IS VITAMIN C AN EFFECTIVE ANTIHYPERTENSIVE SUPPLEMENT? A REVIEW AND ANALYSIS OF THE LITERATURE

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ABSTRACT

Objective: Hypertension is a common condition with high mortality from associated diseases. Epidemiological evidence suggests that a dietary deficiency of vitamin C may be a risk factor for hypertension. However the literature on vitamin C interventional trials appears divided on the efficacy of vitamin C utilization clinically.

Methods: A literature search and review of published trials using vitamin C in treating patients with hypertension was undertaken. Relevant references were located using MEDLINE (1966–2005) and the bibliographies of located articles.

Results: Thirteen trials making up 14 separate groups were identified and analyzed providing a pooled population of 284 hypertensive patients (52% female), with a weighted mean age of 58.8 ± 9.5 years. Median vitamin C dose and study intervention duration was 500mg/day and 6 weeks respectively. The weighted mean baseline and post treatment systolic blood pressures across all 14 groups were 149.6 ± 11.1 and 145.7 ± 11.0 mmHg respectively. This represented a systolic blood pressure decrease of 3.9 mmHg. Seven of the 14 groups ascertained statistically significant reductions ($p < .05$) in systolic blood pressures. However only 2 of the 14 groups found significant reductions in diastolic blood pressure. The weighted mean baseline and post treatment diastolic blood pressures across all 14 groups were 84.6 ± 4.4 and 82.5 ± 4.1 mmHg respec-

tively. This represented a diastolic blood pressure decrease of 2.1 mmHg.

Conclusion: Vitamin C supplementation in hypertensive patients appears to possess modest effects on reducing systolic blood and diastolic blood pressure. (*J Chiropr Med* 2006;5:60–64)

Key Indexing Terms: Vitamin C; Ascorbic Acid; Blood Pressure; Hypertension

INTRODUCTION

Hypertension affects at least one-quarter of the adult population in the United States and is an important determinant of the incidence of coronary heart disease and stroke.¹ Epidemiological evidence suggests that a deficiency of vitamin C may lead to hypertension, and a negative association between plasma vitamin C status and blood pressure has been reported.^{2–7} However this association only suggests, but does not prove, that the intake of extra vitamin C lowers blood pressure. Clinical trials performed to assess the effect of vitamin C supplementation on blood pressure in hypertensive individuals have met with mixed results.^{8–20} In 1997 Ness et al. concluded that there were too few clinical trials, and those reported at that time were generally too small and too varied to provide confirmatory evidence for a casual relationship.²¹ This study was undertaken in order to evaluate the current clinical evidence that vitamin C supplementation lowers both systolic and diastolic blood pressure in hypertensive individuals, and to also review the hypothesized mechanisms of action.

METHODS

A literature search using MEDLINE (January 1966 through October 2005) for published studies that examined the effects of vitamin C on blood pressure was performed using the terms ["Vitamin C" OR "Ascorbic Acid"] AND ["Blood Pressure" OR "Hypertension"]. Studies identified as experimental trials utilizing hypertensive subjects supplemented

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TABLE 1
SUMMARY OF TRIALS INVESTIGATING THE EFFECT OF VITAMIN C ON BLOOD PRESSURE

AUTHOR AND YEAR [REF]	SAMPLE SIZE	MEAN AGE	DOSE VITAMIN C/DAY(MG)	STUDY DESIGN*	DURATION (WEEKS)
KOH 1984 [8]	23	>35	1000	BC	12
OSILESI ET AL. 1991 [9]	20	57.8	1000	CO	6
LOVAT ET AL. 1993 [10]	24	72	400	CO	4
GHOSH ET AL. 1994 [11]	22	73.7	500	RCT	6
ERIKSSON AND KOHVAKKA 1995A [12]	29	43	2000	CO	12
ERIKSSON AND KOHVAKKA 1995B [12]	27	61	2000	CO	12
GOKCE ET AL. 1999 [13]	21	56	500	RCT	4
FOTHERBY ET AL. 2000 [14]	17	72	500	CO	12
ROLLA ET AL. 2000 [15]	8	49.9	1000	RCT	4
DUFFY ET AL. 2001 [16]	19	48	500	RCT	4
DARKO ET AL. 2002 [17]	18	55.5	1500	RCT	4
HAJJAR ET AL. 2002 [18]	24	62	1000	BC	12
MULLAN ET AL. 2002 [19]	15	61	500	RCT	4
MAGEN ET AL. 2004 [20]	17	52.6	500	RCT	8

* BC (BASELINE COMPARISON); CO (CROSS OVER); RCT (RANDOMIZED CONTROLLED TRIAL)

with vitamin C as a mono therapeutic were retrieved for analysis and additional publications were identified from the bibliographies of previously retrieved papers. Data was extracted from the published reports and the following items were entered into an Excel spreadsheet: study design; number of subjects; mean age or age range; vitamin C dose/day; duration of treatment; baseline and post treatment measures for systolic and diastolic blood pressure. Based on population size the weighted mean differences between baseline and post treatment measures for systolic and diastolic blood pressure were calculated and compared. Comparisons were not statistically analyzed because the standard deviation of weighted means does not reflect between-subject variances, but only between-study variances.

RESULTS

Thirteen trials⁸⁻²⁰ making up 14 separate group populations were identified and analyzed providing a total pooled population of 284 hypertensive patients (52% female), with a weighted mean age of 58.8 ± 9.5 years and a weighted mean body mass index of 28.5 ± 1.9 Kg/m². Median vitamin C dose and study intervention duration was 500mg/day and 6 weeks respectively (Table 1).

Seven of the 14 group populations ascertained significant differences ($p < .05$) between baseline and post treatment systolic blood pressure.^{8,9,11,14,15,16,19} The weighted mean baseline and post treatment systolic blood pressures across all 14 group popula-

tions were 149.6 ± 11.1 and 145.7 ± 11.0 mmHg respectively. This represented a systolic blood pressure decrease of 3.9 mmHg.

However, only 2 of the 14 groups found significant differences between baseline and post treatment diastolic blood pressure.^{11,19} The weighted mean baseline and post treatment diastolic blood pressures across all 14 group populations were 84.6 ± 4.4 and 82.5 ± 4.1 mmHg respectively. This represented a diastolic blood pressure decrease of 2.1 mmHg.

Of the 7 of 13 trials which recorded baseline and post treatment plasma vitamin C levels, all 7 showed significant increases in plasma vitamin C concentrations post treatment.^{8,9,11,14,16,17,19} The baseline plasma vitamin C levels ranged between 44 to 74 μ mol, while the range in post treatment levels ranged between 78 to 122 μ mol. The average change between baseline and post treatment levels was 40.7 μ mol.

Five of the 13 trials utilized randomized double-blind placebo controlled parallel designs,^{11,13,16,17,19} 2 utilized randomized single-blind placebo controlled parallel designs,^{15,20} 2 utilized randomized double-blind placebo crossover designs,^{10,14} 1 used a single blind placebo crossover design⁹ and 1 more used a randomized double-blind cross-over design using supplemental magnesium for the other arm of the trial.¹² The remaining two studies were baseline comparisons.^{8,18}

TABLE 1
CONTINUED

SYSTOLIC BLOOD PRESSURE				DIASTOLIC BLOOD PRESSURE			
BEFORE	AFTER	CHANGE	STATED STATISTICAL SIGNIFICANCE	BEFORE	AFTER	CHANGE	STATED STATISTICAL SIGNIFICANCE
143.9	136.3	7.6	0.05	87.8	83.8	4	NS
139	128.8	10.2	0.01	81	78.9	2.1	NS
173	168	5	NS	80	77	3	NS
173.2	162.9	10.3	0.05	90.2	84.3	5.9	0.03
138	143	-5	NS	82	82	0	NS
149	155	-6	NS	87	88	-1	NS
145	142	3	NS	78	79	-1	NS
149	145.3	3.7	0.05	84	82.8	1.2	NS
150.6	141.2	9.4	0.001	93.6	91.2	2.4	NS
155	142	13	0.001	87	79	8	NS
141	141	0	NS	80	81	-1	NS
144	140	4	NS	88	84.7	3.3	NS
142.1	132.3	9.8	0.001	83.9	79.5	4.4	0.003
150.6	150.6	0	NS	86.1	87.4	-1.3	NS

DISCUSSION

Vitamin C supplementation in hypertensive patients appears to possess modest effects on reducing both systolic and diastolic blood pressure. It has been previously estimated that a sustained 2 mmHg reduction of diastolic blood pressure is associated with 14% less stroke and 8% less coronary heart disease.²² From a public health standpoint this is important because the average weighted mean change in diastolic blood pressure observed in this analysis was 2.1 mmHg. But it should be clarified that the change in diastolic blood pressure observed within 12 of the 14 individual study groups was not large enough to be statistically significant, and hence may be nothing more than random fluctuations in blood pressure over time.

Regardless of the observed statistical significant findings within individual studies, the pooled effects of vitamin C supplementation on the reduction of both systolic and diastolic blood pressure is consistent with epidemiologic observations that there exists an inverse relationship between blood pressure and plasma vitamin C status. This finding supports that a modest change in mean population vitamin C intake has the potential to positively impact cardiovascular disease rates in the population.

In comparison to other proposed nutritional supplements for reducing blood pressure, vitamin C may be as beneficial and maybe even superior in its effects on reducing systolic and diastolic blood pressure. A meta-analysis of potassium supplement studies suggests a reduction in both systolic blood

pressure of approximately 3.1 mmHg and diastolic blood pressure of 2.0 mmHg.²³ A meta-analysis of calcium supplement studies suggests an even smaller effect on systolic blood pressure of 1.7 mmHg and no effect on diastolic blood pressure.²⁴

In regard to mechanism of action, hypertension is associated with higher than normal lipoperoxidation and an imbalance in antioxidant status, suggesting that oxidative stress is an important driving factor in the pathogenesis of hypertension.²⁵ Hypertension has been shown to be associated with impaired nitric oxide (NO) production.²⁶ Vascular endothelium derived nitric oxide (eNOS) plays a critical role in the regulation of vascular tone and it appears that vitamin C can improve endothelium vasodilation by augmenting NO bioavailability.²⁷ Because superoxide radicals can degrade NO, it has been proposed that vitamin C improves blood pressure by scavenging superoxide radicals and thereby preventing the inactivation of NO^{28,29} (Fig 1). However, it has been reported that supraphysiological concentrations of vitamin C are required to prevent the superoxide radical destruction of NO.³⁰

It is also known that oxidized LDL inhibits NO release from endothelium cells, and therefore vitamin C may preserve NO by preventing the oxidation of LDL.^{31,32} Vitamin C may also increase NO production by enhancing eNOS activity.³³ This effect appears to be mediated through increasing the intracellular content of tetrahydrobiopterin.³⁴ Tetrahydrobiopterin is as a cofactor for eNOS which requires vitamin C for stabilization as well as protection from oxidation (figure 1). These effects were

Figure 1. Proposed mechanism showing the relation between vitamin C and reducing blood pressure. eNOS, endothelial Nitric Oxide Synthase; H₄B, Tetrahydrobiopterin; O₂⁻, Superoxide Free Radical; oxLDL, Oxidized Low Density Lipoprotein.

evident as an increase in the half-life of tetrahydrobiopterin inside the endothelial cell has been observed.³⁵

If the antihypertensive effects of vitamin C are due to its antioxidant properties, then antioxidants other than vitamin C should also show antihypertensive properties. However, the results of 3 randomized trials to test the effects of vitamin E on hypertension have proven disappointing.^{36,37,38} One explanation for the negative results may be in part due to the use of vitamin E as a sole antioxidant. When vitamin E reacts with a free radical, it subsequently becomes a free radical, which itself may participate in pro-oxidative events leading to LDL oxidation and subsequent NO inactivation. However under normal dietary conditions vitamin C regenerates vitamin E and therefore reduces the pro-oxidant load. Only one clinical trial has investigated a combined antioxidant trial using vitamin C and E on hypertension. This trial found a significant reduction in systolic blood pressure (168.7 to 159.7mmHg) but a non-significant decrease in diastolic blood pressure (89.3 to 85.5 mmHg).³⁹

A major limitation of this study is the pooling together of clinical trials which include a considerable amount of heterogeneity in design and population characteristics. Average subject age varied between 43 and 73 years and it is known that vitamin C concentration in serum decreases with aging, while a concomitant increase in blood pressure occurs.⁴⁰ Differences in age and dietary characteristics may result in unevenly matched baseline plasma vitamin C concentrations. In the 7 studies which observed plasma vitamin C concentrations, the range varied

between 44 to 74 µmol. This may confound both the starting baseline blood pressures as well as the absorbability of vitamin C supplementation which is dependent upon pre-absorption plasma concentrations. Also, not having evenly matched baseline blood pressures could confound the results as populations with higher baseline blood pressures could possibly exhibit more of a hypotensive effect with vitamin C supplementation.

Confounders also included differences between studies with vitamin C supplementation dose (ranged between 400 to 2000mg/day) and study duration (ranged between 4 to 12 weeks). Finally, subject characteristics such as populations with and without type 2 diabetes could result in differences in how the individual populations respond to vitamin C supplementation. Diabetic patients have greater levels of oxidative stress than other groups of patients at risk of cardiovascular disease⁴¹ and therefore may respond more favorably to vitamin C supplementation. Previous studies using type 2 diabetics has revealed diminished tissue levels and impaired vitamin C recycling mechanisms.⁴² However, when comparing the 4 group populations^{12,17,19} comprised of diabetic subjects against the remaining 10 group populations, there was no observable difference between changes in systolic or diastolic blood pressure after vitamin C supplementation between these two groups.

CONCLUSIONS

This analysis and review has shown that supplementation with at least 500mg/day of oral vitamin C for 6 weeks can lower both systolic and diastolic blood pressure, which is known to result in a reduction in the incidence of cardiovascular disease and death due to cardiovascular complications. Although the reduction in systolic and diastolic blood pressure was modest with vitamin C supplementation, any decrease will be beneficial especially in light of the low cost and absence of toxicity within ranges of 500 to 1000mg/day.⁴³

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