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Effects of vitamin C supplementation on essential hypertension
A systematic review and meta-analysis

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Abstract

Background: Vitamin C as a supplement to treat hypertension has been proposed. However, it remains controversial whether vitamin C can improve blood pressure in patients with primary hypertension.

Objectives: To analyze the effect of vitamin C (VitC) supplementation on systolic (SBP) and diastolic (DBP) blood pressure in patients with essential hypertension.

Methods: We searched the Chinese Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, WANFANG Data, Cochrane Library, National Library of Medicine's PubMed, EMBASE, and other databases until June 2019. Eight RCTs involving 614 participants were analyzed. SBP and DBP before and after VitC supplementation were compared between the intervention and control groups. The risk of bias of individual studies was assessed using the Cochrane Collaboration risk of bias tool. Two reviewers selected studies independently of each other. The Cochrane Collaboration Review Manager 5.3 was used to perform the meta-analysis.

Results: There was a significant difference in the change of SBP (weighted mean difference [WMD] = −4.09; 95% confidence interval [CI] −5.56, −2.62; $P < .001$) and DBP (WMD = −2.30; 95% CI −4.27, −.331; $P = .02$) between the groups. Further, there was a significant difference in the SBP (WMD = -3.75, 95% CI -6.24, -1.26, $P = .003$) and DBP (WMD = −3.29, 95% CI −5.98, −.60, $P = .02$) for the subgroup with an age ≥60 years and that with ≥35 participants. In the subgroup analysis, result for SBP with a study duration ≥6 weeks was statistically significant different (WMD = −4.77; 95% CI −6.46, −3.08; $P < .001$). For an intervention dose of VitC ≥500 mg daily, SBP was statistically significant (WMD = −5.01; 95% CI −8.55, −1.48; $P = .005$).

Conclusion: VitC supplementation resulted in a significant reduction of blood pressure in patients with essential hypertension.

Abbreviations: CI = confidence interval, DBP = diastolic blood pressure, PRISMA = Preferred Reporting Items Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial, SBP = systolic blood pressure, SD = standard deviation, SE = standard error, VitC = Vitamin C, WMD = weighted mean difference.

Keywords: arterial blood pressure, essential hypertension, meta-analysis, vitamin C

1. Introduction

One in 4 adults worldwide suffers from high blood pressure, and this ratio is expected to increase to 29% by 2025.[1] The prevalence of hypertension is 37.3% in developed countries and 22.9% in developing countries. Among the population with hypertension, more than 90% have essential hypertension, which makes this type of hypertension without a secondary cause a major global chronic non-communicable disease.[2] Although the pathogenesis of essential hypertension is not entirely clear, recent studies have indicated that oxidative stress and vascular endothelial cell injury might be important factors.[3,4]

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Endothelial cell dysfunction, a characteristic of essential hypertension, is caused by damage to these cells and the release of large amounts of superoxide anions.[5] It is closely related to the development of vascular disease and has been found to promote hypertension and cardiovascular and cerebrovascular diseases.[6–9] Taddei et al[10] noticed abnormal endothelium-dependent vasodilation in descendants of patients with essential hypertension and concluded that endothelial dysfunction might facilitate the development of hypertension. An investigation of the blood pressure of individuals with abnormal L-arginine uptake and a family history of hypertension further confirmed that changes in endothelial function may lead to the development of essential hypertension.[11]

Vitamin C (VitC), or ascorbic acid, is frequently found in fruits, vegetables, vitamin supplements, energy drinks, formulated breakfasts, and dietary cereals.[12] As an essential vitamin involved in human metabolism, it possesses the ability to remove superoxide anions and prevent the formation of peroxynitrite as well as improve vascular endothelial function.[13–16] Numerous clinical studies have assessed the effect of VitC supplementation on blood pressure levels.[17–19] The results were inconsistent, probably because of their heterogeneous methods and the fact that they were small randomized controlled trials (RCTs). Some findings were even contradictory, and no conclusion on the effect of VitC on hypertension has been reached yet. Consequently, we performed a meta-analysis to systematically analyze the effects of VitC supplementation on essential hypertension with the aim to establish current evidence for the role of this intervention.

2. Methods

2.1. Research strategy

We searched the National Library of Medicine's PubMed, Cochrane Library, EMBASE, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, and WANFANG databases for studies published before June 2019. The search terms were as follows: blood pressure, hypertension, hypertensive, primary hypertension, essential hypertension, vitamin C, ascorbic acid, and RCTs. Two independent reviewers selected and screened all results, and if they disagreed, we asked a third reviewer for his/her advice. This meta-analysis complies with the Reviews and Meta-Analyses (PRISMA) statement for reporting items for systematic reviews and meta-analyses.[20]

2.2. Eligibility criteria

The inclusion criteria for this systematic review were as follows:

1) studies with a RCT design related to the therapeutic effect of VitC;
2) the included subjects were explicitly diagnosed with essential hypertension based on laboratory findings, clinical signs, or reported symptoms;
3) the effects of VitC on systolic (SBP) and diastolic (DBP) blood pressure were reported;
4) VitC was included in the trial as a supplement and the study had a control group; and
5) the dose of VitC was >200 mg.

The exclusion criteria were as follows:

1) duplicate publications;
2) non-interventional study designs, such as a case-control study, cohort study, cross-sectional study, case reports and experiences, theory research, and reviews; and
3) non-clinical tests and animal experiments.

2.3. Data extraction

The following information was extracted:

1) participants' basic characteristics, including mean age, sex, and treatment with antihypertensive medications;
2) detailed descriptions of how patients' blood pressure was measured, such as their position (e.g., seated, lying, or standing), the location, device used (e.g., oscillometric monitor, sphygmomanometer cuff; sphygmomanometer, etc.);
3) mean pretreatment SBP and DBP; and
4) mean SBP, DBP, and plasma VitC concentration after the trial.

2.4. Risk of bias assessment

The risk of study bias was assessed using the Cochrane Collaboration risk of bias tool. The risk of bias was evaluated with regard to the following aspects: the method of generating random sequences, allocation of hidden methods, application of the blinding method, incomplete results, selective reporting of results, and other bias. Funnel diagrams were used to detect publication bias.

2.5. Statistical analysis

2.5.1. Extracting and merging data. The Cochrane Collaboration Review Manager 5.3 software was used to extract relevant dichotomous or continuous data from the literature for analysis. The risk ratio was calculated for dichotomous data, whereas the weighted mean difference (WMD) and standard deviations (SD) were calculated for continuous variables. The corresponding 95% confidence interval (CI) and forest plots were used in both cases. In our meta-analysis, we used SD values when data were in the same unit of measure. When they were in different units of measure, we performed a conversion. The chi-square and I^2 (inconsistency) tests were used to detect heterogeneity. A P value < .10 or I^2 > 50% indicated a significant difference in heterogeneity. The fixed-effect model was used when P > .10 and I^2 < 50%, and the random-effect model was used when P < .10 or $I^2 \geq 50\%$.

2.5.2. Data conversion. Mean changes in SBP and DBP were used as indicators to evaluate the effect of VitC in the intervention group and of the placebo in the control group. When there was no explicit reference to SBP or DBP in the studies, we calculated the mean and SD of ΔSBP and ΔDBP using the following formulae.

1) If the number of samples (n) and standard error (SE) were known, the SD was calculated as follows:

$$SD = SE \times \sqrt{n}$$

2) Estimates of SD were calculated if the number of samples (n), mean, and 95% CI[21–23] were known ("a" and "b" are the upper and lower confidence limits, respectively):
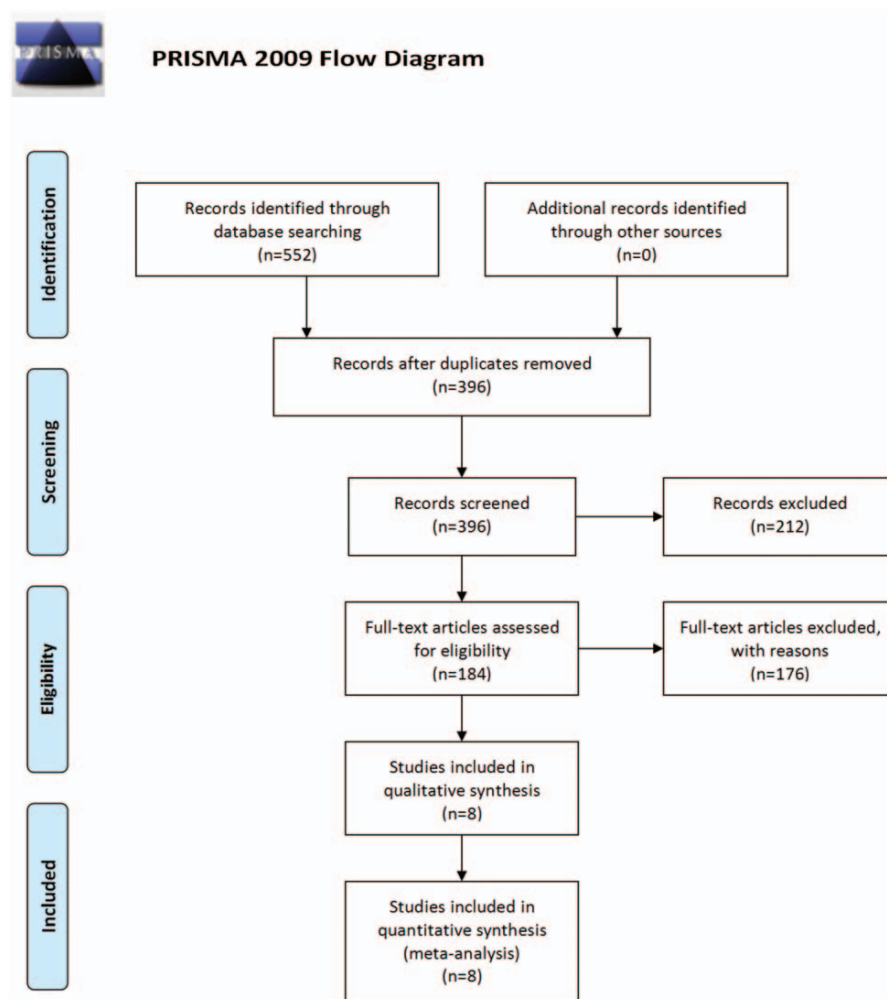
Figure 1. Study selection procedure according to the PRISMA statement.[20] PRISMA = Preferred Reporting Items Systematic Reviews and Meta-Analyses.

$$SD = a - mean \div 1.96\sqrt{n}$$

$$SD = mean - b \div 1.96\sqrt{n}$$

3. Results

3.1. Study selection

We screened 552 study reports, of which 156 were excluded because of duplicate publications. After reading the title and abstract, 212 articles were further excluded, and 184 articles were retained. Among them, 112 articles did not meet the inclusion criteria, 32 studies were improperly compared, and for 32 studies, we could not extract data. Finally, 8 RCTs comprising 614 participants were included. The PRISMA flow diagram is shown in Figure 1.

3.2. Study characteristics

The principal study characteristics are summarized in Table 1. The 8 studies were published between 1991 and 2018. Overall, 614 participants were included. The number of participants in the individual studies ranged from 12 to 480. Participants' mean age ranged from 46 to 78 years. The duration of the intervention varied from 4 to 24 weeks. All participants had essential hypertension. The average SBP and DBP of the participants ranged from 143 to 173 mmHg and from 76 to 97 mmHg, respectively. The supplementary dose of VitC in the treatment group varied between 300 and 1000 mg/dL.

3.3. Quality assessment

Table 2 provides an overview of the risk of bias for the included studies. All included studies used a double-blind approach and reported the number of dropouts. Most trials reported allocation concealment and random allocation but did not mention the specific method used. Selective reporting was unbiased, but without any description to ensure the existence of other biases. Few trials reported adverse events.

Table 1

Randomized controlled trials included in the systematic review of the effects of vitamin C on essential hypertension.

Study	Sample size (intervention/control)	Mean age (years)	Male sex (%)	Country	Study duration (weeks)	Dose of vitamin C supplement (mg/day)	Control	Baseline SBP (intervention/control)	Baseline DBP (intervention/control)	BP measurement details (position, location, device used, number of measurements)
Osilesi et al 1991[24]	12/12	57.8±14.3	50	US	6	1000	placebo	143.4±8/144±4.5	81.8±1.1/81.1±2	Supine, arm, mercury sphygmomanometer, three
Ghosh et al 1994[25]	22/26	73.7±5.1	33	UK	6	500	placebo	173.2±3.2/177±3.3	90.2±2.3/91.1±2.4	Seated, arm, Hawksley Random Zero Sphygmomanometer, three
Fotherby et al 2000[17]	17/17	74±4	58	US	12	500	placebo	149±10/149±10	84±10/84±10	Seated, arm, Hawksley Random Zero Sphygmomanometer, three
Duffy et al 2001[18]	19/21	48.5±12	50	US	4	500	placebo	155±22/156±21	87±9/88±14	Seated, arm, sphygmomanometer, three
Hajjar et al 2002[26]	31/31	62±2	50	US	4	500	placebo	143.6±7.06/144±3	88.24±3.16/88±2	Seated, arm, NA, three
Sato et al 2006[27]	12/12	66.4±5.8	46	Japan	24	600	placebo	154.9±21.6/153.0±19.8	76.3±10.7/90.6±12.6	Seated, arm, oscillometric monitor, three
Bruno et al 2012[28]	32/16	46.7±7.1	71	Italy	20	300	placebo	149.7±17.64/151.6±4.29	97.5±14.49/95.7±9.14	Seated, arm, oscillometric sphygmomanometer (OMRON 705IT), five
Yuan et al 2018[29]	209/126	64.7±9	45	China	24	300	placebo	133.5±14.6/133.4±16.0	82.6±9.0/84.6±9.8	Seated, arm, UA-779 digital monitor, six

NA = not available, UK = United Kingdom, US = United States.

Table 2

Results of the Cochrane Collaboration risk of bias tool for assessing the risk of bias in the 8 randomized controlled trials included in the systematic review of the effect of vitamin C supplementation on essential hypertension.

| Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Osilesi et al 1991[24]	low risk	low risk	low risk	low risk	low risk	unclear
Ghosh et al 1994[25]	low risk	low risk	low risk	low risk	low risk	unclear
Fotherby et al 2000[17]	low risk	low risk	low risk	low risk	low risk	unclear
Duffy et al 2001[18]	low risk	low risk	unclear	low risk	low risk	unclear
Hajjar et al 2002[26]	unclear	low risk	low risk	low risk	low risk	unclear
Sato et al 2006[27]	unclear	unclear	low risk	low risk	low risk	unclear
Bruno et al 2012[28]	unclear	low risk	low risk	low risk	low risk	unclear
Yuan et al 2018[29]	low risk	unclear	unclear	low risk	low risk	unclear
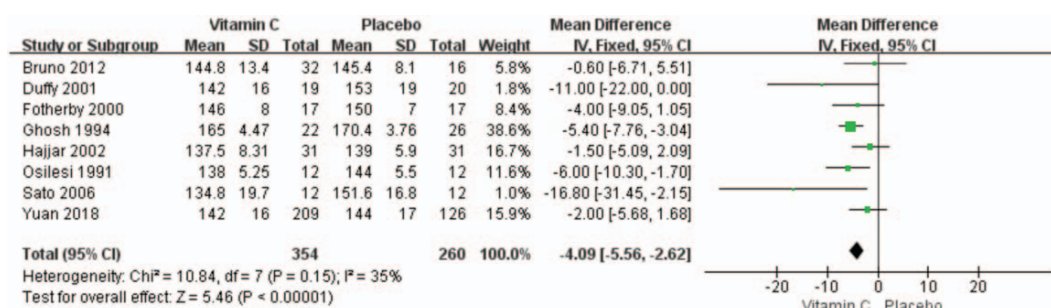
Figure 2. Forest plot of the comparison of mean systolic blood pressure in the 8 randomized control trials on the effect of vitamin C on essential hypertension. CI = confidence interval, SD = standard deviation.

3.4. Study results

3.4.1. Main results. Figures 2 and 3 show the forest plots of the SBP and DBP, respectively. There was a significant difference in SBP between the intervention and control groups (WMD = −4.09; 95% CI −5.56, −2.62; $P < .001$). There was no indication of heterogeneity ($P = .15$, $I^2 = 35\%$, fixed-effect model).

There was a significant difference in DBP between the intervention and control groups (WMD = −2.30; 95% CI −4.27, −.33; $P = .02$). There was an indication of heterogeneity ($P = .0002$; $I^2 = 75\%$; random-effect model).

3.4.2. Subgroup results. There was a significant difference in the SBP (WMD = −3.75, 95% CI −6.24, −1.26, $P = .003$) and DBP (WMD = −3.29, 95% CI −5.98, −.60, $P = .02$) for the subgroup with an age ≥60 years. Combined results of five studies showed that ≥35 participants did significantly reduce DBP (WMD = −2.27, 95% CI −3.42, −1.13; $P < .001$) with relatively low heterogeneity ($I^2 = 49\%$, $P = .10$). In the subgroup analysis, result for SBP with a study duration ≥6 weeks was statistically significant different (WMD = −4.77; 95% CI −6.46, −3.08; $P < .001$), with low heterogeneity ($I^2 = 27\%$, $P = .24$). For an intervention dose of VitC ≥500 mg daily, SBP was statistically significant (WMD = −5.01; 95% CI −8.55, −1.48; $P = .005$), with relatively low heterogeneity ($I^2 = 44\%$, $P = .13$). Results of the analyses of SBP and DBP for different subgroups of the study populations are listed in Table 3.

3.4.2.1. SBP. There was a significant difference in SBP (WMD = −3.75; 95% CI −6.24, −1.26; $P = .003$) and DBP (WMD = −3.29; 95% CI −5.98, −.60; $P = .02$) for the subgroups of age ≥60 years or sample of ≥35 participants compared with the control

group. Compared with the control group, differences in the SBP for the subgroup with a study duration ≥6 weeks (WMD = −4.77, 95% CI −6.46, −3.08, $P < .001$) and that with a VitC dose ≥500 mg (WMD = −5.01, 95% CI −8.55, −1.48; $P = .005$) were statistically significant.

3.4.2.2. DBP. Compared with the control groups, the subgroup analysis for DBP showed that only the subgroup with a sample of ≥35 participants had a significantly different DBP (WMD = −2.27; 95% CI −3.42, −1.13; $P < .001$).

3.5. Publication bias

The publication bias of the 8 RCTs was evaluated with a funnel plot. Figure 4 shows that the publication bias across the studies was small.

4. Discussion

4.1. Effect of VitC supplementation on essential hypertension

VitC is a vitamin found in fresh fruits and vegetables and is an essential water-soluble antioxidant in the human body.[30] According to a review by Taddei et al[31] in 1998, VitC might improve endothelial-dependent vasodilation in patients with essential hypertension and reverse the nitric oxide synthase inhibitor NG-monomethyl-L-arginine 1. Other studies also attempted to explain the possible mechanism of VitC efficacy in the treatment of essential hypertension.[32,33] At present, the main theory is that VitC increases intracellular concentrations of

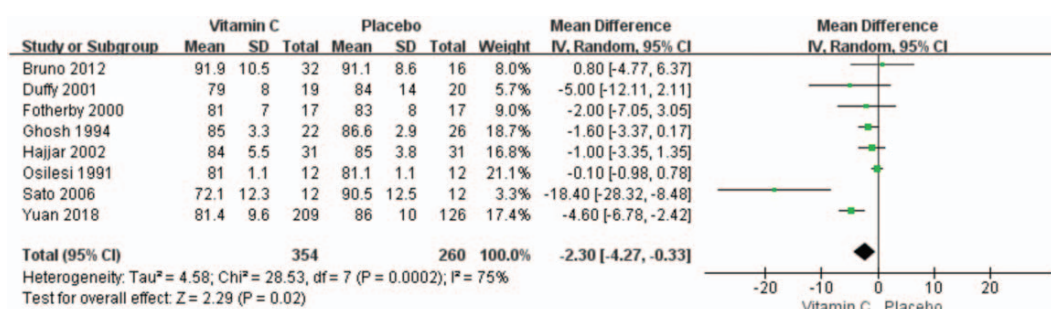

Figure 3. Forest plot of the comparison of mean diastolic blood pressure in the 8 randomized control trials on the effect of vitamin C on essential hypertension. CI = confidence interval, SD = standard deviation.

Table 3

Results of ΔSBP and ΔDBP in different study population subgroups from the 8 randomized controlled trials on the effect of vitamin C supplementation in essential hypertension.

Subgroup	Change in SBP				Change in DBP			
	Number of trials	Heterogeneity	WMD (95% CI)	P value	Number of trials	Heterogeneity	WMD (95% CI)	P value
Mean age								
<60 yr	3	$P=.19$ $I^2=40\%$	−4.87 (−9.67, −.07)	.05	3	$P=.38$ $I^2=0\%$	−.15 (−1.01,.71)	.73
≥60 yr	5	$P=.12$ $I^2=45\%$	−3.75 (−6.24, −1.26)	.003	5	$P=.002$ $I^2=76\%$	−.29 (−5.98, −.60)	.02
Study duration								
<6 weeks	3	$P=.24$ $I^2=30\%$	−1.98 (−4.96, 1.00)	.19	3	$P=.45$ $I^2=0\%$	−1.09 (−3.16,.98)	.30
≥6 weeks	5	$P=.24$ $I^2=27\%$	−4.77 (−6.46, −3.08)	<.001	5	$P=.002$ $I^2=80\%$	−2.26 (−5.15,.63)	.12
Vitamin C dose								
<500 mg	3	$P=.16$ $I^2=46\%$	−3.43 (−6.34,.51)	.02	2	$P=.05$ $I^2=66\%$	−2.41 (−5.07,.25)	.08
≥500 mg	5	$P=.13$ $I^2=44\%$	−5.01 (−8.55, −1.48)	.005	5	$P=.004$ $I^2=74\%$	−2.62 (−5.64,.40)	.09
Country								
America	4	$P=.24$ $I^2=29\%$	−4.13 (−7.10, −1.16)	.006	4	$P=.45$ $I^2=0\%$	−.32 (−1.13,.49)	.44
Other countries	4	$P=.09$ $I^2=54\%$	−3.90 (−7.47, −.41)	.03	4	$P=.001$ $I^2=81\%$	−3.91 (−7.76, −.05)	.05
Sample size								
<35 participants	3	$P=.26$ $I^2=25\%$	−5.92 (−9.92, −1.93)	.004	3	$P=.001$ $I^2=85\%$	−.29 (−.39, 1.34)	.50
≥35 participants	5	$P=.14$ $I^2=42\%$	−4.02 (−6.06, −1.98)	.009	5	$P=.10$ $I^2=49\%$	−2.27 (−3.42, −1.13)	<.001

CI = confidence interval, DBP = diastolic blood pressure, SBP = systolic blood pressure, WMD = weighted mean difference.
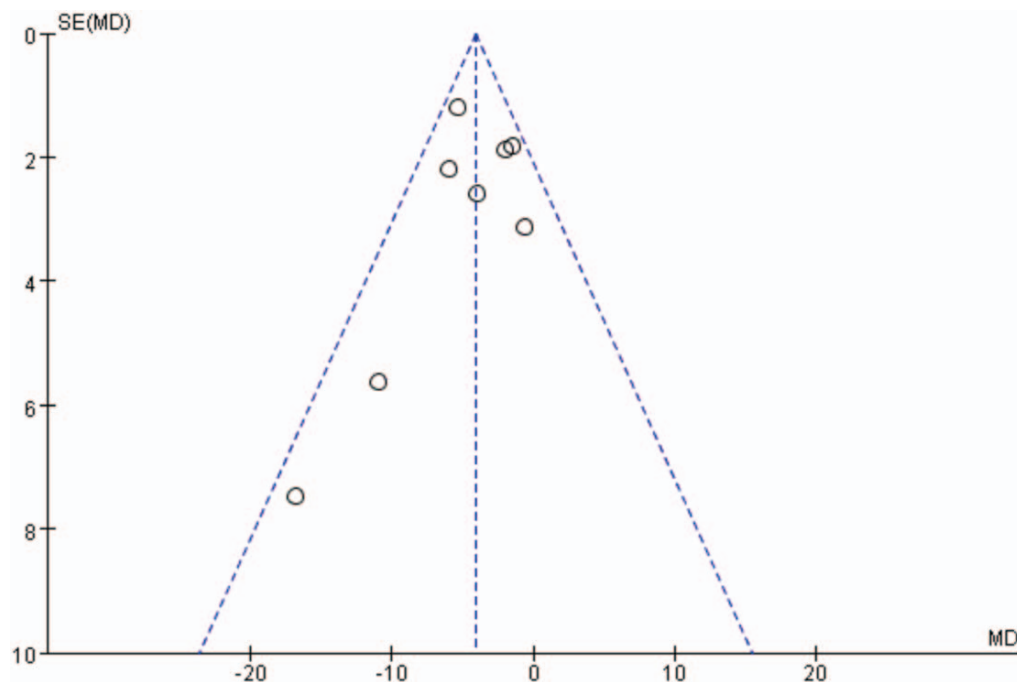

Figure 4. Funnel plot of the 8 randomized control trials on the effect of vitamin C on essential hypertension.

tetrahydrobiopterin, an endothelial nitric oxide synthase cofactor that promotes the production of nitric oxide, which is a potent vasodilator.[34] There is also evidence that VitC enhances the biological activity of nitric oxide.[35] Furthermore, VitC supplementation improved endothelial function in the brachial and coronary arteries in short-term human trials.[36] All aforementioned reports suggest that VitC is an effective preventive and therapeutic supplement in essential hypertension.

However, all studies so far have shown large individual differences and arrived at different conclusions. In several previous meta-analyses,[37,38] the main focus was on the relationship between antioxidants and blood pressure. The present meta-analysis is the first quantitative review of RCTs evaluating the effect of VitC supplementation on essential hypertension. Our meta-analysis included 8 studies with 614 participants and our results showed that VitC supplementation can significantly reduce SBP and DBP in patients with essential hypertension. The meta-analysis by Juraschek et al[39] in 2012 included patients treated with VitC, vitamin E, or magnesium, whereas we focused on participants receiving only VitC. This difference may be the reason why the two studies came to different conclusions.

In the analysis of the subgroup of patients aged ≥60 years, we found a significant difference in SBP and DBP after VitC supplementation as compared to those before supplementation. The reason for this difference is likely the increasing prevalence of hypertension with age. With age, excessive production of reactive oxygen species is observed, resulting in the inability to scavenge all free oxygen radicals and consequently, a decrease in endothelial function.

In the ≥60-year-old subgroup, differences in SBP and DBP between the observation and control groups were statistically significant. The results from Jaja et al's[40] report in 2008 showed that both 6-week and long-term oral VitC in appropriate doses reduced blood pressure levels. These results are consistent with those of our subgroup analyses, where we found a significant difference in SBP between the duration of treatment, VitC dose, country, and sample size.

In the review by Cheng et al[41] in 2017, blood pressure variability also increased with age. This result is because an increase in stiffness of the large arteries is accompanied by early wave reflection, which results in a significant augmentation of the central SBP in the late systole and further adds to the increased cardiac afterload. Blood pressure variability is closely related to the occurrence of heart disease, which can lead to injury of other target organs and increase the risk of vascular and degenerative diseases. Studies have confirmed that blood pressure variability increases the risk of cerebral hemorrhage and Alzheimer disease.[42,43]

Recent studies have shown that the mechanisms of blood pressure variability include endothelial dysfunction and arteriosclerosis; oxidative stress is also often involved.[44] Markers of inflammation and endothelial activation are significantly associated with blood pressure variability, although strong evidence has been found that anti-inflammatory and antioxidant therapies protect target organs from the effect of blood pressure variability.[45] These findings corroborate the results of our study in that antioxidant adjuvant therapy with VitC can reduce blood pressure variability in patients with essential hypertension, thereby protecting the target organs.

Although the exact mechanism of the effect of antioxidant therapy on blood pressure remains to be fully elucidated, there is increasing evidence that antioxidant adjuvant therapy can reduce blood pressure in patients with hypertension to protect the target organs. It is hoped that more detailed information about this mechanism will be obtained in future studies.

4.2. Limitations

This study has several limitations. First, in some cases, we had to calculate and transform data, rather than these being provided directly. Second, the dosage of VitC differed between the 8 RCTs, which may have affected the results of this meta-analysis. In addition, language and publication bias limited our study. Finally, this review included only RCT. In future, there is a need for a greater diversity of research included in the analysis, such as multi-centered studies, more rigorous clinical reports, and prospective studies.

4.3. Clinical implications

Aiming at influencing the pathophysiological mechanisms associated with hypertension, prevention and adjuvant therapy efforts focus on the benefits associated with VitC. Several clinical studies are currently investigating the significance of such potential benefits.[42]

Drug therapy alone does not suffice to effectively treat essential hypertension. Multi-factorial interventions, including increased vitamin intake with defined dosages and duration of treatment, may help to ameliorate and manage the various hypertension-associated vascular endothelial phenomena.

5. Conclusions

Our meta-analysis found that VitC supplementation may play an important role in reducing blood pressure in patients with essential hypertension. However, in view of the current level of evidence, large-scale trials should be conducted, and attention should be paid to the evaluation of blood pressure variability.

Acknowledgments

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Writing – review & editing: Yuanyuan Guan

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