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Full Length Research Paper

A meta-analysis of the efficacy and safety of cilnidipine in Chinese patients with mild to moderate essential hypertension

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The purpose of this study was to evaluate the efficacy and safety of cilnidipine tablets to treat Chinese patients with mild to moderate essential hypertension, and to examine the ability of cilnidipine to lower blood pressure without eliciting unfavorable side effects. Medical databases and review articles were screened for randomized controlled trials (RCTs) that reported the effects of adverse reactions to cilnidipine and amlodipine in treating Chinese patients with mild to moderate essential hypertension. The quality of the included studies was critically evaluated. A total of 547 articles were found, from which 11 articles met the inclusion criteria. The heterogeneity test, the efficacy analysis (Q statistic = 4.62, p = 0.91, I^2 = 0%) and safety analysis (Q statistic = 3.73, p = 0.93, I^2 = 0%) showed that cilnidipine was equally effective and safe compared to amlodipine. The funnel-plot displayed a symmetrical figure, indicating there was no publication bias, and all articles included described high quality trials. In conclusion, cilnidipine is a useful agent to treat mild to moderate essential hypertension.

Key words: Cilnidipine, hypertension, review, meta-analysis.

INTRODUCTION

Hypertension is one of the most common cardiovascular diseases, and prevalence of hypertension continues to increase in China. Each year, it is estimated that an additional 10 million patients will be diagnosed with hypertension, and the current total number of patients nationwide with hypertension surpasses 200 million. Studies completed by the National Health and Nutritional Examination Survey and the World Health Organization estimate that fewer than 30% of hypertensive patients worldwide are adequately controlled and achieve an acceptable lowering of their blood pressure (Papadopoulos and Papademetriou, 2009). The awareness rate, treatment rate, and control rate for the Chinese population are only 30.2, 24.8 and 6.1%, respectively (Liu et al., 2010; Law et al., 2009).

Pharmaceutical intervention is the best way to control hypertensive outpatients in China (Pei-Xi et al., 2012). There are many kinds of antihypertensive drugs nowadays (Du et al., 2012), but calcium antagonist is the most widely used one. Calcium antagonists dilate blood vessels to reduce peripheral vascular resistance to reduce blood pressure. Cilnidipine is a new dihydropyridine calcium antagonist with both L- and N-type calcium channel blocking effects, and has recently been included in the list of first-line antihypertensive agents by the Chinese Guideline for the Prevention and Treatment of Patients with Hypertension in 2009. The antihypertensive effects of cilnidipine are significant, and main features include good oral absorption and a long time of action. After oral administration, drug concentrations peak at 1.8 to 2.2 h and show a long half-life of 7.5 h. Importantly, cilnidipine inhibits sympathetic activation to effectively prevent the reflex tachycardia often reported in similar antihypertensive agents, particularly amlodipine. Cilnidipine, therefore, has the

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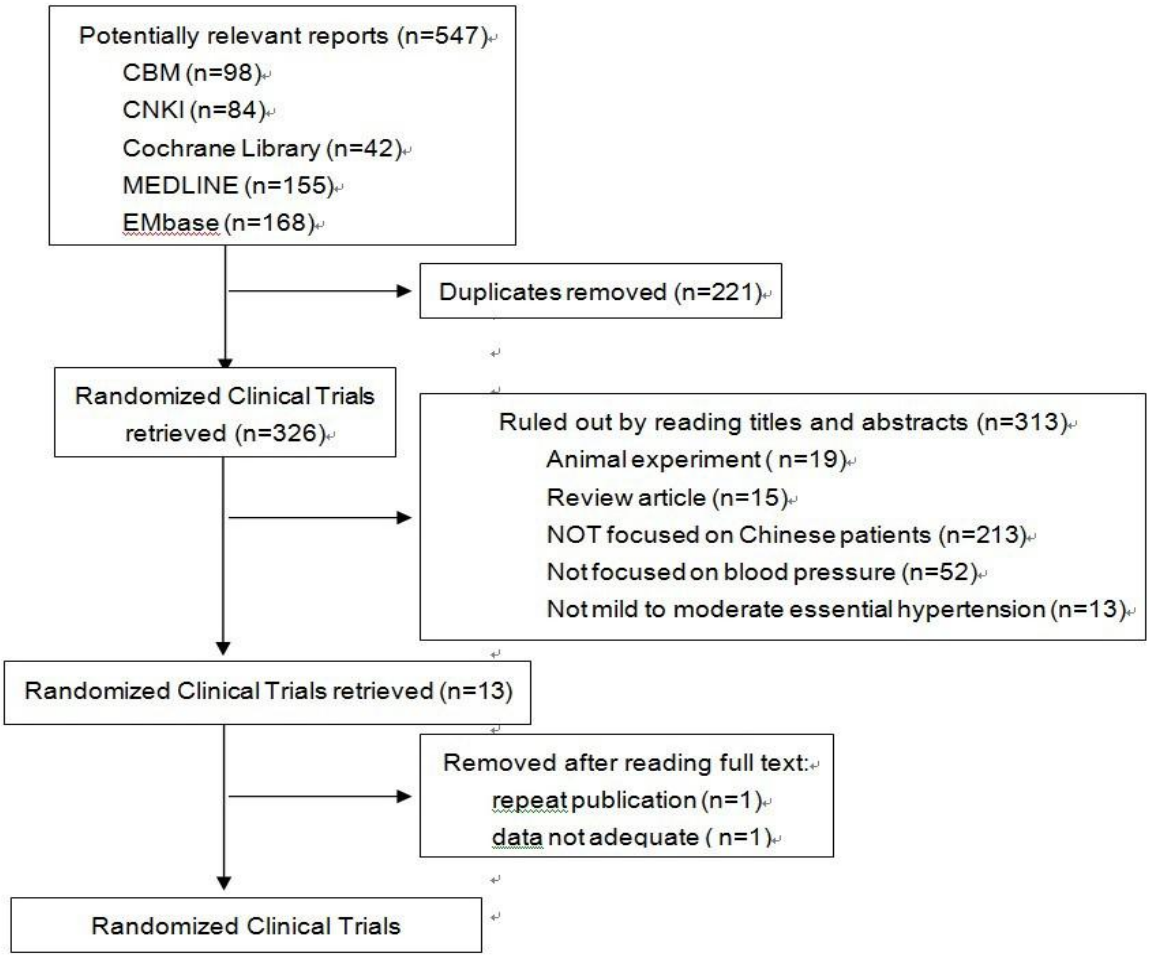

Figure 1. Decision flow chart for article inclusion.

potential to improve patient compliance (Zhang and Zhao, 2003). Cilnidipine tablets first went on the market in Japan in 1995 and were subsequently approved by other countries (for example, China in 2002) to become the primary antihypertensive drug used today.

Although, there have been several small clinical studies that report the use of cilnidipine tablets for the treatment of hypertension, each individual study lacks the power to make strong conclusions because of the individually small sample sizes. For this reason, the goal of the current study was to perform a meta-analysis on clinical randomized controlled trials (RCTs) that focused on using cilnidipine tablets to treat mild to moderate essential hypertension in Chinese patients, in order to better understand the efficacy and safety profiles of cilnidipine.

METHODOLOGY

Search strategy

The search strategy was devised according to the guideline 4.2.7 from the Cochrane collaboration (Sackett et al., 2002). We systematically searched the Cochrane central register of controlled trials (Issue 2, 2011), MEDLINE (1991 to June, 2011), EMbase (1991 to June, 2011), CBM (1991 to June, 2011), and CNKI (1979 to June, 2011) for RCTs that examined the efficacy and safety of using cilnidipine tablets to treat mild to moderate essential hypertension among Chinese people. In addition, we conducted a manual research of abstracts from selected references and searched manually the bibliographies of all relevant trials. The following search criteria were used: ("hypertension" or "essential hypertension") and ("cilnidipine"). The language was limited to peer-reviewed articles written in English or Chinese.

Study selection

Two reviewers independently conducted the literature searches and extracted the relevant articles. The flow chart for article selection is shown in Figure 1. The title and abstract of potentially relevant studies were screened for appropriateness before retrieval of the full articles.

The following selection criteria were used to identify published studies for inclusion in this meta-analysis: (a) the study design was a RCT; (b) the population was Chinese patients with mild to moderate essential hypertension (WHO-ISH Hypertension

Guidelines Committee, 1999 (WHO-ISH Hypertension Guidelines Committee, 1999); Committee of guidebook on prevention and treatment of hypertension, 2000); (c) the intervention was cilnidipine tablets compared to other active anti-hypertensive agents that were being used in a monotherapy strategy; (d) the outcome variables were the overall response rate and adverse reaction rate; (e) the efficacy criteria followed the Guiding Principles for Clinical Research of New Drugs developed by the Chinese Ministry of Health in 1993 (Liu et al., 1998).

Data extraction

From each study, the following information was extracted: author, year of publication, study design, characteristics of the population, sample size, treatment scheme, time of therapy, overall response rate and adverse reaction rate.

Assessment of study quality

The Jadad score was used to assess the quality of the trial methodology, and this assessment was independently performed by each of the two reviewers (Jadad et al., 1996). Articles given 1 to 2 points were regarded as low quality and articles given 3 to 5 points were regarded as high quality. The pre-determined criterion was to exclude articles whose study quality scored below 2 points mark.

Statistical methods

For dichotomous outcomes, we calculated a pooled odds ratio (OR) and 95% confidence interval (CI). The OR was defined as the odds of an outcome in those who received cilnidipine compared with the odds in those who received another active hypertensive agent. The ORs of different randomized clinical trials were combined by using the random-effects model of Der Simonian and Laird if between-study heterogeneity existed. The Mantel and Haenszel fixed-effects model was used if there was no between-study heterogeneity.

Intertribal statistical heterogeneity was explored using the Cochrane Q test with calculated I^2, indicating the percentage of the total variability in effect estimates among trials, due to heterogeneity rather than to chance. The I^2 values of 50% or more indicated a substantial level of heterogeneity. We evaluated the presence of publication bias by means of visual inspection of the funnel plot (whether it was symmetrical or not). To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by excluding those studies with low quality and then rerunning the analysis to assess the change in the ORs.

All p-values were two-sided and statistical significance was set at a level of 0.05. We followed the Quality of Reporting Meta-analysis Guidelines. All the statistical analysis was carried out by the Cochrane collaboration's RevMan 4.2 software (Moher et al., 1999).

RESULTS

Characteristics of the included trials

There were 547 articles relevant to the search terms, from which a total of 11 articles matched inclusion criteria. The most common reason for excluding an article were that, the patient population was not Chinese, the focus of the study was not hypertension, or the patients did not have mild to moderate hypertension. The 11 articles included 790 Chinese patients with mild to moderate essential hypertension (n = 396 on Cilnidipine and n = 394 controls), which were included in this meta-analysis (Zhang and Liu, 2003; Chen et al., 2003; Liang et al., 2003; Ma et al., 2004; Chen et al., 2004; Zhao et al., 2005; Jing et al., 2005; Huang et al., 2006; Huang et al., 2007; Zhao et al., 2008; Zhou, 2011). The antihypertensive agent used for the control group for all of the studies was amlodipine. The mean values for age, gender and initial blood pressure were similar between the two groups ($p > 0.05$). The characteristics of the included trials are shown in Table 1.

Heterogeneity test

We chose the fixed-effect model to perform our meta-analysis because there were no significant heterogeneities among the studies, in both the efficacy analysis (Q statistic =4.62, $p = 1.00$, $I^2 = 0\%$) and the safety analysis (Q statistic =3.73, $p = 0.93$, $I^2 = 0\%$).

Meta-analysis of efficacy

There was 396 of 456 persons in cilnidipine group that is efficacious, the overall response rates were 86.8% (with an average blood pressure lowering of 21 mmHg) and there was 394 of 453 persons in control group that is efficacious, the overall response rates were 87.0% (with an average blood pressure lowering of 21 mmHg). 95% CI [0.68,1.48]. From the meta-analysis, there were no significant differences in efficacy between cilnidipine and amlodipine in treating Chinese patients with mild to moderate essential hypertension (Figure 2).

Meta-analysis of safety

Adverse reaction rates for clnidipine tablets and the amlodipine control group were recorded in all 11 trials. The major adverse reactions for cilnidipine included headache (3.29%), dizziness (4.61%), and facial flushing (5.04%). The major adverse reactions of the control amlodipine group were headache (3.10%), dizziness (6.65%), cough (0.66%) and gastrointestinal symptoms (5.76%). The results of meta-analysis showed that there were no significant differences in safety between cilnidipine and the control amlodipine group in treating Chinese patients with mild to moderate essential hypertension (Figure 3).

Publication bias

An analysis of publication bias was conducted. The

Table 1. Characteristics of the included studies.

Study	Group	Treatment proposal (mg/d)	Times of theraphy (Weeks)	Sample size	Overall response rate (%)	Adverse reaction rate (%)	SBP baseline (mmHg)	SBP after medicine end (mmHg)	DBP baseline (mmHg)	DBP after medicine end (mmHg)	Jadad score
Zhang (2003)	Cilnidipine	5	8	22	86.4	0	149 ± 11	127 ± 13	101 ± 3	84 ± 7	4
	Amlodipine	5	8	24	95.8	0	150 ± 13	118 ± 11	101 ± 4	82 ± 7	
Chen (2003)	Cilnidipine	5	8	109	79.2	16.5	151 ± 13	127 ± 13	99 ± 4	85 ± 9	4
	Amlodipine	5	8	110	83.5	18.2	148 ± 13	130 ± 13	99 ± 4	84 ± 8	
Li (2003)	Cilnidipine	5	8	23	77.3	52.4	165 ± 10	140 ± 18	101 ± 4	86 ± 16	4
	Amlodipine	5	8	20	77.8	40.9	163 ± 12	130 ± 20	102 ± 5	86 ± 13	
Ma (2004)	Cilnidipine	5	8	24	83.3	16.7	151 ± 11	126 ± 8	99 ± 2	86 ± 6	4
	Amlodipine	5	8	24	75.0	12.5	147 ± 11	134 ± 12	100 ± 2	89 ± 6	
Chen (2004)	Cilnidipine	5	8	27	85.2	11.1	144 ± 10	126 ± 7	98 ± 4	86 ± 5	4
	Cilnidipine	5	8	27	88.9	14.8	146 ± 13	126 ± 11	98 ± 3	84 ± 7	
Zhao (2005)	Amlodipine	5	8	19	84.2	0	146 ± 13	126 ± 11	98 ± 3	84 ± 7	4
	Cilnidipine	5	8	21	90.5	9.5	144 ± 10	126 ± 7	98 ± 4	86 ± 5	
Jing (2005)	Amlodipine	5	8	32	90.6	3.1	150 ± 12	128 ± 11	99 ± 3	83 ± 6	4
	Cilnidipine	5	8	32	90.6	0	150 ± 13	133 ± 14	100 ± 5	87 ± 8	
Huang (2006)	Amlodipine	5	8	25	88.0	4.0	146 ± 10	128 ± 8	99 ± 4	86 ± 7	4
	Cilnidipine	5	8	25	88.0	8.0	146 ± 12	127 ± 10	97 ± 3	82 ± 6	
Huang (2007)	Amlodipine	5	8	117	92.5	9.7	148 ± 10	125 ± 11	99 ± 3	77 ± 9	4
	Cilnidipine	5	8	117	87.2	8.6	148 ± 9	127 ± 12	99 ± 3	76 ± 7	
Zhao (2008)	Amlodipine	5	8	24	91.3	21.7	151 ± 10	140 ± 9	97 ± 2	86 ± 4	4
	Cilnidipine	5	8	24	90.5	23.8	150 ± 11	134 ± 7	98 ± 2	84 ± 5	
Zhou (2011)	Amlodipine	5	8	49	93.9	12.2	151 ± 11	132 ± 12	98 ± 4	85 ± 8	3
	Cilnidipine	5	8	49	91.8	16.3	148 ± 3	127 ± 10	98 ± 3	82 ± 5	

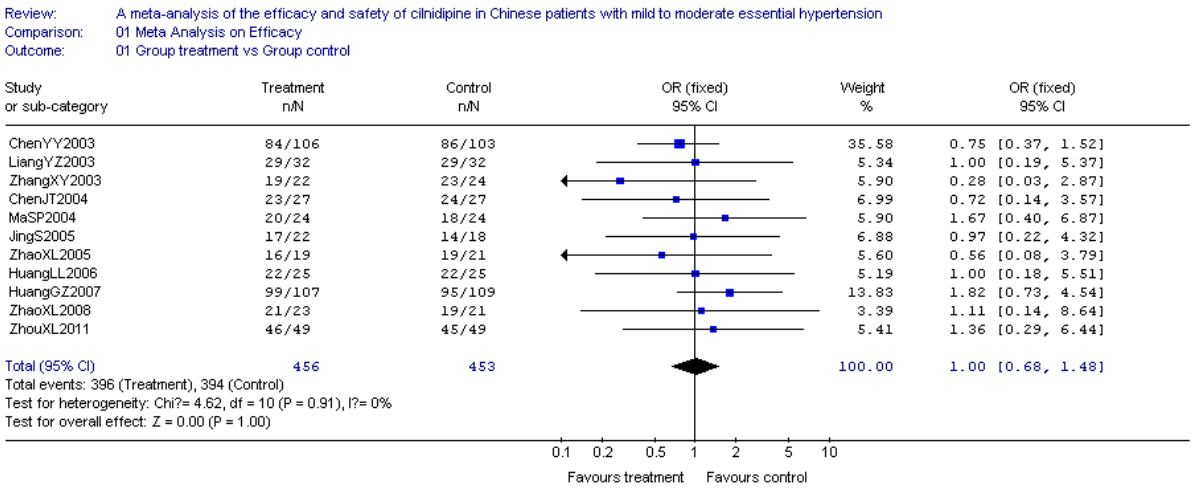

Figure 2. The OR estimates, with the corresponding 95% CI for efficacy. The OR estimates for each study is denoted by a box. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. Note that this line might be contained within the diamond, if the CI is narrow.

funnel plots were symmetrical based on visual analysis, indicating that there was no evidence of publication bias (Figure 4).

Sensitivity analyses

In the efficacy analysis, there was no difference in the overall response rates between cilnidipine and the control amlodipine group [Z = 0.00 (p = 1.00), OR =1.00, 95% CI (0.68, 1.48)]. Further, no difference was found in the adverse reaction rates between cilnidipine and the control amlodipine group in the safety analysis [Z = 0.26 (p = 0.80), OR = 0.95, 95% CI (0.64, 1.41)].

Summary of the literature quality

In an analysis of the articles, we found that all trials that were included in the meta-analysis were of high quality. The Jadad score was at least 2 points for each of the 11 articles. Moreover, there was no evidence of publication bias found and there were no significant heterogeneities between studies in both the efficacy analysis and the safety analysis. Combined, this suggests that the overall quality of the systematic review was high.

There were, however, still a few methodological insufficiencies that should be mentioned. These included: (a) the randomization method for the individual trials may not be rigorous because the specific randomization schemes were inadequately described in all except one article; (b) a selection bias may exist, as the allocation concealment was not described in any of the articles; (c) a measuring bias and implementation bias may exist because one study did not describe whether the trial was a double blind design.

DISCUSSION

Hypertension is a leading cause of cardiovascular morbidity and mortality. In particular, hypertension is a leading cause of congestive heart failure due to the increased pressure overload placed on the myocardium. Cilnidipine is a calcium channel blocker that is widely prescribed in China for the treatment of hypertension. The goal of this study was to use a meta-analysis to examine the efficacy and safety of cilnidipine compared to amlodipine.

The significant finding of this study was that, cilnidipine was equally effective as amlodipine in lowering blood pressure. In addition, cilnidipine shared a similar safety profile with amlodipine. These results indicate that cilnidipine is an effective antihypertensive agent to treat mild to moderate essential hypertension.

Summary of quality of included studies

A total of 11 studies were included in this systematic review, of which all were RCTs. Combined, the 11 studies yielded a total sample size of 790. The Jadad scores of the 11 articles were at least 2 points and the overall quality of this meta-analysis was high.

Meta-analysis of efficacy and safety

In general, calcium channel blockers have a very reliable and stable antihypertensive effect and do not affect

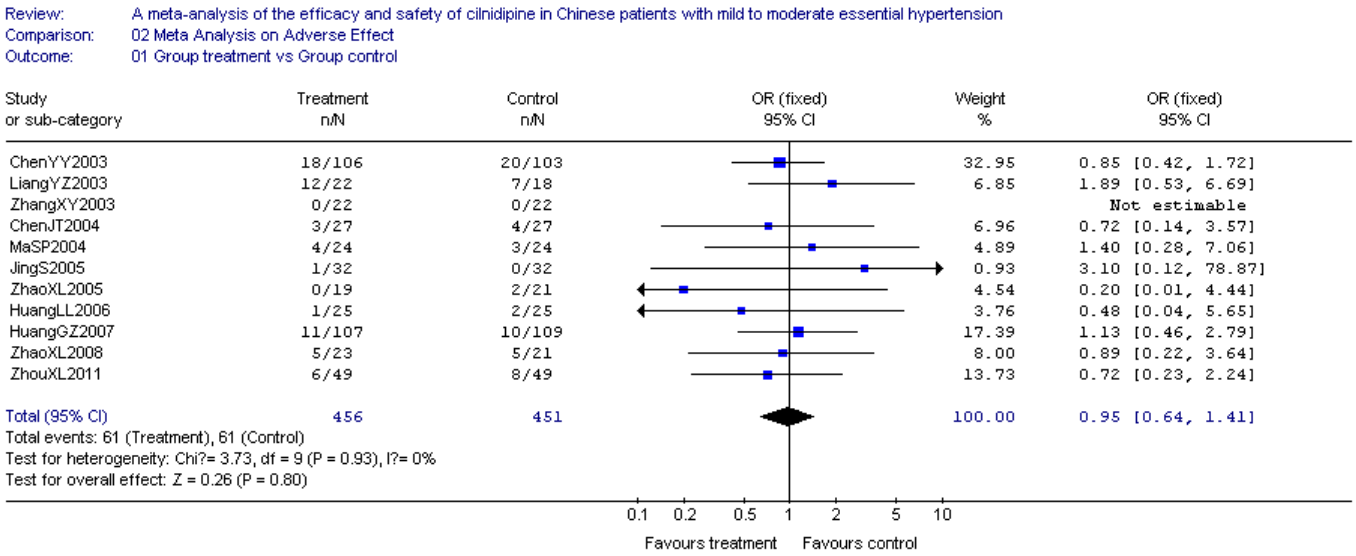

Figure 3. OR estimates, with the corresponding 95% CI for safety. The OR estimate of each study is marked with a box. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond. Note that this line might be contained within the diamond, if the CI is narrow.

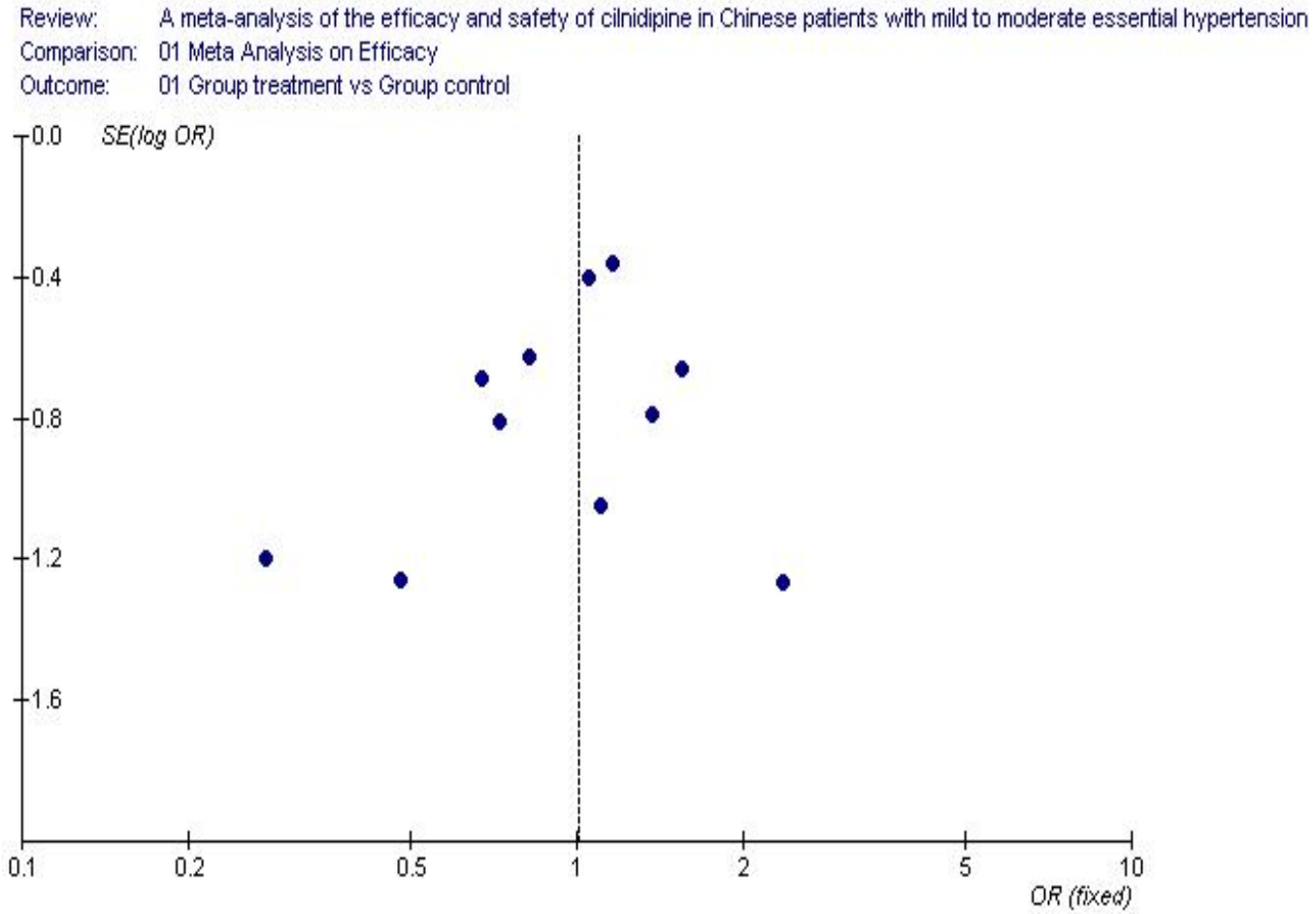

Figure 4. Funnel plot to examine publication bias. Based on the symmetrical shape, there was no publication bias.

glucose and lipid metabolism. As such, calcium channel blockers are useful drugs to control blood pressure and reduce the complications of cardiovascular disease (Wang et al., 2010). In addition to blocking the L-type Ca^{++} channel, cilnidipine has been shown to inhibit the N-type Ca^{++} channel current in sympathetic neurons (Fujil et al., 1997; Hosono et al., 1995). Cilnidipine reduces arterial blood pressure and lowers total peripheral resistance, but does not affect heart rate, cardiac index or cardiovascular structure (Jasmina et al., 2002).

There were several limitations of this study. This study included a meta-analysis of 11 trials, in which the test group had similar treatment doses and times, and all trials used amlodipine as the comparison control. For most of the articles, however, the randomization method was not well-described, which may affect the strength of the meta-analysis. In order to obtain more rigorous and objective clinical evidence, this study should be followed up with a prospective clinical trial with more randomization methods, including a blinding allocation scheme and longer-term follow-up.

Although amlodipine has already been shown to be efficacious, cilnidipine may be selected over amlodipine for the treatment of hypertension. In particular, cilnidipine may be a suitable alternative for patients who experience cough or gastrointestinal symptoms when given amlodipine.

The results of this systematic review revealed that there were no significant differences in efficacy in treating Chinese patients with mild to moderate essential hypertension between cilnidipine and the control amlodipine group.

We can conclude, therefore, that cilnidipine has the same antihypertensive effects compared with a first-line antihypertensive drug.

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