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Efficacy of Amlodipine Combined with Telmisartan or Amiloride in Treating Primary Hypertension: A Meta-Analysis

Tengfei Han[1,a], Huazhong Song[1], Caiyan An[2,b,*]

[1]Inner Mongolia Medical University, Xinhua Street, Huimin District, Hohhot, Inner Mongolia Autonomous Region, China
[2]Hohhot No.1 Hospital, Zhaojun Road Street, Yuquan District, Hohhot, Inner Mongolia Autonomous Region, China
[a]2240454505@qq.com, [b]acy_1999@163.com
**Corresponding author*

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Abstract: Objective is to systematically analyze the efficacy of Amlodipine combined with Telmisartan or Amiloride in the treatment of primary hypertension. Methods about computer and manual retrieval, seven databases of CNKI, VIP, Wanfang, Baidu scholar, China biomedical literature database (CBM), PubMed and SinoMed, and supplemented by other ways, the randomized controlled trials of Amlodipine combined with Telmisartan or Amiloride were screened. With Review Manger 5. 3 software for Meta-analysis. Results: 9 needed literature were finally selected, with a total of 443 patients. Meta-analysis showed that Amlodipine combined with Telmisartan or Amiloride have a positive effect on primary hypertension, and there is no significant difference between the two medication methods under different medication periods (DBP 82. 7 ±6. 5, 95% CI [- 0. 80, 0. 75], P > 0. 05, SBP 131. 1 ±9. 1, 95% CI [- 0. 66, 1. 65], P > 0. 05). Conclusion there is no difference in the treatment of Amlodipine combined with Telmisartan or Amlodipine combined with Amiloride for 4-12 months, but different medication time of studies show significant heterogeneity (I^2 > 50%). Considering the quality and quantity of the included literature, we believe that the research conclusions still need to be confirmed by more clinical reference studies.

1. Efficacy of combined antihypertensive therapy with calcium channel blockers

As the largest chronic disease in China, primary hypertension is harmful badly, according to the China Cardiovascular Health and Disease Report 2019[1], 244. 5 million people over 18 have developed hypertension since 2015, with a rough prevalence of 27. 9% (weighted by 23. 2%), and the prevalence has increased with age. The survey of 2017 appeals, 2. 54 million (95% UI: 2. 26 million to 2. 82 million) people in China died from excessive pressure difference of systolic blood, and the more efficient treatment options for hypertension need to be studied urgently. Previous

surveys have shown that the single efficiency of various kinds of antihypertensive drugs is only 42% to 59%. Many studies have shown that the combination of multiple antihypertensive drugs is the guarantee of reaching the blood pressure standard, and most hypertensive patients need the combination of medication [1-3]. Whether the efficacy of calcium channel blockers combined with angiotensin receptor antagonists better than the combination of calcium antagonists and diuretics is unknown in Chinese primary hypertensive populations. For example, in the research of Huiying Niu, Chang Lili and Jia Ying did not find the comparison between Amlodipine combined with Amiloride or Telmisartan in reducing blood pressure after intervention treatment. In the research of Xiaojuan Jing, Xiaojuan He, Min Zhu , Ying Shu, Mumu Xie and Jicai Chen, it was pointed out that Amlodipine combined with Telmisartan had better therapeutic effect on hypertension than Amlodipine combined with Amiloride, reversed left ventricular hypertrophy and increased EF value, the adverse reaction rate is also lower. This study aims to evaluate the efficacy of calcium channel blocker-based combined antihypertensive therapy and prospectively observe the efficacy of Amlodipine combined with Amiloride or Amlodipine combined with Telmisartan in patients with primary hypertension for further clinical studies.

2. Data and Methods

2.1 Inclusion criteria

In this study, the Han nationality of China was used as the basic population, and the default was Han if no specific mention in the included studies. Accepted languages are Chinese and English. No restrictions on the research institution (hospital or institute) and subject background (from the hospital or general population). Study screening the course of treatment was a minimum of 4 weeks and a maximum of 12 months. In addition, according to the principle of PICO-S (1) P (population): in patients with a clear clinical diagnosis of primary hypertension, there is no limit on the age, gender, disease course and region of patients. (2) I (intervention): The experimental and control groups were based on Amlodipine combined with Amiloride or Telmisartan respectively. (3) C (comparison): Amlodipine combined with Amiloride was used for the experimental group, and Amlodipine combined with Telmisartan for the control group. No limits to medication and dosage. (4) O (outcome): The main indicators are the mean value and the standard deviation of systolic blood pressure (SBP) and diastolic blood pressure (DBP). (5) S (study): The study type is a randomized controlled test (randomized controlled trial, RCT) with blind audit (Blind Review), double simulation (Double-Dummy).

2.2 Exclusion criteria

(1) Republished literature (retained one article) or reused the study data in multiple databases (retained the most complete data article); (2) Amlodipine-based combination therapy was not used in the experimental or control groups; Amlodipine did not combine with Amiloride or Telmisartan or multiple combination treatments; (3) Study subjects, non-primary hypertension; Not cooperative with medication or follow-up investigation; Adverse reactions to the studied combination treatment regimen (Adverse Effects, AEs) with higher odds; (4) Incomplete data or inconsistent data, or no full text of the literature.

2.3 Literature search strategy

The following 7 databases were searched by computer: China Biomedical Literature Database (CBM), CNKI, Wanfang Database (Wanfang), Chinese Technology Journal Full-text Database (VIP),

Baidu Scholar, SinoMed, PubMed; search time until February 2022, with manual search and other ways as addition. English search words include: Primary hypertension, Combined Medication, Amlodipine, Telmisartan, Amiloride. Use the subject words combined with free words.

2.4 Literature screening and data extraction

Two researchers independently screening, used the software End Note X9 for duplicating literature, through manual browsing topic, abstract and full-text reading. Extract the data of which met the included standards. Sort data in Excel form. After the completion of the above work, the two researchers cross check, to the difference of opinion, using review, consultation or the third person assess. Data extraction contents included: the name of the first author, year of publication, literature language, definition standard of primary hypertension, sample race, sample size, sex ratio, mean age, mean and standard deviation of baseline blood pressure, intervention measures, course of treatment, and outcome index.

2.5 Evaluation of the risk of bias

It was conducted independently by 2 researchers, Risk of bias assessment with Review Manger 5. 3 software, seven dimensions of risk of bias according to Cochrane assessment: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias. The quality of the included studies was evaluated by above seven dimensions. Low risk (low risk), high risk (high risk) and unclear risk (unclear risk) are determined in each dimension, Cross-check after completing the determination, Opinions will be resolved by agreement or consultation with a third person.

2.6 Statistical analysis

Meta-analysis was performed by using Review Manager 5. 3 software. Baseline and outcome data are continuous variables, using the mean and standard deviation ($\bar{x} \pm s$) as the effect indicators, and both will calculate the 95% confidence interval (Confidence Interval, CI). Using I^2 as the indicator of test to judge the heterogeneity, we set 25%, 50% I^2 as the criteria to divide the heterogeneity as low, medium, and high. If P> 0. 50, I^2<50% indicates low heterogeneity and fixed effect model (Fixed Effect Model); high heterogeneity and random effect model (Random Effect Model), requiring sensitivity analysis. This study removed the source of heterogeneity, and subgroup analysis to explore whether clinical characteristics or methodology caused significant heterogeneity. Publication bias test was conducted on nine included documents, and a funnel map display was not used because of too few included documents (n <10). （This manuscript had registered on the PROSPERO, and the number of registration is CRD42022322703. PROSPERO: https://www.crd.york.ac. uk/PROSPERO/）

3. Analysis Result

3.1 Literature screening process

A total of 19, 090 related literature were obtained, including CNKI 4232, Wanfang 3658, VIP 3765, CBM 1892, PubMed 1684, Baidu scholar 2967 and SinoMed 892. After excluding duplicate data and non-target studies, 5, 123 preliminary screening literature were obtained, and 993 articles were left after multiple elimination. By browsing 916 titles, abstracts, comments, unreliable literature sources, and case reports, the remaining 77 articles got full-text reading and according to the rejection standards, 9 articles were finally included for Meta-analysis. The flow chart of the literature screening

is shown in Figure 1.

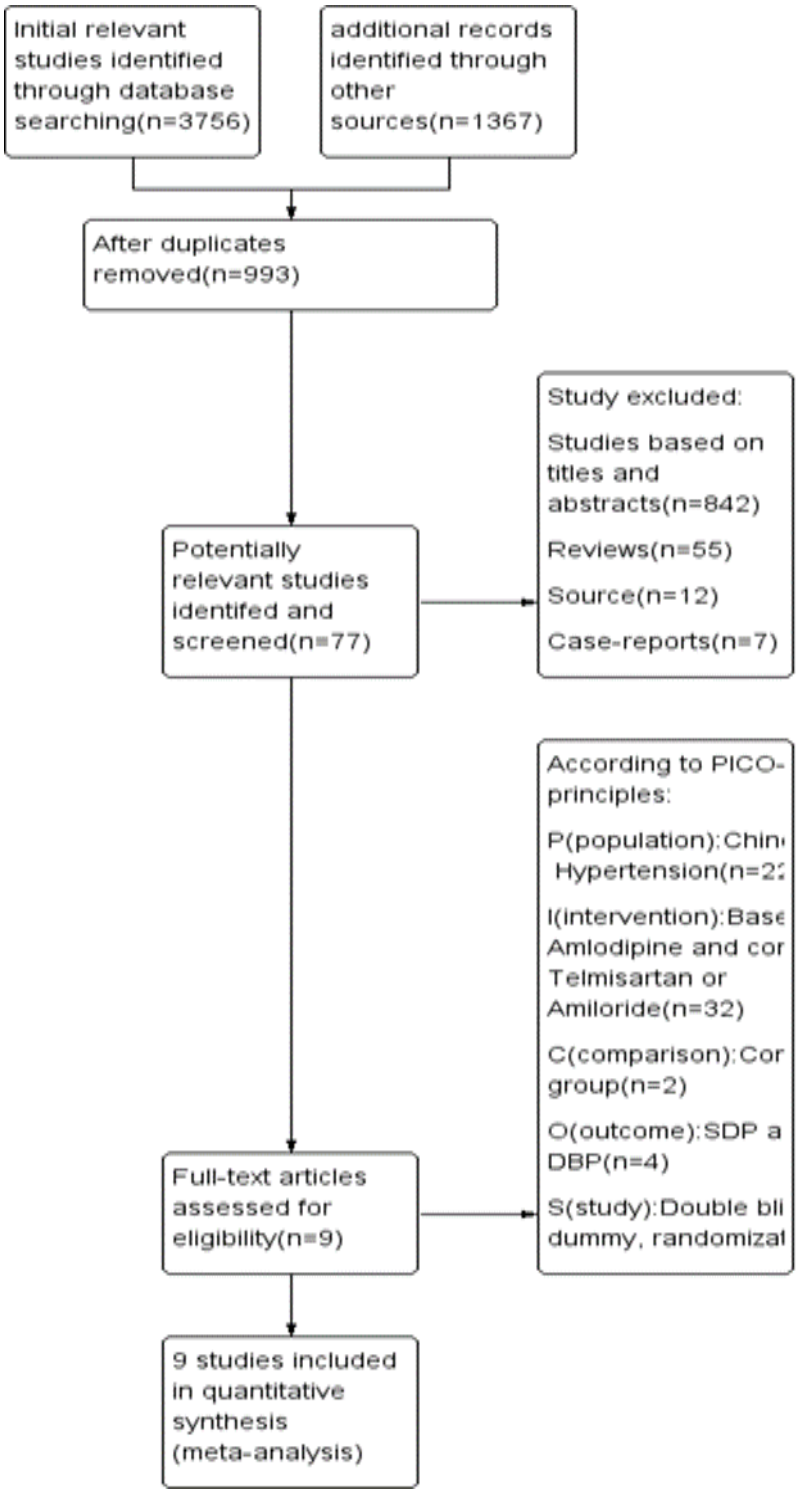

Figure 1 Screening process of literature

3.2 Basic characteristics of the included study

Nine literature included in this study[4-12]. It included 899 patients, 443 patients in the experimental group (with Amlodipine combined with Amiloride), 456 (control group with Amlodipine combined with Telmisartan); 484 males and 415 females; minimum medication course is 4 weeks, maximum

course is 12 months. The general data of age, sex ratio, baseline level and blood pressure in the obtained literature were comparable, and each group was randomized and had double-blind control. One study had a blood uric acid contrast, and all literature outcome indices were expressed by using the mean and standard deviation of SBP and DBP. Basic characteristics of the included studies are presented in Table 1.

First author and year of inclusion	n/例		Sexuality (male/female)		Years of age		Intervening measure		course of treatment/ week	Initial blood pressure (mmHg)		Blood pressure after treatment (mmHg)	
	A	B	A	B	A	B	A	B	A/B	A	B	A	B
HuiyingNiu 2011	32	34	15/17	19/15	65±4	63±4	M	T	12	①148.2±8.6 ②96.6±5.1	①147.3±8.5 ②97.3±5.0	①134.6±8.4 ②84.3±4.5	①133.7±7.9 ②83.6±4.8
XiaojuanJing 2010	46	46	25/21	24/22	65±4	66±3	M	T	4	①156±5 ②97±7	①157±4 ②98±5	①127±5 ②82±5	①123±6 ②76±6
YingShu 2011	48	48	29/19	30/18	61±7	61±6	M	T	48	①159.08±12.5 ②92.71±8.34	①157.60±12.99 ②93.46±8.69	①129.28±10.30 ②79.23±7.95	①132.62±14.9 ②78.62±8.71
MinZhu 2010	25	25	13/12	14/11	66±3	65±4	M	T	8	①173.7±14.2 ②103.5±9.3	①176.4±12.8 ②105.7±8.2	①132.5±12.8 ②84.0±7.9	①123.2±15.3 ②81.8±6.7
XiaojuanHe 2011	73	72	77/74		62.54		M	T	48	①172.6±8.8 ②105.9±4.5	①173.1±9.1 ②106.4±4.9	①130.8±5.6 ②83.0±6.2	①125.3±9.7 ②89.2±7.1
LiliChang 2021	56	60	32/24	34/26	58±6	60±7	M	T	24	①155.4±10.4 ②88.2±8.6	①153.6±9.8 ②90.4±9.3	①126.3±7.8 ②78.9±6.1	①125.3±8.2 ②78.5±5.9
JicaiChen 2017	30	30	16/14	17/13	65±5	66±5	M	T	8	①173±14 ②103±9	①177±13 ②106±8	①133±13 ②85±8	①124±16 ②82±7
YingJia 2010	83	91	36/47	53/38	63±6	64±6	M	T	12	①164.9±13.4 ②95.7±9.3	①163.9±13.8 ②95.8±8.4	①134.9±11.2 ②82.5±7.7	①137.4±13.9 ②80.7±7.5
MamuXie 2010	50	50	46/44		65±14		M	T	4	①165.9±10.8 ②105.7±6.8	①164.4±11.0 ②104.8±6.6	①131.2±7.4 ②85.5±4.7	①148.8±10.3 ②87.5±2.8

Infuse: ① Systolic blood pressure ② represents diastolic blood pressure

M: Amlodipine and amiloride T: Amlodipine and telmisartan

Table 1 General characteristics of include study

3.3 Risk of study bias assessment was included

The risk of bias was evaluated in the nine included literature, based on seven dimensional evaluation, all literature had high risk ratings in one or more items: in the random sequence generation, 2 high risks, 1 unclear risk, high risk ratings are due to the difference in the literature claimed in the abstract section and practical in the experimental implementation; in the allocation concealment, 4 high risks, 1 unclear risk, none of the four studies were assigned to concealment; in the blinding of participants and personnel, 1 high risk; in the blinding of outcome assessment, 2 High risks, 3 items had unclear risks; in the incomplete outcome data, 1 high risk, 1 unclear risk; in the selective reporting, 3 high risks, 1 unclear risk; among the other bias, 2 high risks, 1 unclear risk. Except for the specified high risk item, the remaining high risk was not mentioned in the article, and all unclear risks mean that no judgment basis was not found in the literature. Specific risk assessment of the included studies are shown in Figure 2.

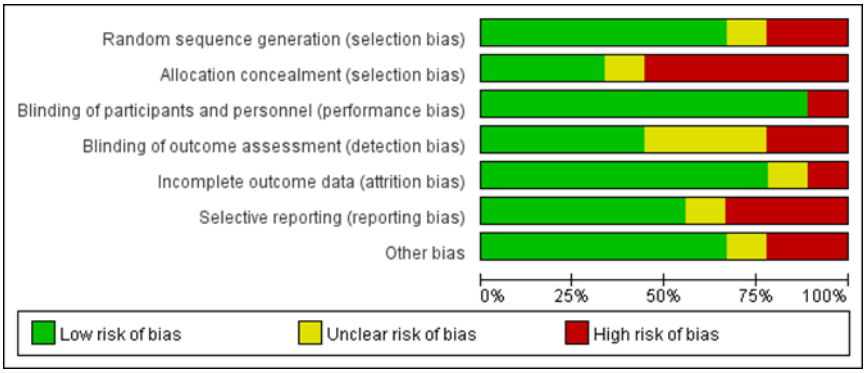

Figure 2: Risk assessment of bias graph of include trails

3.4 Meta-analysis

3.4.1 Post-treatment effect

All included literature showed positive effects of Amlodipine-based combined with Amiloride or Telmisartan on primary hypertension, but no differences between the two regimens were seen. The heterogeneity test results showed high heterogeneity on SBP and DBP(DBP: P=0. 95, I^2 = 89%;SBP:P=0. 4, I^2=94%). Therefore, the random effect model was used, and the results showed that the difference between the experimental and control groups was not statistically significant on SBP and DBP (SBP: CI=0. 49[-0. 66, 1. 65], P>0. 05; DBP: CI=-0. 02[-0. 80, 0. 75], P>0. 05). Specific data are shown in Figure 3 and 4.

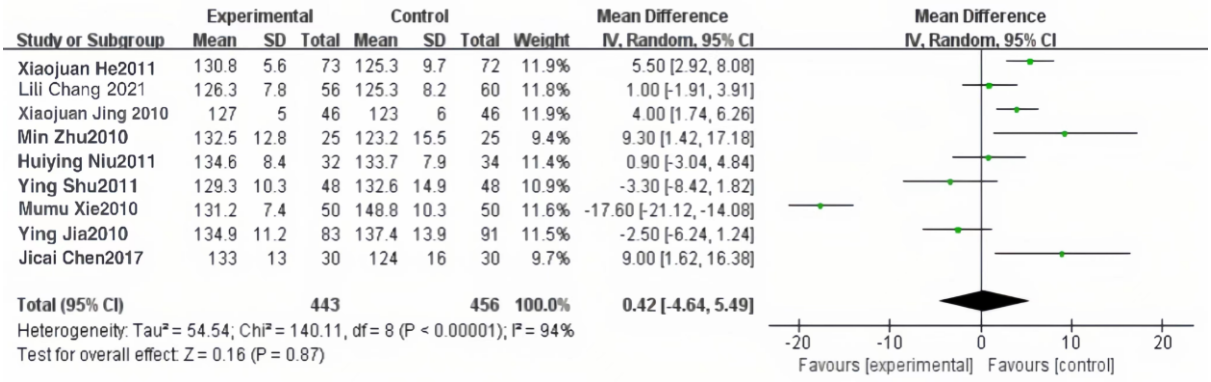

Figure 3 Forest plot of SBP

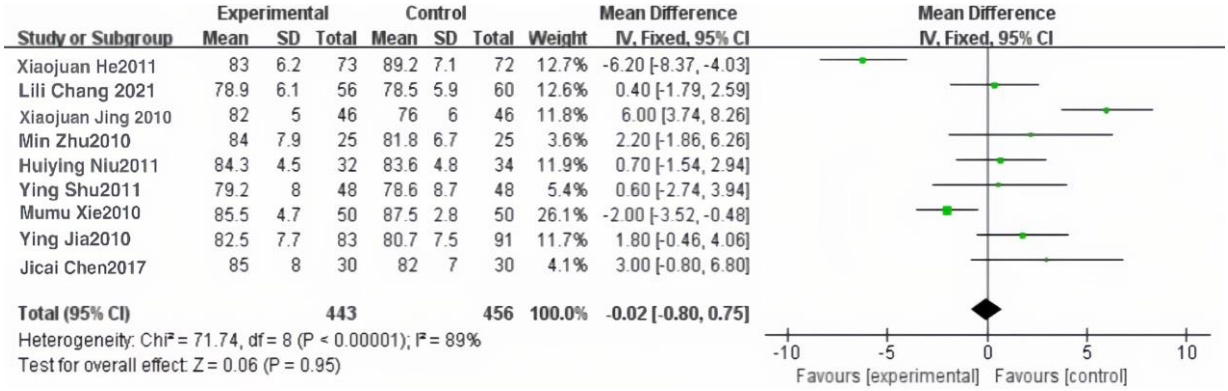

Figure 4 Forest plot of DBP

3.4.2 Sensitivity analysis

There was highly heterogeneity among studies. In order to find the source of heterogeneity, the study conducted sensitivity analysis of each literature by the method of removing literature one by one. The results showed a reduced heterogeneity in He Xiaojuan's study from the diastolic blood pressure results (P=0. 04, I^2=81%). The heterogeneity was also reduced when excluding Jing Xiaojuan's study (P=0. 05, I^2=83%), although there was still high heterogeneity after elimination, the study of the two had a significant effect on the treatment results, and the effect of the combination was greatly affected by the two studies. In addition, it was found that the study did not significantly change the evaluation and heterogeneity of the results (P=0. 14, I^2=89%), but if the three studies were excluded simultaneously, the result changed completely (P=0. 04, I^2=0%), the result that did not appear when excluding any other three studies, indicating that these three articles have a large impact on the meta-analysis results. Through comparison, the course of medication in the three studies was significantly different from other studies. In Jing and Xie's study, the medication course was 4 weeks, and the result of 4-week medication in other literature were used as the baseline of drug adaptation. In He's study, the medication course was 12 months, which was significantly increased compared with the course of other studies. Initially concluded that medication courses may be a source of heterogeneity in this study. The analysis found that the heterogeneity of SBP was significantly reduced in the study of Xie, but still significant (I^2=73%), and the effect result varied significantly (P <0. 0001). We believed that there were also medication variables in addition to the course of treatment factors. After verification, it was found that the medicine: Compound Amiloride contains 1. 25mg Amiloride and 12. 5mg hydrochlorothiazide each half tablet, so we inferred that the addition of hydrochlorothiazide had a great influence on the treatment effect.

3.4.3 Subgroup analysis

Subgroup analysis was based on the treatment course. In the systolic blood pressure subgroup analysis, Xie's study (95%CI=-17. 60[-21. 12, -14. 08]) had great influence, but in the same group, Jin's study (95%CI=4. 00 [1. 76, 6. 26]) showed little effect on the medication course, thus we thought the medication difference was a more significant influencing factor than the treatment duration. In the diastolic blood pressure subgroup analysis, Jin's study (95%CI=6. 00[3. 74, 8. 26]) and Xie's study (95%CI=-2. 00[-3. 52, -0. 48]) were significant in the mean value. In the subgroup analysis of contraction or diastolic blood pressure, although He's study could not contrast within subgroup, the comprehensive forest map found that the contribution heterogeneity and effect difference of He's study were significant. We believe that the medication course was too long to accurately control variables. Analysis of the systolic and diastolic blood pressure subgroups is shown in Figure 5 and Figure 6.

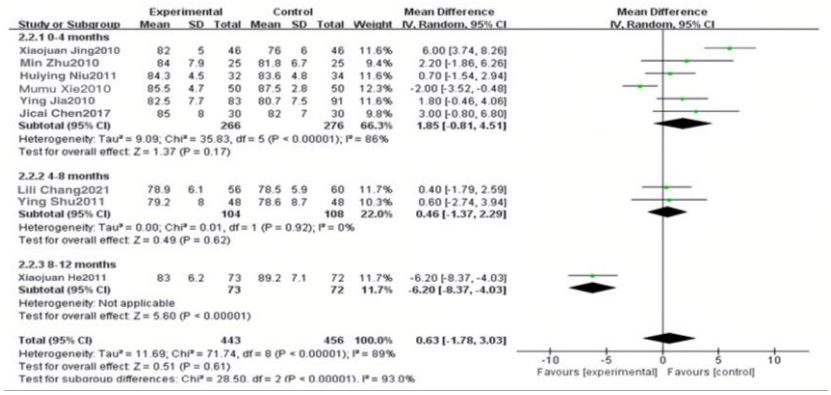

Figure 5 SBP forest plot of subgroup analysis

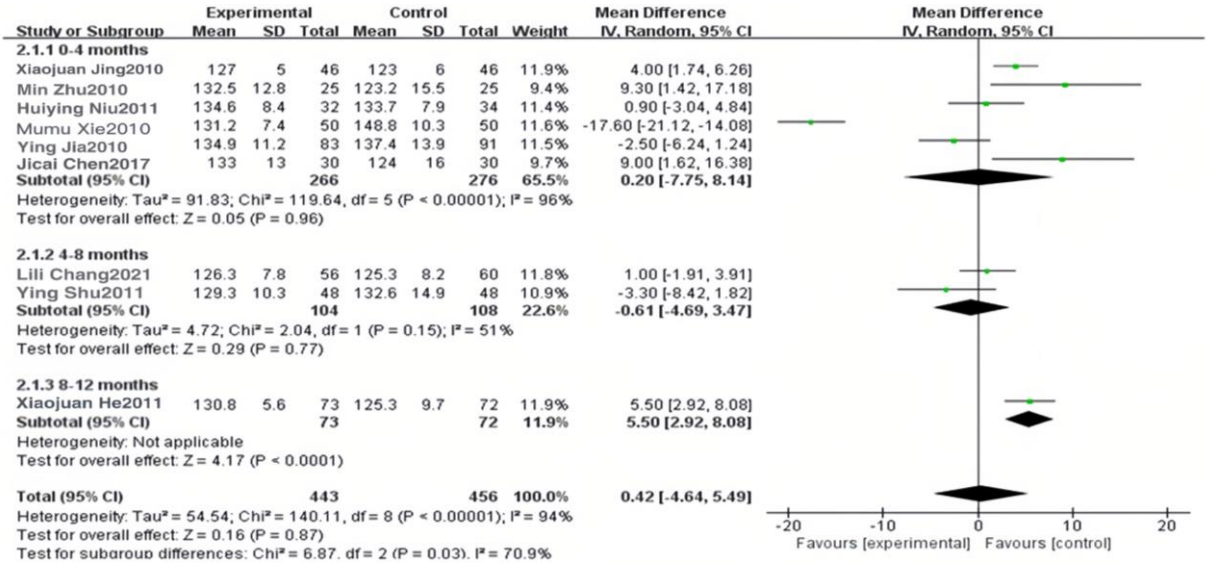

Figure 6 SBP forest plot of subgroup analysis

4. Discussion

Hypertension has become a global health threat, and the long-term state of hypertension leads to a continuous increase in the prevalence of cardiovascular and cerebrovascular diseases[13], stroke, myocardial infarction and other diseases have a very high mortality rate. The renal arteriosclerosis caused by hypertension will seriously affect the kidney function, causing kidney disease. What's more retinal conditions such as arteriosclerosis or retinal artery spasm are mainly caused by hypertension, which brings a heavy burden to the family and society[14]. For patients with hypertension, drug treatment is still the main antihypertensive method of treatment in the current clinic.

There are certain limitations in this meta-analysis:(1)each study is not completely unified in sample size, age, sex ratio, drug volume, course of treatment, and other aspects, such variation led low literature availability, which affected the effectiveness of the Meta-analysis;(2) Comprehensively, the methodological quality of the included studies was low, no clear statement was seen in random sequence generation, random hidden scheme, blind methods of research subjects and researchers, and blind methods of evaluators of results, or the implementation operation is different from the declared operation. These affected the objectivity of the outcome indicators may cause disruption to the credibility of the study findings; (3) Patients were given less long-term follow-up in each study, follow-up results and data were ambiguous. In addition, in the type of medication, the amount of medication, medication duration and many other aspects could not be controlled in the therapy. Therefore, the long-term effect of combination treatment on primary hypertension cannot be confirmed; (4) The written time of the included study is far apart from this study, in the past ten years, the domestic life and eating habits have changed greatly, the proportion of primary hypertension in young and middle-aged people is also increasing, new therapeutic drugs and combination regimens emerge in endlessly. All of these should be paid attention to by the researchers.

This study selected Amlodipine, Amiloride and Telmisartan from the commonly used effective drugs, and the results showed that the combination significantly reduced utility for primary hypertension. For the comparison of the controversial combination, the study concluded through meta-analysis that the combination was not found in the course of 4-48 weeks, and the different conclusions included in the literature may be affected by many factors, especially if the data may be incomplete or publication bias. Additional empirical studies and clinical data are needed.

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