine injection have been reported with potential positive results. However, neither systematic a review nor a meta-analysis on the therapeutic effect of ligustrazine injection as adjunctive therapy for angina pectoris has been reported so far. Therefore, this study offers a comprehensive and PRISMA-compliant systematic review with sensitivity and subgroup analysis for evaluating the efficacy of ligustrazine injection as adjunctive therapy in the treatment of angina pectoris [13].

Material and Methods

Eligibility criteria

The published RCTs were searched independently by 2 reviewers (HK, Shao and LG, Zhao). The participants with angina pectoris were examined according to the World Health Organization guideline [14]. Studies that met the following criteria were included: (a) Studies compared any antianginal drugs combined with or without ligustrazine injection (i.e., ligustrazine injection combined with antianginal drugs *vs.* antianginal drugs alone); (b) Duration of treatment was at least 2 weeks; (c) The sample size of studies was at least 50 patients; and (d) The primary outcome measures in RCTs were symptom improvement and ECG improvement.

Studies were excluded if they did not meet the criteria above and: (a) The RCTs involved animal, human cells or *in vitro* studies; (b) Studies did not include the symptom improvement and ECG improvement as the primary outcome measures; (c) Studies with same authors and similar content; and (d) The dosages of intervention in the treatment and control groups of included studies were not specifically stated.

Information sources

The databases PubMed, Medline, Cochrane Library, Embase, Sino-Med, Wanfang Databases, Chinese Scientific Journal Database, Google Scholar, Chinese Biomedical Literature Database, China National Knowledge Infrastructure and the Chinese Science Citation Database were independently searched and retrieved by 2 authors (HK, Shao and LG, Zhao). The latest search of databases was conducted on 29 May 2015.
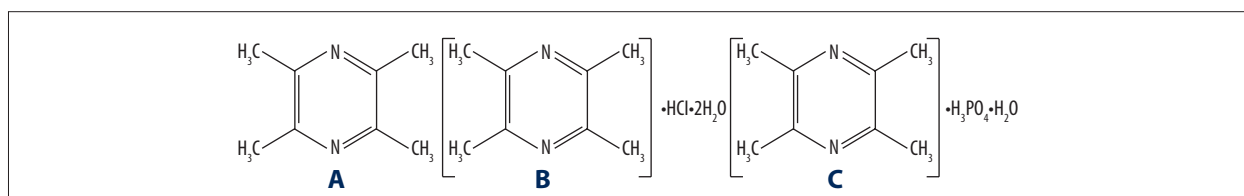

Figure 1. Structure of ligustrazine (**A**), ligustrazine hydrochloride (**B**) and ligustrazine phosphate (**C**) .

Table 1. M scale checklist.

Question	Answer	Score
M1. Were the groups comparable?	Positive in comparability	1
	Negative in comparability	0
M2. Was the study described as randomized?	Randomization procedure was described and the procedure was appropriate	2
	Randomization was mentioned without describing the procedure	1
	Randomization procedure was incorrect	−1
M3. Was the study described as blind?	Double blinding was described with a specific procedure	2
	Double blinding was described without a specific procedure	1
	Single blinding was described with a specific procedure	1
	Single blinding was described without a specific procedure	0.5
	No blinding was described	0
M4. Were withdrawals and dropouts described?	Counts and reasons of withdrawals and dropouts were reported	1
	Only counts or reasons were reported	0.5
	No withdrawal or dropout was mentioned	0
M5. Were the adverse effects described?	Counts and types of adverse effects were reported	1
	Only counts or types of adverse effects were reported	0.5
	No adverse effect was mentioned	0

Search strategies

The following terms were searched in separate or combined ways for English databases: ligustrazine injection, antianginal drugs, angina pectoris, cardiovascular diseases, coronary artery disease. The following terms were searched in separated or combined ways for Chinese databases: Chuanxiongqin zhusheye [ligustrazine injection], Chuanxiongqin [ligustrazine], guanxinbing [coronary artery disease], xinjiaotong [angina pectoris]. Moreover, the references listed in the selected articles were also searched to acquire additional papers related to this study.

Study selection

Two authors (HK. Shao and LG. Zhao) independently screened all titles and abstracts of clinical studies according to the eligibility criteria. Disagreement between the 2 authors was resolved by consensus.

Data collection process

One author (HK, Shao) extracted data from the included RCTs and then put them into Microsoft Excel. Another 2 authors (LG, Zhao and SQ, Liu) examined the accuracy of extracted data. Disagreements between authors were solved through discussion. The software Review Manager 5.0 was used to evaluate the extracted data.

Data items

Two authors (HK. Shao and LG. Zhao) independently extracted the following data items: (a) First author, publication year, and language of RCTs; (b) Characteristics of patients including age and sample size; (c) Intervention (dosages and duration); (d) Outcome measures; and (e) Incidence of adverse reactions.

Risk of bias in individual studies

The methodological quality of included RCTs was independently evaluated by 2 authors (HK. Shao and LG. Zhao) in reporting baseline comparison of participants, randomization methods, concealment of treatment allocation, blinding, and adverse event report according to M score (Table 1) [15].

Quality assessment

Two authors (HK, Shao and LG, Zhao) independently assessed the quality of included RCTs based on M scale (Studies with M scale >3 were considered to be moderate-quality RCTs). Any disagreement among the 2 authors was resolved by consensus.

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[ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica]
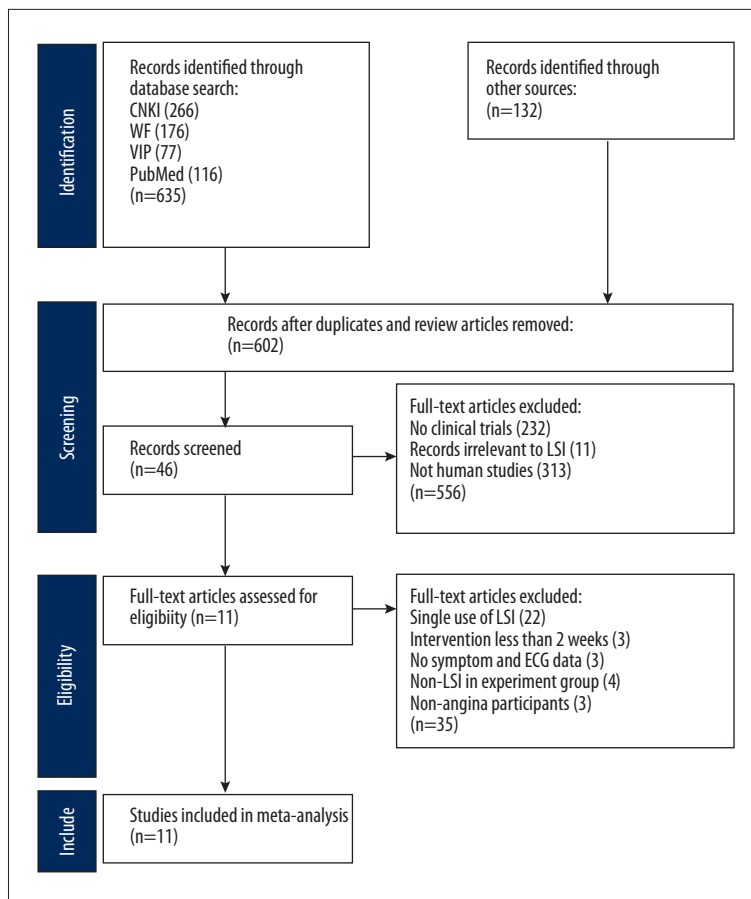[Chemical Abstracts/CAS] [Index Copernicus]

Figure 2. The process of study selection. CNKI is China National Knowledge Infrastructure; WF is WangFang data; VIP is Chinese Scientific Journal Database; Other resoures is Medline, Cochrane Library, Embase, Sino-Med, Google Scholar, Chinese Biomedical Literature Database and the Chinese Science Citation Database. LSI is ligustrazine injection.

Definitions of improvements of symptom and ECG

Improvement in symptom should reduce by at least 50% (i.e., basic improvement in angina symptoms) the frequency and duration of feeling angina chest pain. Improvement in ECG should achieve at least 0.05 mv at ST segment (i.e., basic improvements in ECG) in ECG during an exercise test, as mentioned in ACC/AHA guidelines [16].

Sensitivity and subgroup analysis

Sensitivity analysis was conducted to verify whether the overall efficacy of ligustrazine injection combined with antianginal drugs over antianginal drugs alone would be affected by the low quality of included RCTs. Subgroup analysis was conducted to evaluate the overall effects in subgroups based on sample sizes and publication year of the study.

Risk of bias across studies

The publication bias was assessed by funnel plots, Begg's test, and Egger's test with the software of STATA 12.0.

Statistical analysis

All analyses were performed with RevMan 5.0. For continuous outcome variables, standard mean difference was used with 95% confidence interval (CI). For dichotomous outcome variables, odds ratio (OR) was given with 95% CI. If OR <1, it indicated a lower risk for treatment group than control group. If OR >1, it showed that a greater risk for treatment group than control group. Statistical heterogeneity was measured by using the chi-squared test and I^2 statistic. Significant difference for heterogeneity test was considered when P<0.05 or I^2 statistic >50% [17–19]. The random-effects model was used to analyze the pooled effects when heterogeneity was significantly different, otherwise the fixed-effects model was used. The Z test was used to compare the overall effects of treatment group and control group, and differences were considered to be statistically significant when P<0.05. Results are expressed as pooled odds ratios (OR (95% confidence intervals, CIs)). The Mantel-Haenszel method with fixed-effects model was used to calculate the pooled OR and 95% CI considering the small trials, high event rates, and dichotomous outcome variable in this study.

Supplementary Table 1. Summary of the included studies evaluating the adjunctive therapy of ligustrazine injection in treating angina.

Study	Year	Country	Age	Intervention		Sample	Follow-up (day)	Outcome measures
				Treatment	Control			
Da MF	2008	China	41–83	Ligustrazine injection 80 mg/d, Nitroglycerin 10–15 mg/d, Aspirin 100 mg/d, Metoprolol 50 mg/d	Nitroglycerin 10–15 mg/d, Aspirin 100 mg/d, Metoprolol 50 mg/d	74	14	SYM, ECG
Ji ZJ	2009	China	29–52	Ligustrazine injection 100 mg/d, Aspirin 100 mg/d, Isosorbide dinitrate 30 mg/d, Simvastatin 40 mg/d, Isosorbide-5-mononitrate 20 mg/d	Aspirin 100 mg/d, Isosorbide dinitrate 30 mg/d, Simvastatin 40 mg/d, Isosorbide-5-mononitrate 20 mg/d	80	14	SYM
Li Y	2010	China	42–76	Ligustrazine injection 120 mg/d, Nitroglycerin 10–15 mg/d, Aspirin 100 mg/d, Metoprolol 50 mg/d	Nitroglycerin 10–15 mg/d, Aspirin 100 mg/d, Metoprolol 50 mg/d	68	14	SYM
Liao JQ	2006	China	46–71	Ligustrazine injection 120 mg/d, Nitroglycerin 50 mg/d, Aspirin 150 mg/d	Nitroglycerin 50 mg/d, Aspirin 150 mg/d	68	14	SYM
Liu YJ	2009	China	42–70	Ligustrazine injection 150 mg/d, Isosorbide-5-mononitrate 60 mg/d	Isosorbide-5-mononitrate 60 mg/d	97	28	SYM, ECG
Luo B	2007	China	44–78	Ligustrazine injection 100 mg/d, Nitroglycerin 10 mg/d, Aspirin 75 mg/d	Nitroglycerin 10 mg/d, Aspirin 75 mg/d	80	14	SYM
Sun DN	2007	China	48–80	Ligustrazine injection 120–200 mg/d, Isosorbide dinitrate 30 mg/d, Nitroglycerin 0.3–0.6 mg/d, Aspirin 100 mg/d	Isosorbide dinitrate 30 mg/d, Nitroglycerin 0.3–0.6 mg/d, Aspirin 100 mg/d	96	21	SYM, ECG
Wang QZ	2008	China	48–80	Ligustrazine injection 80 mg/d, Aspirin 75 mg/d, Nitroglycerin 0.3–0.6 mg/d	Aspirin 75 mg/d, Nitroglycerin 0.3–0.6 mg/d	84	14	SYM, ECG
Wang XY	2008	China	44–79	Ligustrazine injection 150 mg/d, Isosorbide-5-mononitrate 60 mg/d	Isosorbide-5-mononitrate 60 mg/d	64	14	SYM, ECG
Yang JX	2008	China	46–78	Ligustrazine injection 100 mg/d, Isosorbide dinitrate 30 mg/d, Aspirin 75 mg/d, Nitroglycerin 0.3–0.6 mg/d	Isosorbide dinitrate 30 mg/d, Aspirin 75 mg/d, Nitroglycerin 0.3–0.6 mg/d	50	14	ECG
Yao MJ	2009	China	43–74	Ligustrazine injection 240 mg/d, Aspirin 100 mg/d, Isosorbide dinitrate 30 mg/d	Aspirin 100 mg/d, Isosorbide dinitrate 30 mg/d	120	15	SYM, ECG

Results

Study selection

The selection process is described in Figure 2. We initially identified 767 potential records, including 266 articles from CNKI, 176 articles from Wanfang data, 77 articles from VIP, 116 articles from PubMed, and 132 articles from Medline, Cochrane Library, Embase, Sino-Med, Google Scholar, Chinese Biomedical Literature Database, and Chinese Science Citation Database. After screening the titles and abstracts, 721 articles were excluded because a large number of records from 3 Chinese databases (CNKI, VIP, and Wanfang) were duplication and a large quantity of RCTs did not meet the inclusion criteria. Full texts of 46 articles were retrieved for further identification according to the pre-defined eligibility criteria; 11 studies were finally selected for quality assessment and meta-analysis.

Table 2. Quality measures of the included studies.

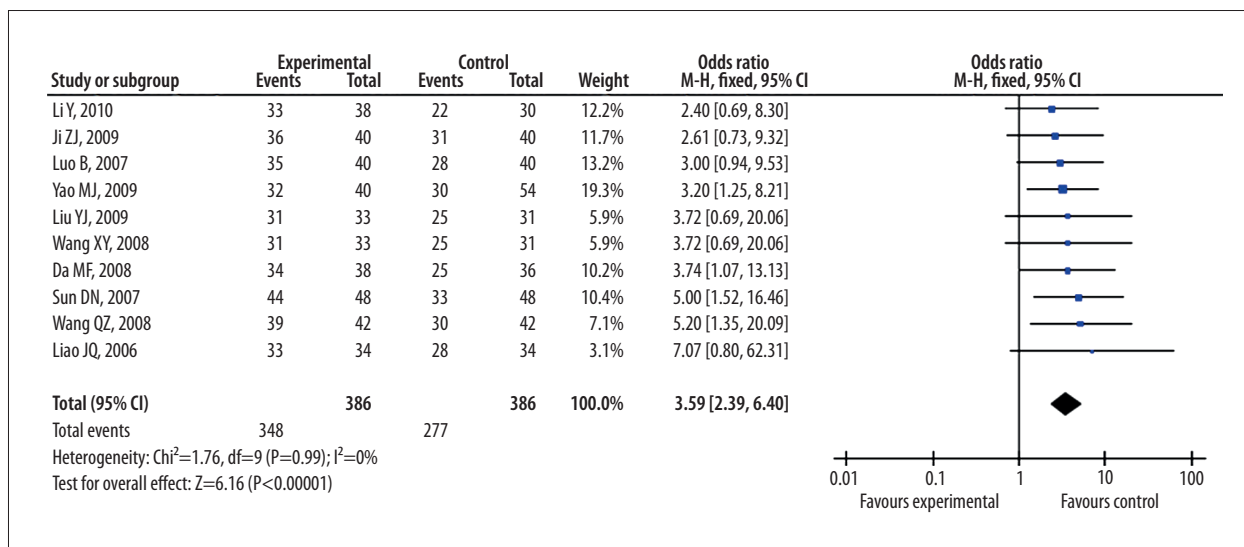| Study	M1	M2	M3	M4	M5	M Score
Da MF, 2008	1	1	0	1	1	4
Ji ZJ, 2009	1	1	0	1	1	4
Li Y, 2010	1	1	0	1	0	3
Liao JQ, 2006	1	1	0	1	1	4
Liu YJ, 2009	1	1	0	1	1	4
Luo B, 2007	1	0	0	1	1	3
Sun DN, 2007	1	1	0	1	0	3
Wang QZ, 2008	1	1	0	1	1	4
Wang XY, 2008	1	1	0	1	1	4
Yang JX, 2008	1	1	0	1	0	3
Yao MJ, 2009	1	1	0	1	0	3

Figure 3. The forest plot of outcome measure symptoms.

Study characteristics

The characteristics of 11 RCTs are summarized in the Supplementary Table 1. The included RCTs were all published in Chinese journals between the 2000 and 2015. The sample size of RCTs ranged from 50 to 120. Eleven RCTs with 870 patients (436 patients in treatment group) were included in this study [20–30]. The duration of treatment ranged from 14 to 28 days. Ten RCTs reported symptoms changes as the outcome measures and 7 studies reported ECG changes. The antianginal drugs used in the control groups included nitroglycerin, metoprolol, aspirin, isosorbide dinitrate, isosorbide-5-mononitrate,

and simvastatin. Based on the drugs used in the control groups, the dosage of ligustrazine injection used in treatment group ranged from 80 to 240 mg daily.

Risk of bias in individual studies

The M scale (between -1 and 7 points) was used to measure the methodological quality of the included studies. The results of quality assessment were provided in Table. 2. Five RCTs scored 3 and 6 RCTs scored 4 according to M scale, indicating the poor methodological quality of most RCTs.
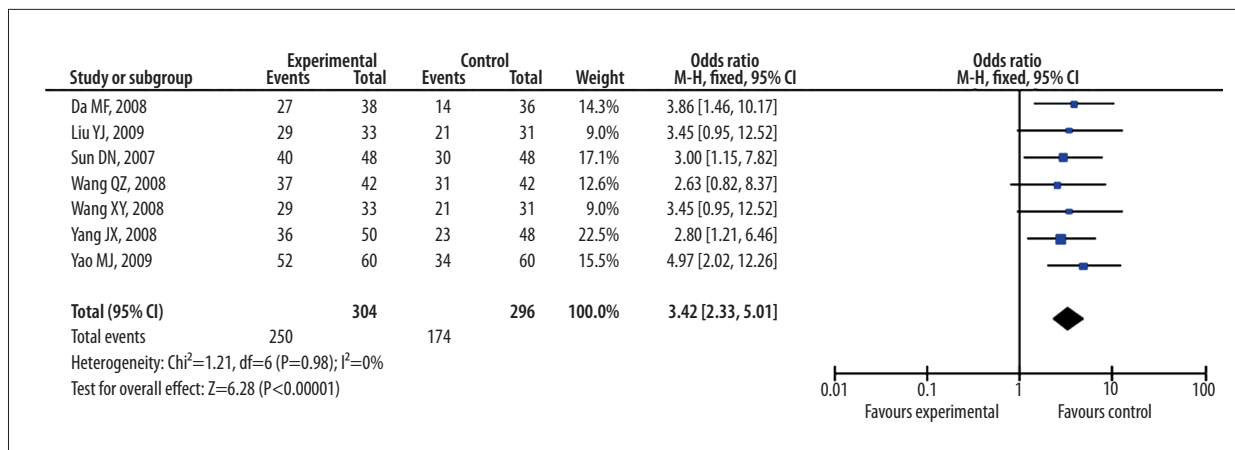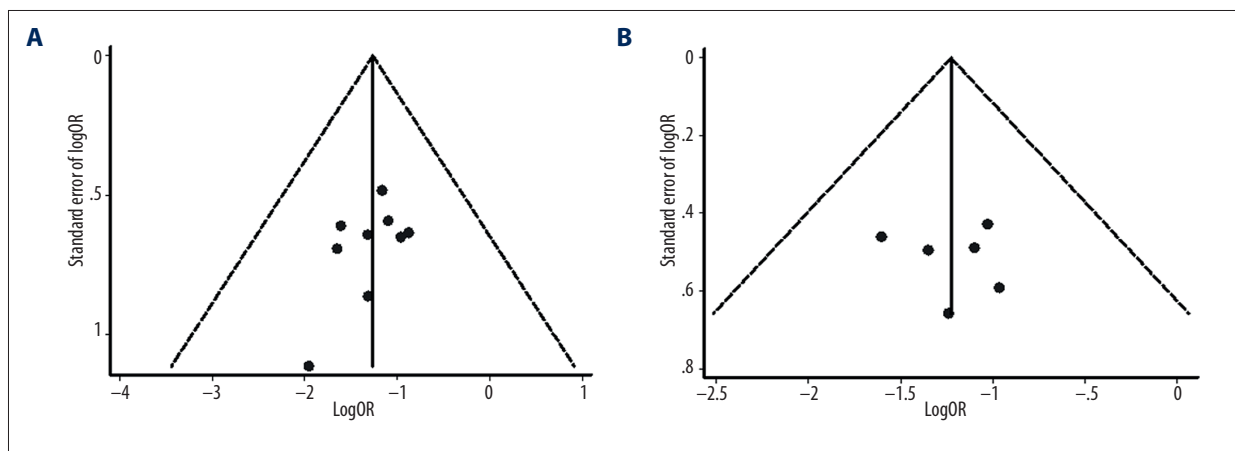
Figure 4. The forest plot of outcome measure ECG.

Figure 5. Funnel plots of the included studies with symptomatic data (**A**); Funnel plots of the included studies with ECG data (**B**).

Results of individual studies and their synthesis

As shown in Figure 3, the Pooled odds ratio of symptoms was 3.59 (95% CI, 2.39 to 5.40, Z=6.16, P<0.00001) with no heterogeneity (I²=0%; χ²=1.76; df=9, P=0.99) among the 10 studies with symptomatic improvements as outcome measure. Figure 4 showed that the Pooled odds ratio of ECG was 3.42 (95% CI, 2.33 to 5.01, Z=6.28, P<0.00001) with no heterogeneity (I²=0%; χ²=1.21; df=6, P=0.98) among the 7 studies with ECG as outcome measure. The Pooled odds ratios of symptoms and ECG indicated that ligustrazine injection as adjunctive therapy for angina pectoris was more effective than antianginal drugs alone.

Risk of bias across studies

As shown in Figure 5, no obvious asymmetry was observed in the funnel plots for symptoms and ECG. Begg's test (symptoms: Z=0.98, P=0.325; ECG: Z=0.15, P=0.881) and Egger's test (symptoms: t=−1.45, P=0.185; ECG: t=0.23, P=0.827) also indicated that there was no statistically significant publication bias.

Adverse events

One RCT reported ligustrazine injection as adjunctive therapy could cause discomfort in stomach for 1 patient. Respectively, 3 RCTs reported that there were 2 patients suffering from headache both in treatment group and control group. The rest of studies did not report the adverse events.

Subgroup and sensitivity analysis

Based on the characteristics of RCTs including publication year (before or after 1 January 2008) and sample size (≤70 or >70), subgroup analysis was performed and the results were shown in Tables 3 and 4. No significant difference was found between the overall odds ratios of subgroups, indicating that the efficacies were consistently stable among all included studies.

Sensitivity analysis based on M scale was conducted in this study. When the lower quality studies (M score ≤3) were excluded, the odd ratio by symptom increased from 3.59 to 3.93 (95%, 2.15–7.19, Z=4.46, P<0.00001) with no heterogeneity

Table 3. Sensitivity and subgroups analysis based on symptoms.

	Group	No. of studies	No. of participants	OR	95% CI	Z	P(effect)	I²	χ²	P(het)
M score	≤3	4	338	3.31	1.91, 5.76	4.24	<0.0001	0%	0.75	0.86
	>3	6	434	3.93	2.15, 7.19	4.46	<0.00001	0%	0.85	0.97
Sample Size	≤70	3	200	3.45	1.42, 8.42	2.27	0.006	0%	0.75	0.69
	>70	7	572	3.63	2.30, 5.74	5.52	<0.00001	0%	0.98	0.99
Publication year	≤2008	6	436	4.24	2.43, 7.39	5.09	<0.0001	0%	0.78	0.98
	>2008	4	306	2.92	1.60, 5.34	3.49	0.0005	0%	0.24	0.97

Table 4. Sensitivity and subgroups analysis based on ECG.

	Group	No. of studies	No. of participants	OR	95% CI	Z	P(effect)	I²	χ²	P(het)
M score	≤3	3	314	3.47	2.08, 5.80	4.74	<0.00001	0%	0.95	0.62
	>3	4	286	3.35	1.88, 5.96	4.11	<0.0001	0%	0.25	0.97
Sample Size	≤70	2	162	2.98	1.48, 6.01	3.05	0.002	0%	0.07	0.79
	>70	5	438	3.62	2.28, 5.72	5.49	<0.00001	0%	0.94	0.92
Publication year	≤2008	5	416	3.09	1.97, 4.85	4.91	<0.00001	0%	0.36	0.99
	>2008	2	184	4.41	2.11, 9.23	3.94	<0.0001	0%	0.21	0.65

(Chi²=0.85, P=0.97, I²=0%). The odd ratio by ECG decreased from 3.42 to 3.35 (95%, 1.88–5.96, Z=4.11, P<0.0001) with no heterogeneity (Chi²=0.25, P=0.97; I²=0%). However, the above results showed that no significant difference happened in odds ratios for symptoms (Table 3) and ECG (Table 4). It had statistical significance (the 95% CI did not contain the value 1) after all low quality studies were excluded during the process of sensitivity analysis. In addition, no obvious heterogeneity was found from the results of sensitivity analysis.

Discussion

Analysis of effectiveness

In recent years, Chinese medicine as adjunctive or alternative medicine for angina pectoris has attracted widely interests because conventional antianginal drugs might sometimes fail to treat angina pectoris. As one of the most popular medicine in China, ligustrazine injection had played a very important role in treating angina pectoris. Although there are many studies about ligustrazine injection, neither systematic review nor meta-analysis has been performed on ligustrazine injection as adjunctive therapy for angina pectoris so far. Therefore, in this study, we firstly provided a comprehensive and PRISMA-compliant systematic review with sensitivity and subgroup analysis for evaluating the efficacy of ligustrazine injection as adjunctive

therapy in the treatment of angina pectoris. PRISMA Checklist was provided in Supplementary Table 2. The results from the 11 included RCTs suggested that ligustrazine injection as adjunctive therapy for angina pectoris was more effective than conventional antianginal drugs alone. Sensitivity and subgroup analysis conducted on M scale, sample size and year of publication also consistently proved that ligustrazine injection as adjunctive therapy has superior effects in the treatment of angina pectoris. Moreover, no publication bias was found in this study.

Limitations

Some limitations existed in this study. The low quality of RCTs included in this study was the major limitation. Only half of RCTs scored 3 or above according to the M scale. Apart from this, the poor design of clinical trials in the RCTs was also an important limitation. The included RCTs were not strictly designed according to the golden standard. Allocation concealment and blinding were not clearly described in majority of the RCTs. Besides, this research had the following defects: (1) All included studies came from mainland China and were published in Chinese. Moreover, no multi-center/country clinical randomized controlled trial was found in this study. (2) The different dosage of ligustrazine injection used in the treatment group might lead to heterogeneity among the included RCTs. (3) Duration of treatment was relatively short as most duration of RCTs was 2 weeks. Therefore, further larger scale,

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Supplementary Table 2. Checklist of items to include when reporting a systematic review or meta-analysis.

Section/topic	#	Checklist item	Section &/or figure reported in
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Title
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	Abstract
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods-Eligibility criteria
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods-Information sources
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeate	Methods-Search strategies
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods-Study selection
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods-Data collection process
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	Methods-Data items
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods-Risk of bias in individual studies
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	Methods-Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis	Methods-Statistical analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	Methods-Risk of bias across studies
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods-Sensitivity and subgroup analysis

Supplementary Table 2 continued. Checklist of items to include when reporting a systematic review or meta-analysis.

Section/topic	#	Checklist item	Section &/or figure reported in
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results-Literature Study selection
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Results-Study characteristics
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	Results-Risk of bias within studies
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Result- Results of individual studies and their synthesis
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Result-Results of individual studies and their synthesis
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15	Result-Risk of bias across studies
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])	Result-Sensitivity and subgroup analysis
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	Discussion-Summary of evidence
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	Discussion-Limitations
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion-Conclusions
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	Funding

higher quality and rigorously designed RCTs were still needed to confirm the efficacy of ligustrazine injection as an adjunctive therapy in the treatment of angina pectoris.

Implications for further research

At present, ligustrazine injection as adjunctive therapies are not well known to most Western physicians and its efficacy in treating angina pectoris has not been evaluated. This study could potentially help physicians manage the problem of drug tolerance and side effects occurred in their patients with angina pectoris.

This study found that a majority of the RCTs on ligustrazine injection had poor methodological quality. The description of randomization methods and concealment of allocation

procedures was not provided in many RCTs. Problems existed in blinding of the patients and researchers were prevalent. In addition, placebo-controlled design was rarely adopted in their study. In some studies, the researchers were not blinded to treatment allocation when they assessed the treatment outcome. The low quality of RCTs included in this study indicated that many researchers might not be aware of the crucial components of RCTs. Therefore, future RCTs about ligustrazine injection should comply with the following recommendations: (1) Researchers should have received some formal educations about clinical trial design when they conducted RCTs; (2) Researchers should register clinical trials and publish their reports in a standard trial registration platforms; (3) The researchers should understand the rationale for selecting different types of control groups; (4) The CONSORT 2010 checklist should be adopted when the researchers reported

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the RCTs about ligustrazine injection. In general, further RCTs with good methodology were still required to accurately verify the efficacy of ligustrazine injection as adjunctive therapy in the treatment of angina pectoris.

This systematic review was more reliable than previous reviews on ligustrazine injection. The previous reviews had the following defects: (1) Non-randomized controlled trials were included in their search strategy; (2) The combination use of other medicines in both treatment and control groups was allowed in their study selection; (3) Sensitivity and subgroup analysis were not provided in their evidence evaluation; (4) Their performance did not follow the PRISMA requirements. On the contrary, this systematic review and meta-analysis included only the RCTs comparing the efficacy of ligustrazine injection combined with conventional antianginal drugs with antianginal drugs alone. Moreover, in order to avoid possible publication biases, subgroup and sensitivity analysis were performed in this study.

In summary, the overall result from the eleven RCTs indicated that the efficacy of ligustrazine injection as adjunctive therapy was more effective than conventional antianginal drugs alone for angina pectoris. Due to the low quality of the included RCTs, more rigorously designed RCTs were still needed to verify the efficacy of ligustrazine injection as adjunctive therapy for angina pectoris.

Conclusions

This study showed that ligustrazine injection combined with conventional antianginal drugs was more effective than conventional antianginal drugs alone in treating angina pectoris. Moreover, sensitivity and subgroup analysis conducted on M scale, sample size, and years of publication also consistently corroborated that ligustrazine injection as adjunctive therapy had superior effect in the treatment of angina pectoris. However, more rigorously designed RCTs were still needed to accurately verify the efficacy of ligustrazine injection as an adjunctive therapy for angina pectoris.

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