



The effect of auricular therapy on blood pressure: A systematic review and meta-analysis

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Abstract

Background: Although a number of clinical studies have investigated the effectiveness and safety of auricular therapy for treating hypertension, the overall evidence remains uncertain.

Aims: We aimed to evaluate the evidence for the effect of auricular therapy on blood pressure using meta-analysis methodology.

Methods: We searched PubMed, Embase, Cochrane Library databases, Clinicalkey, China National Knowledge Infrastructure, China Scientific Journal Database and Wanfang Database and Chinese Biomedicine for trials that compared the effects of auricular therapy to that of sham auricular therapy, antihypertensive drugs, or no intervention on blood pressure. Blood pressure values before and after treatment, magnitude of blood pressure change between baseline and post-intervention, and the efficacy rate, as outcomes, were synthesized by RevMan 5.3. Continuous outcomes were expressed as weighted mean differences, and dichotomous data were expressed as relative risks with 95% confidence intervals.

Results: We systematically reviewed 44 randomized controlled trials (involving 5022 patients through June 2018). Auricular acupressure plus antihypertensive drugs might be more effective than antihypertensive drugs alone in both reducing systolic blood pressure value after treatment ($n=464$ patients; mean difference, -5.06 mm Hg; 95% confidence interval, -6.76 – -3.36 , $p<0.00001$; $I^2=32\%$), decreasing diastolic blood pressure after treatment ($n=464$ patients; mean difference, -5.30 mm Hg; 95% confidence interval, -6.27 – -4.33 , $p<0.00001$; $I^2=0\%$) and the efficacy rate (relative risk, 1.22 ; 95% confidence interval, 1.17 – 1.26 ; $p<0.00001$; $I^2=0\%$).

Conclusion: Auricular therapy could be provided to patients with hypertension as an adjunct to antihypertensive drugs for lowering blood pressure value and achieving blood pressure targets.

Keywords

Auricular therapy, blood pressure, non-pharmacological therapies

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Introduction

Hypertension, defined as values ≥ 140 mm Hg systolic blood pressure (SBP) and/or ≥ 90 mm Hg diastolic blood pressure (DBP), is considered an important and common modifiable risk factor for cardiovascular disease, stroke, renal failure, and death.¹ Overall the prevalence of hypertension appears to be around 30–45% of the general population, affecting over one billion people globally, with a steep increase with ageing. The worldwide prevalence of hypertension in individuals aged ≥ 25 years was estimated

to be approximately 40% in 2008.¹ This is equivalent to almost one billion people and is predicted to increase to over 1.5 billion people by 2025.² The prevalence of hypertension ranges from 24.59% in southern China³ to 36.0%

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in northeastern China,⁴ and 59.4% in Chinese patients aged ≥ 60 years to 72.8% in those aged ≥ 75 years.^{5,6} The current guidelines confirm that angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), calcium antagonists, beta-blockers, and diuretics are all suitable for the initiation and maintenance of antihypertensive treatment.^{7,8} However, the prevalence of resistant hypertension, when a therapeutic strategy that includes appropriate lifestyle changes and a diuretic and two other antihypertensive drugs (ADs) belonging to different classes at adequate doses fails to lower SBP and DBP values to <140 and 90 mm Hg respectively, has been reported to range from 5–30% of the overall hypertensive population, and these common ADs may have side effects, including dizziness, fatigue, headache, depressed mood, and sexual dysfunction.^{9,10}

Meanwhile, lifestyle changes and non-pharmacological therapies such as auricular therapy are considered complementary and alternative methods for hypertension treatment. Auricular therapy is a kind of method of treating physical and psychosomatic diseases by stimulating specific points of ears,^{11,12} which includes various ear stimulating methods like acupressure, acupuncture, electroacupuncture, laser acupuncture, moxibustion, and bloodletting via needles, seeds, magnetic stones, lasers, ultrasound, or massage.^{11,13} Auricular therapy has over 2000 years history of use in China, and Paul Nogier presented the inverted fetus map to describe the holographic theory in 1957,¹¹ which makes it possible to understand the theory of auricular therapy systematically and comprehensively. Since then, auricular therapy has become one of the most popular therapeutic methods in many Western countries.¹⁴ The manipulation of auricular therapy is based on the holographic theory, a sort of assumption that information regarding a part of the entire organism could be retrieved from the corresponding point of the ear, so that stimulation to a specific point of ear could ameliorate the function of the corresponding visceral organ or other part of the body.¹¹ Specifically, the earlobe targets the brain while the concha is related to the visceral organs, the scaphoid fossa refers to the upper extremities while the superior and inferior crus target the lower extremities.¹¹ Nogier believed that the underlying mechanism behind the connections between a part of the body and a point of the ear is related to the autonomic nervous system.¹¹ Despite its obscure mechanism, auricular therapy has been a convenient and fundamental method in traditional Chinese medicine used for returning the body to a harmonized, balanced state and relieving many common symptoms such as pain,^{15–17} fatigue,¹⁸ postoperative nausea and vomiting,¹⁹ hot flushes after cancer treatments,²⁰ xerostomia in maintenance hemodialysis patients,²¹ and some disorders like substance abuse,²² obesity,²³ anxiety,²⁴ sleep disorders,²⁵ and insomnia,²⁶ so that the World Health Organization

(WHO) has recognized it as a promising therapeutic approach for its effectiveness in managing a variety of disorders.²⁷

Auricular therapy is extensively applied by both doctors and nurses as a preventive-therapeutic method for hypertension in China. Although many clinical studies have been conducted to investigate the effectiveness of auricular therapy for treating hypertension, these studies have not yet been systematically summarized and the overall evidence is still uncertain. Herein, it is worthwhile to evaluate the evidence for the effectiveness and safety of auricular therapy for hypertension with a systematic review and to provide recommendations on future research and practice in this field.

Methods

The method used to conduct this systematic review has been previously registered in PROSPERO, an international database of prospectively registered systematic reviews, (CRD42016045832) which is available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016045832. This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Search strategies and selection criteria

The literature search was conducted in PubMed, Embase, Cochrane Library databases, Clinicalkey, China National Knowledge Infrastructure (CNKI), China Scientific Journal Database (VIP), Wanfang Database and Chinese Biomedicine (SinoMed) covering the period from inception to June 2018. Following the Participants, Interventions, Comparisons, Outcomes and Study design (PICOS) principle, the key search terms included hypertension, high blood pressure, essential hypertension, auricular therapy, ear acupoint, acupressure, acupuncture, electroacupuncture, bloodletting, laser acupuncture, laser, moxibustion and random.

Studies meeting the following criteria were included: (a) patients: adults (age >18 years old) with hypertension; (b) intervention: auricular therapy which includes acupressure, acupuncture, electroacupuncture, laser acupuncture, moxibustion, and bloodletting in the auricle; (c) comparison: sham auricular therapy, ADs or no intervention; (d) outcomes: blood pressure (BP) before and after treatment, magnitude of BP change between baseline and post-intervention and the efficacy rate; (e) study design: randomized controlled trial (RCT). The exclusion criteria were as follows: (a) patients with comorbidities and complications of hypertension; (b) trials comparing different methods of auricular therapy

Three researchers (CL, HQH, and QYH) independently screened all records according to the inclusion and exclusion criteria. Any inconsistencies were resolved by

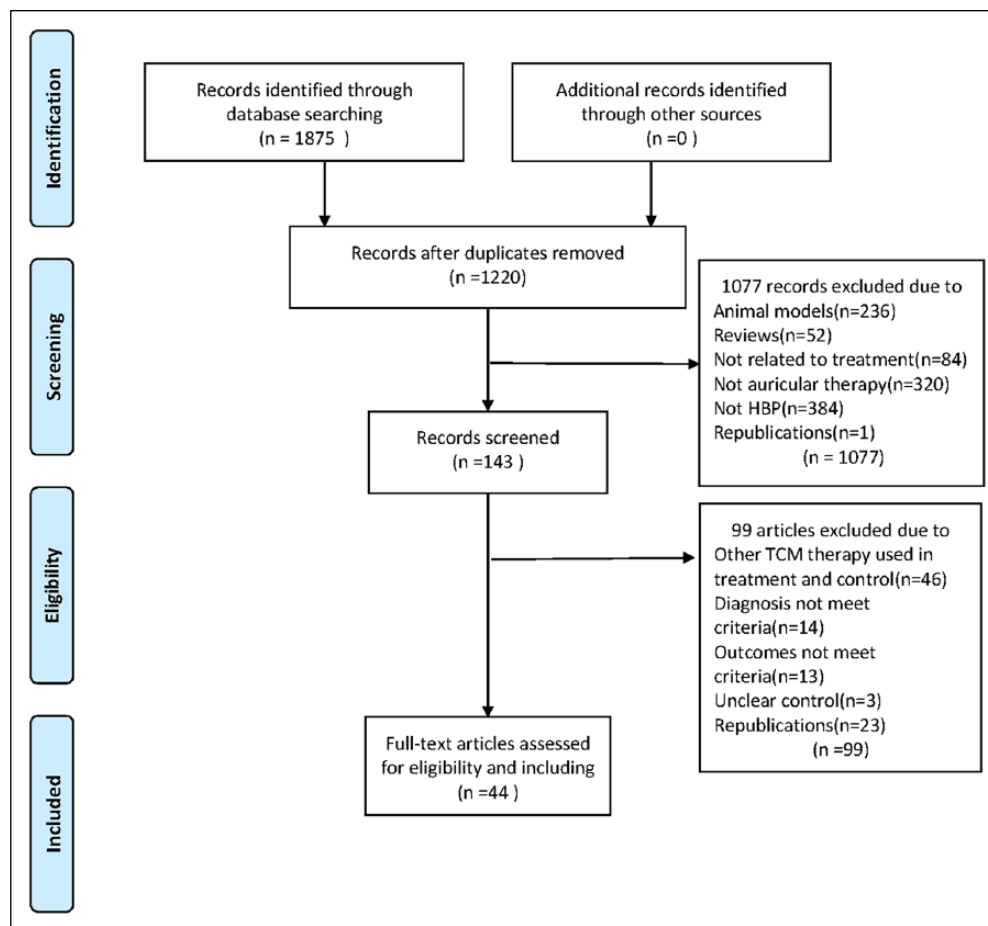


Figure 1. Flow diagram of literature search and selection. HBP: high blood pressure; TCM: traditional Chinese medicine.

discussion among the three authors and were arbitrated by a fourth author (JL). Finally, we identified 44 qualified RCTs that were included in the current analysis.^{28–71} The complete process and the exclusion reasons are shown in Figure 1.

Data extraction and quality assessment

Two investigators (CL, HQH) reviewed the full text of the eligible RCTs and extracted information. The information included setting (in/out patients), diagnostic criteria, sample size, average age, intervention, comparison, outcomes, withdrawal/dropout, and adverse events. All information was double-checked by referring to the original articles when an inconsistency existed.

The quality of the included RCTs was assessed by two investigators (CL, HQT) independently using Cochrane Collaboration's tool for assessing the risk of bias.⁷² Based on the authors' description in the original references, the quality of each of the included studies was classified as having a low, unclear, or high risk of bias, according to the items for judging risk of bias in the 'Risk of bias' assessment tool in the Cochrane handbook.⁷³ Disagreements were

resolved by discussing with the third author (GC) and reaching a consensus among authors.

Data synthesis and analysis

RevMan 5.3.0, the standard software provided by the Cochrane Collaboration, was employed to analyze the results of the RCTs. The meta-analysis model was performed when the patients, interventions, controls, and outcomes were the same or similar and the corresponding data were sufficiently homogeneous,⁷⁴ while results of RCTs were described separately if significant heterogeneity existed. Continuous outcomes were expressed as weighted mean differences (WMDs), and dichotomous data were expressed as relative risks (RRs) with 95% confidence intervals (CIs). In the absence of significant heterogeneity, we explored the possible reasons and conducted a sensitive analysis if necessary. Heterogeneity across the trials was identified using both Chi-squared tests as well as I^2 , considering a value of $I^2 > 50\%$ as indicating substantial heterogeneity.⁷⁵ Funnel plots were generated to detect publication bias when there were more than 10 trials in one comparison.⁷⁶ When necessary data were available, subgroup analysis was conducted.⁷⁷ In order

Table 1. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) summary of 25 randomized controlled trials (RCTs) comparing auricular acupressure plus antihypertensive drugs (AAPADs) to antihypertensive drugs (ADs) alone in hypertension patients.

Patient or population: patients with hypertension

Settings: inpatients/outpatients

Intervention: AAPAD

Comparison: AD

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative effect(95% CI)	No. of participants(studies)	Quality of the evidence(GRADE)	Comments
	Assumed risk	Corresponding risk				
SBP change magnitude between baseline and post- intervention	AD The mean SBP change magnitude between baseline and post- intervention in the control groups was 135.73	AAPAD The mean SBP change magnitude between baseline and post- intervention in the intervention groups was 5.06 lower (6.76 to 3.36 lower)		929 (10 studies)	⊕⊕⊕⊖ Moderate^b	
DBP change magnitude between baseline and post- intervention	The mean DBP change magnitude between baseline and post- intervention in the control groups was 84.75	The mean DBP change magnitude between baseline and post- intervention in the intervention groups was 5.3 lower (6.27 to 4.33 lower)		929 (10 studies)	⊕⊕⊕⊖ Moderate^b	
Efficacy rate	Study population 731 per 1000 Moderate 740 per 1000	892 per 1000 (855–921) 903 per 1000 (866–932)	RR 1.22 (1.17–1.26)	2017 (21 studies)	⊕⊕⊕⊖ Low^{b,c}	

CI: Confidence interval; DBP: diastolic blood pressure; RR: risk ratio; SBP: systolic blood pressure; ROB: risk of bias.

GRADE Working Group grades of evidence: High quality: further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: we are very uncertain about the estimate.

^aThe basis for the assumed risk (e.g. the median control group risk across studies) is provided in these footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bAccording to the ROB graph (Supplementary Material Figure 1).

^cFunnel plot was asymmetrical.

to minimize bias in our findings and recommendations, we graded and assessed the available evidence by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Profiler (pro),^{78,79} with four levels of evidence: high, moderate, low, and very low.

Results

Characteristics of eligible studies

Forty-four studies involving 5022 participants were included. The characteristics of the included studies are summarized in Supplementary Material Table 1. The earliest study was conducted in 1990, while the

latest one was in 2016. The interventions included auricular acupressure and bloodletting in the auricle. The duration of the trials ranged from 20 min to 12 weeks. One trial²⁸ made a comparison between auricular acupressure and sham acupoint, nine trials^{29–37} between auricular acupressure and ADs, five trials^{36,38–41} between auricular acupressure and no intervention, 25 trials^{42–66} between auricular acupressure plus antihypertensive drugs (AAPADs) and ADs alone, one trial⁷⁰ between bloodletting in the auricle and no intervention, two trials^{68,71} between bloodletting in the auricle and ADs, three trials^{67–69} between bloodletting in the auricle plus ADs and ADs alone. In general, all of the trial patients had an average age of 40 years or more.

Methodological quality

All included trials were reported as parallel-group randomized trials, while only 17 trials (38.63%, 17/44) reported the method of sequence generation and, unfortunately, no trial described the process of allocation concealment. Only three trials mentioned the blinding process. For selective reporting, we made judgements by comparing the outcome measures mentioned in the methods section with the results from the original references: all trials were evaluated as low risk. Only four trials mentioned the drop-out of patients. No trial provided a pre-trial sample size estimation. The methodological quality is shown in Supplementary Material Figure 1.

Effects of the interventions

The graded quality of evidence in terms of the outcomes of SBP change, DBP change, and efficacy rate were identified for 25 RCTs (Table 1). Although a total of 44 RCTs were included in this review, of these only 25 RCTs were combined by meta-analysis due to their consistent comparison and high homogeneity, while others were analyzed by qualitative description which could not be given a graded quality of evidence.

Effect of auricular acupressure

As for the comparison of auricular acupressure and sham acupoint, only one trial²⁸ reported the efficacy rate in terms of this comparison, and found a statistical difference between auricular acupressure and sham acupoint, in favor of the experimental group ($n=55$ out of 60 patients; RR, 0.28; 95% CI, 0.10–0.47, $p=0.003$). Moreover, two trials reported the magnitude of BP change between baseline and post-intervention comparing auricular acupressure and ADs. One trial³⁴ comparing auricular acupressure to nifedipine gastrointestinal therapeutic system (GITS) found auricular acupressure was superior to ADs in reducing SBP ($n=118$ patients; MD, -0.92 ; 95% CI, -1.09 – -0.75 , $p<0.00001$), but there was no significant difference between two groups on decreasing DBP ($n=118$ patients; MD, -0.07 ; 95% CI, -0.23 – -0.09 , $p=0.40$). However, the other trial³⁶ comparing auricular acupressure to a kind of AD (the specific medicine is unclear) showed the AD had better effect on reducing SBP ($n=203$ patients; MD, 2.70; 95% CI, 2.37–3.03, $p<0.00001$) as well as on decreasing DBP ($n=203$ patients; MD, 2.50; 95% CI, 1.92–3.08, $p<0.00001$). In addition, five trials reported the outcome by measuring the SBP and DBP before and after the treatment, three found a significant difference between auricular acupressure and ADs in lowering SBP after treatment, in favor of the auricular acupressure group,^{29,31,33} and the others did not. The data of these three trials could not be pooled due to the different kinds of ADs used in the AD

groups. Four of five trials found auricular acupressure significantly effective in reducing DBP after treatment,^{29,31,34,37} and the data of these trials could not be pooled either due to high heterogeneity. Eight trials reported the efficacy rate by counting the number of those who had achieved BP targets after treatment. The meta-analysis from these eight trials showed that there is no statistical difference between groups in efficacy rate ($n=495$ out of 598 patients; RR, 0.99; 95% CI, 0.95–1.03, $p=0.62$; $I^2=0\%$). Furthermore, three trials reported the result from the comparison of auricular acupressure and no intervention, and found a significant difference between auricular acupressure and no intervention group in decreasing SBP, in favor of auricular acupressure,^{38,39,41} nevertheless the data of these trials could not be pooled due to high heterogeneity. In terms of DBP, two of three trials found a significant difference between the two groups and the other did not. Five trials reported the outcome of BP target achievement, and meta-analysis from four trials^{38–41} found a statistical difference between groups in achieving BP targets in favor of the auricular acupressure group ($n=247$ out of 238 patients; RR, 1.27; 95% CI, 1.05–1.55, $p=0.02$; $I^2=0\%$).

Effect of auricular acupressure combined with ADs

Within the comparison between AAPADs and ADs alone, 14 trials^{42,44,46,47,49,52,53,57,59–62,65,66} reported the BP value before and after treatment. Even when we used a random-effect model, heterogeneity was too large ($I^2=82\%$), which might have been due to clinical heterogeneity or low methodological quality. Then, we tried to find the existence of this heterogeneity, and found that if we excluded four trials^{44,47,52,61} with outliers of larger BP value before treatment, the meta-analysis showed AAPADs had a better effect on reducing SBP than ADs alone ($n=464$ patients; MD, -5.06 ; 95% CI -6.76 – -3.36 , $p<0.00001$; $I^2=32\%$) as well as DBP ($n=464$ patients; MD, -5.30 ; 95% CI -6.27 – -4.33 , $p<0.00001$; $I^2=0\%$), which are shown in Figures 2 and 3. Twenty-one trials reported the efficacy rate, and the efficacy rate in the AAPAD group was significantly higher than that in the control group with ADs alone (RR, 1.22; 95% CI, 1.17–1.26; $p<0.00001$; $I^2=0\%$), which is shown in Figure 4.

Effects of bloodletting

Two trials reported the efficacy rate comparing bloodletting in the auricle to ADs, and meta-analysis from these two trials showed that there is no statistical difference between the groups in efficacy rate (RR, 0.65; 95% CI, 0.28–1.51, $p=0.32$; $I^2=0\%$). One trial compared bloodletting in the auricle to no intervention, and found the efficacy rate in the experimental group significantly higher than that in the control group ($n=59$ out of 61 patients; RR, 5.1; 95% CI

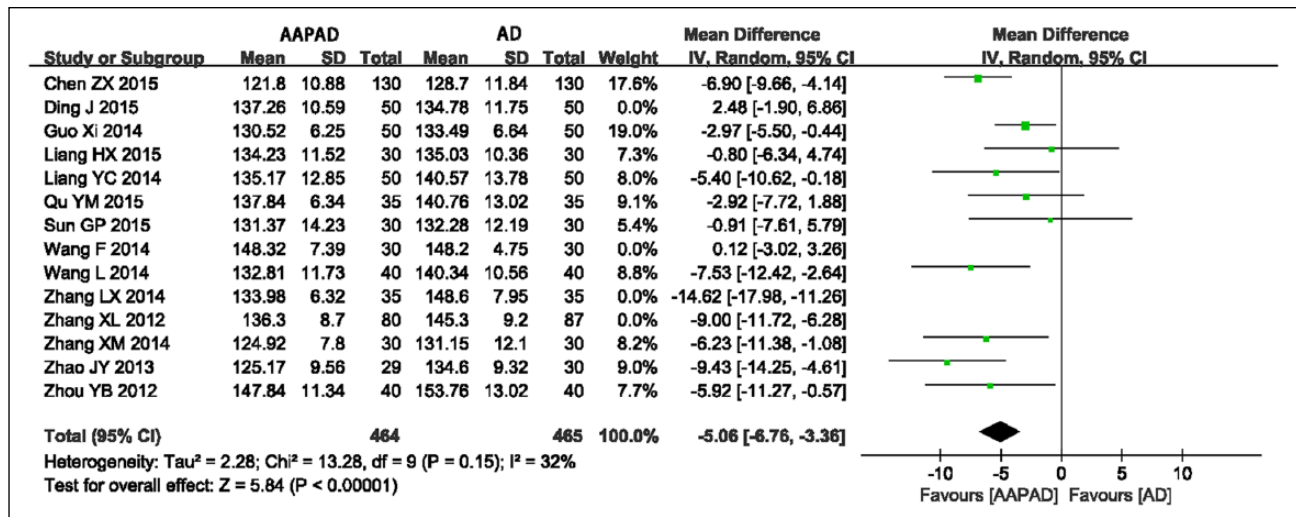


Figure 2. Forest plot of the comparison between auricular acupressure plus antihypertensive drugs (AAPADs) vs antihypertensive drugs (ADs) alone for the outcome systolic blood pressure (SBP) after treatment. CI: confidence interval; SD: standard deviation.

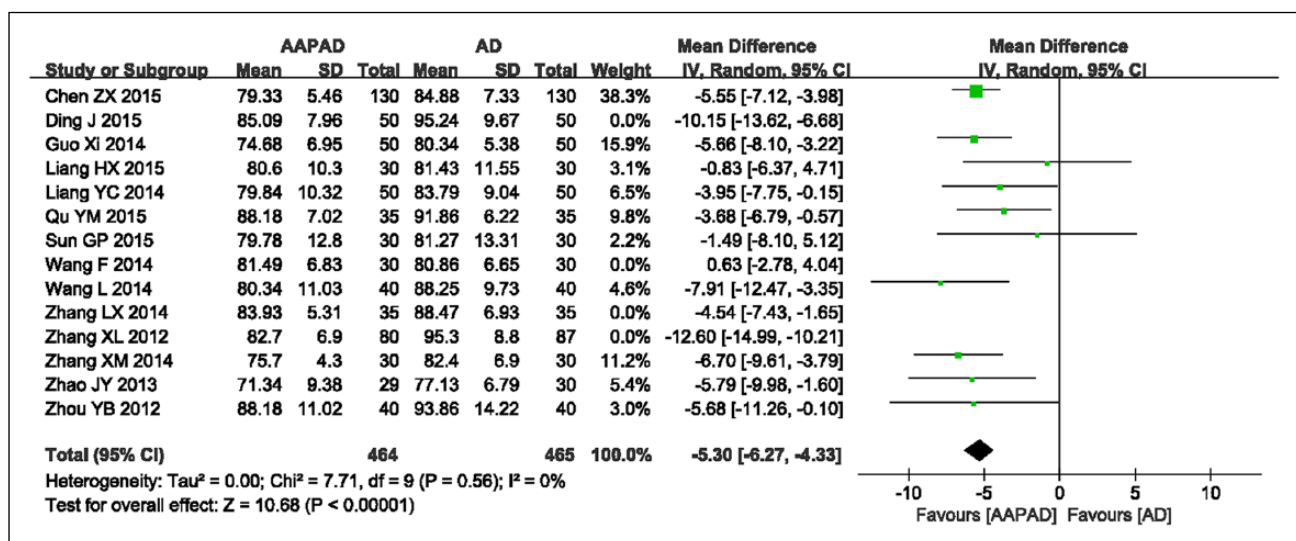


Figure 3. Forest plot of the comparison between auricular acupressure plus antihypertensive drugs (AAPADs) vs antihypertensive drugs (ADs) alone for the outcome diastolic blood pressure (DBP) after treatment. CI: confidence interval; SD: standard deviation.

1.05–24.71; $p=0.04$), and also found a significant difference between the two groups in lowering both SBP ($n=61$ patients; MD, -8.77 ; 95% CI -10.20 – -7.34 , $p<0.00001$) and DBP ($n=61$ patients; MD, -5.50 ; 95% CI -7.24 – -3.76 , $p<0.00001$). As for the comparison of bloodletting in the auricle plus ADs versus ADs alone, three trials reported the efficacy rate, and two of them found a statistical difference between groups, one⁶⁹ compared bloodletting in the auricle plus ADs to felodipine extended-release tablet or irbesartan alone ($n=156$ out of 178 patients; RR, 1.37; 95% CI, 1.21–1.55, $p<0.00001$); one study⁶⁷ used nifedipine in the control group ($n=57$ out of 60 patients; RR, 1.21; 95% CI, 1.05–1.40, $p=0.009$). One trial used amlodipine besylate

tablets in the control group and did not find a statistical difference between groups.⁶⁸

Safety

A total of 42 trials reported on this outcome. In all, four incidents were reported in the bloodletting in the auricle group, while four incidents were reported in the AD group. Side reactions included: hematoma at the bloodletting auricle ($n=2$ patients, 25%), red and swollen at the bloodletting auricle ($n=1$ patient, 12.5%), headache ($n=4$, 50%), palpitation ($n=1$ patient, 12.5%) and ankle edema ($n=1$ patient, 12.5%).

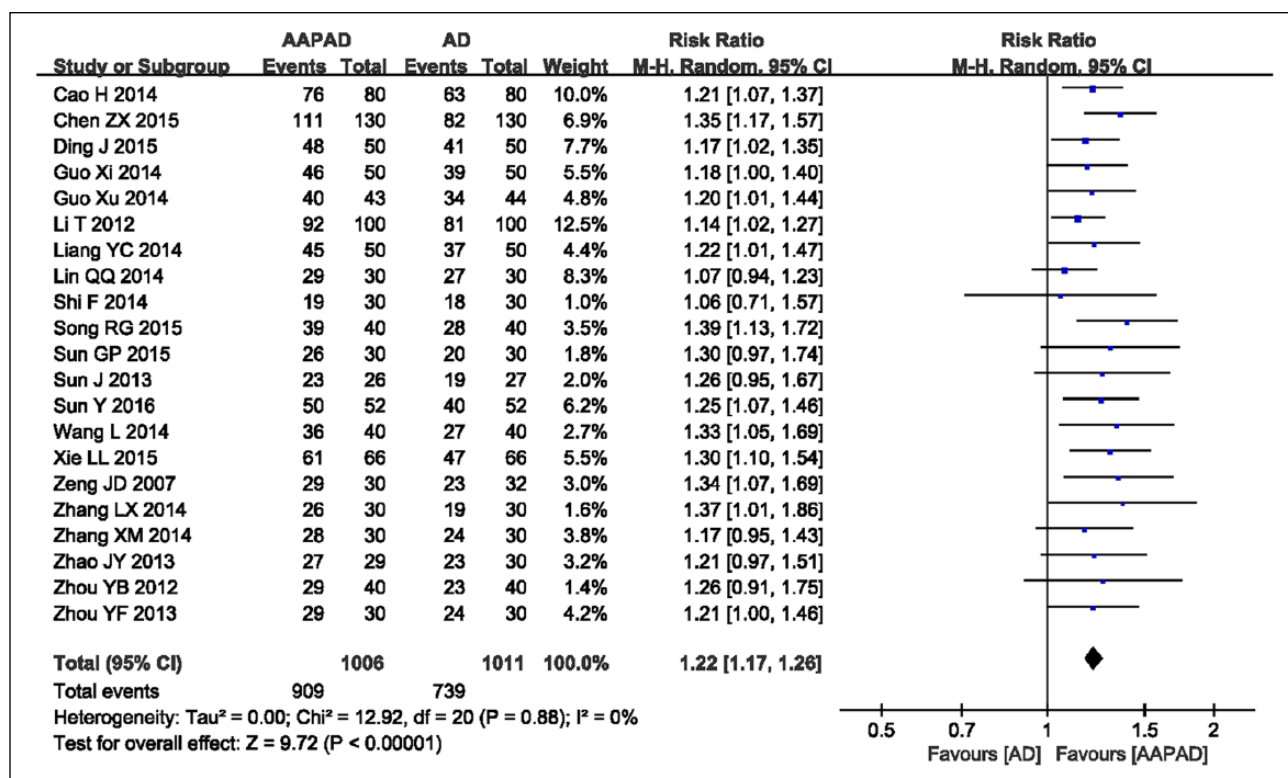


Figure 4. Forest plot of the comparison between auricular acupressure plus antihypertensive drugs (AAPADs) vs antihypertensive drugs (ADs) alone for the outcome efficacy rate. CI: confidence interval; SD: standard deviation.

Extent of publication bias

Conducting the funnel plot (Figure 5) for SBP and DBP after treatment between AAPADs and ADs alone suggested that no evidence of publication bias could be detected.

Discussion

This systematic review of auricular therapy for patients with hypertension provides a comprehensive summary of

such therapy as an alternative and adjunct to routine treatment. The results indicate that there were no consistent results neither in reducing BP nor in efficacy rate between auricular acupressure and ADs. However, auricular acupressure showed favorable changes in efficacy rate compared with sham acupoint and statistically significant changes in BP compared with no intervention. In addition, AAPADs manifest a significantly higher efficacy rate than that of ADs alone. Although the characteristics of included trials varied substantially in both the auricular acupoint

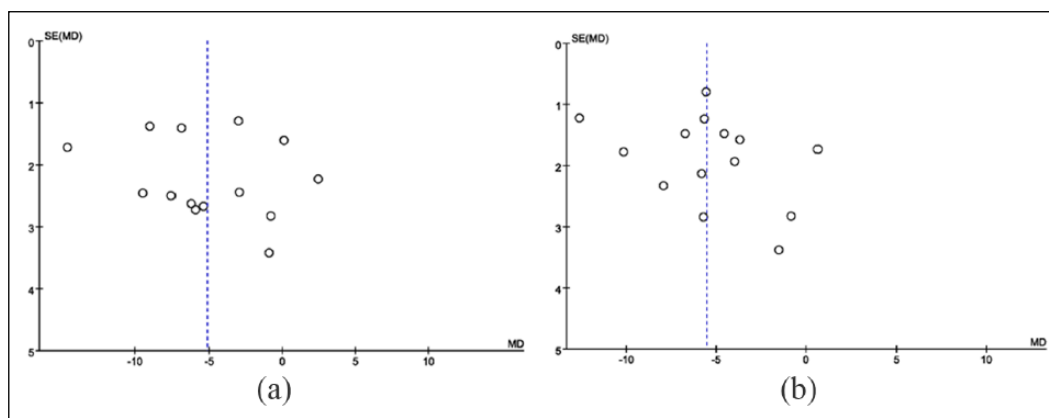


Figure 5. Funnel plot of 14 trials comparing (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP) after treatment. MD: mean difference; SE: standard error.

options and duration of the intervention, all of the included trials except for the comparison between auricular therapy and ADs demonstrated at least one benefit in terms of achieving better BP control.

The auricular therapy included in this systematic review was in diverse forms. Bloodletting in the auricle had better immediate effects than no intervention on both efficacy rate and lowering of BP and bloodletting in the auricle plus ADs showed a favorable difference in efficacy rate compared with ADs alone, while there was no statistical difference between bloodletting in the auricle and ADs in terms of efficacy rate. It is worth mentioning that the safety of bloodletting in the auricle should draw our attention, as it is a kind of traumatic intervention, despite the fact that such therapy has been applied in China for a long period of time.

This review identifies the evidence on effectiveness of auricular therapy based on 44 included trials, and presents a rigorous illustration of the findings, according to the protocol we had registered in PROSPERO, an international prospective register of systematic review, which has also been published. Furthermore, the GRADE summary is presented to assess the quality of the evidence for outcomes, which could contribute to increasing the possibility of adding this kind of therapy to the international guideline for preventing and management of hypertension.

The lack of evaluation of the long-term effectiveness and safety in the included trials limits the finding of such therapy for the primary outcome of hypertension management. In fact, the aim of both non-pharmacological and pharmacological treatment is to prevent adverse outcomes for which high BP is a risk factor, and to achieve better BP control. However, we could not draw a conclusion about the effects of preventing adverse outcomes for auricular therapy, which might be crucial when both the practitioners of this therapy and patients with hypertension weigh the potential benefits and harms before taking the decision to apply such therapy.

This review also has further limitations, partially due to poor methodological quality and insufficient reporting of procedures in the clinical trials that we included. Moreover, we could not make the subgroup analyses detecting the effects of age, disease duration, target auricles, or treatment course because of insufficient data, and a funnel plot for the majority of the included studies was unable to be used to detect potential publication bias due to insufficient number of trials in every comparison and outcome. However, evidence of immediate and long-term effectiveness from auricular therapy could not be found, which was limited mainly to absence of immediate observation and follow-up performance.

In the future, results from studies of high methodological quality which report sufficient outcomes are needed to draw definitive conclusions in terms of the effectiveness of auricular therapy. In further trials, data on all-cause mortality, cardiovascular mortality, cardiovascular morbidity

(non-fatal stroke, myocardial infarction, heart failure) are highly recommended for assessment of effectiveness of treatment of hypertension, while BP after bloodletting in the auricle may be measured immediately for assessment of its instant effectiveness. In addition, the possible effects of auricular therapy for sexual dysfunction caused by routine ADs needs more trials to evaluate.

Conclusions

Despite the significant variation in specific manipulation for auricular therapy and unsatisfactory methodological quality in this review, auricular therapy could be provided to patients with hypertension as an adjunct to AD for reducing BP value and achieving BP targets. Specifically, auricular acupressure, a kind of auricular therapy, showed favorable changes in efficacy rate compared with sham acupoint and statistically significant reductions in BP compared with no intervention, and when combined with routine AD treatment, it manifests a significantly higher efficacy rate than that of AD treatment alone. Bloodletting in the auricle, another auricular therapy, had a better effect than no intervention on both efficacy rate and lowering BP, and bloodletting in the auricle plus ADs showed a favorable difference in efficacy rate compared with ADs alone.

Implications for practice

1. Auricular therapy might significantly lower both systolic blood pressure (SBP) and diastolic blood pressure (DBP) values compared both with sham acupoint and with no intervention, but it is unclear whether this therapy could further lower blood pressure (BP) when compared with antihypertensive drugs (ADs).
2. Auricular therapy combined with ADs may be provided as a kind of alternative therapy to patients with hypertension for achieving BP targets.
3. Bloodletting in the auricle, one of the auricular therapy forms, might have an immediate effect of reducing BP value, while safety issues pertaining to this therapy should be stressed and monitored during the intervention period.

Author contributions

JLG and GC contributed equally to this work and would like to be recognized as co-primary authors. JLG, GC, and JW conceived and designed this study; JLG, GC, HQH, and CL performed this study; HQH, CL, QYH, and JL contributed resources to facilitate the analyses in this study; JLG and GC wrote this article. All authors have read and approved the final manuscript.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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