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Review Article

Chinese herbal medicine for myasthenia gravis: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Background: Myasthenia Gravis (MG) is a disorder of neuromuscular transmission bringing mild ocular weakness to severe generalized muscle weakness and disability. The conventional treatments have long-term side effects, and Chinese herbal medicines (CHM) have shown possible effect and safety for MG patients, but the existing evidence was not robust enough and the results were out of date.

Methods: Searching for randomized controlled trials (RCTs) was conducted in 7 databases and clinical trial registries until July 2021. The ROB 2 tool was used to assess the study quality and GRADE was used to assess the quality of whole evidence. Meta-analyses were conducted and the results were presented as risk ratio (RR) or mean difference (MD) with 95% confidence interval (CI).

Results: Nineteen RCTs (1283 participants) testing 13 kinds of CHM with adequate randomization were included and six RCTs investigating Compound Huangqi were included in the meta-analyses. In addition to conventional treatment, nine CHMs reduced symptom scores of MG. Compound Huangqi plus conventional treatment (pyridostigmine bromide or prednisone or both) reduced the symptom scores compared with conventional treatment (MD = -3.56, 95%CI -4.86 to -2.26). Less adverse events happened in the CHM groups (3/247 in the CHM groups, 52/245 in the control groups, RR = 0.13, 95%CI 0.06 to 0.30, 9 RCTs, a total of 492 participants). The effect on quality of life was inconsistent.

Conclusion: Nine CHMs could probably bring benefit for MG symptom improvement. Moderate to low certainty of evidence supported Compound Huangqi added-on conventional treatment probably bring extra benefit of improving MG symptoms. Adding CHMs could be safer than giving only conventional treatment.

Study registration: The protocol was registered in PROSPERO (ID: 32718).

1. Introduction

Myasthenia Gravis (MG) is a disorder of neuromuscular transmission, resulting from binding of auto-antibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR).[1,2] Clinically, the symptoms range from mild ocular symptoms to severe generalized muscle weakness and disability. Because of the severity of the symptoms, the disease has an extensive impact on physical, psychological and social well-being.[3] The Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America (MGFA) has formed a Task Force to address these issues since 1997. The latest authoritative treatment recommendations in 2020 included thymectomy, rituximab in MG with antibodies to acetylcholine receptors and muscle-specific kinase, eculizumab, and methotrexate.[4] However, pyridostigmine, corticosteroids and immunosuppressive therapy (IS) are still the most common treatments for MG. The use of pyridostigmine and corticosteroids needs to be reduced as much as possible because it is associated with many long-term side effects, often intolerable for patients.[5] Therefore, many studies have been investigating alternative therapies for MG.

Chinese herbal medicine (CHM) has been a popular treatment for MG in China. The possible mechanisms include promoting the expression of transcription factor Forkhead box protein P3 (FoxP3) to up-regulate T regulatory cells (Tregs), and decreasing cytokine expression such as IL- 4 and IL-13 (Astragalus membranaceus);

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increasing number of Tregs and inhibiting Th17 cell differentiation (Radix Ginseng); a decrease of autoantibodies and immunoglobulin G (IgG) (Bupleurum polysaccharides (BPs) from Radix Bupleuri) and anti-acetylcholinesterase effects (flavonoid derivatives from Buzhong Yiqi decoction).[6] A systematic review on CHM for MG was published in 2018, which included 14 randomized controlled trials (RCTs) published before 2017.[6] It concluded that CHM could be used for MG patients, but the conclusion was based on pooled data of different kinds of CHMs, the kind of CHM named HQFF (Compound Huangqi in English) was studied by three included RCTs, but the meta-analysis for this specific kind of CHM was not conducted. Giving only the overall effect of all kinds of CHMs induced more clinical bias in the analysis and the certainty of evidence was not assessed. Besides, the evidence was also out of date. To straighten out the current research progress of CHMs for MG, a more comprehensive search was conducted to include RCTs with more rigorous criteria of reporting quality, the included RCTs were assessed with the advanced risk of bias tool (ROB2)[7] and the certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool.[8] This review is to evaluate the effect and safety of CHM for MG patients, compared with conventional treatment.

2. Methods

The protocol was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=32718), and the deviation from the protocol was explained in the end of this review.

2.1. Eligibility criteria

Types of studies: All RCTs featuring CHM for MG only with clear illustration on the randomization methods. Types of participants: People of any age or sex with an explicit diagnosis of myasthenia gravis. The diagnostic criteria of MG must contain following conditions: 1. Clinical symptoms: some specific striated muscle weakness showed volatility and easy fatigue, extraocular muscle involvement was most common, muscle weakness symptoms were mild in the morning and severe in the evening, after continuous activity, improved after rest. 2. Positive neostigmine test. 3. The results of Repetitive nerves stimulation (RNS) showed that the amplitude of low-frequency stimulation decreased by more than 10%. Single fiber electromyography (SFEMG) results showed "trembling" widening with or without block. 4. Immunological examination: AChR antibody could be detected in the blood of most systemic MG patients, while anti-Musk antibody and anti-LRP4 antibody could be detected in a few MG patients. Based on condition 1, MG could be diagnosed with 2 or 3 or 4. This diagnostic criterion of MG was from the Guidelines for the diagnosis and treatment of myasthenia gravis in China 2015, which was published by China Medical Association.[9] Types of interventions: All traditional CHM treatments for MG were included, with no restrictions on formulation, delivery, dosage, regimen etc. The medicine composition, and method of use should be reported. Trials using CHM combined with any acupuncture treatment would be excluded. Types of comparators: No intervention, placebo, or any conventional treatment for MG patients. The conventional treatment refers to all the recommended therapies from the clinical practice guidelines of MG, such as corticosteroids, immunosuppressive drugs, pyridostigmine bromide, and so on.[2,4] Trials using any CHM treatment including pharmacotherapies and non-pharmaceutical therapies in the control group would be excluded. Types of outcomes and outcome measures: The main outcomes were symptom scores (continuous variable) and the effective rates of treatment (dichotomous variable) within 18 months of MG. The most important measures of symptom scores were The Quantitative Myasthenia Gravis (QMG) Test,[10] and the clinical absolute and relative score system (ARS).[11] The QMG test is a standardized quantitative strength scoring system developed specifically for MG. The QMG has been validated and has been used by the investigators in several previous trials. The higher numbers are representative of more severe impairment. It was recommended by the earlier MGFA Task force report in 2000 as the measure of improvement and worsening. Recent data support the use of a 2- or 3- point of change in QMG as a criterion for minimal clinically significant change and depending on MG severity; in mild (QMG 0–9) to moderate disease (QMG 10–16), a 2-point change is clinically significant, and a 3-point change is significant for severe MG (QMG >16). The clinical absolute and relative score system (ARS) was a standardized quantitative strength scoring system developed specifically for MG. It was developed in China and the reliability of this scoring system was proved by being tested in different observers. It was used popularly in clinical trials of MG in China. The scoring system consisted of two parts, the absolute scores, and the relative scores. The absolute scores included 8 items: ptosis, palpebra superior fatigability, disability of ocular motion, fatigability of the upper and lower extremity muscles, disability of the facial muscles, chewing difficulties, dysphagia, and disability of the respiratory muscles. Each item had five possible scores, ranging from 0 (the signs and symptoms being absent) to 4 (the most severe dysfunction). The relative scores were obtained with the scores before treatment subtracted by the scores after treatment and then divided by the scores before treatment. The higher the relative scores, the more significant the changes of the disabilities. Besides these, other objective and clearly illustrated effectiveness evaluation criteria would also be included. The specific calculation methods of the effective rates were defined by authors of included RCTs. The secondary outcomes including improvement in quality of life (QoL), reduction of the dose of hormone, withdrawal, and adverse events. Measures of QoL included any internationally recognized score and any other validated assessment techniques.

2.2. Searching process

Searching was conducted in the Cochrane Neuromuscular Disease Group Specialized Register, The Cochrane Central Register of Controlled Trials (CENTRAL) (2020, in The Cochrane Library), MEDLINE (January 1966 to September 2020), EMBASE (January 1980 to September 2020), Chinese Bio Medical Database (SinoMed) (1979 to September 2020), Chinese National Knowledge Infrastructure Database (CNKI) (1979 to September 2020), and VIP Chinese Science and Technique Journals Database (1989 to September 2020), and updated in July 2021. We also searched for unpublished literature in the Chinese Conference Papers Database and the Chinese Dissertation Database Ovid Wanfang database (from inception to July 2021). We did not set restriction on the year of dissemination, language, or report status such as unpublished manuscripts and conference abstracts. Other searching resources including the Chinese clinical trial registry and ClinicalTrials.gov for online registration were also searched. We searched searching engines and websites including Microsoft Academic for any missing articles, and opengrey.com for gray literature. We checked the references of studies included in the systematic reviews to identify any missing study. The authors of included RCTs were contacted by email and phone to request further published or unpublished work. The search strategy of PubMed can be reached in https://www.crd.york.ac.uk/PROSPEROFILES/32718_STRATEGY_20210103.pdf.

2.3. Selection and data extraction

Six authors were divided into three groups. In each group, two authors screened each record independently using NoteEx-

pressV3.0 and the disagreements were solved by discussion. Kappa values of each group were calculated to assure the quality of screening and we only started formal screening when the kappa value was above 0.75 in the test. One author (SJZ) collected data from included RCTs and another reviewer (ZYY) checked the extracted data and solved the disagreements by discussion. The data extraction form included study ID, title, first author, type of publication, diagnosis criteria, disease severity of MG, description of participants, complications, number of randomized and completed participants in both groups, drop-out details, type and details of treatment and control, duration of treatment, the measuring methods, and results of all outcomes. When studies reported confusing information including unclear or illogical numbers and figures, we tried to consult the authors to provide raw data.

2.4. Study risk of bias assessment

ROB 2[7] was used to assess risk of bias in the included studies with the excel tool. We assessed the risk of bias of the symptom scores of MG as the main outcome. All domains were assessed including items of the randomization process, deviations from the intended interventions (effect of assignment to intervention), missing outcome data, measurement of the outcome, selection of the reported result and an overall assessment. Two authors (ZSJ and YZY) assessed risk of bias independently and solved the disagreements by discussion. In the randomization section, we considered only studies that explicitly reported the correct randomization method to be truly randomization. In the "deviations from the intended intervention" domain, if the deviations were not reported by the published trial, and no evidence had been shown for deviations, and the trial did not used adjusted statistical methods for deviations such as ITT analysis, we considered the trial to have used an appropriate analysis to estimate the effect of assignment to intervention. In the "missing outcome data" domain, if we did not find the published protocol of the RCT, the included RCT did not report drop-out, and there was no evidence to prove the existence of drop-out, we considered that the data of the outcome of the RCT was available for all. In the "measurement of the outcome" domain, we believed that if the scale used had been tested for reliability and validity, and had been used popularly by many trials, it was an appropriate measurement method. When patients in the CHM group had significantly more visits than those in the control group due to the need to adjust the Chinese herbal medicine formulation, we thought that the measurement or ascertainment of the outcome could have differed between intervention groups. When the study did not report whether the outcome assessors were blinded, we considered they might be aware of the intervention received by participants, because in a hospital environment, outpatients were often treated and evaluated by the same doctor, while the inpatients had daily contact with all the doctors. It was easy for the outcome assessors to know the intervention received by participants. In the "selection of the reported result" domain, we compared reported results with the protocol or the pre-specified analysis plan. If the protocol or the analysis plan was not available, we considered there was no information for this domain. When four or more domains were assessed as "some concerns", the risk of bias of the RCT was accumulated, we considered the overall evaluation should be "high risk", even if there was no "high risk" domain.

2.5. Effect measures

Continuous data were presented as mean difference (MD) with 95% confidence interval (CI) in the symptom score and quality of life. Binary data were presented as risk ratio (RR) with 95% CI for the total effective rate and the curative rate. The random-effects model was used for meta-analysis considering potential clinical heterogeneity. For example, the included CHM could be given in different dosage forms and was compared with different kinds of conventional treatments. We conducted meta-analyses on the results of MG symptom scores, the effective rates, and secondary outcomes. The results of symptom scores would be synthesized into MD with 95% CI, the post treatment score between groups were compared when the difference value between before and after treatment were not reported. The effective rates would be synthesized into RR with 95% CI.

2.6. Synthesis methods

Only studies with accessible full text, reporting outcomes of interest clearly were eligible for each synthesis. Only studies investigating on the "CHMs of the same category" were eligible for meta-analysis. The definition of "CHMs of the same category" was based on the treating principles of traditional Chinese medicine for MG. According to the previous study, spleen and kidney deficiency was the main pathogenesis of MG, and invigorating spleen and kidney was the treating principle for MG.[6,33] The most frequently used herb was Astragali Radix,[6] which was often used as the sovereign drug (main drug) in the prescription. The common minister drug (adjuvant drug) included *Ginseng Radix et Rhizoma*, *Atractylodis Macrocephalae Rhizoma*, *Angelicae Sinensis Radix*, *Lycii Fructus*[6] etc. If the sovereign drugs and the minister drugs were the same in the prescriptions studied in different RCTs, we considered these CHMs to be of the same category. When there was add-and-subtract of the kinds of the herbs or changes of the amount of drug dosage in the prescription for syndrome differentiation, we still considered them to be of the same category if the kinds of sovereign drugs and minister drugs were not changed.

Forest plot was used to present the result of meta-analyses. Review Manager 5.4 was used to implement meta-analyses. The I^2 statistic was referred to judge the heterogeneity among the included RCTs. A smaller I^2 statistic indicates smaller heterogeneity.[12] When $I^2 > 50\%$, the accuracy of the data was checked first. If the data was accurate and appropriate, subgroup analysis would be used to explore possible causes of heterogeneity including different kinds of controls and different outcome scoring systems and the results would be carefully interpreted.[13] The sensitivity analysis would include only blinded outcome assessment to see if the result was stable without placebo effect, based on the meta-analysis. The GRADE online tool was used to assess certainty of the body of evidence which was presented by Summary of Findings table.[8] A funnel plot was used to explore the possibility of publication bias, if ten or more trials were included in a meta-analysis.[14]

3. Results

3.1. Study selection

Overall, 6058 records were identified from database searching and other resources. 4060 records were screened by checking titles and abstracts, and 232 articles were screened by checking the full texts. After full-text screen, 19 RCTs with 1283 participants (46.4% male and 53.6% female) were included in this systematic review (Fig. 1).

3.2. Study characteristics

All trials were conducted in China and published from 2003 to 2020 with only one study (Jiang C 2014) published in English. Five trials were published in journals and 14 were dissertations. Only one trial (Jiang C 2014) had its protocol published online in the Chinese clinical trial registry, and no other protocols or statistics

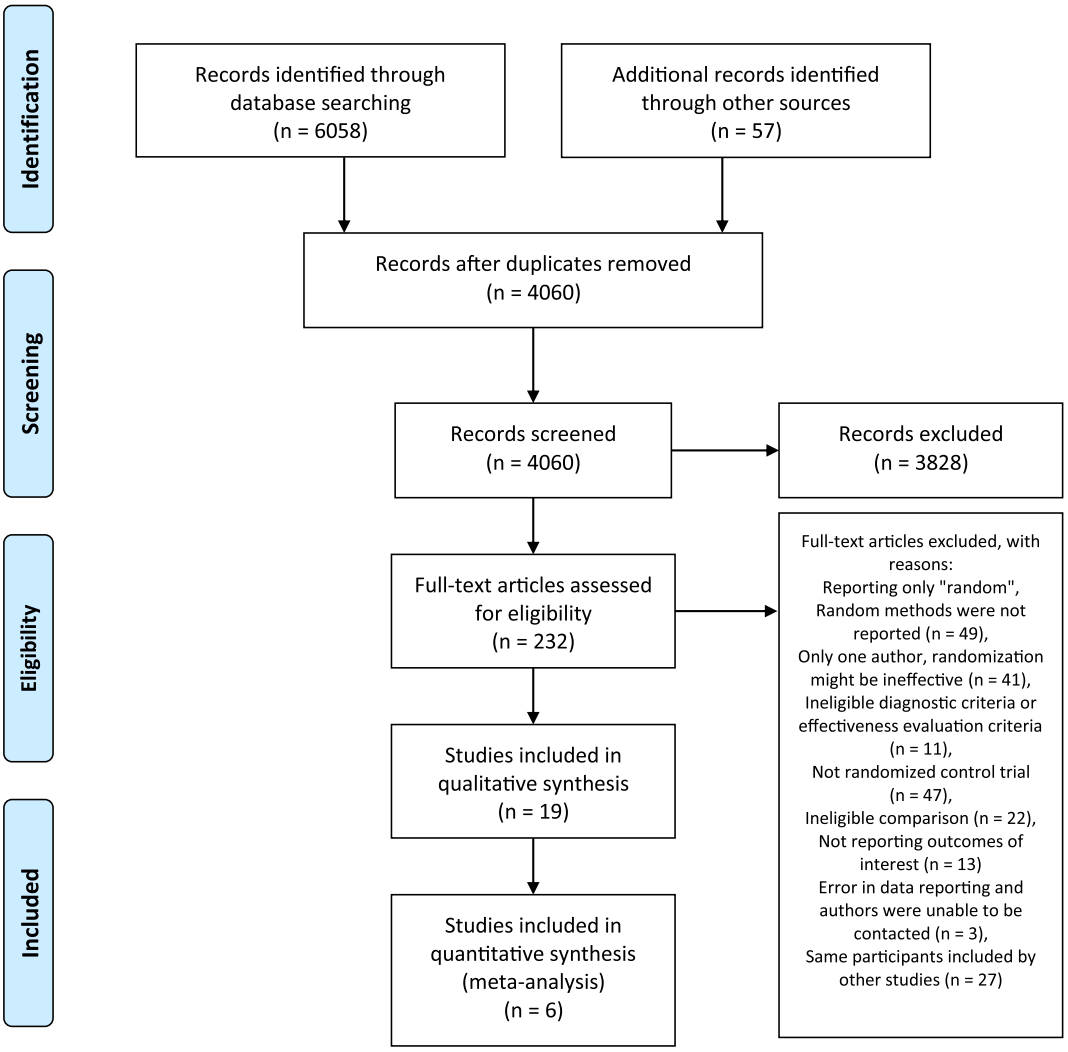

Fig. 1. The PRISMA flow diagram of screening.

analyses plans were identified. All the studies only included patients with mild MG as Osseman or modified Osseman I, IIA, IIB type. Eight studies used diagnosis criteria from Guidelines for the diagnosis and treatment of myasthenia gravis in China 2015[9], 7 used diagnosis criteria from medical textbooks, 2 used the results of academic conference for MG in 1997, 2 used both of guidelines and medical textbooks by combining the criteria. Participants of all ages were covered, only one study focused on the elderly[27] and only one study focused on children.[33] The comparisons between groups were CHM plus conventional treatment versus conventional treatment (15 studies) or CHM plus conventional treatment versus placebo plus conventional treatment (4 studies). Thirteen kinds of CHM were included, comparing with pyridostigmine bromide (PB), prednisone (Pred) or both or dexamethasone acetate. Among them, Compound Huangqi decoction or granules was tested in 6 studies, compared with different conventional treatments and with or without placebo, therefore we conducted meta-analyses on Compound Huangqi. The characteristics of included RCTs were shown in Table 1. The compositions, dosages, dosage forms and treating principles of all the prescriptions of included TCMs were displayed in the supplementary Table S1. We also compared the prescriptions of all the other kinds of CHMs with Compound Huangqi to present the differences between prescriptions of Compound Huangqi given by different RCTs and the similarity between Compound Huangqi and other kinds of CHMs in the supplementary Table S1.

In terms of outcomes, all 19 trials reported the symptom scores and the outcome was evaluated by The Quantitative Myasthenia Gravis (QMG)[10] Test ($n=6$) or the clinical absolute and relative score system (ARS)[11] ($n=13$). The evaluation of effective rates was reported as the total effective rate ($n=16$) and the curative rate ($n=11$). The rule to calculate these two rates was based on symptom scores. The relative score = (total symptom score before treatment - total symptom score after treatment)/total symptom score before treatment. The reporting effect was classified as curative, basically curative, significantly improved, improved, and ineffective, respectively, if the relative score is no less than 0.95, between 0.80 to 0.94, between 0.50 to 0.79, between 0.25 to 0.49, and below 0.25.[11,15] The total effective rate included the curative, the basically curative, the significantly improved and the improved cases. The curative rate included only the curative cases.[11,15] This calculation rule was applied to both the QMG test and the ARS system. Three trials reported the quality of life evaluated by Busch QoL score,[16] and 2 trials reported the reduction of the dose of pyridostigmine bromide (PB). The detailed results of main outcomes of all included studies were presented in Table 2.

3.3. Risk of bias in studies

The risk of bias in the outcome of symptom scores was assessed and shown in Table 3. All the trials reported the method of ran-

Table 1
The characteristics of included RCTs of Chinese herbal medicine for myasthenia gravis.

Article ID	Type of MG	Male/Female	Age(year)	Duration of disease	Complications	Number of patients (T/C)	Treatment group	Control group	Duration of treatment	Outcome
BaoB 2016a[17]	I, IIa, IIb	28/32	28-64	3 months-4 years	NR	30/30	Compound Huangqi granules + pyridostigmine bromide	Placebo + pyridostigmine bromide	36 weeks	1,2
BaoB 2016[18]	I, IIa, IIb	110/131	27-65	11-38 years	No	121/120	Compound Huangqi granules + pyridostigmine bromide	Placebo + pyridostigmine bromide	12 weeks	1,2
ChenML 2020[19]	I	29/37	29-53	2-4 years	No	34/32	Qilian decoction + pyridostigmine bromide	Pyridostigmine bromide	8 weeks	1,2
GuoY 2020[20]	I, IIa	64/56	12-68	3 months-7 years	No	60/60	Yiqi Jianpi decoction + pyridostigmine bromide	Pyridostigmine bromide	3 months	1,2
HeT 2016[21]	I, IIa, IIb	26/35	18-75	1-10 months	No	31/30	Bupi Yishen decoction + pyridostigmine bromide	Pyridostigmine bromide	6 months	1,2,3
JiangC 2014[22]	II	35/25	17-75	1-61 months	No	30/30	JJN granules + pyridostigmine bromide	Pyridostigmine bromide	6 months	1
JuGS 2003[23]	I, IIa	14/26	5-45	2 months-2.5 years	NR	20/20	Tan-wei capsule + prednisone	Prednisone	4 months	1,2
LaiJ 2013[24]	I, IIa, IIb	29/31	7-74	1 month-16 years	No	30/30	Bupi Qiangli decoction + prednisone + pyridostigmine bromide	Prednisone + pyridostigmine bromide	3 months	1,2
LiDF 2012[25]	I, IIa, IIb	22/18	27-52	NR	No	20/20	Yiqi Qushi decoction + pyridostigmine bromide	Pyridostigmine bromide	8 weeks	1,2
LiZQ 2019[26]	I, IIa, IIb	28/32	22-73	NR	No	30/30	Compound Huangqi decoction + pyridostigmine bromide	Pyridostigmine bromide	6 months	1,2
LiuXY 2020[27]	I, IIa, IIb	38/30	60-80	NR	Thymoma 19, thymic hyperplasia 22, hyperthyroidism 27	34/34	Buzhong Yiqi decoction + dexamethasone acetate	Dexamethasone acetate	12 weeks	1
MaY 2016[28]	I, IIa, IIb	23/29	28-61	2.37 years on average	No	26/26	Bupi Yishen decoction + pyridostigmine bromide for type I, Bupi Yishen decoction + pyridostigmine bromide+prednisone for type II	Pyridostigmine bromide for type I, Pyridostigmine bromide+prednisone for type II	3 months	1,2,3
NiuGH 2009[29]	I, IIa, IIb	24/36	24-62	NR	No	30/30	Compound Huangqi granules + prednisone + pyridostigmine bromide	Placebo + prednisone + pyridostigmine bromide	3 months	1,2
OuZH 2005[30]	I, IIa	13/23	6-60	2 months-12 years	No	18/18	Qiangji Jianli oral liquid + pyridostigmine bromide	Placebo + pyridostigmine bromide	60 days	1,2
ShengWD 2018[31]	I, IIa	18/22	38-61	NR	No	20/20	Supplemented Buzhong Yiqi decoction + pyridostigmine bromide	Pyridostigmine bromide	2 months	1
YanJ 2016[32]	I, IIa, IIb	17/23	25-61	NR	NR	20/20	Supplemented Buzhong Yiqi decoction + pyridostigmine bromide	Pyridostigmine bromide	12 weeks	1,2
YuYY 2018[33]	I	27/35	3-16	1-24 weeks	No	31/31	Compound Huangqi decoction + pyridostigmine bromide	Pyridostigmine bromide	6 months	1,2
YuYY 2017[34]	I, IIa, IIb	26/34	16-76	1 month-12 years	No	30/30	Compound Huangqi decoction + pyridostigmine bromide	Prednisone + pyridostigmine bromide	6 months	1,2
YuanYK 2017[35]	I, IIa, IIb	24/33	22-55	NR	No	29/28	Yiqi Bushen granules + prednisone + pyridostigmine bromide	Prednisone + pyridostigmine bromide	4 weeks	1,2,3

Note: NR means not reported, T/C means treatment group / control group. In the outcome column, 1 means symptom score, 2 means overall evaluation of efficacy, 3 means secondary outcomes including drug withdrawal and quality of life.

Table 2
The summary of main outcomes of included RCTs.

Article ID	Number of completed and analyzed participants (Treatment group/Control group)	Name of the CHMs and the component herbs	Symptom scores		Total effective rate	Curative rate
			Measurement	Mean difference (95% CI)	Risk Ratio (95% CI)	Risk Ratio (95% CI)
Chinese herbal medicine + pyridostigmine bromide + prednisone vs pyridostigmine bromide + prednisone						
LaiJ 2013	30/30	Bupi Qiangli decoction: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Angelicae Sinensis Radix, Epimedii Folium, Aconiti Lateralis Radix Praeparata, Smilacis Glabrae Rhizoma	ARS	−1.13 [−3.33, 1.07]	1.07 [0.96, 1.20]	2.00 [0.40, 10.11]
YuYY 2017	30/30	Compound Huangqi decoction: Astragali Radix, Cimicifugae Rhizoma, Saposhnikoviae Radix, Lycii Fructus, Pseudostellariae Radix, Angelicae Sinensis Radix, Atractylodis Macrocephalae Rhizoma, Corni Fructus	ARS	−3.07 [−5.55, −0.59]	1.08 [0.88, 1.32]	2.50 [0.53, 11.89]
YuanYK 2017	29/28	Yiqi Bushen granules: Ginseng Radix et Rhizoma, Astragali Radix, Citri Reticulatae Pericarpium, Atractylodis Macrocephalae Rhizoma, Scutellariae Radix, Taxilli Herba, Ligustri Lucidi Fructus, Paeoniae Radix Rubra	QMG	−1.08 [−2.35, 0.19]	1.22 [0.90, 1.65]	Not Reported
Chinese herbal medicine + pyridostigmine bromide + prednisone vs placebo + pyridostigmine bromide + prednisone						
NiuGH 2009	30/30	Compound Huangqi granules: Astragali Radix, Pseudostellariae Radix, Atractylodis Macrocephalae Rhizoma, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix, Lycii Fructus, Corni Fructus	ARS	−2.81 [−4.36, −1.26]	1.03 [0.94, 1.13]	4.00 [0.47, 33.73]
Chinese herbal medicine + pyridostigmine bromide vs pyridostigmine bromide						
JiangC 2014	30/30	JJN granules: Astragali Radix, Pseudostellariae Radix, Atractylodis Macrocephalae Rhizoma, Aurantii Fructus, Cimicifugae Rhizoma, Leonuri Herba, Angelicae Sinensis Radix, Lycii Fructus, Polygoni Multiflore Radix, Corni Fructus	QMG	−3.22 [−5.47, −0.97]	Not Reported	Not Reported
ChenML 2020	34/32	Qilian decoction: Astragali Radix, Codonopsis Radix, Cimicifugae Rhizoma, Bupleuri Radix, Puerariae Lobatae Radix, Coptidis Rhizoma, Scutellariae Radix, Citri Reticulatae Pericarpium, Pinelliae Rhizoma Praeparatum, Bambusae Caulis in Taenias, Nelumbinis Folium, Chuanxiong Rhizoma, Angelicae Sinensis Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle	ARS	−2.75 [−5.10, −0.40]	1.17 [0.94, 1.44]	1.41 [0.44, 4.55]
GuoY 2020	60/60	Yiqi Jianpi decoction: Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Dioscoreae Rhizoma, Poria, Citri Reticulatae Pericarpium, Astragali Radix, Coicis Semen, Cimicifugae Rhizoma, Bupleuri Radix, Angelicae Sinensis Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle	QMG	−2.12 [−2.72, −1.52]	1.16 [1.03, 1.31]	2.00 [0.52, 7.63]
HeT 2016	31/30	Bupi Yishen decoction: Astragali Radix, Panacis Quinquefolii Radix, Dioscoreae Rhizoma, Cimicifugae Rhizoma, Bupleuri Radix, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium, Atractylodis Macrocephalae Rhizoma, Cistanches Herba, Morindae Officinalis Radix, Polygonati Rhizoma, Smilacis Glabrae Rhizoma, Dendrobii caulis, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle	QMG	−0.83 [−1.42, −0.24]	1.12 [0.93, 1.35]	2.42 [0.51, 11.53]
LiDF 2012	20/20	Yiqi Qushi decoction: Astragali Radix, Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Angelicae Sinensis Radix, Atractylodis Rhizoma, Alismatis Rhizoma, Cimicifugae Rhizoma, Phellodendri Chinensis Cortex	QMG	−1.00 [−1.79, −0.21]	1.12 [0.91, 1.38]	Not Reported
LiZQ 2019	30/30	Compound Huangqi decoction: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix etc.	ARS	−2.26 [−4.07, −0.45]	1.69 [1.18, 2.41]	Not Reported
ShengWD 2018	20/20	Supplemented Buzhong Yiqi decoction: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Curculiginis Rhizoma, Epimedii Folium, Cimicifugae Rhizoma, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium	ARS	−1.70 [−2.59, −0.81]	NR	Not Reported
YanJ 2016	20/20	Supplemented Buzhong Yiqi decoction: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Curculiginis Rhizoma, Epimedii Folium, Cimicifugae Rhizoma, Angelicae Sinensis Radix, Citri Reticulatae Pericarpium	ARS	−3.20 [−4.19, −2.21]	1.00 [0.91, 1.10]	3.00 [0.34, 26.45]
YuYY 2018	31/31	Compound Huangqi: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix etc.	ARS	−2.45 [−3.86, −1.04]	1.20 [1.00, 1.44]	2.38 [1.23, 4.59]

(*continued on next page*)

Table 2 (*continued*)

Article ID	Number of completed and analyzed participants (Treatment group/Control group)	Name of the CHMs and the component herbs	Symptom scores		Total effective rate	Curative rate
			Measurement	Mean difference (95% CI)	Risk Ratio (95% CI)	Risk Ratio (95% CI)
Chinese herbal medicine + pyridostigmine bromide vs placebo + pyridostigmine bromide						
BaoB 2016a	30/30	Compound Huangqi: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix etc.	ARS	−8.20 [−11.91, −4.49]	3.25 [1.77, 5.98]	Not Reported
BaoB 2016	121/120	Compound Huangqi: Astragali Radix, Lycii Fructus, Cimicifugae Rhizoma, Saposhnikoviae Radix, Angelicae Sinensis Radix etc.	ARS	−4.93 [−6.63, −3.50]	3.93 [2.71, 5.68]	Not Reported
OuZH 2005	18/18	Qiangji Jianli oral liquid: Astragali Radix, Codonopsis Radix, Atractylodis Macrocephalae Rhizoma, Dioscoreae Rhizoma, Angelicae Sinensis Radix, Cimicifugae Rhizoma, Bupleuri Radix, Citri Reticulatae Pericarpium, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Humulus Scandens	ARS	−2.41 [−3.33, −1.49]	1.12 [0.93, 1.36]	2.00 [0.20, 20.15]
Chinese herbal medicine + prednisone vs prednisone						
JuGS 2003	20/20	Tan-wei capsule: Astragali Radix, Hominis Placenta, Strychni Semen, Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle	ARS	−2.40 [−3.28, −1.52]	1.05 [0.92, 1.20]	2.00 [0.20, 20.33]
Chinese herbal medicine + dexamethasone acetate vs dexamethasone acetate						
LiuXY 2020	34/34	Buzhong Yiqi decoction: Polygoni Multiflore Radix, Atractylodis Macrocephalae Rhizoma, Corni Fructus, Paeoniae Radix Alba, Angelicae Sinensis Radix, Flycyrrhizae Radix et Rhizoma Praeparata Cum Melle, Bupleuri Radix, Cuscutae Semen, Cimicifugae Rhizoma, Polygonati Rhizoma, Polygoni Multiflori Caulis	QMG	−1.14 [−1.86, −0.42]	Not Reported	Not Reported
Different conventional treatment for different type of MG in one study						
MaY 2016	26/26	Bupi Yishen decoction: Astragali Radix, Codonopsis Radix, Rehmanniae Radix Praeparata, Angelicae Sinensis Radix, Corni Fructus, Lycii Fructus, Mori Fructus, Atractylodis Macrocephalae Rhizoma, Poria, Morindae Officinalis Radix, Cistanches Herba, Cuscutae Semen, Citri Reticulatae Pericarpium, Bupleuri Radix, Cimicifugae Rhizoma, Platycodonis Radix	QMG	Not Reported	1.14 [0.95, 1.36]	3.00 [0.33, 26.99]

ARS, clinical absolute and relative score system; CI, Confidence interval; QMG, Quantitative Myasthenia Gravis Test.

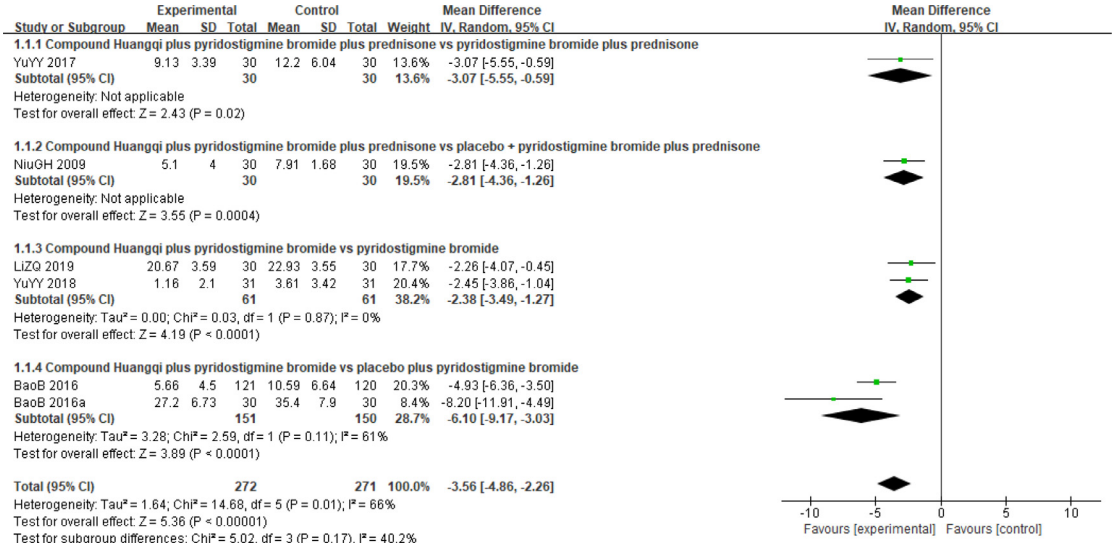

Fig. 2. The forest plot of the symptom score of the comparison: Compound Huangqi plus conventional treatment vs conventional treatment (plus placebo of Compound Huangqi).

domization generation, but only 4 trials concealed the randomization by using central pharmacy. Only four trials conducted blinding by using the placebo of CHM in the control group. No study reported the blinding the outcome assessor. Three trials reported the existence of drop-out and the details and they all used naive 'per-protocol' analyses which may induce bias due to deviations from the intended interventions, but the drop-out rates were all below 5% and the observed events were not rare, so it was unlikely to induce risk of bias due to missing outcome data. The included two scales of MG symptom scores were the most objective and reliable measure assessed by health care professionals, so the assessment of the outcome would be less likely influenced by the knowledge of intervention received. Since only the protocol of one trial[22] was accessible, the risk of bias in selection of the reported result was mostly unclear. But since all the included RCTs reported the important clinical outcomes such as the symptom score, the lack of

Table 3
The risk of bias of included RCTs reporting the outcome of symptom scores.

Study ID	Domain 1. Randomization process		Domain 2. Deviations from intended interventions		Domain 3. Missing outcome data		Domain 4. Measurement of the outcome		Domain 5. Selection of the reported result		Overall Judgement
	1.1–1.3	Judgement	2.1–2.7	Judgement	3.1–3.4	Judgement	4.1–4.5	Judgement	5.1–5.3	Judgement	
BaoB 2016a	Y/NI/N	Some concerns	PY/PY/NI/NA/NA/Y/NA	Some concerns	Y/NA/NA/NA	Low	N/N/PY/PN/NA	Low	NI/NI/NI	Some concerns	Some concerns
BaoB 2016	Y/PY/N	Low	PN/PN/NA/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PN/NA/NA	Low	NI/NI/NI	Some concerns	Some concerns
ChenML 2020	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/PN/PN	Some concerns	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	High
GuoY 2020	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
HeT 2016	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/PN/PN	Some concerns	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	High
JiangC 2014	Y/Y/PN	Low	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	Y/Y/N	High	High
JuGS 2003	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/PY/NI	High	High
LaiJ 2013	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
LiDF 2012	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
LiZQ 2019	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/PY/NA/NA/NA	Some concerns	NI/NI/NI	Some concerns	Some concerns
LiuXY 2020	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
MaY 2016	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
NiuGH 2009	Y/PY/N	Low	N/N/NA/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/N/NA/NA	Low	NI/NI/NI	Some concerns	Some concerns
OuZH 2005	Y/PY/N	Low	PN/PN/NA/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PN/NA/NA	Low	NI/NI/NI	Some concerns	Some concerns
ShengWD 2018	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
YanJ 2016	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
YuYY 2018	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
YuYY 2017	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/Y/NA	Low	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	Some concerns
YuanYK 2017	Y/NI/N	Some concerns	PY/PY/PN/NA/NA/PN/PN	Some concerns	Y/NA/NA/NA	Low	N/N/PY/PY/PN	Some concerns	NI/NI/NI	Some concerns	High

Y, Yes; NI, no information; N, no; Low, low risk of bias; High, high risk of bias; Some concerns, some concerns on the risk of bias.

protocol might not induce strong bias. We contacted the authors of 19 included RCTs for more details and any unpublished trials but we did not get any response.

3.4. Meta-analyses of compound Huangqi

We conducted meta-analyses to investigate the effect of Compound Huangqi on all the main outcomes, which were all measured by the clinical absolute and relative score system. The forest plot (Fig. 2) showed that when Compound Huangqi was given added on conventional treatment, the symptom score was reduced, comparing the post treatment score between groups (MD=−3.56, 95% CI −4.86 to −2.26, $I^2 = 66\%$, 6 RCTs, $n = 543$). The subgroup analyses were conducted in different control and use of placebo. The results of subgroup analyses were Compound Huangqi plus pyridostigmine bromide (PB) plus prednisone (Pred) versus PB plus Pred (MD = −3.07, 95% CI −5.55 to −0.59, 1 RCT, $n = 60$); Compound Huangqi plus PB plus Pred versus placebo plus PB plus Pred (MD = −2.81, 95% CI −4.36 to - 1.26, 1 RCT, $n = 60$); Compound Huangqi plus PB versus PB (MD = −2.38, 95% CI −3.49 to −1.27, $I^2 = 0\%$, 2 RCTs, $n = 122$); Compound Huangqi plus PB versus placebo plus PB (MD = −6.10, 95% CI −9.17 to −3.03, $I^2 = 61\%$, 2 RCTs, $n = 301$). The possible reasons for the heterogeneity in the last subgroup between BaoB 2016 and BaoB 2016a might be that BaoB 2016 was a multi-center RCT with 241 participants, but BaoB 2016a was a single center RCT with only 60 participants.

In terms of other outcomes, the confidence interval of the total effective rate was too wide and overlapped the null (RR=1.71, 95% CI 0.95 to 3.09, $I^2 = 98\%$, 6 RCTs, $n = 543$). The heterogeneity was also too high which indicated the calculation of total effective rate might induce statistical bias into the pooled result. But the curative rate was significantly increased in the CHM group (RR=2.49, 95% CI 1.39 to 4.46, $I^2 = 0\%$, 3 RCTs, $n = 182$). However, the result should be interpreted carefully because of its small sample size. Details of the meta-analyses were shown in Fig. 3 and Fig. 4.

3.5. Secondary outcomes

Three studies reported the quality of life measured by Busch QoL score. The MD with 95% CI varied a lot among three studies, including 0.93 (0.24, 1.62),[21] −0.64 (−1.80, 0.52)[28] and −2.72 (−4.17, −1.27).[35] Because these 3 RCTs studied different kinds of CHMs with different controls, it would be inappropriate to pool the results. In addition, the different directions of results showed that the evidence is very uncertain. No study reported the reduction of the dose of corticosteroids, but 2 studies reported the reduction of PB. Since the evaluation criteria of drug dose reduction were different in these 2 studies, the result cannot be pooled. He T 2016 defined successful drug withdrawal as patients achieving complete remission of symptoms or clinical absolute score of basically curative standard with stable condition and no recurrence after withdrawal for more than one month. Five out of 30 participants achieved successful drug withdrawal, one out of 30 in the control group. Yu YY 2018 reported the change of daily dosage consumption of PB and PB withdrawal. The daily dosage consumption of PB reduced from 88.06±39.95 mg/d (before treatment) to 30.00 ± 36.33 mg/d (after treatment) in the CHM group, and from 89.68 ± 38.94 mg/d to 86.13 ± 42.24 mg/d in the control group (only PB). Seventeen participants achieved PB withdrawal in the CHM group, and only 2 achieved in the control group.

In terms of adverse events (AEs), 3 trials reported no AE in two groups. Seven trials reported no AE in the CHM group, but AEs happened in the control groups. These AEs including gastrointestinal reaction ($n = 22$), consisting of diarrhea, bloating, nausea, and vomiting; hormone side effects, consisting of moon-shaped face ($n = 2$), elevated fasting blood glucose ($n = 4$), and central obesity

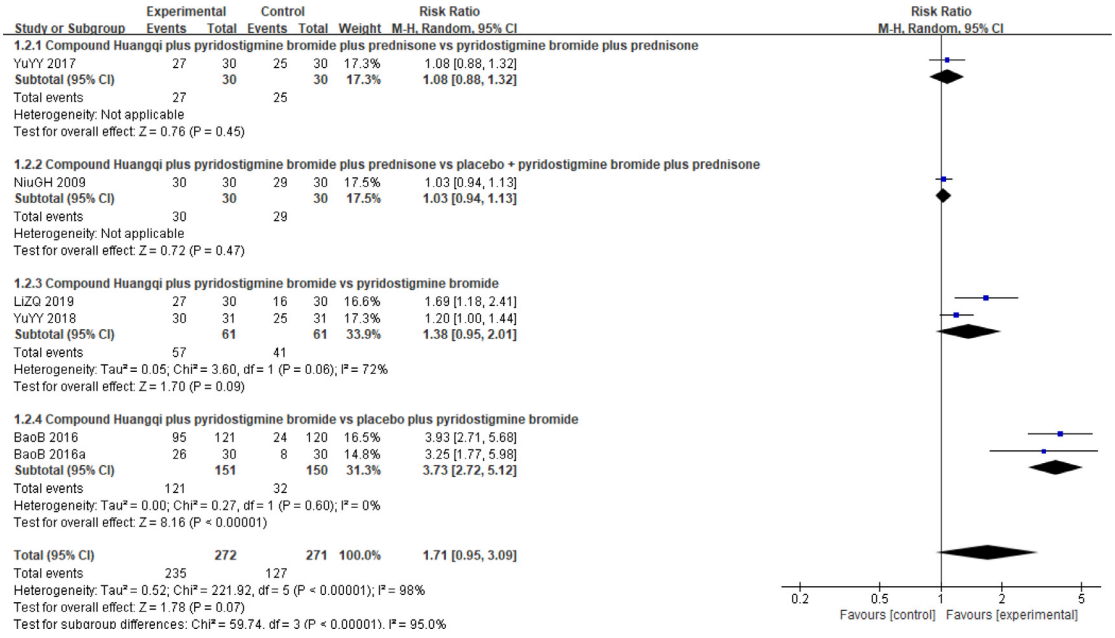

Fig. 3. The forest plot of the total effective rate of the comparison: Compound Huangqi plus conventional treatment vs conventional treatment (plus placebo of Compound Huangqi).

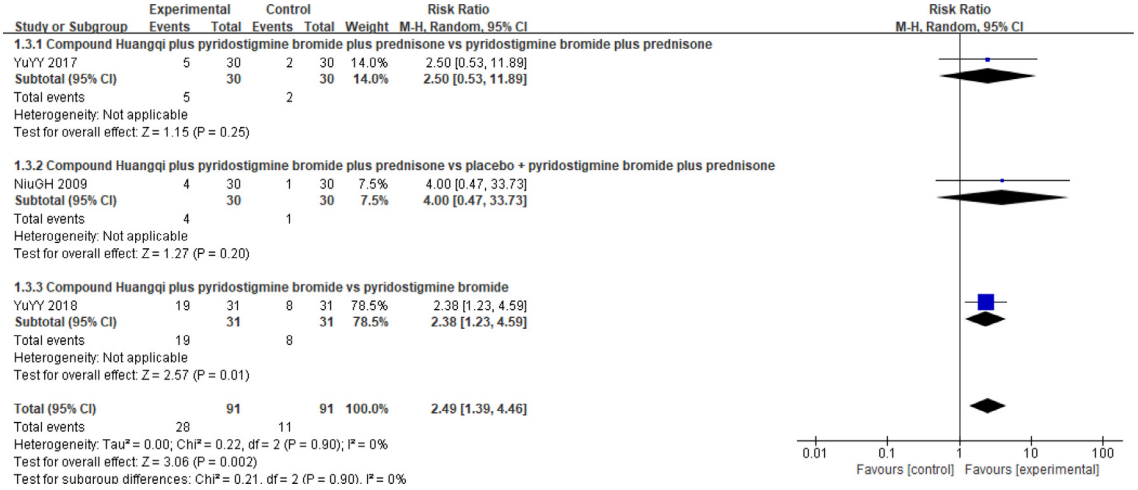

Fig. 4. The forest plot of the curative rate of the comparison: Compound Huangqi plus conventional treatment vs conventional treatment (plus placebo of Compound Huangqi).

($n = 2$); upper respiratory infection ($n = 2$); mild abnormal liver function ($n = 2$). Two trials reported AEs occurred in both groups, but they occurred less in the CHM group. Yu YY 2017 reported 2 cases of stomach discomfort in the Compound Huangqi decoction plus PB group, and 4 cases of stomach cramps, 6 cases of diarrhea, 3 cases of nausea and vomiting, 1 case of bradycardia, 2 cases of increased sputum in the Prednisone Acetate plus PB group. Yuan YK 2017 reported 2 patients in the Prednisone plus PB group and 1 patient in the Yiqi Bushen granules plus Prednisone plus PB group with mild diarrhea and vomiting, which were attributed to unclean diet after medical history inquiry. Seven trials did not reported information about the occurrence of AEs. Overall, nine studies reported adverse events happened in both groups, 3 adverse events happened in the CHM groups ($n = 247$) and 52 adverse events happened in the control groups ($n = 245$), and the pooled data of adverse events was RR=0.13 (95% CI 0.06 to 0.30, 9 RCTs, 492 participants).

3.6. Sensitivity analysis

We did not conduct sensitivity analysis because there was only 1 or 2 included RCTs in each comparison of the meta-analyses. The amount of included RCTs was not enough for us to conduct a meaningful sensitivity analysis.

3.7. Reporting bias

The funnel plot was not conducted as only 6 RCTs were included in the meta-analysis. There were not enough included RCTs to detect reporting bias.

Table 4
The summary of evidence using GRADE method.

Question 1: Compound Huangqi plus pyridostigmine bromide plus prednisone compared to pyridostigmine bromide plus prednisone for myasthenia gravis patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Compound Huangqi plus pyridostigmine bromide plus prednisone	pyridostigmine bromide plus prednisone	Relative (95% CI)	Absolute (95% CI)		
Symptom score (assessed with: the clinical absolute and relative score system)												
2[26,31]	randomised trials	serious [a]	not serious	not serious	not serious	none	60	60	-	MD **2.88 lower** (4.2 lower to 1.57 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
The total effective rate (assessed with: the clinical absolute and relative score system)												
2[26,31]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	57/60 (95.0%)	54/60 (90.0%)	RR 1.04 (0.96 to 1.13)	**36 more per 1,000** (from 36 fewer to 117 more)	⨁⨁◯◯ LOW	IMPORTANT
The recovery rate (assessed with: the clinical absolute and relatie score system)												
2[26,31]	randomised trials	serious [a]	not serious	not serious	serious [b]	none	9/60 (15.0%)	3/60 (5.0%)	RR 2.95 (0.84 to 10.37)	**98 more per 1,000** (from 8 fewer to 469 more)	⨁⨁◯◯ LOW	IMPORTANT

Question 2: Compound Huangqi plus pyridostigmine bromide compared to pyridostigmine bromide for myasthenia gravis patients

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Compound Huangqi plus pyridostigmine bromide	pyridostigmine bromide	Relative (95% CI)	Absolute (95% CI)		
Symptom scores (assessed with: the clinical absolute and relative score system)												
4[14,15,23,30]	randomised trials	serious [a]	serious [c]	not serious	not serious	none	212	211	-	MD **4.01 lower** (6 lower to 2.02 lower)	⨁⨁◯◯ LOW	CRITICAL
The total effective rate (assessed with: the clinical absolute and relatie score system)												
4[14,15,23,30]	randomised trials	serious [a]	serious [c]	not serious	serious [b]	none	178/212 (84.0%)	73/211 (34.6%)	RR 2.22 (0.99 to 4.98)	**422 more per 1,000** (from 3 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Note: a. The protocol of included RCTs were inaccessible, so there were some concerns about reporting bias. b. The confidence interval overlapped the null. c. The confidence interval was wide and the I square is over 50%. **CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

3.8. Certainty of evidence

The certainty of the recovery rate in the comparison of CHM plus PB versus PB was not assessed. Because there was only one study included, and GRADE method does not apply to single study. Moderate to low certainty of evidence supported that Compound Huangqi combined with conventional treatment for MG patients probably reduced more symptom scores than conventional treatment (Table 4). However, the certainty of the total effective rate and the curative rate was low to very low.

4. Discussion

According to former studies, CHM as adjunctive therapy for MG could reduce the QMG scores or MG clinical absolute and relative scores and improve total clinical effective rate. In addition, fewer adverse events happened in the CHM groups. But there were still some weaknesses in the primary study. The previous systematic review included 14 RCTs published before March 2017, the conclusion was based on the pooled data of all kinds of CHMs, and the certainty of the evidence was not assessed. This update of systematic review included 19 RCTs, eight of which were published after March 2017 involving 533 participants. This systematic review was conducted with updated methodological tools such as ROB2 and GRADE and the conclusion was based on RCTs studying CHMs of the same category of Compound Huangqi. Twelve kinds of CHM were included, in forms of decoction, granules and oral liquid. We found that most kinds of CHM added on conventional treatment might reduce symptom scores of MG compared with conventional treatment alone. Compound Huangqi showed significantly effect on improving the symptoms of MG, tested by 6 RCTs. As to adverse events, in the newly included RCTs, 3 studies reported adverse events happened in both groups, 3 adverse events happened in the CHM groups ($n = 90$) and 29 adverse events happened in the control groups ($n = 89$). Overall, twelve studies reported less AEs in the CHM group and no AE was caused by CHM, which indicated CHM was probably safe to use. Five studies of Compound Huangqi reported none or much less adverse events happened in the treatment group which indicated that Compound Huangqi was safe to use.[17,26,29,33,34]

In clinical practice, it is important to apply CHM under the guidance of traditional Chinese medicine's theory. In this review, most CHMs were formulated with the principle of tonifying the spleen, nourishing the kidney, dissipating dampness, and rising the Yang. The most used herbs were also well-known to reflect the treatment principles. Among all the tested CHMs, Compound Huangqi has representative characteristics on ingredients and principles of formulated prescription. This formula was invented by Jingsheng Zhang, a well-known traditional Chinese medicine doctor in Liaoning University of Traditional Chinese Medicine, and it was tested for MG in clinical practice for more than 20 years.[33] Compound Huangqi decoction was produced by the Pharmaceutical Bureau of the First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine. Compound Huangqi is not on the market yet and it's only tested in the MG outpatient service of Affiliated Hospital of Liaoning University of Traditional Chinese Medicine in China. This kind of CHM might bring more benefit to MG patients and further clinical trials might unveil the accurate efficacy of Compound Huangqi in the future.

The basic mechanism of included CHMs is still not clearly investigated, but it can be inferred from published articles about the mechanisms of the components. In terms of the components of Compound Huangqi, studies have shown that Astragali radix possesses potent immunomodulation, antioxidant, and anti-inflammation functions.[36] Cimicifugae Rhizoma was reported to have anti-inflammatory, antioxidant, anti-complement, and

anticancer effects.[37] Saposhnikoviae Radix may enhance the effectiveness of prescriptions by promoting distribution of other herbs in brain.[38] Pharmacological studies indicated that Atractylodis macrocephalae rhizoma possessed antitumor activities, neuroprotective effect, anti-hepatotoxicity, immune and anti-inflammatory activity, etc.[39] Crude extracts and pure compounds isolated from Radix Bupleuri exhibited various biological activities, such as anti-inflammatory, anticancer, antipyretic, antimicrobial, antiviral, hepatoprotective, neuroprotective, and immunomodulatory effects.[40] Angelicae sinensis radix played a therapeutic role for asthma with Yin deficiency syndrome and improved airway inflammation by inhibiting the expression of RORγt in lung tissues and regulating the balance of Th1/Th2 and Th17/Treg.[41] Lycii fructus exhibits a cytoprotective effect, possibly through the enhancement of the antioxidant gene expression.[42]

The limitation of RCTs included in this review was that the risk of bias was assessed to be unclear in many domains. There was no information about randomization concealing or the assessor to measure or assess the outcome. Seventeen studies did not publish or register the protocol and the only one study had its protocol registered online but did not mention it in the full text. We tried to contact the authors, but no one answered us. Another limitation is all studies of Compound Huangqi were conducted in the MG outpatient service of Affiliated Hospital of Liaoning University of Traditional Chinese Medicine in China. Compound Huangqi was applied in decoction or granules for 3 to 9 months, combined with pyridostigmine bromide or prednisone. When it was applied as decoction, the prescription was adjusted based on syndrome differentiation, and when it was given to children, the dosage was reduced according to their age. The study design did not adopt stratification of the patients according to their syndrome differentiation. The different treating strategies between children and adults were mixed when reporting the effect. The reduction of pyridostigmine bromide and prednisone was not following the same pattern, which might also induce bias in the meta-analyses.

In general, with the promising effect, if Compound Huangqi can be tested in different experimental environments, with more elaborate study design, it might have a larger and more precise clinical value. The mechanisms of the most used herbs in treating MG are still under investigation. Large, well-designed RCTs with a low risk of bias are still in great need.

Author contributions

Conceptualization: LJP. Methodology: LJP, ZSJ, and WRT. Writing – review & editing: LJP. Writing – original draft: ZSJ and WRT. Investigation: WRT, YZY, LCH, ZRX, ZYY, and FM. Formal analysis: ZSJ, YZY, and HM. Data curation: ZSJ, YZY, and HM.

Conflict of interest

JL is an editorial board member of this journal but the member status had no bearing on editorial consideration. The authors declare that they have no other conflicts of interest.

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Ethical statement

Not applicable.

Data availability

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

Deviation from protocol

We did not search AMED database because of network limits but we added search engines and websites follow the recommendation from Cochrane. Since the protocol has been registered for a long time and the ROB tool recommended by Cochrane has been updated, we decided to use ROB 2 to assess the risk of bias of studies. In terms of the inclusion criteria, since the published systematic review[5] used a limit related to risk of bias to narrow the range of studies included in the meta-analysis, we decided to include studies with clearer reporting of the implementation of studies to achieve more reliable evidence. To give more practical recommendation for clinical practice, we only conducted meta-analysis of RCTs on same kind of CHM and assessed the certainty of evidence with GRADE.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100806.

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