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Evidence-Based Integrative Medicine

Blood-Letting Therapy for Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*

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ABSTRACT **Objective**: To evaluate the efficacy and safety of blood-letting therapy (BLT) in treatment of hypertension. **Methods**: A comprehensive electronic and manual bibliographic searches were performed in Cochrane Central Register of Controlled Trials, Excerpt Medica Database (EMBASE), PubMed, China National Knowledge Infrastructure, Chinese Scientific Journal Database, Chinese Biomedical Literature Database, and Wanfang Database to identify randomized controlled trials (RCTs) in which hypertensive patients were treated with BLT or BLT plus antihypertensive drugs (BPAD) against placebo, no treatment or antihypertensive drugs. The Cochrane Risk Assessment Tool was used to assess the methodological quality of trials. The Review Manager 5.3 software was used for meta-analysis. **Results**: A total of 7 RCTs with 637 hypertensive patients from 1989 to 2017 were identified. Compared with antihypertensive drugs, blood pressure was significantly reduced by BLT (RR=1.21, 95% CI: 1.01 to 1.44, P=0.03; heterogeneity: P=0.06, I^2=60%) and BPAD (RR=1.25, 95% CI, 1.02 to 1.53, P=0.03; heterogeneity: P= 0.01, I^2=71%). Moreover, a significant improvement in Chinese medicine syndrome by BLT (RR=1.32; 95% CI: 1.14 to 1.53, P=0.0002; heterogeneity: P=0.53, I^2=0%) and BPAD (RR=1.47; 95% CI: 1.06 to 2.04, P=0.02; heterogeneity: P=0.13, I^2=56%) was identified. The reported adverse effects were well tolerated. **Conclusions**: Although some positive findings were identified, no definite conclusions regarding the efficacy and safety of BLT as complementary and alternative approach for treatment of hypertension could be drew due to the generally poor methodological design, significant heterogeneity, and insufficient clinical data. Further rigorously designed trials are warranted to confirm the results.

KEYWORDS blood-letting therapy, phlebotomy, blood pressure, Chinese medicine, complementary and alternative medicine, systematic review, meta-analysis, randomized controlled trials

As the leading risk factor for cardiovascular disease, hypertension is an important public-health challenge faced by both primary care physicians and other health practitioners, which accounts for a large proportion of premature deaths worldwide.[1] To reduce the high frequency and concomitant risks of cardiovascular diseases and stroke, strict control of blood pressure (BP) is suggested by various updated guidelines for hypertension treatment from the Eighth Joint National Committee (JNC8) and European Society of Hypertension (ESH).[2,3] Despite well-established approaches to diagnosis and treatment, inadequately controlled BP is found in approximately half of all hypertensive subjects,[4,5] and successful treatment of hypertension has not yet fulfilled the great expectations.[6] Currently, complementary and alternative medicine (CAM) is becoming increasing popular for lowering BP and improving hypertension-related symptoms in hypertensive patients.[7-10] The commonly used CAM strategies included herbal medicine,[11,12] dietary supplements,[13] acupuncture,[14] moxibustion,[15] massage,[16] spinal manipulation,[17] qigong,[18] yoga,[19] Tai Chi,[20] aromatherapy,[21] and blood-letting therapy (BLT).[22]

BLT, also known as phlebotomy, blood donation, or collateral pricking therapy, is a well-documented traditional healing art used in Eastern

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Asia and European countries.[23] It is often undertook by the experienced practitioners using a triangle-edged needle to prick the superficial blood vessels and remove a few drops of blood from the patient. Currently, a large number of clinical researches ranging from case reports, case series, controlled trials, and randomized controlled trials (RCTs) supported the use of BLT for treatment of hypertension.[24-27] The potential mechanisms may be related to the increase of serum nitric oxide concentration.[28-30] The article aims to evaluate the efficacy and safety of BLT in treatment of hypertension.

METHODS

Eligibility Criteria

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[31]

Types of Studies

Only RCTs that evaluated the effect of BLT in hypertensive patients were included. There are no restriction on blinding, publication status, and language. Quasi-randomized trials, non-randomized studies, and animal studies were excluded for analysis.

Types of Participants

Participants suffering from and being treated for hypertension were enrolled in this systematic review. The diagnosis criteria was made based on at least one of the current or past guidelines or definitions of hypertension.[2,3] No restriction on age, gender, or ethnic origin was predefined.

Types of Interventions

The participants in the treatment group received BLT used alone or BLT plus antihypertensive drugs (BPAD), while the participants in the control group received placebo, no intervention, or antihypertensive drugs. The antihypertensive drugs used in treatment group should be similar to control group. There is no limitation on the duration or frequency of BLT treatment.

Types of Outcome Measures

The primary outcome measure was defined as categorical or continuous BP, while the secondary outcome measure was defined as Chinese medicine (CM) syndrome. As shown in Table 1, the effectiveness on categorical BP was categorized into 3 grades according to the evaluation criteria from China Food and Drug Administration (available at http://www.sda.gov.cn) and the Guidelines of Clinical Research on New Drugs of Traditional Chinese Medicine (GCRNDTCM).[32] In this systematic review, the outcomes of "significant improvement" and "improvement" were considered successful treatments, and grouped together as "effective", whereas the outcome of "no improvement" was regarded unsuccessful and grouped as "ineffective".

Table 1. Evaluation Criteria on Effectiveness of Categorical BP Recommended by CFDA and GCRNDTCM

Graded criteria	Detailed description
Significant improvement	(a) DBP decreased by 10 mm Hg and reached the normal range (b) DBP did not return to normal but decreased by more than 20 mm Hg
Improvement	(a) DBP decreased by less than 10 mm Hg but reached the normal range (b) DBP decreased by 10 to 19 mm Hg but did not reach the normal range (c) SBP decreased by more than 30 mm Hg
No improvement	Not reaching the above standards

Notes: BP: blood pressure; CFDA: China Food and Drug Administration; DBP: diastolic blood pressure; SBP: systolic blood pressure; GCRNDTCM: Guidelines of Clinical Research on New Drugs of Traditional Chinese Medicine

Literature Search

An extensive literature search in the 7 electronic databases were conducted as follows: Cochrane Central Register of Controlled Trials (CENTRAL, 1996–2017), EMBASE (1980–2017), PubMed (1959–2017), Chinese National Knowledge Infrastructure (CNKI, 1980–2017), Chinese Scientific Journal Database (VIP,1989–2017), Chinese Biomedical Literature Database (CBM,1978–2017), and Wanfang Database (1998–2017), for relevant publications that examined the effect of BLT for hypertension. Details of search terms used in the literature search were as follows: ("hypertension" OR "high blood pressure" OR "blood pressure" OR "gao xue ya") AND ("blood-letting therapy" OR "blood-letting" OR "bloodletting" OR "phlebotomy" OR "blood donation" OR "collateral pricking therapy" OR "collateral pricking" OR "fang xue") AND ("clinical trial" OR "randomized controlled trial" OR "randomised controlled trial" OR "lin chuang yan jiu"). All potentially relevant studies were retrieved for further evaluation according to the inclusion criteria. References of all relevant publications were also hand-searched for additional studies, such as unpublished trials, conference proceedings, and

trial registries, that might be missed in the databases searching.

Study Selection

Two reviewers independently screened the potentially relevant studies based on the titles and abstracts. Duplications were excluded, and the remaining studies were further assessed according to the previously defined inclusion and exclusion criteria. Reasons for exclusion were documented in detail. Copies of the full-text of the eligible studies were identified. When uncertainty regarding eligibility arose, a third party was consulted. Figure 1 summarizes the algorithm followed for the selection of studies.

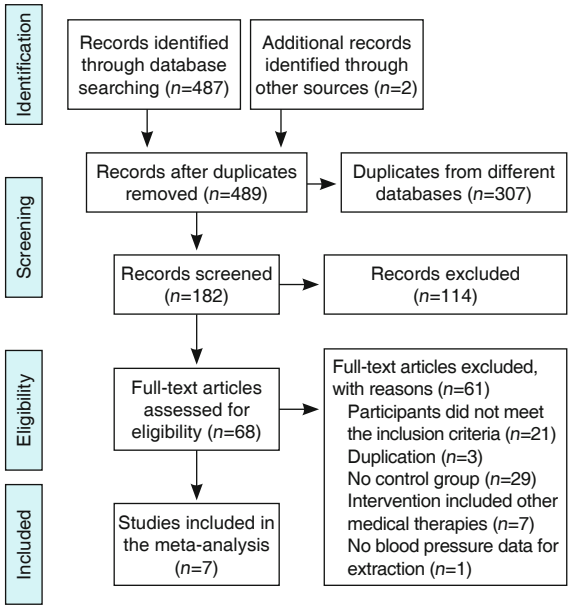

Figure 1. Flow Diagram of Study Selection and Identification

Data Collection

Two independent reviewers conducted the data extraction. Disagreements were resolved by discussion between the reviewers. The following data were extracted from the studies that met the inclusion criteria: the name of the first author, year of publication, the age and gender of included participants, sample size, diagnosis standard, study design, regimen of medications in both BLT group and antihypertensive drugs group (dose, frequency, route of administration, and duration), length of follow-up, outcome measures, and adverse effects. When insufficient or incomplete data were identified, the corresponding authors of included trials were contacted via e-mail, fax, or telephone.

Quality Assessment

Two reviewers independently evaluated the methodological quality of included trials on the basis of following 7 domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other sources of bias.[33]

Statistical Analysis

As only outcomes of dichotomous BP and CM syndrome could be extracted, risk ratio (RR) with 95% confidence intervals (CIs) were calculated using the Review Manager software (RevMan, Version 5.3, Copenhagen, the Nordic Cochrane Centre, the Cochrane Collaboration, 2014). Q and I^2 statistic were calculated to evaluate the heterogeneity among the studies. For Q statistic, $P<0.10$ was considered to be statistically significant heterogeneity. For I^2 statistic, 0%–24% means no heterogeneity, 25%–49% means moderate heterogeneity, 50%–74% means large heterogeneity, and 75%–100% means extreme heterogeneity. A random-effects model was applied for the meta-analysis if substantial heterogeneity was observed ($I^2>50\%$ or $P<0.1$). Otherwise, a fixed-effects model was recommended.

RESULTS

Study Identification

The literature search in the 7 electronic databases yielded a total of 489 potential publications. After screening the titles and abstracts of these articles, we excluded 307 duplicates from different databases and 114 articles because they were irrelevant: not about hypertensive subjects, reviews, expert commentaries, case reports, case series, uncontrolled studies, nonclinical trials, or mechanism studies. Then, full texts of the remaining 68 articles were retrieved, which excluded an additional 61 articles for the reasons mentioned in Figure 1. Finally, a total of 7 studies met the inclusion criteria and were included in the meta-analysis.[34-40]

Study Characteristics

Table 2 summarizes the basic characteristics of the included trials. All the trials were conducted in China and published in Chinese between 1989 and 2014. The number of participants with hypertension in each study ranged from 60 to 160, with a total of 637 patients (355 patients treated by BLT or BPAD and 282

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Table 2. Basic Characteristics of Included Trials

Authors	Sample size (randomized/ analyzed), Male/ Female	Age (year)	Diagnosis standard	Intervention	Control	Treatment duration	Adverse effects report	Main outcomes
Wang, et al 1999[34]	107/107 T: 26/28 C: 23/30	T: 50.8 C: 51.5	WHO-ISH GMH-1978; CM syndrome (NDI)	BLT (2 times/week)	Compound antihypertension tablet (2-6 tablets/day)	5 weeks	N	BP, CM syndrome
Hu, et al 2012[35]	60/60 T: 21/9 C: 19/11	T: 32–63 C:28–65	CGMH-2005; GCRNDTCM	BLT (10 times)	Amlodipine besylate (5 mg, qd)	20 days	N	BP, CM syndrome
Deng 1989[36]	160/160 T: 56/44 C: 60	NR	WHO-ISH GMH-1978; CM syndrome (NR)	BLT (10 times)	Antihypertensive drugs	10 days	N	BP
Chen, et al 2004[37]	90/90 T1: 11/19 T2: 9/21 C: 12/18	T1:42–70 T2:38–70 C:29–70	WHO-ISH GMH-1999; SPCDTTTCM	T1: BLT (3 times/week) T2: T1+C	Amlodipine besylate (5 mg, qd)	4 weeks	N	BP, CM syndrome
Wang, et al 2014[38]	60/60 T: 30 C: 30	NR	CGMH-2010; GCRNDTCM	BLT (3 times/week)+C	Enalapril (5 mg, bid)	7 weeks	N	BP, CM syndrome
Wen, et al 2014[39]	100/100 T: 51 C: 49	NR	Hypertension (NDI); CM syndrome (NR)	BLT (1 time/day)+C	Telmisartan (40 mg, qd)	2 weeks	Y	BP
Zhang 2014[40]	66/60 T: 18/12 C: 17/13	T: 37–53 C: 34–57	IM-2006; CM syndrome (NR)	BLT (1 time/day)+C	Captopril (10 mg, bid)	4 weeks	N	BP

Notes: BLT: blood-letting therapy; BP: blood pressure; C: control group; T: treatment group; CGMH: Chinese guidelines for the management of hypertension; GCRNDTCM: Guidelines of Clinical Research on New Drugs of Traditional Chinese Medicine; IM: internal medicine; N: no; Y: yes; NDI: no detailed information; NR: not reported; SPCDTTTCM: the syndrome part of clinical diagnosis and treatment terms in traditional Chinese medicine; CM: Chinese medicine; WHO-ISH GMH: WHO-ISH guidelines for the management of hypertension

patients treated by antihypertensive drugs). The age of the participants ranged from 28 years to 70 years. Patients recruited in these 7 studies were diagnosed as hypertension, which were based on criteria of WHO-ISH guidelines for the management of hypertension, 1978 (WHO-ISH GMH-1978),[34,36] Chinese guidelines for the management of hypertension, 2005 (CGMH-2005),[35] WHO-ISH GMH-1999,[37] CGMH-2010,[38] and internal medicine-2006 (IM-2006), respectively.[40] Only one trial declared patients with hypertension but without a description of the detailed diagnostic criteria.[39] The diagnostic standards of CM syndromes were reported in 3 trials, including GCRNDTCM[35,38] and the syndrome part of clinical diagnosis and treatment terms in Chinese medicine (SPCDTTTCM).[37] Another trial declared that hypertensive patients with certain CM syndromes were included; however, no detailed information was provided.[34] No diagnostic standard of CM syndrome was considered in the rest 3 trials.[36,39,40]

Among them, 3 RCTs compared the effect of BLT *vs*. antihypertensive drugs,[34-36] 3 RCTs compared the effect of BPAD *vs*. antihypertensive drugs,[38-40] and 1 RCT compared the effect of BLT and BPAD *vs*. antihypertensive drug, respectively.[37] Hypertensive patients in the treatment groups were given the same type and dosage of antihypertensive drugs as the control groups.[37-40] Total treatment duration varied from 10 days to 7 weeks. Baseline characteristics of hypertensive patients for the comparability and categorical BP outcome data were reported in all the identified studies. The outcomes of CM syndromes were reported in 4 trials.[34,35,37,38] Adverse effects about BLT were recorded in 1 trial.[39]

Quality Assessment of Included Studies

The assessment of methodological quality of included trials was described in Table 3. It was assessed to be generally poor, providing inadequate information to draw definitive conclusions on whether or not the random sequence generation, concealment of allocation, and double-blinding were conducted accurately. Although all studies reported randomization, only 3 trials provided the concrete method of random sequences generation. Allocation concealment and blinding procedures were not reported in all of the included studies. Selective reporting was evaluated to be unclear risk of bias

as no study protocols could be identified. No trials reported the drop-outs, pre-trial estimation of sample size, and source of funding.

Table 3. Quality Assessment of Included Trials

Included trials	A	B	C	D	E	F	G
Wang, et al 1999[34]	?	?	?	?	+	?	?
Hu, et al 2012[35]	?	?	?	?	+	?	?
Deng,1989[36]	?	?	?	?	+	?	?
Chen, et al 2004[37]	+	?	?	?	+	?	?
Wang, et al 2014[38]	+	?	?	?	+	?	?
Wen, et al 2014[39]	+	?	?	?	+	?	?
Zhang, 2014[40]	?	?	?	?	+	?	?

Notes: A: adequate sequence generation; B: concealment of allocation; C: blinding (participants and personnel); D: blinding (assessor); E: incomplete outcome data addressed (intention-to-treat analysis); F: free of selective reporting; G: other potential threat to validity; +: low risk; ?: unclear

Effect Estimation

Primary Outcome in BP Level

BLT vs. Antihypertensive Drugs

Four trials evaluated the effect of BLT on categorical BP in patients with hypertension compared to antihypertensive drugs.[34-37] There were 214 patients in BLT group and 173 patients in antihypertensive drugs group. Because significant heterogeneity was identified (P=0.06, I^2=60%), a random-effects model was used for statistical analysis. The combined effects of these 4 independent trial results revealed that BP was significantly reduced by BLT (n=387, RR=1.21, 95% CI: 1.01 to 1.44, P=0.03, Figure 2A).

BPAD vs. Antihypertensive Drugs

Four trials compared BPAD with antihypertensive drugs for the outcome of categorical BP in hypertension patients.[37-40] There were 141 patients in BPAD group and 139 patients in antihypertensive drugs group. A random-effects model was applied for statistical analysis as data extracted from 4 studies showed significant heterogeneity among trials (P=0.01, I^2=71%). The meta-analysis identified a remarkable reduction on BP by BPAD (n=280, RR=1.25, 95% CI: 1.02 to 1.53, P=0.03, Figure 2B).

Secondary Outcome in CM Syndrome

BLT vs. Antihypertensive Drugs

Three trials assessed the effect of BLT on CM syndrome compared to antihypertensive drugs used alone.[34,35,37] There were 114 patients in BLT group and 113 patients in antihypertensive drugs group. A fixed-effects model was used according to the test of heterogeneity (P=0.53, I^2=0%). Meta-analysis revealed a significant improvement on the outcome of CM syndrome by BLT (RR=1.32; 95% CI: 1.14 to 1.53, P=0.0002, Figure 3A).

BPAD vs. Antihypertensive Drugs

Two trials evaluated the effect of BPAD on

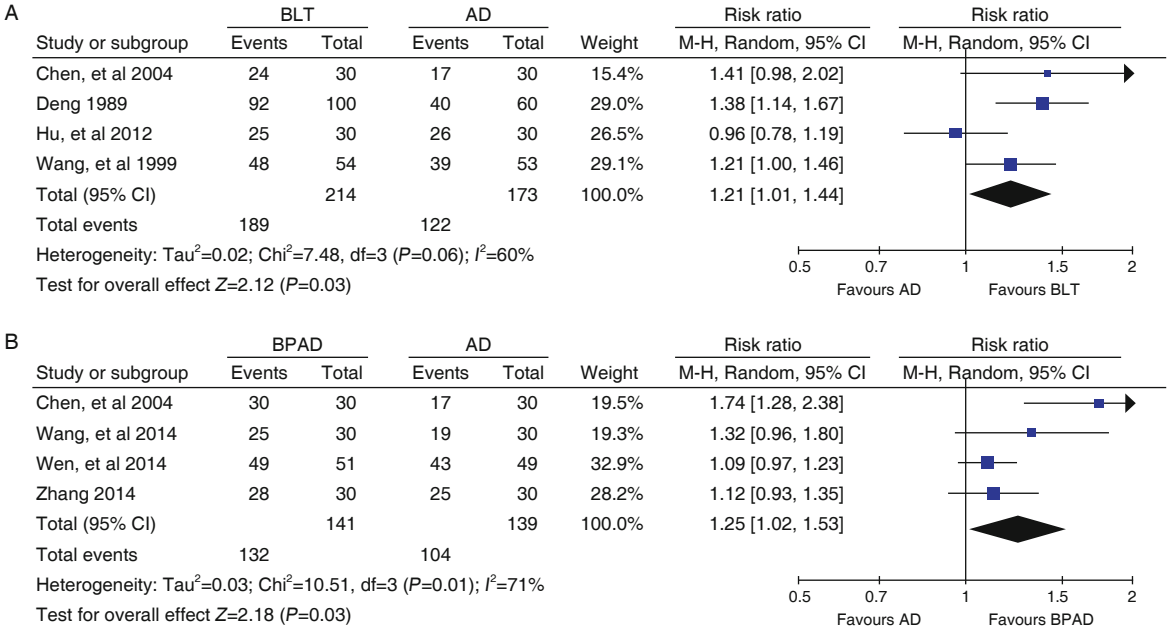

Figure 2. Effect of BLT on BP Level

Notes: A: BLT *vs*. AD; B: BPAD *vs*. AD. AD: antihypertensive drugs; BLT: blood-letting therapy; BP: blood pressure; BPAD: blood-letting therapy plus antihypertensive drugs

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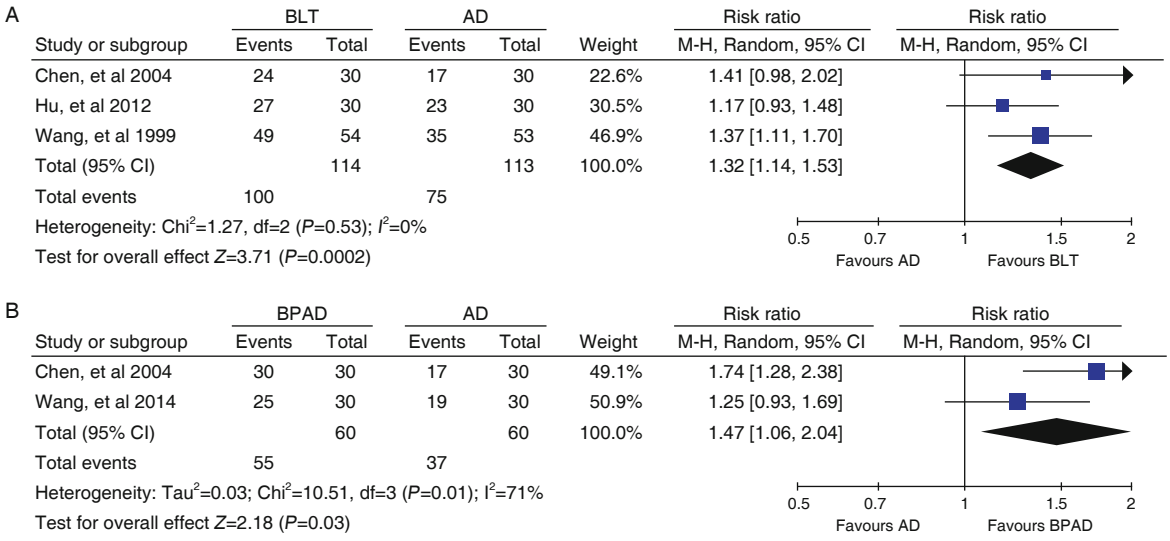

Figure 3. Effect of BLT on CM Syndrome

Notes: A: BLT *vs*. AD; B: BPAD *vs*. AD. AD: antihypertensive drugs; BLT: blood-letting therapy; BPAD: blood-letting therapy plus antihypertensive drugs; CM: Chinese medicine

CM syndrome when comparing to antihypertensive drugs.[37,38] There were 60 patients in BPAD group and 60 patients in antihypertensive drugs group. As significant heterogeneity was identified (P=0.13, I^2=56%), a random-effects model was selected for statistical analysis. Pooled analysis also demonstrated a significant improvement on CM syndrome by BPAD therapy when compared to the antihypertensive drugs (RR=1.47; 95% CI: 1.06 to 2.04, P=0.02, Figure 3B).

Safety Evaluation

Adverse effects related to treatment occurred in only 1 trial.[39] No adverse effect was observed in the other 6 trials. Specific adverse effects included vomiting and fainting in BPAD group and abdominal pain, diarrhea, and palpitation in antihypertensive drugs group. Meta-analysis showed no significant difference between BPAD and antihypertensive drugs (RR=0.32, 95% CI: 0.07 to 1.51, P=0.15). The reported adverse effects were generally well tolerated and no trial was stopped.

DISCUSSION

BLT is one of the oldest CAM remedies used in China, Mongolia, United States, Norway, Italy, and other countries. In Western countries, it was still being practiced as recently as the 19th century for hypervolemic conditions, including acute congestive heart failure and pre-eclampsia. Holsworth, et al[41] validated the benefits of BLT approach, which could reduce the cardiovascular risks through reductions in whole blood viscosity, excessive iron, oxidative stress and inflammation. Moreover, the hypotensive responses to BLT, with about 20 mm Hg reduction in systolic BP, have been observed in patients with essential hypertension, resistant hypertension and secondary hypertension induced by erythropoietin.[42]

A comprehensive and rigorous literature search with a coverage of relevant publications across several electronic databases and other resources were carried out. Finally, a total of 7 RCTs involving 637 patients were identified, with the comparison of BLT *vs*. antihypertensive drugs and BPAD *vs*. antihypertensive drugs on the effect of BP level and CM syndrome. The pooled analysis of these selected trials revealed the beneficial role of BLT either used alone or in combined with antihypertensive drugs for hypertension. Results from the meta-analysis suggested that, as an alternative medicine, BLT appeared to present certain BP-lowering and CM syndrome-improving effects; and as a complementary approach, BLT could enhance the BP-lowering and CM syndrome-improving effects of conventional antihypertensive drugs.

Although significant positive conclusions regarding BLT were identified, it should be treated with caution due to insufficient data reporting and poor methodological design. The following limitations should be considered. Firstly, only categorical BP was reported and no trial provided the continuous

BP data at baseline and after treatment. Therefore, how much BLT could decrease the exact BP data at last is still unclear. Secondly, as only 4 trials reported CM syndrome, more attention should be paid to the reporting and application of CM syndrome in further studies. Thirdly, poor methodological quality regarding randomization, blinding, and reporting according is another critical issue.

In conclusion, whether therapeutic blood loss leads to beneficial effects on hypertension is an interesting question. This review provided the evidence regarding the efficacy and safety of BLT for the treatment of hypertension. Although some positive findings were identified, no definite conclusions regarding BLT as complementary and alternative approach for hypertension could be drew due to the generally poor methodological design, significant heterogeneity, and insufficient clinical data. Further rigorously designed trials are warranted to confirm the results.

Conflict of Interest

None

Author Contributions

Xiong XJ designed the study and drafted the full text. Xiong XJ, Wang PQ, Li SJ searched the databases, screened the trials, extracted the data, assessed the quality of the included trials, and performed the meta-analysis. All authors reviewed the manuscript.

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