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Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Efficacy and safety of Yangxue Qingnao Granules in treatment of migraine：A Systematic Review and Meta-analysis	1
ABSTRACT			
Structured summary	2	**Background** Yangxue Qingnao Granules (YXQN) is a clinical Chinese Patent medicine that has been commonly used in the treatment of migraine. The aim of this meta-analysis was to assess the efficacy and safety of YXQN alone in the migraine. **Methods** We searched 10 databases to identify relevant randomized controlled trials (RCTs) published before September 2022. Two review authors independently searched and screened the literature, extracted the data as well as assessed the methodological quality of the included studies by using criteria from the ROB 2.0, and analyzed via using Review Manager 5.4 software. **Results** A total of 12 trials including 767 participants with migraine met the selection criteria. We divided these studies into comparisons of YXQN with placebo, routine treatment drugs and other Chinese patent medicine, respectively. The results of the meta-analysis showed that ①Clinical trial efficacy analysis: the YXQN group outperformed the placebo group (RR = 0.29, 95% CI[0.15, 0.43], P＜0.00001), the routine treatment group (RR = 0.18，95% CI[0.09, 0.27]，P＜0.0001) and the Chinese patent medicine group (RR=0.27, 95% CI[0.13, 0.41], P＜0.001). ②Frequency of headache: meta-analysis showed a statistically significant difference in the YXQN group versus placebo group (MD=-1.25, 95% CI[-1.60, -0.90], P＜0.00001) , the routine treatment drugs (MD=-0.85, 95% CI [-1.15, -0.56], P<0.00001) and the Chinese patent medicine (MD=-0.91, 95%CI [-1.35, -0.46], P< 0.0001) . ③headache duration: meta-analysis results showed great heterogeneity between studies, with no differences between YXQN and place (MD = -0.61，95%CI [-1.53, -0.31], P=0.19) and routine treatment drugs (MD = -0.22, 95%CI [-0.89, -0.46], P<0.53); YXQN was more effective than other Chinese patent medicine in reducing headache duration (MD=-1.24, 95%CI [-1.70, -0.77], P<0.00001). ④The headache pain degree: meta-analysis results showed no significant difference in the YXQN group versus placebo control (MD= -1.67, 95%CI[-3.52, 0.19], P=0.08), routine treatment drugs (MD=-0.53, 95%CI [-2.02, 0.96], P=0.68) and other Chinese patent medicine (MD=-0.49, 95%CI [-2.83, 1.85], P=0.68). Occurrence of adverse reactions/events: 3 cases were reported, all of which were mild gastrointestinal adverse reactions. **Conclusions** Compared with placebo,routine treatment drugs and other Chinese patent medicines, YXQN can improve the clinical efficiency and reduce the frequency of headache attacks. Compared with other Chinese patent medicines, YXQN can significantly reduce the duration of headache, but it has no obvious advantages in reducing the intensity of headache. This systematic review revealed YXQN is effective and safe in the treatment of migraine. However, in view of the low quality of the studies included in this subset, which affects the reliability of the results, more high-quality, large-sample, multi-centre, double-blind randomised controlled trials are still needed for further validation in the future to make better recommendations for clinical.	2
INTRODUCTION			
Description of the condition	3	Migraine is a chronic, neurological disease found to be 1 of the top 10 global causes of disease-related disability[1, 2].Migraine is a prevalent disease characterized by headaches that are often severe and throbbing and accompanied by associated symptoms, such as photophobia, phonophobia, nausea, vomiting, vertigo, cutaneous allodynia, and	3

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		cognitive dysfunction[3-7].Migraine is a leading cause of neurological disability worldwide and has a substantial effect on society[8-10]. Prophylaxis of headache episodes may be achieved with calcium channel blockers, beta-blockers, anti-depressives, antiepileptic drugs and triptans[11]. However, high dropout rates in most clinical trials suggest that these drugs are not well tolerated by patients[12]. It therefore seems that development of new agents which combine good efficacy and safety may be helpful in the treatment of patients with migraine. Traditional Chinese medicine is a good choice, because migraine has tolerance and limited adverse reactions to supplements and substitute drugs[13].	
Description of the intervention	4	YXQN is a kind of Chinese patent medicine for migraine consists of more than ten species Chinese herbal medicines, including Angelica, Ligusticum chuanxiong, Radix paeoniae alba, Radix rehmanniae, Uncaria, Caulis spatholobi, Prunella vulgaris, Cassia seed, Mother of pearl, Corydalis and Asarum. Clinical studies have confirmed the effectiveness of YXQN in treating It can improve the overall efficiency of treatment, reduce the duration of headache and increase cerebral blood flow[14]. In terms of adverse reactions, there were nausea, dizziness, fatigue, lethargy and other symptoms, which did not affect the treatment. Most of them could recover without special treatment. A few of them were relieved after symptomatic treatment[15].	4
Significance of the review	4	However, there is still insufficient evidence to evaluate the efficacy of YXQN in migraine. Therefore, this meta-analysis aims to systematically integrate these clinical trials to evaluate the efficacy and safety of YXQN alone in the treatment of migraine and provide evidence based basis for further clinical application and research.	4
Objectives	4	The aim of this meta-analysis was to assess the efficacy and safety of YXQN alone in the migraine.	4
Methods	5	This protocol follows the guidelines according to the preferred reporting items for systematic reviews and meta-analysis protocol (PRISMA-P) and the Cochrane Handbook for Systematic Reviews of Interventions.	5
Types of studies	4	We will only adopt RCTs (parallel groups as well as crossover) using well-described randomization methods. We will exclude quasi-randomized clinical trials.	4
Types of participants	5	(1) Research Subjects: the subjects were migraine patients, all of whom met the relevant diagnostic criteria of the international classification of headache diseases; (2) Interventions: The treatment group used YXQN treatment along for migraine; the control group used conventional treatment for migraine: calcium ion antagonists, calcium channel blockers, antiepileptic Drugs, Chinese patent medicine, placebo,etc; (3) Efficacy evaluation index: The primary outcome was clinical effectiveness: migraine responder rate reduced to at least 50% of the original number[16]. Secondary outcomes include frequency of headache, duration of headache, intensity of headache and adverse reactions.	5
Types of intervention	5	IThe treatment group used YXQN treatment along for migraine; the control group used conventional treatment for migraine: calcium ion antagonists, calcium channel blockers, antiepileptic Drugs, Chinese patent medicine, placebo,etc	5
Types of outcome measures	5	Efficacy evaluation index: The primary outcome was clinical effectiveness: migraine responder rate reduced to at least 50% of the original number[16]. Secondary outcomes include frequency of headache, duration of headache, intensity of headache and adverse reactions.	5
Search methods for identification of studies	4	**Electronic searches.** We will search CNKI (China National Knowledge Infrastructure), CBM (Chinese Biomedicine Database), VIP (Chinese Scientific Journals Database), Wanfang, Web of Science, Pubmed, EBSCO, CENTRAL, the Cochrane Library, and Embase. The search strategy for MEDLINE is shown in table 1. This search strategy will be modified as required for other electronic databases	4

Data collection and analysis	5-6	**Selection of studies.** Two of us (Bo zhou，Huanqin Li) independently screened titles and abstracts and then independently read full texts to confirm eligibility. Any disagreements were resolved by consensus and by another one of us (Kegang Cao). Two of us (Bo zhou, Huanqin Li) independently piloted a data collection form and then independently extracted outcome data. Extracted data were compared by 2 of us, and any discrepancies were resolved through discussion. **Assessment of Risk of Bias.**Two reviewers (Bo Zhou, Guishu Wang) independently rated the risk of bias of the RCTs using the revised Cochrane risk of bias, version 2 (RoB 2) tool[17]. The assignment or intention to treat was the outcome of interest. Disagreements were resolved by consensus. We contacted authors when information was not reported in the article and/or needed clarification. **Certainty of Evidence.**Two of us (Bo Zhou, Huanqin Li) independently rated the certainty for each comparison and outcome based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method, who consulted with a third reviewer when there were discrepancies. Using the online program GRADEpro (https://gradepro.org/), we assessed the risk of bias; inconsistency, indirectness, and imprecision of the results; and the probability of publication bias with a four-item scale (“Very Low”, “Low”, “Moderate, or “High”). **Statistical Analysis.**Statistical analysis was performed on the collected data using Revman 5.3, statistical software provided by the International Evidence-Based Medicine Collaboration Network. The count data are expressed as odds ratio (OR) or relative risk (RR). For continuous variables, if the measurement units and methods are inconsistent, the standardized mean.difference (SMD) is used as the effect index. When the measurement unit and measurement method are consistent, the measurement data are expressed as mean difference (MD). Both of them are expressed as 95% confidence interval (CI). When the results showed that I2 < 50%, they were considered to be less heterogeneous or non-existent. When I2 > 50%, heterogeneity was considered to exist, indicating that the cause of heterogeneity should be analyzed by a sensitivity or subgroup analysis. In addition, sensitivity analyses were performed to identify the robustness of meta-analysis results by excluding: (1) studies with high risks of bias and (2) outliers that are numerically distant from the rest of the data. If more than ten trials were included in the meta-analysis, reporting funnel plots assessed biases such as publication bias.	5-6
DISCUSSION			
Summary of evidence	18-20	In recent years, there has been a significant increase in public and medical interest in the use of traditional Chinese medicines for the treatment of migraine, i.e., of which Nourishing Blood and Clearing Brain Granules has been a proprietary Chinese medicine for the treatment of migraine for many years.The present study showed that the prophylactic use of blood-clearing pellets significantly reduced the positive rate of dural mast cell degranulation and significantly decreased the expression level of c-Fos protein in the nucleus of the trigeminal spinalis. The mechanism may be related to the stabilization of mast cell membranes to reduce their degranulation and the reduction of c-Fos protein expression in the nucleus of the trigeminal spinal tract[23, 24]. Meanwhile, the Blood Clearing Granules can reduce the blood viscosity of migraine patients and improve the blood rheological indicators such as red blood cell deformation ability, red blood cell aggregation index, low-cut viscosity, high-cut viscosity and fibrinogen to achieve the purpose of treating headache[25].Adverse reactions are gastrointestinal symptoms, none of which affect the treatment, most of which recover on their own without special treatment, and a few of which resolve with symptomatic treatment[26]. There is evidence to support the efficacy of Nourishing Blood and Clearing Brain Granules in the treatment of migraine, which is consistent with the results of this study. To ensure consistency in the study, the clinical efficacy was set at a uniform 50% reduction in the frequency of headache attacks as the efficacy criterion. This study systematically	18-20

		reviewed the Chinese and English literature to determine the effectiveness and safety of Nourishing Blood and Clearing Brain Granules in the treatment of migraine. 12 randomised controlled trials, including a total of 1210 migraine patients, met the inclusion criteria. The main finding of this review was that Nourishing Blood and Brain Granules appeared to be more effective than controls in the treatment of migraine as assessed by various headache-related measures, including the number and duration of headache attacks. In terms of clinical efficiency and number of attacks, Nourishing Blood and Clearing Brain is more effective than positive drugs, placebo and other proprietary Chinese medicines. Compared with flunarizine and western medicine, nourishing blood and clearing brain can effectively reduce the clinical incidence and the number of headache attacks with fewer adverse effects. Compared with placebo, there was no significant advantage of nourishing blood and clearing brain in terms of duration and degree of headache, which may be related to the inconsistent statistical methods and evaluation criteria of the investigators. Compared with other proprietary Chinese medicines, Nourishing Blood and Clearing Brain could significantly reduce the duration of headache, but there was no significant improvement in the degree of headache. Although the findings appear to be valid, the poor methodological quality and clinical heterogeneity of the included studies limit the evidence supporting the use of blood-raising and brain-clearing granules for migraine. **Limitation** There are some limitations to this study.①The large heterogeneity of this study may be related to the risk of bias in the included studies, which was not uniform; the use of subgroup analysis did not reduce the heterogeneity, so the accuracy of the results may have been affected; (2) The data analysis used published trials with positive results, indicating that trials with negative results may have been missed, which would make the true effect very different from the estimate of the effect.（3）The quality of the included literature was evaluated using ROB2.0, but the results will vary from person to person③The small sample sizes of the included studies, the lack of large sample trials and the small number of included studies affect the reliability of the results; ④The included literature used multiple outcome indicators and even though SMD was used to remove the heterogeneity caused by different outcome indicators, the accuracy of the final conclusions was still weakened⑤Some of the included studies did not describe in detail the occurrence of adverse reactions. The GRADE evidence grading system was used to evaluate the quality of the evidence, and the results showed that the evidence level for all the outcome indicators was very low, except for the low level of evidence for the frequency of headache attacks in the Nourishing Blood and Clearing Brain Granules compared with the control group. The main reasons for this were: (i) limitations, mainly due to the low quality of the original literature, which only mentioned randomisation without specifying blinding and allocation concealment; (ii) inconsistency, mainly due to the high heterogeneity between studies; (iii) imprecision, as the number of included studies was small; and (iv) possible publication bias. The results of the study suggest that the use of blood-raising and brain-clearing pellets alone is safer and more effective in the treatment of migraine compared with other treatment modalities. However, due to the small number of included studies and the low and very low quality of evidence according to the GRADE system, more high-quality, large-sample, multi-centre, double-blind randomised controlled trials are needed to further validate the study and make better recommendations for clinical use. Therefore, the following five issues should be noted in future clinical studies: (i) adopt the correct randomisation method, allocation concealment and blinding; (ii) conduct large sample clinical trials; (iii) strengthen and improve safety studies; and (iv) when conducting randomised controlled trials, the efficacy assessment of the included studies must be strictly based on uniform requirements and standards.	
CONTRIBUTORS			

Contributors	21	Bo Zhou and Kegang Cao designed the study, conducted the analysis, and drafted the manuscript. Guishu Wang and Yuning Yao performed the literature selection. Huanqin Li and Kegang Cao did the quality assessment. Huanhuan Fan and Tong Hao performed the data extraction. Bo Zhou, and Guishu Wang did part of the statistical work. Kegang Cao and Huanqin Li critically revised the manuscript.	21
FUNDING			
Funding	21	This study was supported by The Fourth Batch of National TCM (Clinical and Basic) Excellent Talents Training Project.	21
COMPETING INTERESTS			
Competing interests	21	None.	
PATIENT CONSENT			
Patient consent	21	Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.	
PROVENANCE AND PEER REVIEW			
Provenance and peer review	19	Not commissioned; externally peer reviewed.	
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References

[1]. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet, 2016. 388(10053): p. 1545-1602.

[2]. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Neurol, 2017. 16(11): p. 877-897.

[3]. Burstein, R., R. Noseda and D. Borsook, Migraine: multiple processes, complex pathophysiology. J Neurosci, 2015. 35(17): p. 6619-29.

[4]. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia, 2013. 33(9): p. 629-808.

[5]. Lipton, R.B. and S.D. Silberstein, Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. Headache, 2015. 55 Suppl 2: p. 103-22; quiz 123-6.

[6]. Lipton, R.B., et al., Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache, 2001. 41(7): p. 646-57.

[7]. Goadsby, P.J., et al., Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol Rev, 2017. 97(2): p. 553-622.

[8]. Buse, D.C., et al., Impact of Migraine on the Family: Perspectives of People With Migraine and Their Spouse/Domestic Partner in the CaMEO Study. Mayo Clin Proc, 2016.

[9]. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet, 2017. 390(10100): p. 1211-1259.

[10]. Lipton, R.B., et al., Migraine prevalence, disease burden, and the need for preventive therapy. Neurology, 2007. 68(5): p. 343-9.

[11]. Nandha, R. and H. Singh, Renin angiotensin system: A novel target for migraine prophylaxis. Indian J Pharmacol, 2012. 44(2): p. 157-60.

[12]. Sadowsky, C.H., et al., Switching From Donepezil to Rivastigmine Is Well Tolerated: Results of an Open-Label Safety and Tolerability Study. Prim Care Companion J Clin Psychiatry, 2005. 7(2): p. 43-48.

[13]. Assarzadegan, F. and M. Sistanizad, Tolerability and Efficacy of Memantine as Add on Therapy in Patients with Migraine. Iran J Pharm Res, 2017. 16(2): p. 791-797.

[14] Lei Lin et al., systematic evaluation and meta-analysis of the efficacy and safety of Yangxue Qingnao Granule in treating migraine Chinese Journal of Traditional Chinese Medicine, 2020 45 (21): Page 5093-5102

[15] Chen Fuchao et al. Meta analysis of Yangxue Qingnao Granule combined with flunarizine hydrochloride in the treatment of migraine Journal of Modern Integrated Chinese and Western Medicine, 2013 22 (02): Page 146-148

[16]. Tfelt-Hansen, P., et al., Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia, 2012. 32(1): p. 6-38.

[17]. Sterne, J., et al., RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, 2019. 366: p. l4898.

[18] Li Zhiwei, A control study of Yangxue Qingnao Granule in treating migraine Chongqing Medical Journal, 2003 (05): 628-629

[19] Li Zhao, Li Chunyu and Liu Kai. Yangxue Qingnao Granule in the Treatment of 79 Cases of Migraine Journal of Practical Chinese Medicine, 2003 (03): 230

[20] He Fayi, Clinical observation of Yangxue Qingnao Granule in the prevention and treatment of migraine Journal of Luzhou Medical College, 2005 (05): 39-41

[21]. Baihu Ming and Yangxue Qingnao Granules were used to treat 28 cases of migraine China Modern Drug Application, 2011 5 (16): Page 67-68

[22]. Zhang Zhongshao and Kuang Suya, Clinical Study on Yangxue Qingnao Granule in Treating Migraine Modern Diagnosis and Treatment, 2015 26 (04): Page 766-768

[23]. Zhao Pei et al., Effect of Yangxue Qingnao Granule on Degranulation of Dural Mast Cells in Migraine Rats Journal of Cardiovascular and Cerebrovascular Diseases of Integrated Traditional Chinese and Western Medicine, 2013 11 (11): Page 1364-1366

[24] Lei Xiaofeng et al., Effect of Yangxue Qingnao Granule on c-Fos protein expression in spinal trigeminal nucleus of migraine model rats induced by nitroglycerin Chinese Journal of Modern Neurology, 2014 14 (08): Page 708-716

[25]. Li Yanshun, Effect of Yangxue Qingnao Granule on headache symptoms and hemorheology in migraine patients Electronic Journal of Clinical Medicine Literature, 2016 3 (58): Page 11617-11618

[26]. Lei Lin et al., systematic evaluation and meta-analysis of the effectiveness and safety of Yangxue Qingnao Granule in treating migraine Chinese Journal of Traditional Chinese Medicine, 2020 45 (21): Page 5093-5102