Iran J Public Health, Vol. 53, No.12, Dec 2024, pp.2683-2693

Review article

Clinical Advantages of Phlebotomy: An Umbrella Review of Meta-Analyses

Shabnam Khatami [1,2]***, Maryam Rahimzade*** [1]***, Narges Lavari*** [1,3]***, Taha Jadidi*** [4]***, *Mohammad Sadegh Adel-Mehraban*** [1,2]

1. *Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran*
2. *Traditional Persian Medicine and Complementary Medicine (PerCoMed) Student Association, Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran*
3. *The Persian Gulf Tropical Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran*
4. *Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Tehran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Email: sadeghadel@gmail.com

(Received 10 Mar 2024; accepted 26 May 2024)

Abstract

Background: Phlebotomy has been used as a non-pharmacological treatment for different types of diseases, regarding the philosophy of humors in traditional medicines, such as Persian Medicine. However, according to the narrow-approved indications for phlebotomy in Western Medicine, we aimed to systematically summarize high-level of evidence on safety and efficacy of phlebotomy in treatment of human diseases.

Methods: In this umbrella review, to identify meta-analysis studies of clinical trials on phlebotomy, four electronic databases, including PubMed, web of science, Scopus, and Cochran library were searched until Jun 18, 2022 with relevant keywords for 'phlebotomy' and 'meta-analysis' according to PRISMA guidelines and PICO questions. After excluding irrelevant studies, data on subject characteristics, method of intervention, and adverse events were extracted. To evaluate the quality of the methodology of the systematic reviews, AMSTAR2 scale was utilized.

Results: From 327 identified studies, 7 full texts met the inclusion criteria, consisting of 56 clinical trials on 5648 subjects. These meta-analysis studies reported effects of phlebotomy on hypertension, acute gouty arthritis, skin disease (chronic urticaria and porphyria), and liver diseases (non-alcoholic fatty liver disease, chronic hepatitis C, and liver surgery). Our results showed significant improvements in different outcomes, while the most common adverse event was hematoma.

Conclusion: The level of evidence on the efficacy and safety of phlebotomy in some specific health conditions was substantial; however, to investigate the efficacy and safety of phlebotomy in management of other health problems more clinical studies with high sample sizes are needed.

Keywords: Phlebotomy; Persian medicine; Bloodletting; Traditional medicine; Meta-analysis

Introduction

Phlebotomy, also called venesection, refers to a type of blood pooling in traditional medicines, such as Persian Medicine, in which blood is removed by incising a vein. Phlebotomy serves two

main purposes: first, to reduce the patient's hemoglobin concentration by reducing blood volume and second, to treat diseases and inflammations. The instruments, locations, methods, and volume of bloodletting vary in different diseases and cultures but usually the technique of bloodletting involves incision of the median cubital vein using a lancet (1).

The Egyptians used phlebotomy in 1000 BC. Passages in the Ebers Papyrus that have been taken as evidence that scarification was an accepted procedure (2). Galen and Hippocrates were also advocates of bleeding and cupping regarding the philosophy of humors in medicine. Celsus, in 100 BC, was a strong advocate of phlebotomy by scarification (3). Phlebotomy was part of Arab traditional medicine, and it was mentioned by Prophet Mohammed (621 AD). The procedure was prescribed by the Arab physicians of the Middle Ages and soon spread to the Middle East and eventually to the rest of Europe during the Renaissance. The art of phlebotomy also appears to have been practiced in other parts of the world for Uganda in Africa, to the North Australia and in England during feudal times (3). In China, phlebotomy originated from primitive societies and was usually used for patients who have excessive, heat or stasis syndromes, according to the Chinese medicine philosophy (4).

Phlebotomy is one of the important bases of the development of the surgery profession (5). In Western medicine, bloodletting was in use until the 1920s. One of its main indications was febrile illness, of which malaria and plague were the frequent and dreaded causes (6). John Hunter (father of modern surgery) was commended for using bleeding in his practice, particularly for the treatment of inflammation as well as for apoplexy (3). In the 18th century, this procedure was widely used in almost all diseases from febrile conditions such as plague and cholera to fractures and dislocations. Despite there are currently only three accepted indications for therapeutic phlebotomy including hemochromatosis, polycythemia vera, and porphyria cutanea tarda (7), strong evidence exists for benefits of phlebotomy in the treatment of some other diseases such as type II diabetes mellitus (8, 9), hypertension (10, 11), neuralgias like sciatica (12), carpal tunnel syndrome (13), acute gouty arthritis(14), osteoarthritis (15), none alcoholic fatty liver (NAFL) (16, 17), skin diseases (4, 18), and acute brain injury (19). As an example, hypertension is one of the most challenging health problems that is in charge of a high percentage of deaths worldwide due to cardiovascular disease and stroke (20). The Eighth Joint National Committee (JNC8) and European Society of Hypertension (ESH) suggestion is strict control of blood pressure (BP) to reduce risks of cardiovascular diseases and stroke (21, 22) but uncontrolled BP is found in approximately half of all diagnosed cases (23, 24), and treatment of hypertension has not been satisfactory(25) in spite of new approaches. On the other hand, there are concerns about the side effects of phlebotomy, including hypovolemic shock, anemia, and phlebitis.

Hence, according to the controversial evidence on the efficacy and safety of phlebotomy, we aimed to summarize a high level of evidence on the use of phlebotomy.

Methods

Data sources

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PICO questions as follows: Participants: systematic reviews with meta-analysis, Interventions: phlebotomy, Comparison: all types of comparisons, and Outcome: any outcomes. To identify systematic reviews of clinical trials on phlebotomy, four electronic databases, including PubMed, Web of Science, Scopus, and Cochran Library were searched from insertion until Jun 18, 2022, using the following formula: ("venesection"[Title/Abstract] OR "phlebotomy"[Title/Abstract] OR "bloodletting"[Title/Abstract] OR "venipuncture"[Title/Abstract] OR "phlebotomy"[MeSH Terms] OR "bloodletting"[MeSH Terms]) AND "systematic review"[Title/Abstract]. Two inde-

pendent investigators evaluated all papers based on the titles and abstracts, and relevant studies were assessed based on the full texts. Then, to avoid missing related papers, the reference lists of the remaining studies were manually searched. Any discrepancies in all the above processes were resolved by discussing with the third researcher.

Eligibility criteria and study selection

The inclusion and exclusion criteria of this review were as follows: systematic review and meta-analyses of clinical trials conducted to investigate the effect of phlebotomy on various diseases with English language full-texts were included, and systematic review and meta-analyses of *in vitro*, observational, or animal studies were excluded.

Data Extraction

The following information was extracted from included papers by two independent researchers: authors' names, publication year, number of included studies, disorders, participants' characteristics (sex, age, sample size), intervention, type of comparison, adverse events, and significant main outcomes.

Quality Assessment

To evaluate the quality of the methodology of the systematic reviews, the Assessment of Multiple Systematic Reviews 2 (AMSTAR2) scale was utilized (26). The AMSTAR2 evaluates different domains of the study. It represents the quality assessment qualitatively and does not generate an overall score to assess the quality. According to this guideline, each domain obtains YES, partially YES (PYES), or NO.

Results and discussion

Among the initially 327 identified studies, 93 were excluded due to duplication and 237 were excluded after reviewing titles and abstracts. Finally, after evaluating full texts 7 studies were included in the present umbrella review (Fig. 1).

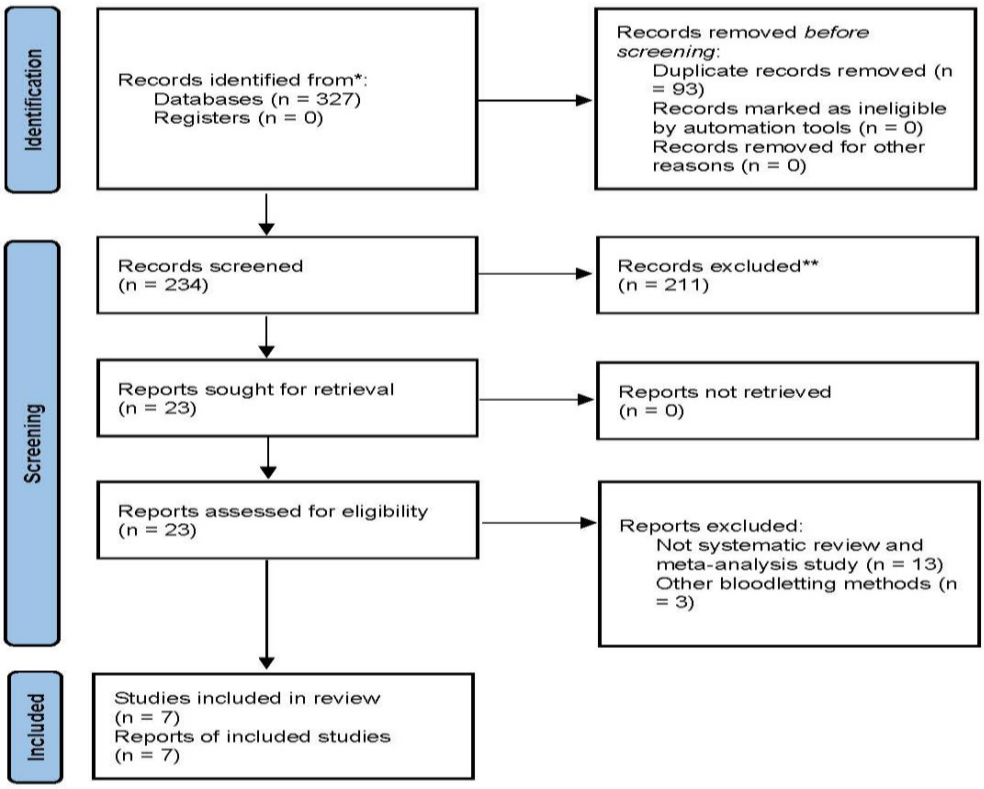

Fig. 1: Flow diagram of the study selection processes

All the systematic reviews included meta-analysis, were in English language, and only four of them included randomized control trials (RCT)(4, 10, 14, 27). Included studies evaluated the effects of phlebotomy on gouty arthritis, liver surgery, hypertension, chronic urticaria, porphyria, non-alcoholic fatty liver disease, and chronic hepatitis C (4, 10, 14, 27-30) (Table 1). The total number of included studies was 56 articles (maximum = 12; minimum = 4) published between 2008 and 2022. Three studies were conducted in China (4, 10, 14) and others were in Texas (29), Thailand (30), Michigan (27), and Canada (28). The total number of included patients was 5648 subjects of both genders, aged from 11 to 71 yr old. The amount of removed blood during phlebotomy was from 10 to 500 mL within 1 to 10 times and the phlebotomy was compared with different medications depending on the type of the disease. Reported adverse events were subcutaneous hematoma, vomiting, and fainting in the phlebotomy group and gastrointestinal reactions, headache, dizziness, and fatigue in the control group. Table 2 shows the quality assessment of included studies based on the AMSTAR2 criteria: one article was defined as "high quality"(4), four articles as "low quality"(10, 14, 28, 30), and two articles were assessed as "critically low quality"(27, 29). Main concerns about methodological quality were detected as: a) the absence of a comprehensive search strategy; b) Lack of detailed descriptions of included studies; c) No declaration of funding sources for the studies included in the review; d) Failure to interpret or discuss the risk of bias in the results; and f) inattention to publication bias (small study bias).

We summarized included studies in 3 groups:

Group1: Skin diseases (chronic urticaria, porphyria)

Group2: Liver diseases (non-alcoholic fatty liver disease, chronic hepatitis C, liver surgery)

Group3: Other diseases (hypertension, acute gouty arthritis).

Skin diseases

Two studies evaluating skin disorders were included in this study: chronic urticaria (4) and porphyria (29) including 512 patients with chronic urticaria in 7 trials and 525 porphyria cutanea tarda (PCT) patients in 12 studies. The volume of BLT was 300 ml, The duration of the intervention was from 4 d to 4 wk and 1 to 10 times. These 2 studies reported significant clinical improvements in controlling disease activity, decreasing recurrence rate, and increasing response rate to standard medications.

Chronic Urticaria

According to the literature, chronic urticaria is an allergic condition and inflammatory disease with unknown pathogenesis that lasts more than 6 wk (31). Although this health problem is not life-threatening, it influences the functions and well-being of affected individuals and imposes a significant financial burden on healthcare systems. Meta-analysis of Yao et al. compared phlebotomy alone with phlebotomy plus pharmacological medications (cetirizine, mizolastine, and loratadine)(4). This study evaluated the results as primary outcome (disease activity control) and secondary outcomes (recurrence; response rate; adverse events). Disease activity control according to the Cochrane Handbook was reported in only one study (32), in which it identified the significant difference between phlebotomy and cetirizine. Although 2 clinical trials reported a remarkable statistical difference in the response rate between BLT plus pharmacological medication group and just the same medicine, meta-analysis showed no significant difference in the response rate between BLT and pharmacological medication. Furthermore, two clinical trials reported a lower recurrence rate in the phlebotomy group compared to cetirizine. The quality assessment of the study in this part was very low (high risk of bias, lack of consistency, imprecision and sparseness of the data) and no serious side effects were reported in this trials (4). Stressful events in the life of each person have an effect on the route of skin diseases (33). Psychological stress may cause degranulation of mast cells that are dependent on corticotropin-releasing hormone (CRH), thus related mechanisms may be linked to urticaria

(34). Stress can be an independent factor in the onset and amplification of urticarial, and BLT improves mental status and quality of life (35). Thus, by reducing stress, it helps to reduce disease activity; however, the exact mechanism of action of BLT is not specified (4).

Table 1: Characteristics of the included studies

Num.	*Study*	*Number of included studies/ disorders*	*Participants*			*Intervention*			*Adverse events*		*Outcomes*
			Sample size (n)	Age (yr)	Sex	Amount of received blood	Phlebotomy protocol	Comparison	phlebotomy	Control	
1	Li et al., 2022(14)	12/ gouty arthritis	894	Mean: 30 - 55	Both	Mean: 10 mL	1 to 3 times/ 1 to 9 d	Colchicine, NSAIDS, Allopurinol	Subcutaneous hematoma (3 patients)	Gastrointestinal reaction, Diarrhea, Abdominal pain, Abdominal distention, Vomiting	↓ VAS, severe symptoms, and CRP ↔ Uric acid and ESR
2	Park et al., 2020(28)	8/ liver surgery	2275	Mean: 35-65	Both	Mean: 7 mL/kg	1 time	None	NR	NR	↓ Need for blood transfusion
3	Xiong et al., 2019(10)	7/ hypertension	637	28-70	Both	NR	1 to 10 times/ 10 d to 5 w	Amlodipine, enalapril, telmisartan, captopril	Vomit and faint	Abdominal pain, diarrhea, palpitation	↓ Hypertension
4	Yao et al., 2019(4)	7/ chronic urticaria	512	11-71	NR	NR	1 to 10 times/ 4 d to 4 w	Cetirizine, loratadine, mizolastine	Hematoma	Dry mouth, headache, drowsiness, vomiting, dizziness, and fatigue	↑ Control of disease activity, ↓ Recurrence rate, ↑ Response rate
5	Salameh et al., 2018(29)	12/ porphyria	525	Mean: 43-55.3	Both	300 mL	2 times within 3 to 7 d	4-aminoquinoline	NR	NR	↓ Relapse rate
6	Jaruvongvanich et al., 2016(30)	4/ non-alcoholic fatty liver disease	438	49-55	Both	250-350 mL	Every 1-3 w until ferritin<30-80 ng/mL	Diet, lifestyle modification, exercise	NR	NR	↓ HOMA-IR, ALT, TG ↑ HDL-C
7	Desai et al., 2008(27)	6/ chronic hepatitis C	367	NR	Both	250-500 mL	Every 1 to 2 w	Interferon alone	NR	NR	↑ Sustained viral response rate, liver histology, hepatic activity index ↓ inflammation score

Legend: ↑: significant increase; ↓: significant decrease; ↔: no significant change; ALT: alanine transaminase; CRP: C-reactive protein; d: day; ESR: erythrocyte sedimentation rate; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; mL: milli liter; NR: not reported; NSAIDS: Non-steroidal anti-inflammatory drugs; TG: triglyceride; VAS: visual analog scale; w: week; yr: years old

Table 2: Quality assessment of the studies based on AMSTAR2 criteria[1]

Study	*1. Pico components*	*2. protocol*	*3. study design*	*4. comprehensive search strategy*	*5. study selection*	*6.data extraction*	*7. details of excluded extraction*	*8. description of included studies*	*9a. risk of bias(ROB)*	*9b. risk of bias(ROB)*	*10. Funding sources*	*11. Analysis method*	*12. ROB on Meta analysis*	*13. ROB on Individual studies*	*14. Discuss heterogeneity*	*15. Publication bias*	*16. Conflict of interest*	*Quality assessment*
Li et al., 2022/ China	YES	YES	YES	PYES	YES	YES	YES	PYES	YES	Includes only RCTs	NO	YES	YES	NO	YES	YES	YES	LOW
Park et al., 2020/ Canada	YES	YES	YES	YES	YES	YES	YES	PYES	YES	YES	NO	YES	YES	YES	YES	NO	YES	LOW
Xiong et al., 2019/ China	YES	YES	YES	PYES	YES	YES	YES	YES	PYES	Includes only RCTs	NO	YES	NO	YES	YES	NO	YES	LOW
Yao et al., 2019/ China	YES	YES	YES	PYES	YES	YES	YES	YES	YES	Includes only RCTs	YES	YES	YES	YES	YES	YES	YES	HIGHT
Salameh et al., 2018/ Texas	YES	YES	YES	NO	YES	YES	PYES	YES	Includes only NRSI	YES	NO	YES	YES	NO	YES	NO	YES	Critially Low
Jaruvongvanich et al., 2016/ Thailand	YES	YES	YES	NO	YES	YES	YES	PYES	YES	YES	NO	YES	YES	YES	YES	YES	YES	LOW
Desai et al., 2008/ Michigan	YES	YES	YES	NO	NO	YES	NO	PYES	YES	Includes only RCT	NO	YES	YES	NO	YES	YES	no	Critially Low

AMSTAR: Assessment of Multiple Systematic Reviews; PYES: partially yes. Reference: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. bmj. 2017 Sep 21;358

Porphyria cutanea tarda (PCT)

Porphyria cutanea tarda (PCT), the most common porphyria caused by uroporphyrinogen III decarboxylase (UROD) enzyme deficiency, must be distinguished from other porphyrias. Deficiency of this enzyme leads to the accumulation of uroporphyrinogen in the liver, which then oxidized porphyrin enters the plasma. High levels of these porphyrins lead to photosensitivity and chronic blistering skin disease in sun-exposed areas (29). The study of Salameh et al. evaluated the relapse of patients with PCT in remission treated with phlebotomy, high dose 4-aminoquinolines or low dose 4-aminoquinolines(29). The relapse rate in patients treated with high dose 4-aminoquinolines (hydroxychloroquine or chloroquine) has been reported at 35.4% (69 of the 195 patients). In this group, patients have been followed up for 2.4 to 11 yr, while the pooled relapse rate in the high dose 4-aminoquinolines group without previous phlebotomy and with previous phlebotomy were 12.2 and 10 per 100 person-years, respectively. The relapse rate in the group that received low dose 4-aminoquinolines has been reported at 36.3% (88 of the 242 patients). In this group, participants have been followed up for 1 to 4 yr, while the pooled relapse rate was 17.5 per 100 person-years. In the phlebotomy group, 18 patients from 88 relapsed after a follow-up period of 1-6 yr (20.5%), the relapse rate varied from 10% to 29%. The pooled relapse rate was 6.5 per 100 person-years(29). Although recent studies showed that one of the most effective treatments in PCT is phlebotomy (36), its mechanism is not clear, yet. Iron overload and ferritin level are two

important factors in the pathogenesis of PCT. Iron overload in the body may facilitate the formation of some radicals, which leads to the production of UROD inhibitor and, as a result, increases photosensitivity. Any condition that leads to iron overload in a PCT patient is an obvious indication for phlebotomy (37). In the phlebotomy method, serial and accurate monitoring of ferritin level is performed. The goal of phlebotomy is to reduce the serum ferritin level (less than 20 ng/ml) (38, 39). Phlebotomy triggers the production of new red blood cells (RBC) by bone marrow. During the process of making new RBCs, iron reforms to the ferritin to produce more hemoglobin resulting in the reduction of overall iron serum level in patients(40). Moreover, for initiation of treatment, therapeutic phlebotomy in several hematologic diseases such as acquired iron overload in sickle cell anemia and thalassemia, hereditary hemochromatosis, and polycythemia vera is the best choice(40).

Liver diseases

Three studies on liver diseases were included in this review: non-alcoholic fatty liver disease (NAFLD), chronic hepatitis C, and liver surgery. 438 patients with NAFLD in 4 trials, 367 Chronic Hepatitis C patients in 6 studies, and 2275 liver surgeries in 8 articles were included. The volume range of BLT was from 250 to 500 mL. The frequency of BLT was different: in liver surgery, it was only once, but in the next 2 articles, it was almost every 1 to 3 wk.

Nonalcoholic Fatty Liver Disease (NAFLD)

Overall, 438 patients with NAFLD (197 underwent phlebotomy and 241 controls) in 4 studies were evaluated in this systematic review. The average age was 49 to 55 yr. The duration of follow-up varied from 6 to 24 months. In the phlebotomy group, the homeostasis model of insulin resistance (HOMA-IR), alanine aminotransferase (ALT) serum level, and the triglyceride level decreased, and high-density lipoprotein cholesterol (HDL-C) level increased significantly. in comparison with the control group (30). In chronic liver disease such as NAFLD, serum level of ferritin is associated with iron deposition in the liver, and hyperferritinemia with normal transferrin saturation has been reported in almost one-third of NAFLD patients. High level of serum iron influences insulin sensitivity and leads to insulin resistance. Hence, in order to improve insulin resistance and iron overload-induced liver damage, phlebotomy can be beneficial by iron-depleting effects (30, 41).

Chronic Hepatitis C

Meta-analysis of Desai et al. evaluated the effects of phlebotomy on total inflammation, liver function, and sustained viral response (SVR) of chronic hepatitis C (CHC) patients. The treatment period varied from 6 to 12 months, the amount of obtained blood ranged from 250 to 500 mL, and phlebotomy was done weekly in all studies to reach the target hemoglobin(27). SVR rate was significantly higher in CHC patients who received phlebotomy (27%), compared to the control group (12%). Comparing pre- and post-treatment liver biopsy samples in three studies demonstrated significant histological improvement in the phlebotomy group. Moreover, phlebotomy improved the hepatic activity index and inflammation score (27). Phlebotomy reduces blood aminotransferase levels and reverses the fibrosis process in CHC patients by reducing liver iron overload. Some studies have reported histological recovery and even regression of cirrhosis after phlebotomy. High level of hepatic iron in CHC patients reduces the SVR rate to monotherapy with interferon and phlebotomy can strengthen the treatment by removing excess iron from the body (27).

Blood loss in liver surgery

Blood loss during major hepatectomy is remarkable, and it requires a high amount of blood transfusions. Because low central venous pressure (CVP) aids in reducing blood loss during liver resection, hypovolemic phlebotomy is one of the emerging techniques that reduces CVP. A meta-analysis by Park et al. evaluated the effects

of phlebotomy on RBC transfusion and blood loss in liver surgery (28). They reported a reduced amount of blood loss in phlebotomy group compared to control group, but the difference was not remarkable; however, phlebotomy significantly reduced the need for RBC transfusion. Among included studies, the relationship between CVP and blood loss was controversial. This study showed no substantial differences between groups considering complications, except the study of Putchakayala that revealed an elevated morbidity rate in the phlebotomy group. Phlebotomy mildly reduces CVP and splanchnic blood flow leading to a decreased amount of blood loss during parenchymal transection and the final result depends on the methodology of the surgery (42).

Other diseases

Acute gouty arthritis (AGA)

Li et al. evaluated the pain relief effects of phlebotomy in AGA patients. The sample size of these studies was 894 participants and the age range was 30 to 55 yr old for both genders (14). The average amount of removed blood was 10 mL in each session, 3 to 7 sessions with 0 to 3 d intervals. This meta-analysis study reported that phlebotomy significantly reduced visual analog scale (VAS) scores and the severe symptoms of the disease were remarkably ameliorated compared to the control group. In comparison with standard treatment, the serum level of C-reactive protein (CRP) was significantly decreased after phlebotomy and both groups induced similar reductions in erythrocyte sedimentation rate (ESR) and uric acid levels. Accordingly, phlebotomy is useful in reducing pain and alleviating CRP level in AGA patients(14). The mechanism of action of phlebotomy in AGA is not clearly known, but BLT can improve damaged tissues by eliminating algesic substances from the body and promoting local microcirculation (43). Phlebotomy improves hemodynamics by increasing blood flow, ameliorating vascular spasm, decreasing blood viscosity, and promoting blood circulation leading to improvement of ESR and uric acid levels (14). Phlebotomy accelerates pain relief by reducing inflammatory biomarkers such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) and stimulating gene expression of anti-inflammatory markers such as IL-10 that results in restoration of endothelial damage and improvement of platelet aggregation and blood hypercoagulation (44).

Hypertension

In Western countries, phlebotomy has been used for hypervolemic diseases, including pre-eclampsia and acute congestive heart failure. BLT decreases cardiovascular risks by reducing whole blood viscosity, oxidative stress, iron overload, and inflammation (45). Phlebotomy reduces blood pressure with the same mechanisms. This meta-analysis demonstrated a significant reduction in blood pressure following phlebotomy alone or in combination with antihypertensive medicines in comparison with antihypertensive drugs alone with no adverse effects. In another study, in patients with resistant hypertension, essential hypertension and erythropoietin-induced secondary hypertension that received phlebotomy systolic blood pressure and diastolic blood pressure decreased by 20 mmHg and 10 mmHg respectively and reached the normal range or decreased by more than 20 mmHg, without returning to the normal range (46).

Strengths and limitations

Strengths of this study includes: to the best of our knowledge, it is the first umbrella review that summarizes systematic review and meta-analysis studies on the efficacy of phlebotomy in different diseases. Moreover, we utilized AMSTAR2 to assess the quality of the studies. Due to the small number of clinical trials and meta-analyses on phlebotomy, our overview study was limited only to 7 studies. According to the heterogenicity of studies, concluding a comprehensive summarized result was not possible.

Conclusion

Traditional medical systems, such as Persian medicine, are full of innovative therapeutic

methods of which some patients prefer to use herbal treatments and others prefer non-pharmacological treatments like phlebotomy. On the other hand, if physicians become ensured about the efficacy and safety of these methods, they can use them in the treatments of the patients. This study showed that provided a high level of evidence on the efficacy and safety of phlebotomy in some specific conditions such as gouty arthritis, liver disorders, skin disease, and hypertension. However, according to the low-quality included studies, more well-designed clinical studies with high sample sizes are needed to investigate the efficacy and safety of phlebotomy in the management of other health problems.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This study was not supported financially by any organization.

Conflict of interest

Authors declare no conflict of interest.

References

1. Xia YB, Cheng J Fau, Tong L, et al (2012). [Comparative study of bloodletting therapy between traditional Chinese medicine and Tibetan medicine]. *Zhongguo Zhen Jiu,* 32(5):464.
2. Schneeberg NG (2002). A twenty-first century perspective on the ancient art of bloodletting. *Trans Stud Coll Physicians Phila,* 24:157-85.
3. Parapia LA (2008). History of bloodletting by phlebotomy. *Br J Haematol,* 143 (4):490-495.
4. Yao Q, Zhang X, Mu Y, et al (2019). Bloodletting Therapy for Patients with Chronic Urticaria: A Systematic Review and Meta-Analysis. *Biomed Res Int,* 2019:8650398.
5. DePalma RG, Hayes VW, Zacharski LR (2007). Bloodletting: Past and Present. *J Am Coll Surg,* 205(1):132-44.
6. Denic S, Agarwal MM (2007). Nutritional iron deficiency: an evolutionary perspective. *Nutrition*, 23 (7-8):603-614.
7. Kim KH, Oh KY (2016). Clinical applications of therapeutic phlebotomy. *J Blood Med,* 7:139-144.
8. FA FAS (1998). Effect of Phlebotomy on Plasma Glucose and Insulin Concentrations. *Diabetes Care,* 21 (12):2190.
9. Guillygomarc'h A, Mendler MH, Moirand R, et al (2001). Venesection therapy of insulin resistance-associated hepatic iron overload. *J Hepatol,* 35 (3):344-349.
10. Xiong XJ, Wang PQ, Li SJ (2019). Blood-Letting Therapy for Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Chin J Integr Med,* 25 (2):139-146.
11. Jeitler M, Roth S, Steckhan N, et al (2022). Therapeutic Phlebotomy in Patients with Grade 1 Hypertension: A Randomized-Controlled Trial. *J Integr Complement Med,* 28 (6):530-539.
12. Amini MH, Esmaeili SS, Barzi DM, Fesharaki MG (2018). The effect of FASD (blood-letting) in the treatment of sciatica: a randomized clinical trial study. *Ann Med Health Sci Res*, 8:391-396.
13. Chelavi LH, Ilkhani R, Azadvari M, et al (2021). The effect of phlebotomy (Fasd) on carpal tunnel syndrome; a randomized clinical trial. *Oncology and Radiotherapy,* 15(5): 8-12.
14. Li SH, Hu WS, Wu QF, Sun JG (2022). The efficacy of bloodletting therapy in patients with acute gouty arthritis: A systematic review and meta-analysis. *Complement Ther Clin Pract,* 46: 101503.
15. Khan SA, Rehman S, Jamil SS (2012). Safety and Efficacy of Fasd (Blood Letting through Venesection) in the Cases of Osteoarthrosis – A Randomized Controlled Study. *Hippocratic J. Unani Med,* 7(2):1-140.
16. Adams LA, Crawford DH, Stuart K, et al (2015). The impact of phlebotomy in nonalcoholic fatty liver disease: A prospective, randomized, controlled trial. *Hepatology,* 61 (5):1555-1564.

17. Valenti L, Moscatiello S, Vanni E, et al (2010). Venesection for non-alcoholic fatty liver disease unresponsive to lifestyle counselling—a propensity score-adjusted observational study. *QJM,* 104 (2):141-149.
18. Liu C, Lei B, Zheng J (2008). Randomized control study on the treatment of 26 cases of acne conglobata with encircling acupuncture combined with venesection and cupping. *Zhen Ci Yan Jiu,* 33 (6):406-408.
19. Vaghebin R, Khalili M, Amiresmaili S, et al (2022). Saphenous vein phlebotomy alleviates neuroinflammatory response and oxidative stress following traumatic brain injury. *Interdisciplinary Neurosurgery,* 30:101626.
20. T. U (2014). Decade in review—hypertension: the past decade in hypertension—facts, hopes, and hypes. *Nat Rev Cardiol,* 11:633-635.
21. James PA, Oparil S, Carter BL, et al (2014). 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *JAMA,* 311 (5):507-520.
22. Mancia G, Fagard R Fau, Narkiewicz K, et al (2013). 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press,* 22(4):193-278.
23. Chow CK, Teo Kk Fau, Rangarajan S, et al S (2013). Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA,* 310(9):959-68.
24. Guo F, He D Fau, Zhang W, et al (2012). Trends in prevalence, awareness, management, and control of hypertension among United States adults, 1999 to 2010. *J Am Coll Cardiol,* 60(7):599-606.
25. Bauchner H, Fontanarosa PB, Golub RM (2014). Updated Guidelines for Management of High Blood Pressure: Recommendations, Review, and Responsibility. *JAMA,* 311 (5):477-478.
26. Shea BJ, Reeves BC, Wells G, et al (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ,* 358:j4008.
27. Desai TK, Jamil LH, Balasubramaniam M, et al (2008). Phlebotomy improves therapeutic response to interferon in patients with chronic hepatitis C: A meta-analysis of six prospective randomized controlled trials. *Dig Dis Sci,* 53(3):815-22.
28. Park L, Gilbert R, Baker L, et al (2020). The safety and efficacy of hypovolemic phlebotomy on blood loss and transfusion in liver surgery: a systematic review and meta-analysis. *HPB (Oxford),* 22 (3):340-350.
29. Salameh H, Sarairah H, Rizwan M, et al (2018). Relapse of porphyria cutanea tarda after treatment with phlebotomy or 4-aminoquinoline antimalarials: a meta-analysis. *Br J Dermatol,* 179 (6):1351-1357.
30. Jaruvongvanich V, Riangwiwat T, Sanguankeo A, et al (2016). Outcome of phlebotomy for treating nonalcoholic fatty liver disease: A systematic review and meta-analysis. *Saudi J Gastroenterol,* 22 (6):407-414.
31. Ma B, Chen X, Liang Y, et al (2020). Efficacy of bloodletting therapy in patients with chronic idiopathic urticaria: a randomized control trial. *Evid Based Complement Alternat Med,* 2020:6598708.
32. Cumpston M, Li T, Page MJ, et al (2019). Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev,* 10(10):ED000142.
33. Picardi A, Abeni D (2001). Stressful life events and skin diseases: disentangling evidence from myth. *Psychother Psychosom,* 70 (3):118-136.
34. Theoharides TC, Singh KL, Boucher W, et al (1998). Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. *Endocrinology,* 139 (1):403-413.
35. Ma H, Kui Y, Li Y, et al (2013). Bloodletting therapy combined with paroxetine hydrochloride for generalized anxiety disorder: A randomized controlled trial. 2013 IEEE International Conference on Bioinformatics and Biomedicine, IEEE, pp. 174-176.

36. Badminton MN, Elder GH (2002). Management of acute and cutaneous porphyrias. *Int J Clin Pract,* 56 (4):272-278.
37. Shah A, Bhatt H. Porphyria Cutanea Tarda. 2023 Apr 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
38. Rocchi E, Gibertini P, Cassanelli M, et al (1986). Serum ferritin in the assessment of liver iron overload and iron removal therapy in porphyria cutanea tarda. *J Lab Clin Med,* 107 (1):36-42.
39. Easterbrook M (1999). An ophthalmological view on the efficacy and safety of chloroquine versus hydroxychloroquine. *J Rheumatol,* 26 (9):1866-1868.
40. Zubair A (2014). Therapeutic phlebotomy. *Clin Liver Dis (Hoboken),* 4 (5):102-106.
41. Trasolini R, Cox B, Galts C, et al (2022). Elevated serum ferritin in non-alcoholic fatty liver disease is not predictive of fibrosis. *Can Liver J,* 5 (2):152-159.
42. Rekman J, Wherrett C, Bennett S, et al (2017). Safety and feasibility of phlebotomy with controlled hypovolemia to minimize blood loss in liver resections. *Surgery,* 161 (3):650-657.
43. Yang J, Jiao L (2012). Discussions on history of the bloodletting therapy overseas. *Zhongguo Zhen Jiu,* 32 (6):553-557.
44. Jiang H, Qiu L-L, Li YY, et al (2020). Efficacy and mechanism of fire needling bloodletting for lower extremity varicose veins. *Zhongguo Zhen Jiu,* 40 (9):953-956.
45. Holsworth RE, Jr, Cho YI, et al (2014). Cardiovascular benefits of phlebotomy: relationship to changes in hemorheological variables. *Perfusion,* 29 (2):102-16.
46. Kuchel GA, Avorn J, Reed MJ, et al (1992). Cardiovascular responses to phlebotomy and sitting in middle-aged and elderly subjects. *Arch Intern Med,* 152 (2):366-370.