The Efficacy and Tolerability of Ubrogepant for Episodic Migraine: A Systematic Review and Meta-Analysis

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Abstract

Background: The aim of this review was to evaluate the efficacy and tolerability of ubrogepant in patients with episodic migraine. Methods: We systematically searched PubMed, Embase, MEDLINE, Cochrane Library, and clinicaltrials.gov from inception to JULY, 2019. Randomized controlled trials of the efficacy and/or tolerability of ubrogepant for migraine were included. Meta-analysis was conducted by RevMan 5.3 software. Results: A total of 4 RCTs involving 4 163 patients were included. The meta-analysis showed that there were significant differences in the percentage of subjects with PF, PR, SPF, SPR, sound without phobia, light without phobia and nausea compared with the control group. (RR=1.31,95%CI:1.18~1.45，P<0.00001, RR=1.63,95%CI:1.46~1.82，P<0.00001, RR=1.22,95%CI:1.15~1.29，P<0.00001, RR=1.32,95%CI:1.22~1.42，P<0.00001, RR=1.16,95%CI:1.05~1.27，P=0.002), all the differences were statistically significant. Conclusions: For adult patients with episodic migraine, ubrogepant could effectively abort the acute attack. High-quality, adequately powered RCTs are needed to fully evaluate the efficacy and tolerability of ubrogepant for episodic migraine.

Background

Migraine is a common neurovascular disease in clinic, recurrent pain is the main manifestation of migraine, it is more common on both sides than on one side, the symptoms are aggravated during exercise and usually last for 1~72 hours. The attack is accompanied by nausea, vomiting, photophobia and other symptoms, which seriously affect the normal life, work and study quality of the patients.[1,2] Epidemiological investigation shows that the prevalence rate of migraine in China is 9.3%.[3] It is listed as the third most common disease in the world and highly specific globally The seventh cause of sexual disability.[4,5]

At present, the clinical drugs used to prevent and treat migraine are adrenoceptor blockers, calcium channel blockers, antiepileptic drugs, antidepressants, non-steroidal anti-inflammatory drugs, triptan drugs and ergotoxine derivatives.[6] However, currently, the drug specificity of intermittent preventive treatment is not high, and the efficacy is not satisfactory.[7,8] Calcitonin gene-related peptide (CGRP) is a 37-amino acid neuropeptide commonly found in trigeminal nerve endings and ganglion as well as higher-order neurons and glia, which plays a key role in the pathophysiological mechanism of migraine in the central and peripheral regions.[9,10] In the peripheral nervous system, the release of CGRP causes vasodilation and inflammation.[11] CGRP regulates pain transmission in the central nervous system.[10,12] Ubrogepant is a novel, highly effective oral antagonist of calcitonin gene-related peptide (CGRP) receptor, which is expressed in the nervous system related to the pathogenesis of migraine.[13] At present, there are no scholars studying Ubrogepant at home and abroad.The purpose of this study was to evaluate the efficacy and safety of Ubrogepant in the treatment of episodic migraine, so as to provide evidence basis for the clinical treatment of migraine.

Methods

Protocol and registration

This review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42019145125). It was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

Population, Interventions, Comparators, Outcomes, Study Designs (PICOS)

We considered all parallel and crossover randomized controlled trial (RCT) designs reporting efficacy and/or tolerability of commercially available ubrogepant for episodic migraine in adult (≥18 years) patients. We defined our study population as average-risk individuals (no history of head trauma or neurological disease), irrespective of health status, with a history of migraines. We defined our study population as average-risk individuals (no history of head trauma or neurological disease), irrespective of health status, with a history of migraines. We considered RCTs in which the intervention was administered in the form of a tablet (irrespective of dose and frequency of administration), and the comparator was a placebo-matching ubrogepant tablet(active agents were excluded). Our primary outcome measures were pain freedom(PF) at 2 hours after initial dose and pain relief(PR) at 2 hours after initial dose. Secondary outcomes were sustained pain freedom (SPF), sustained pain relief (SPR). Tolerance includes the absence of phonophobia in sound the absence of phonophobia in light and the absence of nausea.

Trial Identification

Computer search PubMed, Embase, Web of Science (SCI), Cochrane Library and other databases, the retrieval time from the establishment of the database to July 2019. In order to identify ongoing or unpublished trials, we supplemented the bibliographic database search with a search of clincialtrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) website.

According to the criteria of inclusion and exclusion of the literature, two independent researchers carried out data extraction and literature quality evaluation according to the criteria of inclusion and exclusion of the literature. In case of differences, they were resolved in consultation with the third evaluator. The extracted data included the baseline situation of patients, intervention measures, the number of cases, average age, final index and so on.

Risk of Bias Assessment

According to the inclusion and exclusion criteria of the literature, 2 independent researchers read the title and abstract to extract data and evaluate the quality of the literature. In case of any disagreement, they should negotiate with the third evaluator. Based on the bias risk assessment form provided by the Cochrane system Evaluation Manual, The evaluation contents include: random method, assignment concealment, blind method, whether the data is complete, whether to report withdrawal / loss of follow-up, intentionality analysis (ITT analysis), whether selective reporting results.

Data Synthesis and Analysis

Where possible, we conducted meta-analyses using inverse variance, random effects models implemented in RevMan (version 5.3.5). Meta-analysis was conducted when analyzable data were available from at least two trials. Relative risk (RR) and 95% confidence interval (95%CI) were used as effect quantities, and weighted mean difference (WMD) and 95%CI were used as effect quantities. I^2 test and *P* value were used to analyze heterogeneity in the inclusion study. If $P > 0.1$ and $I^2 < 50\%$ indicated no significant heterogeneity between studies, fixed-effect model analysis was adopted. If there is significant heterogeneity ($P \leq 0.1$, $I^2 \geq 50\%$), sensitivity analysis will be conducted on the factors that may cause heterogeneity. If the heterogeneity is still large after sensitivity analysis, random effect model will be adopted.

Results

Literature search results

According to the retrieval strategy, a total of 259 English literatures were obtained. After reading the topic, abstract and full text, 4 items of RCT[14-17] were included. The process of literature retrieval and screening is shown in Figure 1, and the basic characteristics of the included studies are shown in Table 1. The studies included in this system review were randomized, double-blind and multicenter clinical trials. ITT analysis was used to analyze the effectiveness indicators. The specific methods of generating random sequences are described, and the allocation and concealment are all interactive voice response systems. The number of people who quit and lose visits are reported, and the quality of the study is high.

Risk of Bias

We judged a high proportion of the trials to have low risk of bias for sequence generation (100%), and low risk of bias for allocation concealment (100%), complete outcome reporting (100%), blinding of participants and personnel (100%), and outcome assessment (100%) ,but other bias is unclear(100%) (Figure 2,3). Overall,4 trials[13-16] were judged to be of low risk.Supplementary Figure 2 and 3 summarizes the reasons for the risk of bias judgment decisions.

Primary Outcomes

Percentage of Participants Reporting Pain Freedom (PF)

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants reporting pain freedom (PF), RR=1.99,95%CI:1.51~2.63 *P*<0.00001. (Supplementary Figure 4).

Percentage of Participants With Pain Relief (PR)

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants with pain relief (PR), RR=1.31,95%CI:1.20~1.42，*P*<0.00001. (Supplementary Figure 5).

Secondary Outcomes

Percentage of Participants With Sustained Pain Freedom (SPF)

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants with sustained pain freedom (SPF), RR=1.31,95%CI:1.18~1.45，*P*<0.00001. (Supplementary Figure 6).

Percentage of Participants With Sustained Pain Relief (SPR)

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants with sustained pain relief (SPR), RR=1.63,95%CI:1.46~1.82，*P*<0.00001. (Supplementary Figure 7).

Tolerability

Phonophobia is sensitivity to sound

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants with the absence of phonophobia in sound, RR=1.22,95%CI:1.15~1.29，*P*<0.00001. (Supplementary Figure 8).

Photophobia is sensitivity to light

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants with the absence of phonophobia in light, RR=1.32,95%CI:1.22~1.42，*P*<0.00001. (Supplementary Figure 9).

Absence of Nausea

Compared with placebo, ubrogepant was found to be statistically significantly associated with a reduction in percentage of participants with absence of nausea, RR=1.16,95%CI:1.05~1.27，*P*=0.002. (Supplementary Figure 10).

Discussion

Migraine, as one of the three most common diseases in the world, can cause disability, seriously affect the quality of study and life of patients, and increase the burden on patients' families and the whole society and economy. About 38.8% of migraine patients have access to prophylactic treatment, but only 12.4% of them are on treatment[4], an area where there is still an unmet medical need for prophylactic

treatment. CGRP can cause cerebral artery dilatation in cerebral circulation and mediate dural neurogenic inflammation, which plays a key role in the pathophysiological mechanism of migraine.[18] As an oral CGRP receptor antagonist, ubrogepant mainly ACTS on smooth muscle cells in the microvascular wall to control peripheral vascular resistance.[19]

In this systematic review and meta-analysis examining the use of ubrogepant for episodic migraine, including 4 high-quality RCTs with episodic migraine, the percentage of participants with PF, the percentage of participants with PR, the percentage of participants with SPF, and the percentage of participants with SPR in the trial group were significant better than that in the control group. Subgroup analysis of different doses in the experimental group showed that when the dose was increased, the efficacy of the experimental group was significantly better than that of the placebo group, which was consistent with the study results of (Do TP, etc.)[20] and the recommended starting dose was at least 25mg/d. In terms of tolerance, the absence of phonophobia in sound the absence of phonophobia in light and the absence of nausea were significant better than that in the control group.

Defects in this study: the number of RCT is limited to 4 studies without a large number of patients; due to the lack of original literature, no comparison was made with other migraine drugs and similar drugs erenumab and galcanezumab.

Conclusions

Ubrogepant could improve acute headache in adult patients with episodic migraine. And compared with placebo, ubrogepant is effective and well tolerated. However, more high-quality studies and clinical applications are needed.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

all authors have read and approved the manuscript.

Competing interests

Uncontested interest

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Authors Contributions

Category 1

(a) Conception and Design

YD, BD

(b) Acquisition of Data

YD, HY, BD

(c) Analysis and Interpretation of Data

YD，HY, CZ, BD

Category 2

(a) Drafting the Manuscript

YD, HY, BD

(b) Revising It for Intellectual Content

YD, HY, BD

Category 3

(a) Final Approval of the Completed Manuscript

YD,HY, CZ, BD

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Figures

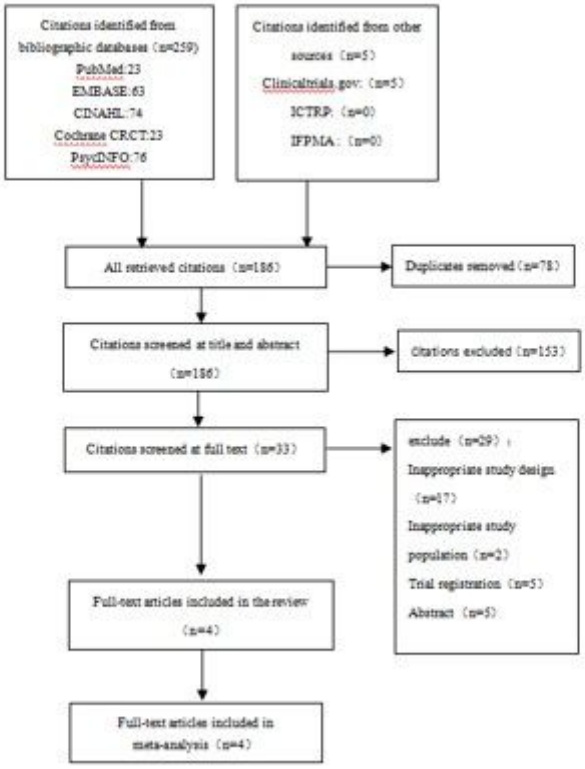

Figure 1

flowchart of literature retrieval and selection

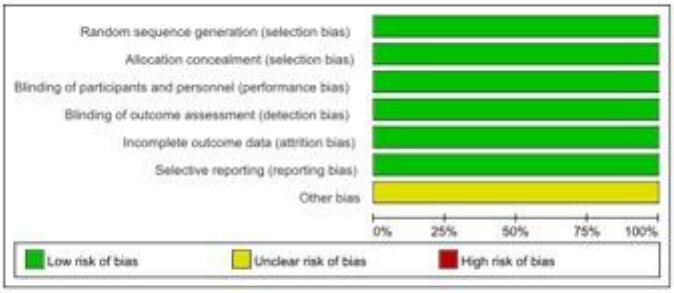

Figure 2

Risk of bias graph

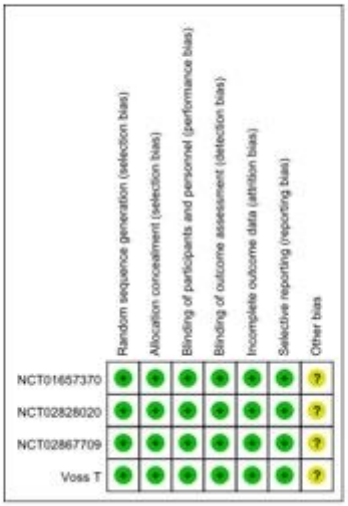

Figure 3

Risk of bias summary

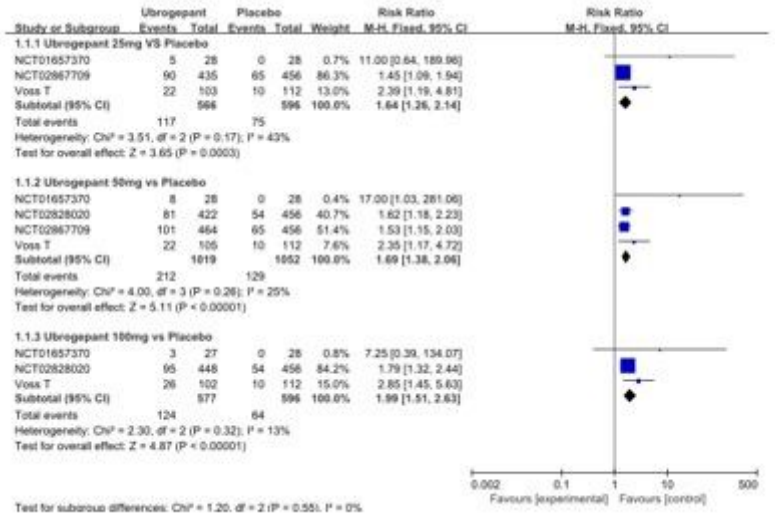

Figure 4

Forest plot for PF

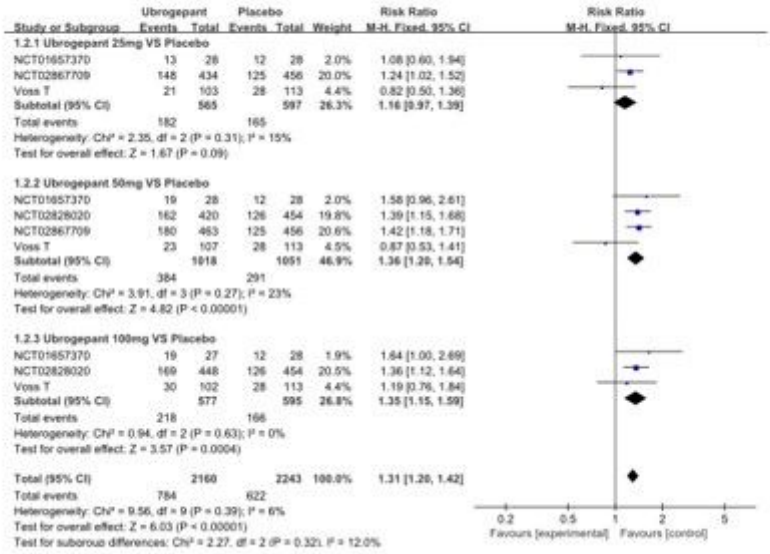

Figure 5

Forest plot for PR

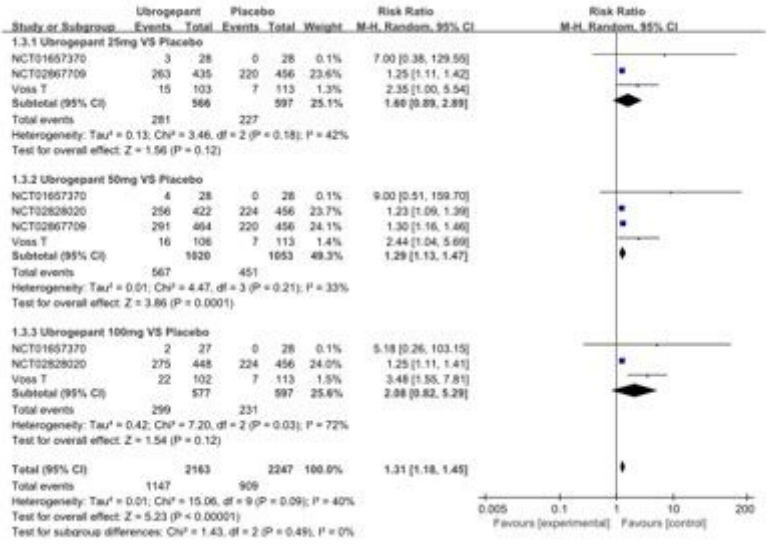

Figure 6

Forest plot for SPF

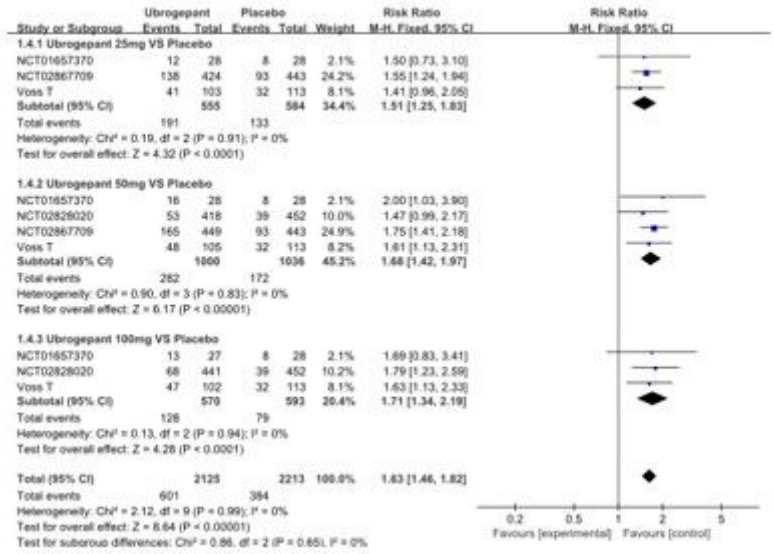

Figure 7

Forest plot for SPR

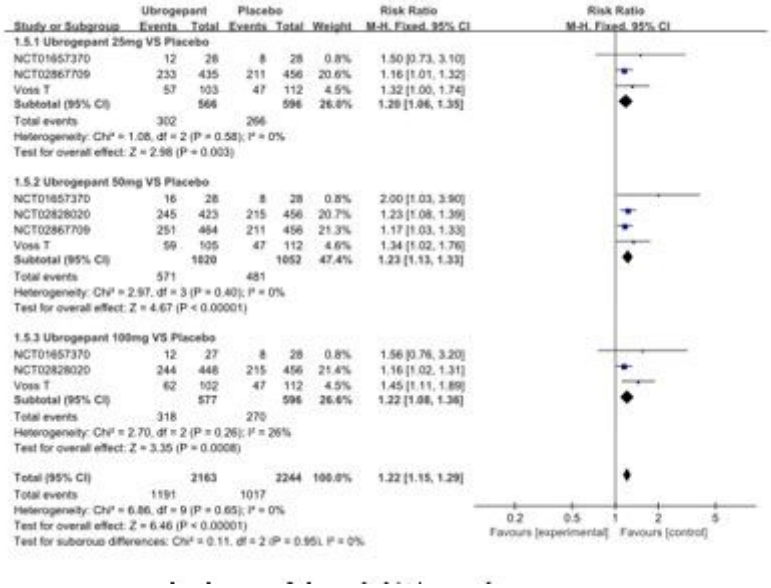

Figure 8

Forest plot for the absence of phonophobia in sound

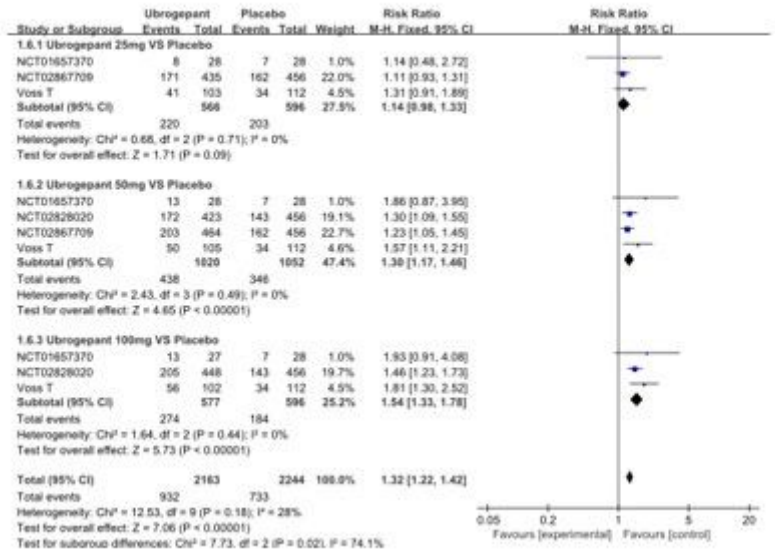

Figure 9

Forest plot for the absence of phonophobia in light

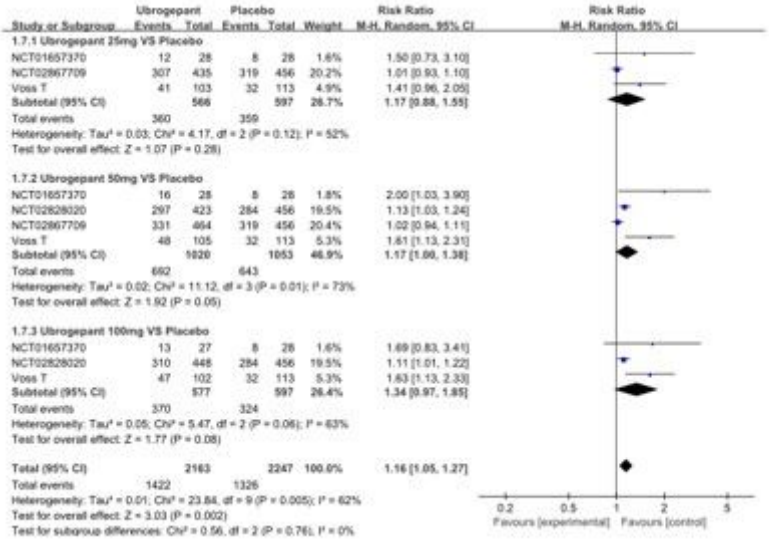

Figure 10

Forest plot for the absence of nausea

Supplementary Files

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- PRISMA2009checklist.doc