Postprint of a Study on the Current Status of Outcome Measure Selection in Randomized Controlled Trials of Traditional Chinese Medicine for Myasthenia Gravis

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Abstract

Traditional Chinese medicine (TCM) therapies such as herbal medicine and acupuncture are widely employed in the treatment of myasthenia gravis; however, high-quality evidence-based medical evidence validating their efficacy and safety is lacking. One contributing factor is the absence of recognized, unified outcome measures in trial design, which subsequently prevents data pooling in secondary research such as meta-analyses due to inconsistent indicators. Developing a core outcome set for TCM treatment of myasthenia gravis would facilitate clinical research design and the accumulation of high-quality evidence-based evidence. To describe the current status of outcome measure selection in randomized controlled trials of TCM for myasthenia gravis, analyze existing problems, propose recommendations, and promote the development of a TCM core outcome set. Comprehensively search Chinese and English databases, screen randomized controlled trials of TCM treatment for myasthenia gravis, extract outcome measure information, categorize and tally frequencies, partition indicator domains, analyze existing problems, and propose corresponding recommendations. Eight major databases were searched, yielding 186 included articles. Outcome measures were utilized 724 times cumulatively and classified into 7 major categories: myasthenia gravis severity scales, myasthenia gravis quality of life scales, TCM syndrome scores, safety indicators, blood biochemical indicators, muscle strength changes, and others. Identified problems include unclear distinction between primary and secondary outcome measures, lack of internationally recognized indicators, insufficient emphasis on safety, substantial variation in the number of outcome measures and evaluation time points, presence of evaluation bias, omission of health economic evaluation, and non-standardized TCM efficacy evaluation criteria. Based on the identified prob-

lems, specific recommendations are proposed: promoting the construction of a core outcome set for clinical research on TCM treatment of myasthenia gravis, selecting internationally recognized outcome and safety indicators with explicit primary/secondary designation, choosing appropriate treatment cycles and evaluation time points, conducting clinical trial registration, implementing blinding, and standardizing reporting.

Full Text

Preamble

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Abstract

Background: Traditional Chinese medicine (TCM) therapies, including herbal medicine and acupuncture, are widely used in myasthenia gravis (MG) treatment. However, high-quality evidence verifying their efficacy and safety remains lacking. One major reason is the absence of recognized, unified outcome indicators in trial design, which prevents data pooling in secondary studies such as meta-analyses. Developing a core outcome set (COS) for TCM treatment of MG would facilitate clinical research design and accumulation of high-quality evidence.

Objective: To describe the current status of outcome selection in randomized controlled trials (RCTs) of TCM for MG, analyze existing problems, and propose recommendations to promote the development of a COS for TCM in MG treatment.

Methods: We comprehensively searched Chinese and English databases to screen RCTs of TCM for MG. Outcome indicator information was extracted, classified, and frequency was counted. Indicators were categorized into domains, and selection characteristics and existing problems were analyzed to propose recommendations.

Results: Eight databases were searched, yielding 186 included publications (149 journal articles, 32 dissertations, and 5 conference papers). Outcomes were used 724 times total and classified into seven categories: MG severity scales (133 times), MG quality of life scales (20 times), TCM syndrome scores (70 times), safety indicators (66 times), blood biochemical indicators (224 times), muscle strength changes (3 times), and others (208 times). Problems identified included: unclear primary/secondary distinction, lack of internationally recognized indicators, insufficient attention to safety, large variation in outcome quantity and evaluation timepoints, evaluation bias, absence of health economic assessment, and non-standardized TCM efficacy evaluation criteria.

Conclusion: Based on identified problems, we propose specific recommendations: promote construction of a COS for TCM treatment of MG; select internationally recognized primary and secondary outcomes with clear hierarchy; choose appropriate treatment duration and evaluation timepoints; register clinical trials; implement blinding; and standardize reporting.

Keywords: Myasthenia gravis; Outcome indicators; Randomized controlled trials; Traditional Chinese medicine; Core outcome set

Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease characterized by impaired neuromuscular junction transmission [1]. The incidence of MG in China is approximately 6.8 per million [2]. Existing RCTs and meta-analyses suggest that TCM therapies, including herbal medicine and acupuncture, may benefit MG patients by alleviating clinical symptoms and improving quality of life [3, 4]. However, high-quality evidence verifying their efficacy and safety remains insufficient [5]. One primary reason is the lack of recognized, unified outcome indicators in clinical trial design, which limits the generalizability of research conclusions and prevents data pooling in meta-analyses and other secondary studies due to outcome heterogeneity [6].

This study comprehensively searched RCTs of TCM for MG to describe outcome selection patterns, construct an outcome indicator pool and domain classification system, analyze existing problems, and propose recommendations. Our aim is to promote the development of a core outcome set (COS) for TCM treatment of MG, providing a foundation for outcome selection in clinical trial design and acquisition of high-quality evidence [7].

Methods

1.1 Literature Inclusion Criteria

Studies were included if they met the following criteria: (1) Participants: MG patients; (2) Study design: RCTs evaluating clinical efficacy of TCM therapies, with no language restrictions; (3) Interventions: TCM-based treatments including herbal medicine, acupuncture, moxibustion, massage, cupping, scraping, Daoyin, Qigong, or other therapies based on TCM theory, either alone or combined with Western medicine; (4) Publication types: journal articles, dissertations, and conference papers.

1.2 Literature Exclusion Criteria

Studies were excluded if they: (1) Had research objectives limited solely to exploring TCM mechanisms of action; or (2) Had missing key information or were duplicate publications.

1.3 Retrieval Strategy

For Chinese databases, we combined subject headings, keywords, abstracts, and titles using search terms including "myasthenia gravis," "Wei syndrome," "Wei disease," "muscle weakness," "traditional Chinese medicine," "herbal medicine," "acupuncture," "moxibustion," and "cupping." Chinese databases searched included CNKI, VIP, WanFang, and CBM. For English databases, we combined MeSH terms and free-text terms including "Myasthenia Gravis," "Acupuncture," and "Medicine, Chinese Traditional." English databases searched included PubMed, Cochrane Library, Embase, and Web of Science. The search timeframe spanned from database inception to April 2022. All retrieved literature was imported into NoteExpress V3.5.0.9054 for duplicate removal.

1.4 Data Extraction

Using Excel 2019, we extracted the following information: title, authors, publication year, journal, randomization method, blinding, interventions and duration, primary and secondary outcomes, efficacy evaluation criteria, follow-up timepoints, and dropout rates.

1.5 Statistical Analysis of Outcome Indicators and Domain Classification

We counted the frequency of each outcome indicator used in TCM RCTs for MG and classified them. Following the "Technical Procedures Standard for Developing Core Outcome Sets for Clinical Trials of Traditional Chinese Medicine" [8], indicators were categorized into seven functional domains: TCM disease/syndrome, symptoms/signs, laboratory tests/examinations, quality of life, long-term prognosis, economic evaluation, and safety events.

Results

2.1 Literature Retrieval Results

Eight Chinese and English databases were searched. Based on inclusion and exclusion criteria, 186 publications were included: 149 journal articles, 32 dissertations, and 5 conference papers.

[Figure 1: see original paper] Flowchart of screening RCTs about traditional Chinese medicine for myasthenia gravis

2.2 Basic Characteristics of Included Literature

The earliest TCM intervention RCT for MG was published in 1992, with an increasing publication trend in recent years. Treatment duration across all included RCTs ranged from 1 week to 208 weeks (4 years), with the majority (60.75%) selecting 4-16 weeks. Eighteen studies (9.68%) did not report treatment duration. Most studies (83.33%) used three follow-up assessments, while eight studies (4.30%) did not report follow-up frequency. Only 12 studies (6.45%) reported blinding of participants and personnel, while 174 studies (93.55%) did not report blinding status. The number of outcome indicators per study ranged from 1 to 12, with most studies (85.48%) selecting 1-6 indicators.

Basic characteristics of randomized controlled trials of myasthenia gravis treated with traditional Chinese medicine

2.3 Outcome Indicator Frequency Statistics and Indicator Domains

Across the 186 included studies, outcome indicators were used 724 times total. The maximum number of indicators per RCT was 12, and the minimum was 1. For analysis, all outcomes were classified into seven major categories: (1) MG severity scales: 133 uses; (2) MG quality of life scales: 20 uses; (3) TCM syndrome scores: 70 uses; (4) Safety indicators: 66 uses; (5) Blood biochemical indicators: 224 uses; (6) Muscle strength changes: 3 uses; and (7) Others: 208 uses. Detailed classification and frequency are shown in Table 2 . The indicator domains are illustrated in Figure 2 [Figure 2: see original paper].

Classification and frequency of outcomes used in randomized controlled trials of myasthenia gravis treated with traditional Chinese medicine

[Figure 2: see original paper] Outcome domain of RCT of myasthenia gravis treated with traditional Chinese medicine

Discussion

3.1 Characteristics of Outcome Selection in TCM RCTs for MG

Analysis of outcome selection and efficacy evaluation criteria in TCM RCTs for MG reveals several characteristics: MG scales and response rates were the primary outcome forms; studies emphasized exploring TCM mechanisms from perspectives of immune homeostasis, cytokines, and inflammation; TCM syndrome scores reflected the distinctive features of TCM clinical research; and safety evaluation was emphasized.

3.2 Problems in Outcome Selection

3.2.1 Unclear Distinction Between Primary and Secondary Outcomes Primary outcomes should reflect trial objectives, have the closest relationship with clinical endpoints, and typically feature quantifiability, objectivity, and high reproducibility, preferably using domain-recognized standards [9]. Clinical trials need to specify one or two primary outcomes to guide sample size calculation, statistical methods, results interpretation, and efficacy evaluation [10]. Secondary outcomes should provide auxiliary support for the primary objective. Among the 186 included RCTs, only two (1.08%) explicitly defined primary and secondary outcomes [11, 12], reflecting non-standardized outcome specification in TCM clinical trials.

3.2.2 Lack of Internationally Recognized Outcomes Outcome selection, particularly for primary outcomes, should use domain-recognized indicators. Using non-internationally recognized outcomes to evaluate TCM efficacy inevitably affects the acceptance of research results and conclusions. Among the 186 RCTs, 104 (55.91%) used the MG Absolute and Relative Scoring (MG-ARS) system. Developed by renowned Chinese neuroimmunologist Professor Xu Xianhao and widely used in China after modification, MG-ARS can evaluate MG severity and treatment improvement but is not internationally adopted [13]. In contrast, MG-ADL, QMG, MG-QOL, and MGC have higher international recognition and utilization rates [14].

3.2.3 Insufficient Attention to Safety Evaluation Safety evaluation is as important as efficacy assessment for any intervention [15]. For complex herbal formulations with unclear adverse reaction profiles, standardized safety evaluation is fundamental for improving TCM acceptance and informing clinical decisions [16]. Only 66 of the 186 RCTs (35.48%) explicitly evaluated TCM safety. In TCM clinical trials, vital signs, blood routine, urine routine, liver/kidney function, and electrocardiogram should be dynamically monitored according to intervention and follow-up duration, with detailed documentation of adverse events, management, and outcomes [17]. For physical therapies like acupuncture and cupping, adverse reactions such as skin damage, bleeding, needle fainting, needle sticking, and infection should be meticulously recorded in addition to standard safety indicators [18].

3.2.4 Large Variation in Outcome Quantity and Evaluation Timepoints The number of outcome indicators per study ranged from 1 to 12, showing substantial variation. Too few outcomes limit study richness and depth, while too many consume human and financial resources. No reference standards exist for optimal outcome quantity, which requires comprehensive consideration of research objectives, duration, and funding.

Treatment duration ranged from 1 week to 208 weeks, and follow-up frequency varied from 2 to 7 times, with no standardized references [19]. Short treatment duration and few follow-ups save resources and maintain participant compliance but cannot evaluate long-term TCM efficacy and safety. For MG, a chronic neuroimmune disease prone to fluctuation and relapse requiring long-term treatment, extended monitoring and follow-up are necessary. Conversely, overly long studies waste resources, and continued intervention may not yield obvious clinical improvement once patients achieve minimal manifestation status (MMS) [20], making long-term follow-up inappropriate for stable MG patients.

Due to MG' s fluctuating nature, factors including medication, diet, fatigue, and emotion can significantly affect muscle weakness symptoms. Evaluations conducted within 4-6 hours after taking pyridostigmine (during the drug' s action window), after meals, or after rest may yield artificially favorable results. Therefore, follow-up assessments for MG participants should specify and unify exact timepoints and precautions, such as medication status and fasting/postprandial state, to exclude these confounding factors. None of the included studies mentioned specific follow-up timing or requirements, introducing potential bias in outcome evaluation.

3.2.5 Risk of Bias in Outcome Evaluation Lower risk of bias increases result reliability. Blinding in outcome evaluation, particularly for subjective indicators like TCM syndrome scores and MG-QOL, can minimize placebo effects. Only 12 of the 186 TCM RCTs for MG (6.45%) explicitly mentioned blinding participants and personnel. No studies reported blinding of outcome assessors, introducing potential bias [16]. Regarding data integrity and selective reporting, no RCTs provided clinical registration information, making bias assessment impossible [21].

3.2.6 Absence of Health Economic Evaluation Economic factors in treatment are increasingly important, with epidemiologists recommending inclusion of health economics in clinical research analysis [10]. As MG patients require long-term or lifelong medication, both TCM and Western medicine impose economic burdens on individuals and national healthcare systems. Economic-benefit evaluation of TCM therapies compared with standard Western treatment would help MG patients make informed treatment choices. None of the 186 RCTs conducted health economic evaluation, possibly due to incomplete relevant outcome indicators [22].

3.2.7 Non-Standardized TCM Efficacy Evaluation Indicators and Overuse of Response Rate Seventy of the 186 RCTs (37.63%) used TCM syndrome efficacy indicators, reflecting TCM research characteristics. However, studies varied substantially in primary/secondary symptom selection, scoring values, and indicator combinations, lacking unified standards. One hundred seventy-five studies (94.1%) used "response rate" as an outcome. Response rate is a composite indicator typically calculated based on TCM syndrome score or scale score change rates to determine efficacy grades and calculate overall response. Its ambiguous meaning complicates result interpretation [23], and its use is generally discouraged.

3.3 Recommendations

3.3.1 Promote Core Outcome Set Development A COS represents the minimum set of clinical outcomes and indicators recognized by the field, specifying "what" outcomes should be measured and reported in all clinical trials for a health condition [24]. COS development can standardize clinical research outcomes, reduce publication bias and selective reporting, and enable horizontal comparison across treatments and vertical meta-analysis across studies [25]. Since the COS concept was introduced to China, discussion and practice of developing core outcome sets for TCM clinical trials (COS-TCM) have increased [23], but no COS exists for TCM treatment of MG. Following internationally recognized procedures [26, 27], a COS-TCM for MG should be developed and refined under the leadership of evidence-based medicine experts with participation from clinical researchers.

3.3.2 Select Internationally Recognized Outcomes and Safety Indicators with Clear Hierarchy Jan et al. [28] analyzed primary outcome selection in major MG clinical trials from 2016-2020, finding QMG most frequently used, followed by MG-ADL. Primary outcomes should reference QMG and MG-ADL. TCM syndrome scores should be included as secondary outcomes. Depending on research objectives, other secondary indicators such as MG-QOL, MG-ARS, MG-related antibodies, and blood biochemical indicators may be selected. Safety indicators should include vital signs, blood/urine/stool routine, liver/kidney function, and electrocardiogram. Selected outcomes should be used to systematically evaluate TCM efficacy and safety. Additionally, health economics experts should be invited to assist with economic-benefit evaluation.

3.3.3 Select Appropriate Treatment Duration and Evaluation Timepoints Treatment duration and evaluation timepoints should be selected based on research objectives, participant characteristics, and intervention features [29]. Based on literature analysis, treatment duration of 4-16 weeks is appropriate, with evaluation nodes every 4-6 weeks and three follow-up assessments. To exclude effects of medication, diet, fatigue, and emotional fluctuations on MG muscle weakness, outcome evaluations should be standardized

to occur after medication intake, post-meal, and when participants are free from fatigue and emotional disturbance.

3.3.4 Clinical Trial Registration, Blinding Implementation, and Standardized Reporting Following the three principles of RCT design (randomization, control, blinding) and the PICOS principle, trial design should be improved with clinical trial registration specifying primary/secondary outcomes and follow-up timepoints. Blinding should be properly implemented for outcome evaluation, ideally achieving triple blinding of researchers, assessors, and data analysts to reduce bias. Outcome and safety evaluation results should be reported according to CONSORT guidelines [30].

3.4 Study Limitations

This study did not conduct longitudinal temporal comparisons, preventing analysis of outcome selection characteristics across different time periods and understanding of development trends in TCM treatment of MG. Additionally, this study only included TCM clinical trials and did not comprehensively compare outcome selection with Western medicine studies. Future research should conduct such comparisons to understand the advantages and disadvantages of outcome selection in TCM clinical trials.

Author Contributions

Shaohong Li and Wenzeng Zhu conceived and designed the study, proposing primary research indicators and objectives. Yukun Tian, Linghao Meng, and Ruiying Fang conducted literature screening and data analysis and created tables. Siyang Peng drafted the initial manuscript. Siyang Peng and Wenzeng Zhu were responsible for quality control and final review, with overall responsibility for the article.

Conflict of Interest

The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.