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Full Length Research Paper

A meta-analysis of the efficacy and safety of lacidipine 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 lacidipine tablets to treating Chinese patients with mild to moderate essential hypertension. We systematically searched the Cochrane central register of controlled trials (Issue 2, 2011), Medline (1966 to June 2011), EMbase (1966 to June 2011), CNKI (1993 to June 2011), WANFANG (1981 to June 2011), VIP (1989 to June 2011) and CBM (1991 to June 2011) through the computer and manually retrieved the relevant literature with pre-specified criteria. Then, we evaluated the quality of selected articles, extracted data and used Revman 5.1 software to do a meta-analysis. A total of 819 articles were found and 13 articles finally included were all randomized clinical trials that examined the efficacy and safety of using lacidipine tablets to treat mild to moderate essential hypertension among Chinese people. For the heterogeneity test, the efficacy analysis (Q statistic = 12.02, I^2 = 0%, Z = 3.43, *P* = 0.0006) and safety analysis (Q statistic = 15.77, p = 0.20, I^2 = 24%, Z = 3.58, P= 0.0003) showed that lacidipine was more effective and safer than other currently available antihypertensive agents. Meta-analysis showed that there was a significant difference between the total efficiency and adverse effect of lacidipine and other antihypertensive drugs. The evidence currently available shows that lacidipine tablets have a better efficacy and safety compared with other active antihypertensive agents used to treat mild to moderate essential hypertension.

Key words: Lacidipine, essential hypertension, systematic review, meta-analysis.

INTRODUCTION

Hypertension is the most important risk factor of cardiovascular, cerebrovascular and kidney diseases occurrence and death (Zhao et al., 2012). It is the most common chronic non-infectious diseases worldwide. The prevalence rate of hypertension continues to increase in China. It is estimated that the total number of patients nationwide with hypertension had reached 200 million (Liu et al., 2010), which accounted for one-fifth of the world's population with hypertension. But the awareness rate, treatment rate, and control rate of the Chinese population is only 30.2, 24.8 and 6.1%, respectively (Law et al., 2009). For decades, despite that anti-hypertension, drugs of different mechanisms all achieve positive effect however (Du et al., 2012), calcium antagonists have been the main antihypertensive agent, they act through dilating blood vessels to reduce peripheral vascular resistance. And the calcium antagonist was included to the list of first-line antihypertensive agents by the domestic and foreign numerous guidelines (Committee of guidebook on prevention and treatment of hypertension, 2011). Lacidipine is the third-generation dihydropyridine calcium antagonist, first produced by Italy GSK, and put into market in 1991. It works with voltage-dependent L-type calcium channel blocking effects to reduce the transmembrane Ca^{2+}, cause vasodilation thus leading blood pressure to decrease (Zhang, 2004). Lacidipine was used for many years in Europe and the United States because of its unique high lipophilicity, high vascular selectivity, good tolerability and longer half-life,

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so it achieved a desired antihypertensive effect. Domestic lacidipine was approved in China in 1995, gradually, to become one of the agents for treatment of mild to moderate essential hypertension (Wu, 2005). Although domestic lacidipine has made a positive efficacy and there are several studies about lacidipine tablets for the treatment of hypertension, the studies lack strong conclusions because the quality of research is without systematic evaluation. For this reason, the goal of the current study was to perform a meta-analysis on clinical random control trials (RCTs) that focused on using lacidipine tablets to treat mild to moderate essential hypertension in Chinese patients, in order to obtain evidence on the efficacy and safety.

METHODOLOGY

Search strategy

The search strategy was devised according to the working handbook 5.1 from the Cochrane collaboration. We systematically searched the Cochrane central register of controlled trials (Issue 2, 2011), Medline (1966 to June 2011), EMbase (1966 to June 2011), CNKI (1993 to June 2011), Wangfang (1981 to June 2011), VIP (1989 to June 2011), and CBM (1991 to June 2011) for randomized clinical trials that examined the efficacy and safety of using lacidipine tablets to treat mild to moderate essential hypertension among Chinese people. In addition, we conducted a manual search of abstracts from selected references and we also searched by hand the bibliographies of all relevant trials. The following search criterion was used: hypertension, essential hypertension and lacidipine, and 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 randomized clinical trial; (b) the population - was Chinese patients with mild to moderate essential hypertension (WHO-ISH Hypertension Guidelines Committee, 1999; Committee of guidebook on prevention and treatment of hypertension, 2000); (c) the intervention - was lacidipine tablets versus other active antihypertensive agents as monotherapy; (d) the outcome variables — was the overall response rate and adverse reaction rate; and (e) the efficacy criteria — was the Guiding Principles for Clinical Research of New Drugs developed by the Chinese Ministry of Health in 1993 (Liu et al., 1988). Subjects were excluded if they had severe heart, brain, lung, liver, kidney organ dysfunction and diabetes, combination therapy and those who cannot complete the follow-up.

Data extraction

From each study, the following information was extracted: author, year of publication, study design, characteristics of the population, simple size, treatment proposal, time of the therapy, overall response rate, and adverse reaction rate. The total effective rate and adverse effect incidence rate of used drugs was considered the ultimate goal of observation.

Assessment of study quality

The Jadad score was used to assess the quality of the trials methodology, and this assessment was independently performed by each of the two reviewers (Sackett et al., 2002). Articles given 1 to 2 points were regarded as low quality and the ones given 3 to 5 points were regarded as high quality through Jadad scale method (Jadad et al., 1996).

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 lacidipine compared with the odds in those who received other active hypertensive agents. 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 were used if there was no between-study heterogeneity. Intertribal statistical heterogeneity was explored using the Cochrane Q test with the calculated I^2, indicating the percentage of the total variability in effect estimates among trials that is, 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 odds ratios. All p-values were two-sided with statistical significance set at a level of 0.05. All the statistical analysis was carried out by the Cochrane collaboration's RevMan 5.1 software.

RESULTS

Characteristics of the included trials

There were 819 articles relevant to the search terms and a total of 13 articles matched inclusion criteria (Sun et al., 1995; Zhu, 1997; Zhang et al., 1999; Wu and Fu, 2001; Yi et al., 2001; Zhou et al., 2001; Xue 2001; Fang et al., 2001; Jiang et al., 2002; Duan et al., 2003; Xu et al., 2004; Li et al., 2005; Wu and Xiong, 2007). The 13 researches included 1348 Chinese patients with mild to moderate essential hypertension, 688 patients used Lacidipine tablets and 660 patients used Nitrendipine (229 patients), Captopril (108 patients), Nifedipine (85 patients), Lisinopril (51 patients), Amlodipine (85 patients), and Benidipine (102 patients) in controls. The 13 articles included in this meta-analysis were all randomized controlled trials. There were 11 high quality articles, in which 9 researches got 4 points and 2 researches got 3 points, the remaining 2 researches got 2 scores which were considered low quality through Jadad scale method. The characteristics of the included trials are shown in Table 1.

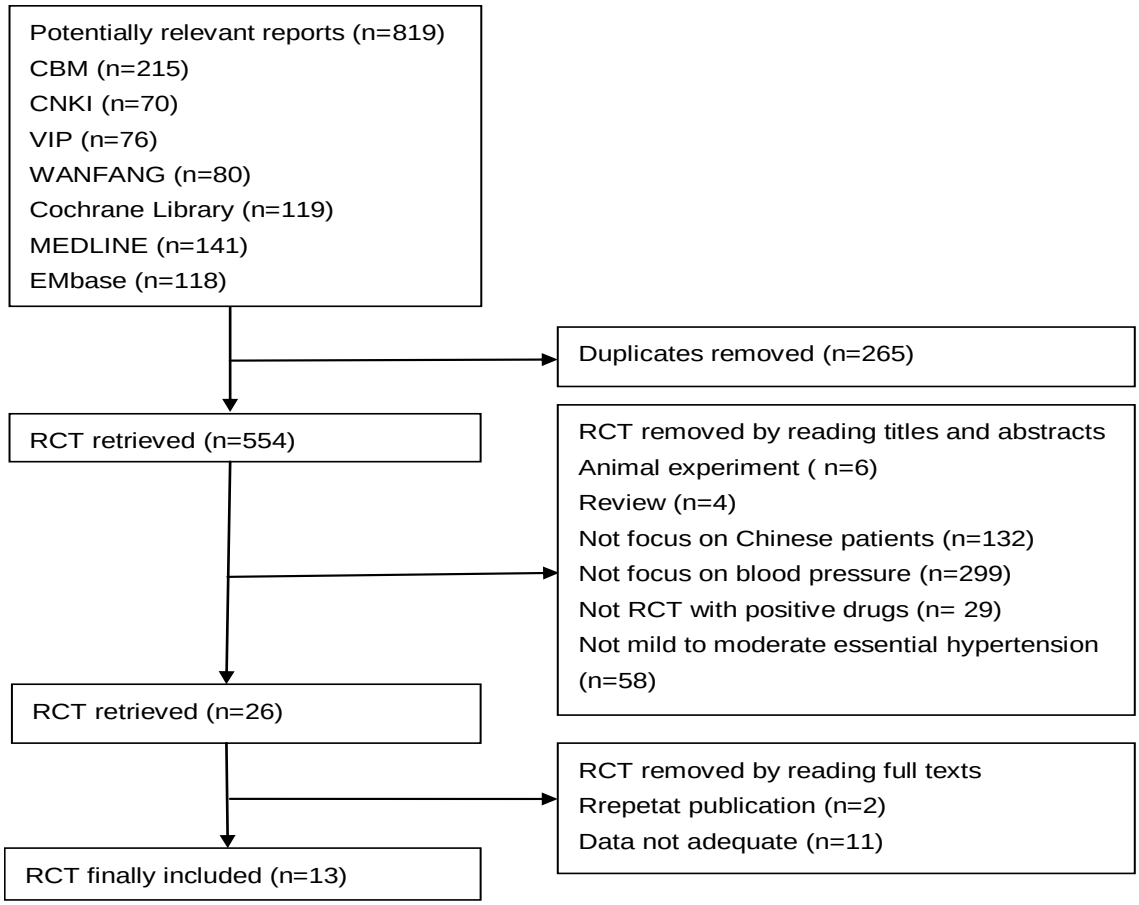

Figure 1. Flow chart of article selection.

Heterogeneity test

We chose the fixed-effect model to perform our meta-analysis, because there were no significant heterogeneities among the-studies, in both efficacy analysis (Q statistic = 12.02, p = 0.44, I^2 = 0%) and safety analysis (Q statistic = 15.77, p = 0.20, I^2 = 24%).

Meta-analysis of efficacy

The overall response rates were 89.2% for lacidipine and 82.7% for the control group. From the meta-analysis, there were significant differences in efficacy between lacidipine group and control group in treating Chinese patients with mild to moderate essential hypertension (Figure 2).

Meta-analysis of safety

The major adverse reactions of lacidipine tablets were mild headache (1.3%), dizziness (0.9%), facial flushing (3.9%), palpitations (0.5%), and mild edema (2.0%). The major adverse reactions of control group were cough (2.4%), headache (1.5%), dizziness (0.6%), facial flushing (4.8%), mild edema (3.4%), and gastrointestinal symptoms (1.1%). The results of meta-analysis showed that the incidence of the adverse reactions in lacidipine tablets were lower than the controlled groups, there were significant differences in treating Chinese patients with mild to moderate essential hypertension (Figure 3).

Publication bias

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

Sensitivity analyses

In an analysis excluding the 2 low quality trials, our results were consistent with those found in our main

Table 1. Characteristics of important studies admitted.

Studies	Group	Treatment proposal (mg/d)	Times of therapy (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
Sun (1995)[11]	Lacidipine	2-6	6	61	98.4	5	164 ± 17	139 ± 12	100 ± 6	82 ± 6	4
	Nitrendipine	20-40	6	60	88.3	30	166 ± 16	140 ± 17	100 ± 5	83 ± 7	
Zhu (1997)[12]	Lacidipine	5	8	40	92.5	16.5	151 ± 13	127 ± 13	99 ± 4	85 ± 9	4
	Amlodipine	5	8	40	95.0	18.2	148 ± 13	130 ± 13	99 ± 4	84 ± 8	
Zhang (1999)[13]	Lacidipine	2-6	4	32	93.7	6.3	160 ± 12	133 ± 9	101 ± 7	84 ± 8	4
	Nitrendipine	10-20	4	28	85.7	17.9	159 ± 9	136 ± 6	102 ± 7	84 ± 8	
Wu (2001)[14]	Lacidipine	4	4	30	96.7	0	162 ± 19	147 ± 10	101 ± 7	86 ± 6	4
	Captopril	50	4	26	95.0	19.2	163 ± 19	142 ± 13	100 ± 6	91 ± 6	
YI (2001)[15]	Lacidipine	2-8	4	60	96.7	20.0	160 ± 10	1127 ± 9	98 ± 7	80 ± 8	2
	Nifedipine	30-60	4	60	95.0	21.7	162 ± 8	123 ± 4	96 ± 7	83 ± 7	
Zhou (2001)[16]	Lacidipine	2-8	4	60	96.7	20.0	169 ± 13	134 ± 18	105 ± 7	82 ± 6	3
	Nitrendipine	30	4	50	84.0	24.0	168 ± 12	142 ± 15	102 ± 6	89 ± 6	
Fang (2001)[17]	Lacidipine	5	4	30	73.3	13.3	169 ± 13	134 ± 18	105 ± 7	82 ± 6	4
	Nitrendipine	10	4	30	73.0	13.3	154 ± 11	140 ± 14	105 ± 8	87 ± 6	
Xue (2001)[18]	Lacidipine	4-8	8	51	72.5	5.9	156 ±14	139 ± 7	105 ± 7	89 ± 8	4
	Lisinopril	10-20	8	51	70.6	2.0	156 ± 12	142 ± 16	102 ± 5	90 ± 8	
Jiang (2002)[19]	Lacidipine	4-8	8	68	93.0	1.5	160 ± 10	127 ± 9	98 ± 7	80 ± 8	4
	Nitrendipine	20	8	61	83.0	8.2	162 ± 8	123 ± 14	96 ± 7	83 ± 7	
Duan (2003)[20]	Lacidipine	4	6	45	92.0	13.3	160 ± 12	136 ± 6	102 ± 7	84 ± 8	2
	Amlodipine	5	6	45	93.0	11.1	159 ± 9	127 ± 10	97 ± 3	82 ± 6	
Xu (2004)[21]	Lacidipine	4	4	25	88.0	8.0	155 ± 15	135 ± 19	104 ± 6	90 ± 12	4
	Nifedipine	30	4	25	76.0	16.0	154 ± 13	134 ± 14	98 ± 4	85 ± 8	
Li (2005)[22]	Lacidipine	4-8	8	104	78.4	11.5	152 ± 12	137 ± 16	98 ± 4	87 ± 10	4

Table 1. Contd.

	Benidipine	2	8	102	74.4	10.8	150 ± 11	134 ± 7	98 ± 2	84 ± 5	
Wu (2007)[23]	Lacidipine	4-6	8	82	91.6	4.9	175 ± 3	135 ± 5	105 ± 2	81 ± 2	3
	Captopril	50	8	82	80.7	9.8	162 ± 5	149 ± 6	111 ± 6	89 ± 6	

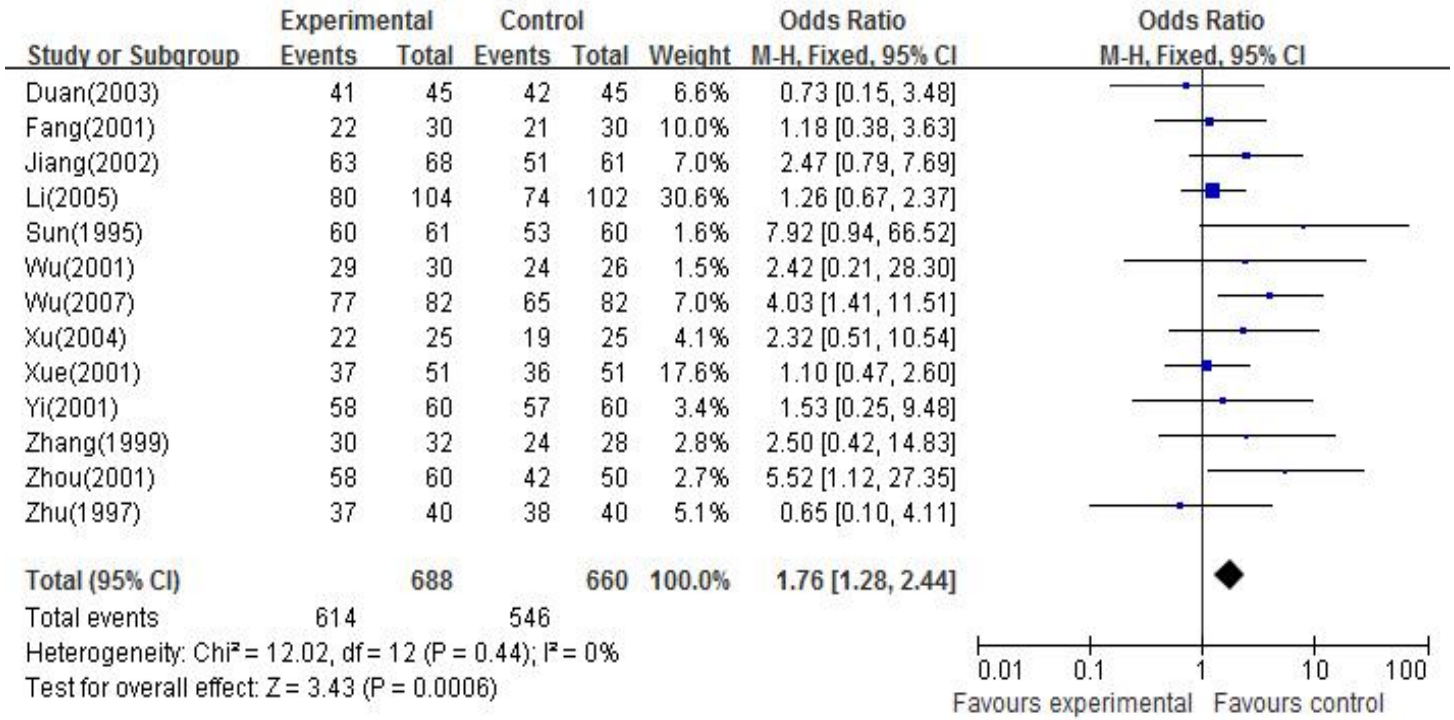

Figure 2. OR estimates with the corresponding 95% CI for the efficacy. The OR estimate of each study is marked with a ■. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond;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

analysis described earlier: in the efficacy analysis, there was a significant difference in overall response rates between lacidipine group and control group [Z = 3.43 (p = 0.0006), OR = 1.76, 95% CI (1.28 to 2.44)], furthermore, a significant difference was found in adverse reaction rates

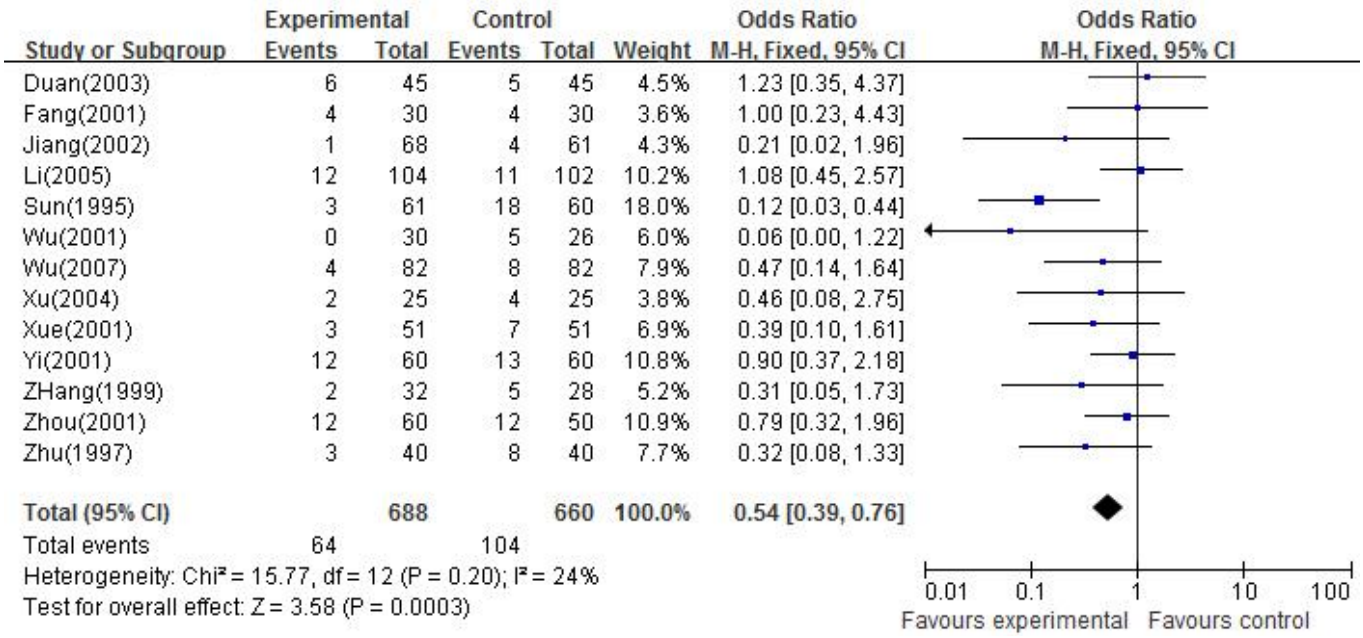

Figure 3. OR estimates with the corresponding 95% CI for the safety. The OR estimate of each study is marked with a ■. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The CIs of pooled estimates are displayed as a horizontal line through the diamond;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

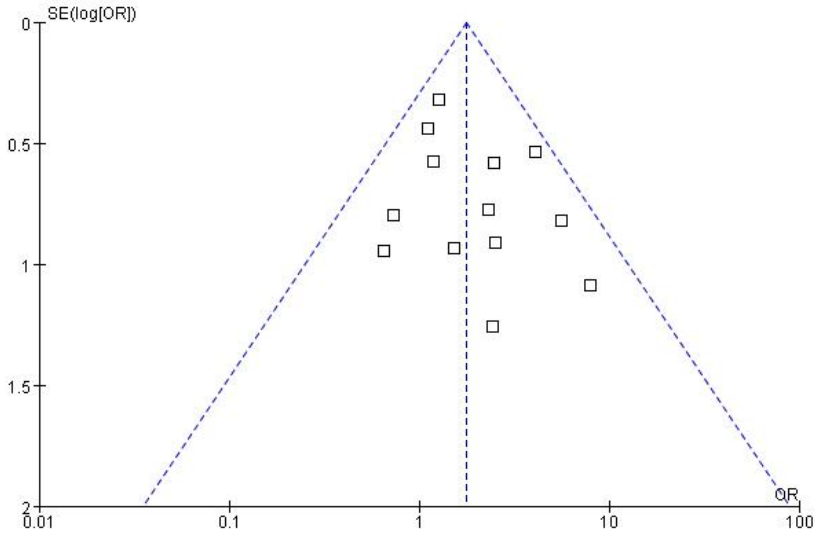

Figure 4. Funnel plot to examine publication bias.

between lacidipine group and control group in the safety analysis [Z = 3.58 (p = 0.003), OR = 0.54, 95% CI (0.39 to 0.76)].

DISCUSSION

Summary of the literature quality

A total of 13 articles were included in this systematic review. From these articles, we included a total sample size of 1348 patients for the meta-analysis. The Jadad score was at least two points for each of the 13 articles.

Moreover, no evidence of publication bias was found and there were no significant heterogeneities between studies in both efficacy analysis and safety analysis. Combined, this suggests that the overall quality of the systematic review was high. However, there were still a few methodological insufficiencies. 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; and (c) a measuring bias and implementation bias may exist, because 4 studies did not describe whether the trial was a double blind design.

Analysis of efficacy and safety

According to the drug core molecular structure and the role of L-type calcium channels in different sub-units, calcium channel blockers are divided into dihydropyridine and non-dihydropyridine. The long-acting and high vascular selective dihydropyridine calcium have been recognized at home and abroad, its antihypertensive effect acts by blocking extracellular calcium through voltage-dependent L-type calcium channels into vascular smooth muscle cells, then reduce excition-contraction coupling, lowering the contractile response of resistance vessels. Its advantages include rapid effect, relative stronger antihypertensive effect and magnitude, and do not affect glucose and lipid metabolism.

As a long-lasting and high vascular selective calcium antagonist, the fat-soluble of lacidipine is significantly higher than other calcium antagonist; it can accumulate in the lipid bilayer of the cell membrane, continually released in the cleanup phase (Sidorenko et al., 2002). It has a complete oral absorption, drug concentrations peak-at 3 to 5 h, has a nearly 99% binding rate with plasma protein. The half-life is 14 h, but has a long-lasting anti-hypertension effect. Its metabolism is in the liver, especially for patients with renal insufficiency. As lacidipine has a high selectivity on vascular smooth muscle, thus rarely case reflex tachycardia (McCormack and Wagstaff 2003).

This study included a meta-analysis of 13 articles, in which the trial designs are all clinical randomized controlled, the total sample is 1348 cases. 11 articles had Jadad scores of more than 2 points, and the overall quality is acceptable. The study showed that lacidipine had a significant efficacy on treatment of mild to moderate essential hypertension compared with the controlled group. The results demonstrate that the main adverse reactions of lacidipine are mild headache, face flushing, palpitations, mild edema, but it had a low incidence and a lesser extent, and all can be tolerated without stopping halfway. The incidence of adverse reactions was significantly compared with the controlled group, which suggests that it had a better security.

Conclusion

The study also showed that lacidipine had a significant hypertension compared with the controlled group, which efficacy on treatment of mild to moderate essential indicated that lacidipine had a better antihypertensive effect compare with other first-line antihypertensive agents. In this study, there were so many types in the controlled group. Although the doses, the period of treatment were basically the same, some studies were not described in detail for the random method. These factors may affect the credibility of the results of meta-analysis. Therefore, more and more double-blind randomized controlled trials are needed to get better clinical evidence.

REFERENCES

Committee of guidebook on prevention and treatment of hypertension (2011). Guidebook on prevention and treatment of hypertension. Chinese J. Cardiol. 39(7):579-615.

Committee of guidebook on prevention and treatment of hypertension (2000). Guidebook on prevention and treatment of hypertension. Chinese J. Hypertens. 8(2):103-112.

Du B, Cui WP, Xu GL (2012). A meta-analysis of the efficacy and safety of arotinolol in the treatment of Chinese patients with essential hypertension. Afr. J. Pharm. Pharmacol. 6(1):36-42.

Duan YJ, Zhang C, Ji YJ (2003). Clinical study of Lacidipine in treatment of essential hypertension. China Prescription Drug, 12(12):70-72.

Fang GQ, Yan WG, Shen LL (2001). The treatment of lacidipine for essential hypertension. Capital Med. 8(4):44.

Jadad AR, Moore A, Carroll D (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin. Trials 17(1):1-12.

Jiang B, Chen JM, Wang JX (2002). The comparition of efficacy on treatment of hypertension between Lacidipine and Nitrendipine, Captopril. Strait Pharm. J. 14(1):46.

Law MR, Morris JK, Wald HJ (2009). Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies. BMJ 338:1665.

Li XF, Ke YN, Jiang H (2005).Study of the anti-hypertensive efficacy and safety of Benidipine in patients with essential hypertension. Pharm. J. Chinese People's Libetation Army 21(6):429-432.

Liu GZ, Hu DY, Hu P (1998). Recommendations on evaluation of clinical trials of cardiovascular drugs. Chinese J. Cardiol., 26(1): 7-9.

Liu LS, Wang W, Yao CH (2010). Hypertension prevention guide (2009 grass-roots version). Chinese J. Hypertens. 18(1):11-30.

McCormack PL, Wagstaff AJ (2003). Lacidipine: a review of its use in the management of hypertension. Drugs, 63(21): 2327-2356.

Sackett DL, Clarke M, Oxman AD (2002). Cochrane Reviewers, Handbook 4.2, In Renew Manager. Oxford: The Cochrane Collaboration. pp.13-36.

Sidorenko BA, Stetsenko TM, Preobrazhenskii DV (2002). Third generation of calcium antagonists: focus on lacidipine. Kardiologiia 42(12):81-90.

Sun XC, Tao P, Xu CB (1995). Clinical effects of Lacidipine in the treatment with essential hypertension. Chinese J. Clin. Pharmacol., 11(2): 78-83.

WHO-ISH Hypertension Guidelines Committee (1999). 1999 World Health Organization- International Society of Hypertension Guidelines for the Management of Hypertension Hypertens. 17(2):151-183.

Wu GP (2005). Research progress of Lacidipine. Chinese J. Cardiovascular Rev. 3(6):468-470.

Wu SG, Fu YQ (2001).Evaluate the efficacy of treatment of hypertension with Captopril and lacidipine China Pharmaceuticals 10(10):49.

Wu SM, Xiong GH (2007).Clinical study of 82 cases of Lacidipine in patients with essential hypertension.. China Practical Med. 2(32):34-36.

Xu CY, Zheng CS, Wang ZC (2004).The efficacy of Lacidipine in treatment of mild to moderate hypertension. Chongqing Med. J.

33(12):1911-1912.
Xue ZL (2001).Efficacy and safety of Lacidipine in treatment of essential hypertension. Chinese J. Modern Appl. Pharm. 18(2):150-152.
Yi M, Li GM, Huang R (2001). The comparition of efficacy on treatment of hypertension between Lacidipine and Nifedipine Controlled Release Tablets. Chinese J. Clin. Pharmacol. 8(10):2-3.
Zhang SH, Cui WD, Zhang RH (1999). Clinical study of Lacidipine in treatment of hypertension. J. Shanghai Tiedao Univ. 20(9):42-44.
Zhang WZ (2004).The antihypertensive mechanism and application of calcium antagonist. Chinese J. Cardiol. 32(sup2):43-44.
Zhao PX, Wang C, Qin L (2012). Effect of clinical pharmacist's pharmaceutical care intervention to control hypertensive outpatients in China. Afr. J. Pharm. Pharmacol. 6(1):48-56.
Zhou SG, Hu LL, Shi TF (2001).Lacidipine treatment of hypertension in 60 cases. China Pharm. 10(6):46-47.
Zhu JH (1997). Clinial efficacy of Lacidipine in treatment of essential hypertension J. Nantong Medical College 17(4):527-528.