Systematic Review and Meta-Analysis

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Nondrug therapies for hypertensive patients complicated with cervical spondylosis

A systematic review and meta-analysis

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Abstract

Purpose: The aim of this study was to systematically evaluate the efficacy and safety of nondrug therapies for hypertensive patients complicated with cervical spondylosis.

Methods: Randomized controlled trials (RCTs) concerned with nondrug therapies for hypertensive patients complicated with cervical spondylosis were identified by searching 5 English and Chinese databases. Study selection, data extraction, and risk of bias assessment were conducted independently by 2 authors. RevMan 5.3 software was used for meta-analysis with effect estimate presented as relative risk (RR) and mean difference (MD) with a 95% confidence interval (CI).

Results: A total of 13 studies involving 929 patients were included. The majority of the included trials were assessed to be of high clinical heterogeneity and high risk of bias. The results of meta-analysis showed that there was a significant improvement in the effectiveness rate of cervical vertebra symptoms (RR = 1.67, 95% CI [1.33, 2.10], $P < .0001$), effectiveness rate of blood pressure lowering (RR = 1.35, 95% CI [1.06, 1.71], $P = .02$), systolic blood pressure reduction (MD = −11.05, 95% CI [−14.12, −7.98] mmHg, $P < .0001$), and diastolic blood pressure reduction (MD = −6.96, 95% CI [−8.89, −5.04] mmHg, $P < .00001$). Nondrug therapies had no significant difference compared with drugs in the effectiveness rate of overall improvement (RR = 1.3, 95% CI [0.93, 1.82], $P = .12$). There were no serious adverse effects related to nondrug therapies in the included trials.

Conclusion: The results show sound advantages of nondrug therapies over conventional medicine or sham procedure in efficacy. However, the evidence remains weak because of the high clinical heterogeneity and high risk of the included trials. Therefore, further thorough investigation, large-scale, proper-designed, randomized trials of nondrug therapies for hypertension complicated with cervical spondylosis are warranted.

Prospero registration number: CRD2019123175.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitors, ACS = acute coronary syndrome, ARB = angiotensin receptor blocker, CBM = the Chinese Biomedical Literature Database, CCB = scalcium channel blockers, CI = confidence interval, CNKI = the China National Knowledge Infrastructure, CSM = cervical spondylotic myelopathy, DBP = diastolic blood pressure, MD = mean difference, NUCCA = National Upper Cervical Chiropractic, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, RCTs = randomized clinical trials, RR = relative risks, SBP = systolic blood pressure, SCG = superior cervical ganglion, SD = standard deviation, TCM = traditional Chinese Medicine.

Keywords: cervical spondylosis, hypertension, meta-analysis, nondrug therapy, systematic review

1. Introduction

Hypertension is an important worldwide public-health challenge, which has been identified as the leading risk factor for mortality and ranked third as a cause of disability-adjusted life-years.[1] The data showed that 26.4% of the adults in 2000 had hypertension. Meanwhile, the proportion of people projected to have this condition by 2025 is 29.2%, suggesting that the prevention, detection, treatment, and control of this condition should receive high priority.[2]

The cervical spondylosis is an age-related degeneration disease. Previous studies showed that the proportion of cervical

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spondylosis was dropping with aging in the elderly, whereas increasing with aging in the young and the adults.[3] Cervical spondylosis not only affects the life quality, but also increases the economic burden, since high-cost surgery is a regular treatment method. Therefore, the cervical spondylosis might become a public health concern.[4]

During the last years, close relationship was observed between cervical spondylosis and cardiovascular diseases such as acute coronary syndrome, arrhythmia, and hypertension, which had attracted more and more close attention.[5–7] Akimura et al examined hypertensive patients with MR and compared them with normal blood pressure group. The results showed that 90.6% of vertebral arteries were compressed in essential hypertension group and only 22% in the control group.[8] Ning and Mo[9] analyzed cervical x-ray of 232 patients with and without hypertension and found that the incidence of cervical spondylosis was 83.0% in hypertension group and 42.5% in control group.

Nondrug therapies are main component of traditional Chinese Medicine (TCM), including manipulation, acupuncture, massage, needle-knife, Qigong, and so on. Nowadays, nondrug therapies have been widely used as alternative and effective methods for the treatment of hypertension complicated with cervical spondylosis in China. In recent years, many clinical studies in this field reported the therapeutic effect ranging from case reports and case series to randomized clinical trials (RCTs). However, there is no critically appraised evidence such as systematic reviews or meta-analysis on potential benefits and harms of nondrug therapies for hypertension complicated with cervical spondylosis to justify their clinical use and recommendation.

The aim of this systematic review is to assess RCTs testing the efficacy and safety of non-drug therapies for hypertensive patients complicated with cervical spondylosis.

2. Methods

This study was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (see Supplemental Content, http://links.lww.com/MD/D684. PRISMA 2009 checklist)[10] and was registered in PROSPERO (ID: CRD42019123175, https://www.crd.york.ac.uk/prospero/). Since this study is a secondary study of past clinical trials, the ethical approval is not necessary.

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria for studies. All paralleled RCTs were included to access the efficacy and safety of nondrug therapies for hypertension complicated with cervical spondylosis, regardless of blinding. There were no restrictions on population characteristics, language, and publication type.

2.1.2. Inclusion criteria for participants. Participants had been diagnosed as hypertension complicated with cervical spondylosis, regardless of the disease course and severity and meet the following criteria.

(a) Diagnostic criteria of hypertension: systolic blood pressure [SBP] ≥140 mmHg, or diastolic blood pressure [DBP] ≥90 mmHg;
(b) Diagnostic criteria of cervical spondylosis: Diagnosis of cervical spondylosis by computed tomography (CT), magnetic resonance imaging (MRI) and other imaging methods.

2.1.3. Inclusion criteria for the interventions. All the RCTs of nondrug therapies were included which were compared with no treatment, placebo, or drug therapy. RCTs combined nondrug with drug therapy compared with drug therapy were included as well. If these experimental groups used antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blocker (ARB), calcium channel blockers (CCBs), and so on, we included the trials as long as the drugs were used equally across the experimental and control groups.

2.1.4. Outcomes. Outcomes were effectiveness rate (blood pressure lowering, cervical vertebra symptoms improvement, overall improvement [including both blood pressure and cervical spondylosis]; SBP reduction and DBP reduction; and adverse effects.

2.1.5. Exclusion criteria. We excluded trials as follows: nondrug therapies were used in the control group; Quasi-randomized trials which methods of allocation use date of birth, date of admission, hospital numbers, or alternation; the secondary hypertension caused by craniocerebral injury, kidney, adrenal gland, goiter, and so on; duplicated publications reporting the same groups of participants; studies that could not be contacted with the author to judge the correctness of the randomization method; studies with incorrect randomization method; studies containing inaccurate or incomplete data.

2.2. Database and search strategy

RCTs assessing the administration of nondrug therapies for hypertensive patients complicated with cervical spondylosis were located by searching the following databases: PubMed, Embase, CBM, CNKI, and Wan Fang. All of those searches ended before January, 2019. The following search strategy was used for PubMed and modified to suit other databases.

PubMed search strategy:

- #1 hypertension [Me SH Terms]
- #2 blood pressure, high [Title/Abstract]
- #3 blood pressures, high [Title/Abstract]
- #4 high blood pressure [Title/Abstract]
- #5 high blood pressures [Title/Abstract]
- #6 OR #1-#5
- #7 cervical vertebra [Me SH Terms]
- #8 vertebrae [Title/Abstract]
- #9 cervical [Title/Abstract]
- #10 OR #7-#9
- #11 clinical trial [Publication Type]
- #12 #6 AND #10 AND #11

2.3. Selection of studies

Eligible studies were selected and checked independently by 2 authors (XW and JJ). Search results from different databases were imported into the document management software Note Express 2.0. Studies for inclusion were identified by the inclusion criteria. Repeated and nonrelevant studies were rejected by screening the titles and abstracts. The full text of studies of potential relevance to the review was downloaded. For the research in which randomization methods were not clearly described, we confirmed the validity by contacting the authors through telephone or email. A final decision was made on

whether to include the study. The 2 authors (XW and JJ) cross-checked the results with each other. Disagreements were resolved by discussing with a third author (HX).

2.4. Data extraction and risk of bias assessment

Two authors (XW and JJ) independently extracted the data from the selected studies. The extracted data included the author names, year of publication, study size, age and sex of the participants, disease duration, treatment process, details of the control interventions, outcomes, course, follow-up, and adverse effects for each study. The data were entered into an electronic database by the 2 reviewers separately to avoid duplicate entries. In the case where the 2 entries did not match, an inspection will be conducted and a third person may be involved for verification. Disagreement was resolved by discussion and reached consensus through a third author (HX).

Two reviewers (XW and JJ) independently assessed the risk of bias of each trial using a tool developed by the Cochrane Collaboration. The following types of bias were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias (defined as baseline data comparability). Each item was categorized as low/unclear/high risk of bias. Disagreements were resolved through discussion.

2.5. Data synthesis

Revman 5.3 software provided by the Cochrane Collaboration was used for data analysis. Dichotomous data were expressed as relative risks (RRs) and continuous data were expressed as mean differences (MD) both with 95% confidence interval (CI). Statistical heterogeneity was evaluated with the Cochran χ^2 and quantified with I^2. A random-effect model was used to estimate the overall effect instead of a fixed-effect model because the former weighs study outcomes according to within-trial as well as between-trial variance, thus providing a more conservative result.[11] To deal with possible heterogeneity and perform secondary analysis, subgroup analysis was conducted according to whether combined with antihypertensive drugs in the experiment group. Publication bias would be explored by funnel plot if sufficient studies were found.

3. Results

3.1. Description of included studies

As shown in Figure 1, the flow chart showed the search process and study selection. After primary searches from the above 5 databases, 618 articles were retrieved: CNKI (n = 108), CBM (n = 312), Wan fang database (n = 154), PubMed (n = 38), and Embase (n = 6). A total of 531 articles were screened after removing 87 duplicates. After reading the titles and abstracts, 488 articles were excluded. Full texts of 43 articles were retrieved and 30 articles were excluded with reasons listed as below: not randomized controlled trials (n = 2), participants did not meet the inclusive criteria (n = 2), duplication (n = 1), the control group was treated with nondrug therapies (n = 25). Finally, 13 RCTs were included. The selection process was summarized in a PRISMA 2009 flow diagram (Fig. 1).

3.2. General data of included studies

Thirteen independent studies were included. Two RCTs were published in English[12,13]; 11 RCTs were published in China.[14–24] The experimental groups included a total of 8 types of nondrug therapies, whereas some included ≥2 nondrug therapies, including acupuncture (n = 3), needle knife (n = 2), massage (n = 7), cervical traction (n = 1), Baduanjin (n = 1), fire needle (n = 1), spinal manipulation (n = 2), catgut-imbedding (n = 1). When it comes to the control measures, 2 studies used sham procedure,[12,13] 1 study used antihypertensive drugs in combination with drugs for cervical spondylosis,[15] other 10 studies used conventional antihypertensive drugs, including ACEI, ARB, and CCB.[14,16–24]

Ten trials[12,13,14–16,18,19,22–24] investigated nondrug therapies using alone versus drug therapy or sham procedure. Three trials[12,21,24] investigated nondrug therapies plus antihypertensive drugs versus drug therapy. A total of 929 participants with hypertension complicated with cervical spondylosis were included. The number of participants varied from 50 to 104 and the duration of treatment was between 10 days and 6 months. The primary characteristics of included trials were summarized in Table 1. All of the 13 trials used the blood pressure and cervical vertebra symptoms as the outcome measure.

3.3. Risk of bias assessment of included studies

The risk of bias assessment of included trials has been recorded in Table 2. The randomized allocation of participants was mentioned in all trials. However, only 6 trials[12,13,15,17–19] stated the methods for sequence generation including random number table and computer-generated random number. No detailed information was provided in the other 7 trials to judge whether or not it was conducted properly.[14,16,19–21,23,24] None of the trials mentioned the adequate allocation concealment. Three trials[12,13,19] mentioned blinding. One of them[19] only mentioned double-blinding but did not describe in detail. The other 2 trials[12,13] introduced the blinding in detail. None of trials had a pretrial estimation of sample size, which indicated the lack of statistical power to ensure appropriate estimation of the therapeutic effect. Two trials[12,20] reported dropout or withdraw. One study[20] reported 3 cases of voluntary withdrawal during the observation period and 2 cases were lost to follow. Another study[12] mentioned 1 case lost to follow-up in the third week. All trials provided baseline data for the comparability among groups. The results of the assessment of risk of bias were presented in a "risk of bias summary" figure produced by RevMan 5.3 automatically (Fig. 2).

3.4. The effectiveness rate of nondrug therapies for cervical vertebra symptom improvement

Two trials[17,18] reported the effect of cervical vertebra symptom improvement. Compared with drug therapy alone (RR = 1.67, 95% CI [1.33, 2.10], $P < .0001$, $I^2 = 0\%$), the nondrug therapies showed significant improvement in the cervical vertebra symptom. One trial[17] showed that nondrug therapies combined with drugs were more effective than drug therapy alone (RR = 1.59, 95% CI [1.14, 2.22], $P = .007$). Another trial[18] indicated that nondrug therapies alone also showed significant benefit in improving cervical vertebra symptom than using drugs alone (RR = 1.74, 95% CI [1.28, 2.38], $P = .0005$) (Fig. 3).

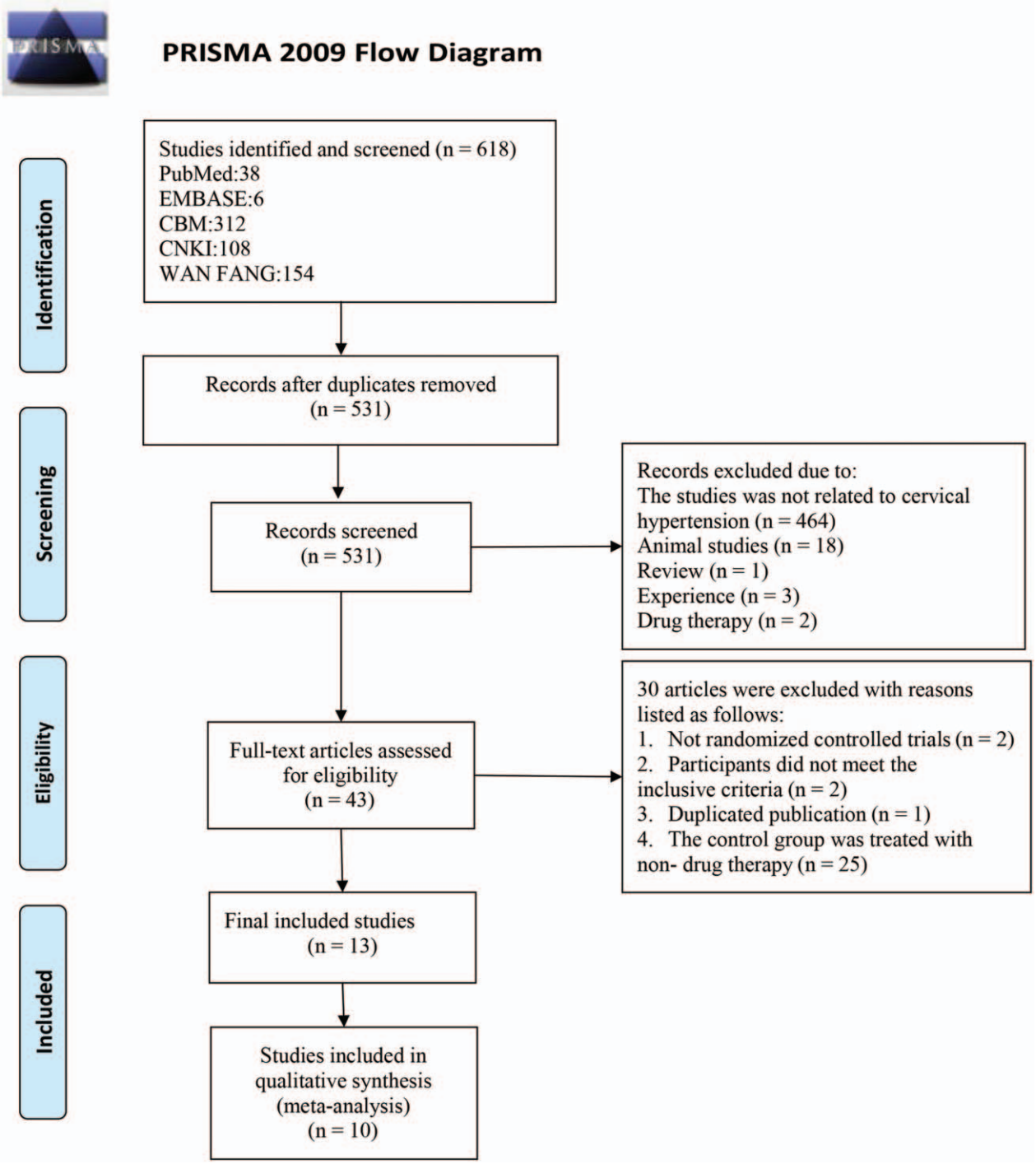

Figure 1. Flow diagram of the search method and selection process.

3.5. The effectiveness rate of nondrug therapies for overall improvement

Three studies reported the overall improvement[14,16,23] and all patients in the experimental group used nondrug therapies alone. No significant difference between nondrug and drug therapies was identified in overall improvement (RR = 1.30, 95% CI [0.93, 1.82], $P = .12$, $I^2 = 79\%$) (Fig. 4). One trial[16] failed to find a significant difference between the experimental and control group (RR = 0.99, 95% CI [0.82, 1.20]). The other 2 trials[14,23] demonstrated better effect favoring nondrug therapies.

3.6. The effectiveness rate of nondrug therapies for blood pressure lowering

Six studies reported the effectiveness rate of blood pressure lowering.[15,18,21–24] The result of Zhang[24] was negative among

Table 1

Summary of the characteristics of the included trials.

First author, year	No. of participants (R/A)	Female (%)	Age (mean ± SD), y	Disease duration	Intervention	Control	Course
Yu, 2018[14]	T 30/30 C 29/29	T 20 (66.67%) C 18 (62.07%)	T 46.82 ± 10.12 C 44.96 ± 11.02	T 4.75 ± 1.20 y C 5.0 ± 1.19 y	Needle knife, massage	Amlodipine besylate tablets 5 mg qd	1 mo
Kong and Shen, 2017[15]	T 48/48 C 48/48	T 19 (39.58%) C 21 (43.75%)	T 47.22 ± 13.05 C 46.73 ± 12.76	T 18.13 ± 10.33 mo C 17.94 ± 10.27 mo	Acupuncture	Jingfukang granule, felodipine sustained-release tablets 5 mg qd	28 days
Lu, 2009[16]	T 36/36 C 30/30	T 20 (55.55%) C 17 (56.67%)	T 30–60 C 40–58	T 10 days–2 yC 13 days–3 y	Cervical traction, acupuncture	Nifedipine sustained-release tablets 10 mg bid	20 days
Wang et al, 2018[17]	T 30/30 C 30/30	T 16 (53.33%) C 15 (50.00%)	T 50.68 ± 6.82 C 49.74 ± 6.94	T 6.28 ± 2.24 y C 6.16 ± 2.38 y	Baduanjin, oral Enalapril Maleate tablets 10 mg qd	Enalapril Maleate tablets 10 mg qd	6 mo
Zhu, 2013[18]	T 30/30 C 30/30	T 19 (63.33%) C 17 (56.67%)	T 41.85 ± 5.75 C 43.32 ± 4.80	T 1.27 ± 0.75 y C 1.33 ± 0.62 y	Massage	Nifedipine sustained-release tablets 20 mg qd	1 mo
Chen, 2018[19]	T 52/52 C 52/52	T 25 (48.08%) C 28 (53.85%)	T 46.82 ± 10.12 C 44.96 ± 11.07	T 8.64 ± 1.96 y C 9.02 ± 2.13 y	Massage	Nifedipine sustained-release tablets 20 mg qd	1 mo
Abdosalam et al, 2014[20]	T 45/45 C 46/46	T 7 (15.56%) C 8 (17.39%)	T 48.96 ± 6.93 C 49.93 ± 7.14	T HBP: 9 (7–16) y, CS: 8 (5–13) y C HBP: 10 (7–15) y, CS: 9 (6–15) y	Massage, conventional antihypertensive drugs	Conventional antihypertensive drugs	3 mo
Lv, 2012[21]	T 32/32 C 31/31	Unclear	18–70	Unclear	Massage, oral Nifedipine sustained-release tablets 20 mg qd	Nifedipine sustained-release tablets 20 mg qd	4 wk
Wang et al, 2014[22]	T 50/50 C 50/50	T 29 (58.00%) C 26 (52.00%)	T 48.3 ± 3.4 C 42.3 ± 2.6	T 0.25–2 y C 0.1–2 y	Fire needle, spinal manipulation	Nifedipine controlled release tablets 30 mg qd	20 days
Li and Rao, 2014[23]	T 30/30 C 30/30	32 (53.33%)	30–70	10 days–5 y	Sequential therapy (needle knife, massage, Catgut-imbedding)	Felodipine tablets 5 mg qd	10 days
Zhang, 2017[24]	T 35/35 C 35/35	T 18 (51.43%) C 16 (45.71%)	T 31–50 C 32–50	T 7 –66 wk C 7–66 wk	Acupuncture	Levamlodipine besylate tablets 2.5 mg qd	1 mo
Goertz et al, 2016[12]	T 24/24 C 27/26	T 9 (37.5%) C 12 (44.44%)	T 57.6 ± 8.5 C 54.9 ± 12.1	Unclear	Toggle recoil spinal manipulation	Sham procedure	6 wk
Bakris et al, 2007[13]	T 25/25 C 25/25	T 10 (40.00%) C 5 (20.00%)	T 53.6 ± 8.3 C 51.8 ± 10.9	Unclear	NUCCA	Sham procedure	2 mo

A = number subjects analyzed, bid = twice a day, C = control, CS = cervical spondylosis, NUCCA = national upper cervical chiropractic, qd = once a day, R = number subjects randomized, T = treatment, tid = three times a day.

Table 2

The risk of bias assessment of included trials.

First author, year	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Baseline data comparability
Yu, 2018[14]	Unclear	Unclear	Unclear	No	No	Yes
Kong and Shen, 2017[15]	Random number table	Unclear	Unclear	No	No	Yes
Lu, 2009[16]	Unclear	Unclear	Unclear	No	No	Yes
Wang et al, 2018[17]	Random number table	Unclear	Unclear	No	No	Yes
Zhu, 2013[18]	Random number table	Unclear	Unclear	No	No	Yes
Chen, 2018[19]	Unclear	Unclear	Double blind	No	No	Yes
Abdosalam et al, 2014[20]	Unclear	Unclear	Unclear	Yes	No	Yes
Lv, 2012[21]	Unclear	Unclear	Unclear	No	No	Yes
Wang et al, 2014[22]	Random number table	Unclear	Unclear	No	No	Yes
Li and Rao, 2014[23]	Unclear	Unclear	Unclear	No	No	Yes
Zhang, 2017[24]	Unclear	Unclear	Unclear	No	No	Yes
Goertz et al, 2016[12]	Computer-generated random number	Unclear	Double blind	Yes	No	Yes
Bakris et al, 2007[12]	Random number table	Unclear	Double blind	No	No	Yes

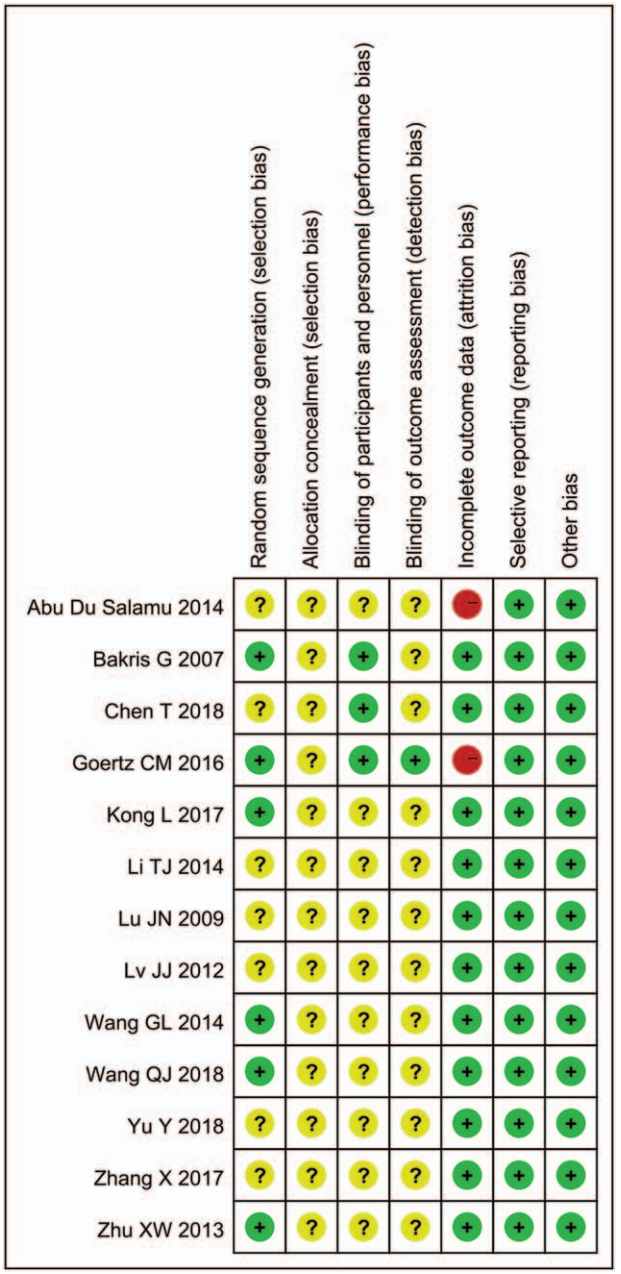

Figure 2. Risk of bias summary (presentation of the risk of bias summary of the review author's judgments about each risk of bias item for each included study).

the 6 studies. Pooled data of the 6 trials found that nondrug therapies were more effective than drugs alone (RR = 1.35, 95% CI [1.06, 1.71], $P = .02$, $I^2 = 85\%$) (Fig. 5). Subgroup analysis showed that either nondrug therapies ($RR = 1.32$, 95% CI [1.01, 1.72], $P = .04$, $I^2 = 87\%$) or plus drugs (RR = 1.54, 95% CI [1.08, 2.19], $P = .02$) appeared more effective than drug therapies alone.

3.7. The efficacy of nondrug therapies on blood pressure

Meta-analysis of 5 studies[15,17–19,24] showed that nondrug therapies demonstrated a superior effect in SBP reduction (MD = −11.05, 95% CI [−14.12, −7.98] mmHg, $P < .00001$) (Fig. 6A). Subgroup analysis of studies which used nondrug therapies alone[15,18,19,24] revealed a greater SBP reduction than control group (MD = −11.63, 95% CI [−15.11,−8.05] mmHg, $P < .00001$). Subgroup analysis of the remaining studies which used nondrug plus drug therapies[17] also showed significant difference between the experimental and control groups (MD = −7.40, 95% CI [−13.93, 0.87] mmHg, $P = .03$).

Meta-analysis of 5 studies[15,17–19,24] about the efficacy of nondrug therapies on DBP also showed a significant difference between the experimental and control groups (MD = −6.96, 95% CI [−8.89,−5.04] mmHg, $P < .00001$) (Fig. 6B). Subgroup analysis of studies which used nondrug therapies alone[15,18,19,24] revealed a significant difference between the treatment and control groups. The results indicated that nondrug therapies were more effective in reducing DBP than drug therapies alone (MD = −6.41, 95% CI [−7.66, −5.17] mmHg, $P < .00001$). Similarly, subgroup analysis of nondrug plus drug therapies[17] was also significant (MD = −13.10, 95% CI [−18.35, −7.85] mmHg, $P < .00001$).

We had originally intended to include the 3 trials[12,13,20] to conduct this meta-analysis. However, statistical and clinical heterogeneity prevented us from doing so. The descriptions of the 3 individual studies are as follows. The Chinese study[20] tested the therapeutic effects of massage on controlling SBP in patients with hypertension complicated with sympathetic cervical spondylosis. A total of 91 patients were randomized into 2 groups, namely massage invention group (n = 45) and antihypertensive drugs (control) group (n = 46). The result showed that massage intervention had certain curative effect on controlling SBP in patients with hypertension complicated with sympathetic cervical spondylosis ($P < .005$), but may not have definite effect on controlling DBP ($P > .05$). One of the 2 English trials[12] investigated the effects of toggle recoil spinal manipulation in participants with prehypertension or stage 1 hypertension. A total of 51 patients were allocated by an adaptive design to 2 treatments: toggle recoil spinal manipulation (n = 24) or a sham procedure (n = 27). Adjusted mean change from baseline to week 6 was greater in the sham group (systolic, −4.2 mmHg; diastolic,−1.6 mmHg) than in the spinal manipulation group (systolic, 0.6 mmHg; diastolic, 0.7 mmHg), but the difference was not statistically significant. Another English study[13] assessed the effectiveness of National Upper Cervical Chiropractic (NUCCA) on blood pressure reduction. A total of 50 hypertensive patients complicated with Atlas misalignment (through supine leg-length check protocol) were divided randomly into 2 groups, namely NUCCA group (n = 25) and placebo (control) group (n = 25). This study cohort had a mean age 52.7 ± 9.6 years, consisted of 70% males. At week 8, there were differences in SBP (−17 ± 9 mmHg, NUCCA versus −3 ± 11 mmHg, placebo; $P < .0001$) and DBP (−10 ± 11 mmHg, NUCCA vs −2 ± 7 mmHg; $P = .002$). This study concluded that restoration of atlas alignment was associated with marked and sustained reductions in blood pressure, which was similar to the use of 2-drug combination therapy.

3.8. Assessment of publication bias

We conducted funnel plots to detect the publication bias (Fig. 7A and B). It demonstrated asymmetrical funnel plots, suggesting potential publication bias. The funnel plots were made according to trials which used SBP or DBP as outcomes.

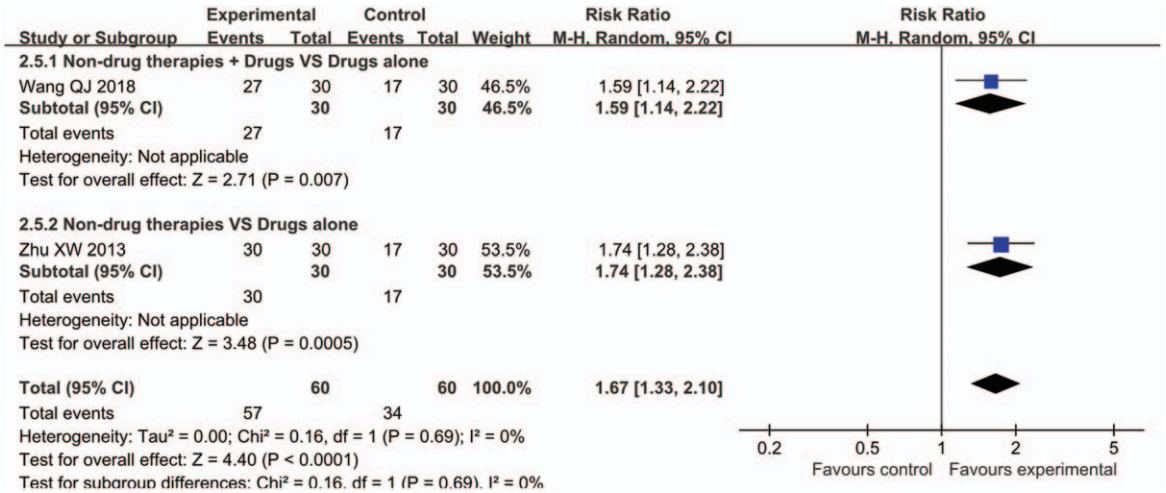

Figure 3. Forest plot of the effectiveness rate of nondrug therapies for cervical vertebra symptom improvement.

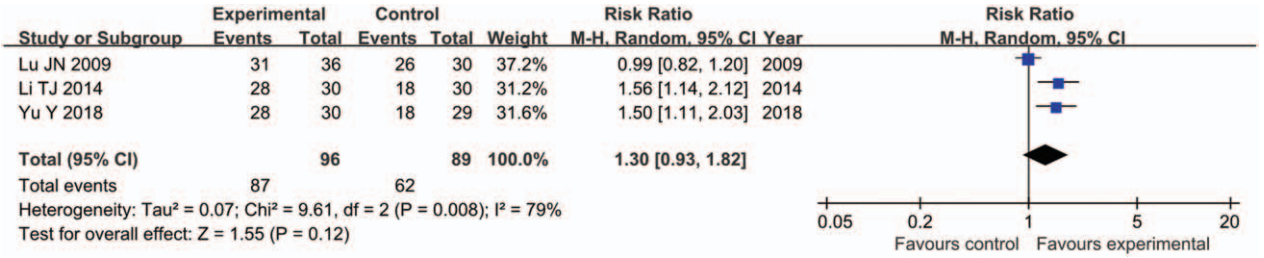

Figure 4. Forest plot of the effectiveness rate of nondrug therapies in overall improvement.

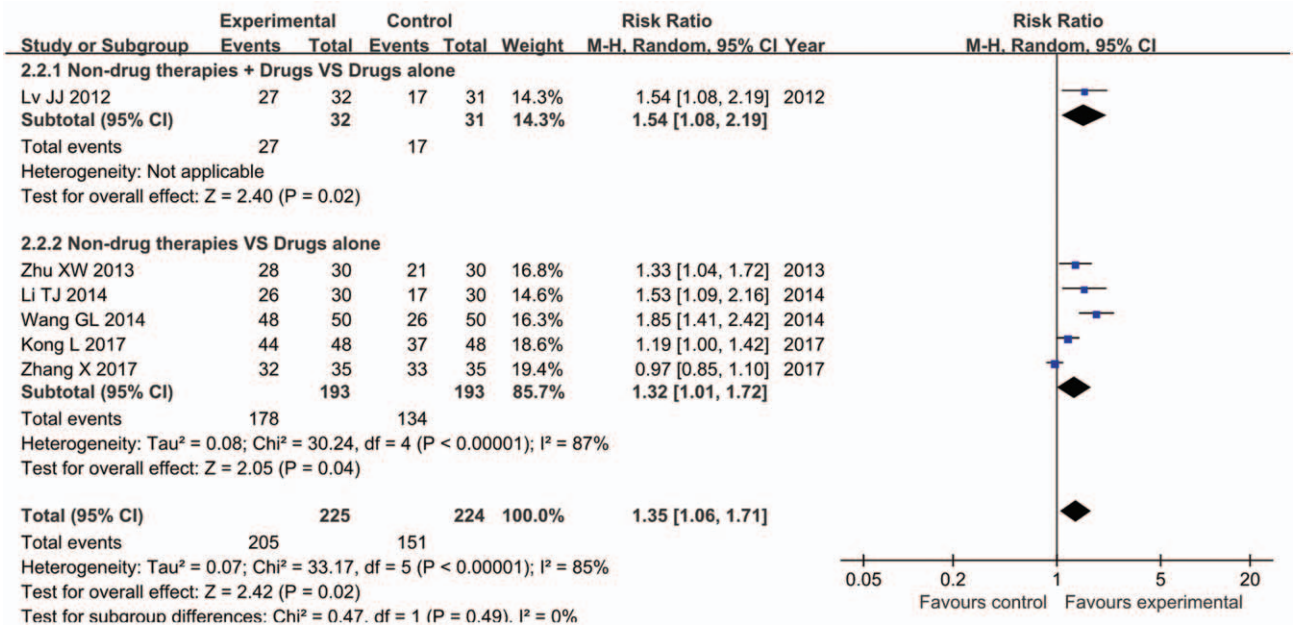

Figure 5. Forest plot of the effectiveness rate of nondrug therapies for blood pressure lowering.

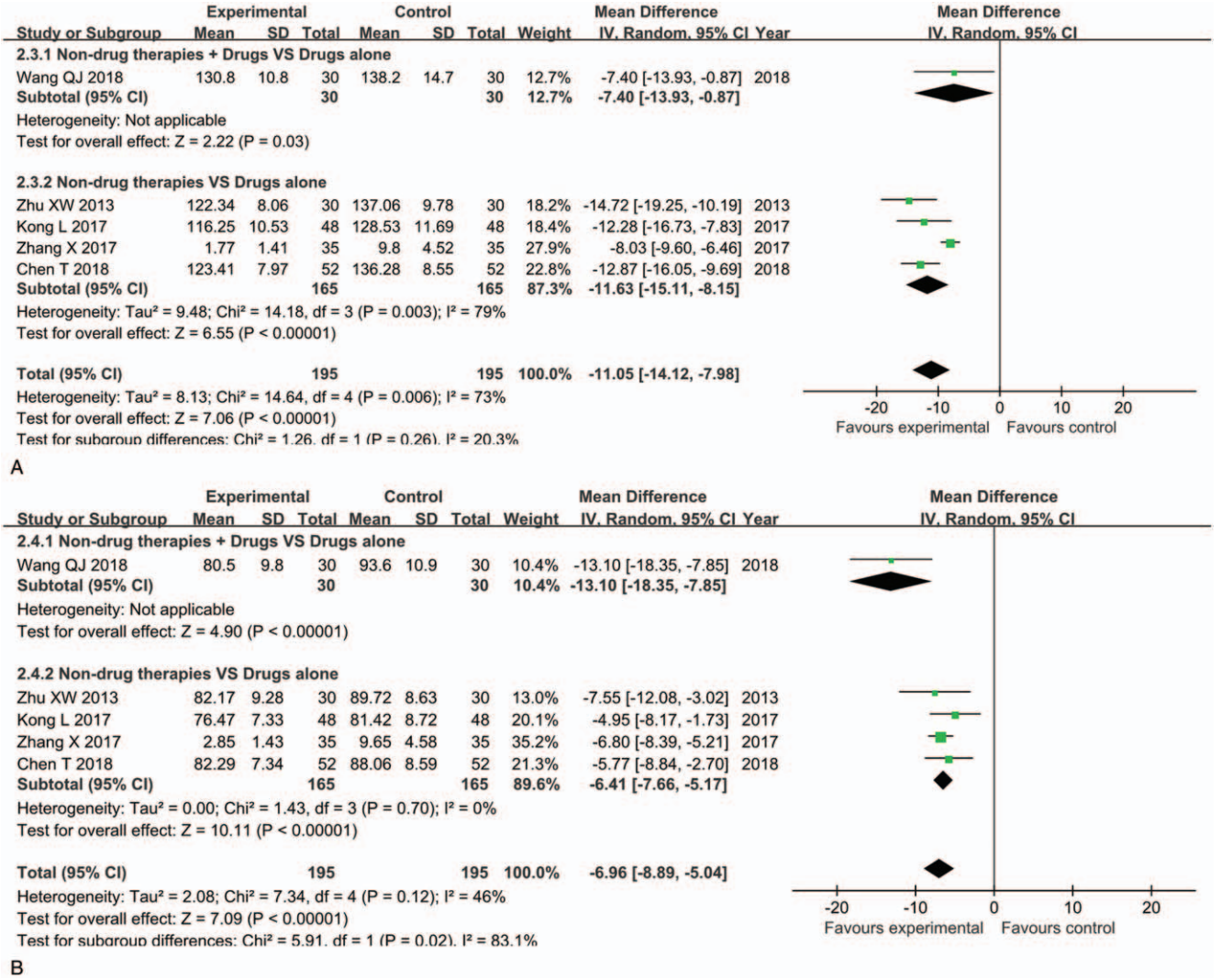

Figure 6. a Forest plot of the efficacy of nondrug therapies on systolic blood pressure (A). Forest plot of the efficacy of nondrug therapies on diastolic blood pressure (B). Notes: SD = standard deviation.

3.9. Adverse effect

Among the 13 trials, 8 trials did not report information about adverse events,[14–16,19,20,22–24] 3 trial reported that none of the participants had any advertise events,[13,17,21] and the remaining 2 trials described the adverse events in detail.[12,18] One study[18] reported headache aggravation, dizziness aggravation in the control group, and illustrated that massage was safer compared with taking antihypertensive drugs. Another case reported 4 adverse events related to study treatments resolved within 48 hours and required only self-care: 3 headaches of mild to moderate severity and 1 episode of neck and upper thoracic pain and muscle tension of moderate severity.[12] No trial reported severe adverse events possibly related to nondrug therapies.

4. Discussion

4.1. Summary of evidence

In this systematic review, 13 studies were included and 10 studies were put into meta-analysis to explore the efficacy of nondrug therapies for hypertensive patients complicated with cervical spondylosis. In this review, we found that compared with conventional drugs or sham procedure, nondrug therapies demonstrated a potential beneficial effect on relieving cervical vertebra symptom (RR = 1.67, 95% CI [1.33, 2.10], $P < .0001$), the effectiveness of blood pressure lowering (RR = 1.35, 95% CI [1.06, 1.71], $P = .02$), SBP reduction (MD = −1.05, 95% CI [−14.12, −7.98] mmHg, $P < .0001$), and DBP reduction (MD = −6.96, 95% CI [−8.89, −5.04] mmHg, $P < .00001$).

The subgroup analysis showed that the nondrug therapies were not inferior or even superior to conventional drugs regardless of whether combined with antihypertensive drugs or not, although it was possibly because of the small sample size, flawed methodology of the included trials, and the no or short follow-up duration. Combination of drug and nondrug therapies can further help reduce blood pressure.

As an important composition of TCM, nondrug therapies have made great contributions to essential hypertension,[25–27] including acupuncture, massage, auricular point sticking, and so on. A meta-analysis[28] found that nondrug therapy combined

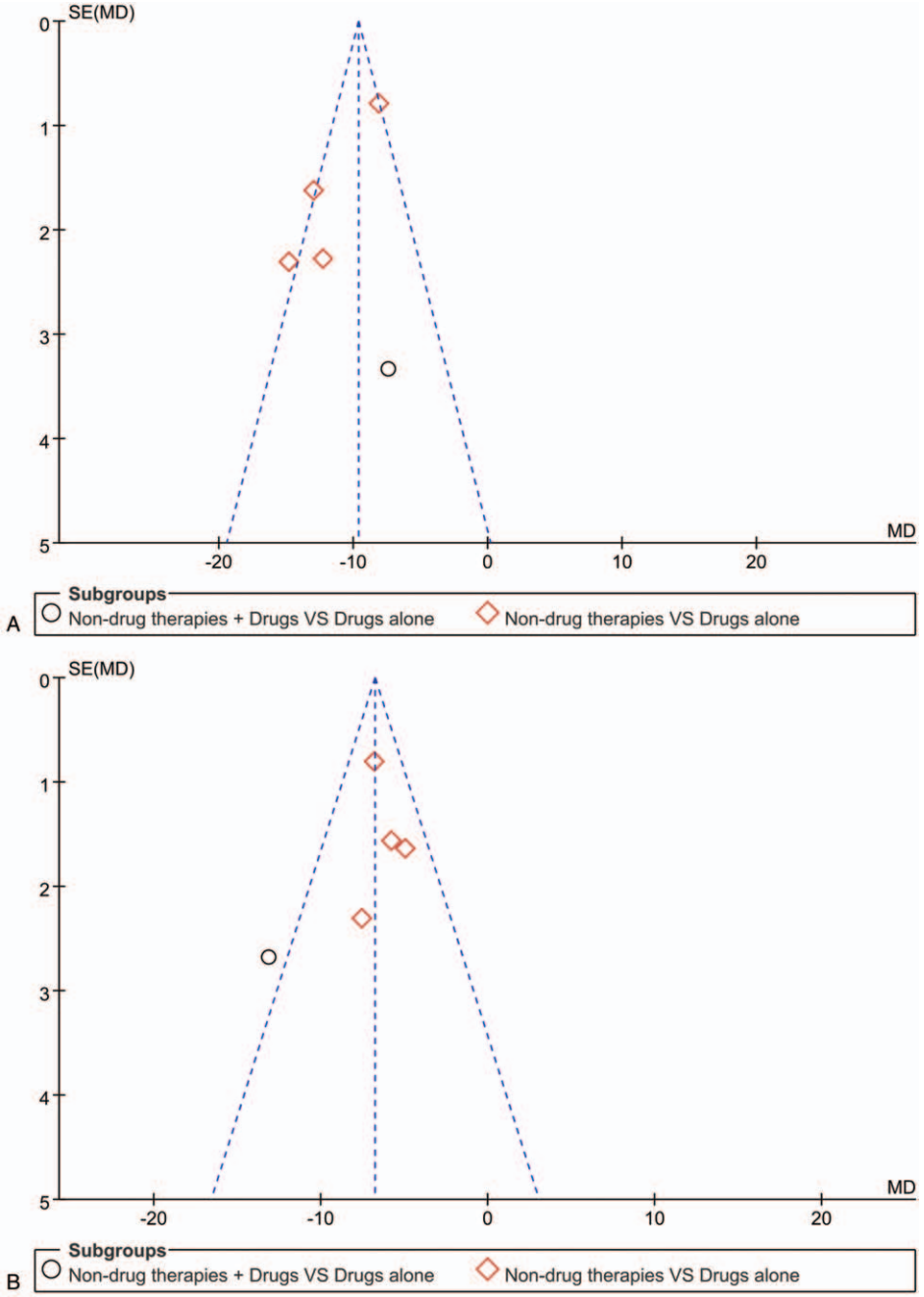

Figure 7. (A) Funnel plot of the efficacy of nondrug therapies on systolic blood pressure for assessing publication bias. (B) Funnel plot of the efficacy of nondrug therapies on diastolic blood pressure for assessing publication bias.

with drug therapy for the treatment of essential hypertension was superior to drug therapy alone. Nondrug therapies are also effective for cervical spondylosis.[29–31] However, there is no systematic review evaluating nondrug therapies for hypertension complicated with cervical spondylosis until now, so it is necessary to conduct this study. As far as we know, this is the first systematic review and meta-analysis of RCTs in this field.

4.2. Cervical spondylosis and hypertension

The occurrence of hypertension complicated with cervical spondylosis is very common as such patients accounted for 6.7% of cervical spondylosis and 15% to 21.9% of hypertensive patients.[32] Cervical spondylosis is reported to be associated with increased sympathetic activity and hypertension.[6] One research showed that persistent hypertension in outpatients was associated with worsened clinical status and increased markers of spinal cord damage on magnetic resonance imaging (MRI).[33] It is known that the excitability of sympathetic nerve is closely related to hypertension.[34] Sympathetic cervical spondylosis is one of the most common types of cervical spondylosis and the main mechanism is considered as cervical instability and sympathetic nerve compression.[35] Meanwhile, superior cervical ganglion (SCG) plays an important role in the formation of hypertension.

Preganglionic fibers of SCG originate in the lateral horn of the spinal cord from T1 to T6 in the upper thoracic segment and are directly related to the ventrolateral medulla cephalic area (pressor area) of the autonomic nervous center in the brain stem through the spinal cord.[36] Some studies found that stimulations of rabbit anterior cervical ganglion but not tractions of vertebral artery would induce increasement of blood pressure.[37–40]

Many reports showed that treatment of cervical spondylosis can help control blood pressure effectively. Liu et al[41] found that the high blood pressure in 12 of 30 (40%) hypertensive patients was reduced to normal levels following the cervical decompressive surgery, which resulted in a termination of the antihypertensive medications. They also designed a time series cohort study about the effects of decompressive cervical surgery on blood pressure in cervical spondylosis patients with hypertension in 2016, to make contributions for the development of new methods of hypertension treatment and prevention. Peng et al[42] reported 2 patients of cervical spondylosis with concomitant cervical vertigo and hypertension who were treated successfully with anterior cervical discectomy and fusion. Itoki et al[43] reported 68 consecutive cervical spondylotic myelopathy (CSM) patients who underwent surgery with myoarchitectonic spinolaminoplasty and a significant blood pressure reduction was observed in the hypertension group 6 months after surgery, but not in the normotensive group. Yang et al[44] performed decompression surgery or conservative treatments on 135 CSM patients with concomitant hypertension and conducted follow-up assessments up to 1 year to examine the change of blood pressure, spinal cord function, and cervical pain. They found that cervical decompression surgery could reduce concomitant high blood pressure in CSM patients, indicating a significant association between the decrease in blood pressure and the improvement of spinal cord function.

The mechanism of nondrug therapies improving blood pressure by treating the cervical spine remains unclear. At present, it is believed that acupuncture plays a hypotensive role through multisystem, multitarget, and multilevel regulation mechanisms, including inhibition of central and peripheral sympathetic nerve activity, and so on.[45] Wang and Ding[46] held the view that massage could correct joint dislocation, restore the displaced vertebra to normal, and eliminate neck muscle spasm, so as to alleviate the cardiocerebrovascular spasm, improve the blood supply of brainstem reticular structure, and gradually reduce blood pressure to normal.

4.3. Limitations

Before recommending the conclusion of this review to clinical practice, we have to consider the following weaknesses.

First, there are a variety of nondrug therapies which are relatively broad concepts, including acupuncture, massage, Qigong, and so on. It is hard to evaluate the differences among various kinds of nondrug therapies. We took the clinical heterogeneity into consideration; thus, we used a random-effect model instead of a fixed-effect model to provide a more conservative conclusion. Until now, there are few researches estimating the effect of different nondrug therapies because even the same nondrug therapy may have some differences. For example, when it comes to acupuncture treatments, the selection of acupoints, the method of needling, the time of needling, and the length of needle retention will be somewhat different so that these factors could influence the results.[47,48]

Second, one of the limitations of our study is the high risk of the original studies, as it is likely to influence the reliability of final results. Most trials only provided inadequate reporting of study design, allocation sequence, allocation concealment, intention-to-treat analysis, and drop-outs account in the majority of trials.

Third, we noticed that the outcomes were not uniform in these current clinical trials, including various relevant indicators of cervical vertebra or blood pressure. It might be one of the factors that caused high clinical heterogeneity. For example, when estimating cervical spondylosis symptoms, the Neck Disability Index, Visual Analogue Score, or range of motion was used in different trials.

Fourth, the duration of treatment was from 10 days to 6 months. The difference of duration may have an impact on the meta-analysis results. Furthermore, some studies did not mention long-term follow-up and lack observation of long-term efficacy. A longer follow-up period with serial measurements of outcomes is suggested to determine the long-term efficacy of nondrug therapies.

Fifth, only 5 of the 13 trials mentioned adverse effect.[12,13,17,18,21] Even for the trials that reported adverse events, their reports were very brief, providing limited information. Therefore, a conclusion about the safety of nondrug therapies cannot be drawn clearly. Four trials[15,16,23,24] reported information on follow-up, but gave no details. To properly assess the safety of nondrug therapies, large-scale clinical trials with long-term follow-up are required.

In addition, all the trials did not describe the blinding in detail. It may directly lead to performance bias and detection bias due to patients and researchers being aware of the therapeutic interventions for the subjective outcome measures. In non–placebo-controlled and non–double-blind trials, placebo effects might add to the complexity of interpreting the conclusion. Although it was difficult to perform double-blinding because of certain features associated with nondrug therapies, blinding to the outcome assessors and data analyzer could be feasible.

5. Conclusion

To our knowledge, this meta-analysis is the first review of RCTs yielding information on efficacy and safety of nondrug therapies for treatment of hypertension complicated with cervical spondylosis. This research unprecedentedly evaluated the efficacy of nondrug therapies for blood pressure lowering and cervical vertebra symptoms improvement in hypertensive patients complicated with cervical spondylosis objectively and comprehensively. The results show sound advantages of nondrug therapies over conventional medicine or sham procedure in efficacy. In clinic, patients with hypertension are mostly treated with antihypertensive drugs, but the influence of cervical spondylosis on blood pressure is often ignored. This can result in a lot of uncontrolled hypertension. Our research provides a new idea for clinical doctors, which is very likely to benefit patients. However, the evidence remains weak due to the high clinical heterogeneity and high risk of the included trials. Therefore, further thorough investigation, large-scale, proper-designed, randomized trials of nondrug therapies for hypertension complicated with cervical spondylosis are warranted.

Author contributions

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Writing – review & editing: Xinyi Wang, Jianqing Ju, Hao Xu.

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