A Double-Blind, Placebo-Controlled Parallel Trial of Vitamin C Treatment in Middle Aged Patients (35-50 Years Old) with Mild Primary Hypertension

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Abstract

Objective- An evaluation of the effect of vitamin C on blood pressure is very important because hypertension is a major risk factor for cardiovascular, cerebral and renal diseases. We studied the effect of vitamin C on the blood pressure of patients between 35-50 years old with mild primary hypertension in Kerman.

Methods- We conducted a prospective one-year double-blind, placebo controlled parallel trial on 42 middle aged patients with mild primary hypertension at the hypertension clinic in Kerman University of Medical Sciences. Following a 2-week run-in phase, two age and sex matched groups of untreated hypertensive subjects received 8 weeks oral treatment with either vitamin C, 250 mg twice daily (n=21; 8 M/13F, mean age 42.7 ± 5.3 years) or placebo one tablet twice daily (n=21; 10 M/11F, mean age 42.7 ± 5.9 years). Blood pressure was measured in the sitting position on three occasions during the run-in phase, and again at 1, 2, 4 and 8 weeks after commencing treatment. Venous blood samples for the measurement of plasma ascorbic acid were measured at baseline and at 1, 2, 4, 8 weeks after treatment.

Results- Plasma ascorbic acid level in vitamin C group significantly changed from 8.8 ± 3 umol/l at baseline to 32.3 ± 12 umol/l at 8 weeks, but in placebo-treated group, it changed from 13.8 ± 6 umol/l at baseline to 9.01 ± 4.1 umol/l at 8 weeks during the study period. A more significant fall in mean blood pressure was observed in the vitamin C group than the placebo-treated group such that the mean systolic blood pressure decreased from 153.1± 5 to 144±5.3 mmHg in vitamin C group and from 154.1±4.9 to 149±4.9 mmHg in the placebo group. The mean diastolic blood pressure decreased from 95.7±1.4 to 91.4±1.7 mmHg in the vitamin C group and from 96.2±1.6 to 94.0±1.6 mmHg in the other group.

At 8 weeks, the significant difference in the reduction of systolic blood pressure (p<0.05) and diastolic blood pressure (p<0.001) between the two groups became apparent.

Conclusion- Vitamin C intake has a useful effect on lowering blood pressure. **(*Iranian Heart Journal.* 2002, 2003; 3(2&3): 49-53)**

Key word: systolic blood pressure < diastolic blood pressure vitamin C < antioxidant.

Hypertension is multifactorial disease that can be influenced by genetic, race diet, hormonal and geographical conditions. Many studies have related hypertension to the intakes of sodium, potassium, calcium and energy. The role of dietary antioxidants in relation to blood pressure is of recent interest. Epidemiologic data support an inverse association between circulating antioxidants such as vitamin C and blood pressure.[7,14] Other investigators in the United States and Japan have reported the same results.[10,11,16]

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Ulrich Solzbach also found that vitamin C improves the endothelium-dependent vasomotor capacity of coronary arteries in patients with hypertension and patent coronary arteries.[15]

Duffy in 1999 showed that an intake of 500mg vitamin C daily for one month decreased systolic blood pressure significantly, but diastolic blood pressure change was not clear.[3] He measured plasma vitamin C level only at base and the end of the study and its changes throughout the study period was not evaluated.

Doing this research is necessary for the following reasons:

1- it is not clear whether the effect of vitamin C on blood pressure is the same in different races, geographical situations and dietary habits. The amount of vitamin C intake is especially different depending on the dietary habits in different countries.
2- In many previous studies, the subjects had been old (>65 years) or with no special age limit, while with aging and progression of atherosclerosis, endothelial dysfunction appears and this may influence the effect of vitamin C on blood pressure in young and old patients.
3- In other studies, the time of the effect of vitamin C on BP and the time needed to observe the highest level of the effect were not clear, so we planned this research to investigate these above items.

Methods

This double blind, placebo-controlled parallel trial was done in two groups (the vitamin C group and the placebo one).

Patients

Patients were recruited into the study from the hypertension clinic in cardiovascular research center of Kerman University of Medical Sciences. None was receiving any antihypertensive drugs. Inclusion criteria included those with a constant SB_P* 140-159 mmHg and D_{BP}** 90-99 mmHg, which were recorded on three separate occasions. They were selected because patients with such blood pressure (mild primary HTN) did not need drug treatment.

All the patients had normal renal, liver and cardiac functions according to the clinical and routine lab examinations. They had no history of cardiovascular diseases such as angina pectoris, MI and CHF and no change in dietary habits during the 8 weeks prior to the study. Moreover, they did not use tobacco, alcohol, sympathomimetic drugs, vitamins, antidepressants and antiarrhythmic drugs and were matched according to dietary habits and the amount of daily vitamin C intake.

Study Design and Measurements:

Prior to commencing the study, all patients under went a dietary review by a hospital dietician to ensure that none were taking nutritional or vitamin supplements and none were followers of unusual diets all patients were asked not to take any vitamin supplements during the study. But to take prescribed vitamin C or placebo tablets regularly and refer to clinic on the special dates. During a 2-week run-in phase, the blood pressure was taken in sitting position after 15 min rest by a mercury sphygmomanometer on three separate occasions and each time twice. Base line blood pressure values were taken as the mean of the last two measurements obtained during the run-in phase. Following a 2-week run-in phase, two age- and sex-matched groups of untreated hypertensive subjects were randomized in a double-blind study to receive 8 weeks oral treatment with either vitamin C, 250 mg twice daily (n=21; 8 M/13F, mean age

*SBP: Systolic Blood Pressure
**DBP: Diastolic Blood Pressure

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42.7±5.3 years) or placebo, one tablet twice daily (n=21; 10M/11F mean age 42.7±5.9 years) vitamin C tablets were prepared by Daro Pakhsh company and matching placebo tablets by Kerman pharmaceutics faculty.

Blood pressure and plasma Ascorbic Acid were measured at base line and at 1, 2, 4 and 8 weeks after commencing treatment.

Fasting venous blood for measurement of plasma ascorbic acid was taken one hour after using of prescribed tablets.

Compliance with treatment was assessed using tablet counts and by the plasma ascorbate concentrations in those patients receiving vitamin C.

Plasma Ascorbate level analysis:

5ml fasting blood samples was obtained by venipuncture and promptly centrifuged for 10min at 4°c to separate the plasma. Immediately after harvesting the plasma, ascorbic acid was stabilized by 10% (w/v) metaphosphoric acid. Samples were vortex mixed, centrifuged for 10min at 4°c and stored at-25°c in the dark for ≤ 2 months. Ascorbic acid was measured by high performance liquid chromatography using a modification of the method of Lunec and Blake.[8]

Statistical analysis:

Data analysis was performed using SPSS 10. The analysis used paired t. test, independent t. test and regression analysis.

Results

Mean blood pressure changes (baseline vs. 8 weeks) in both groups was as following:

In vitamin C- treated group, systolic blood pressure (mean change 9.1 with 95% CI* 6.3- 9.95) mmHg, P<0.0001 and diastolic blood pressure (mean change 4.3 with CI 95% 4.1-4.5) mmHg, P<0.0001.

In placebo-treated group, S_{BP} (mean change 5 with 95% CI 4.9-5.3) mmHg, P<0.001 and D_{BP} (mean change 2.2 with 95% CI 2-2.3) mmHg, P<0.001 (table 1).

Table I. The mean systolic and diastolic blood pressure measurements in the vitamin c-treated and placebo treated groups at baseline, 1, 2, 4 and 8 weeks.

Blood pressure (mmHg)	0 weeks	1 weeks	2 weeks	4 weeks	8 weeks
Vit.C group (n=21) S_{BP}	153.1 (5)	152 (5.2)	150.8 (5.1)	148.9 (5.3)	144 (5.3)
D_{BP}	95.7 (1.4)	95.1 (1.8)	94.8 (1.6)	93.9 (2)	91.4 (1.7)
Placebo group (n=21) S_{BP}	154.1 (4.9)	153.5 (4.8)	151.4 (4.2)	150.9 (4.6)	149.1 (4.9)
D_{BP}	96.2 (1.6)	95.7 (1.7)	94.7 (1.2)	94.7 (1.4)	94.0 (1.6)

During the study period, more significant fall in mean blood pressure was observed in the vitamin C group than placebo-treated group so that the mean S_{BP} decreased from 153.1 ± 5 to 144 ± 5.3 mmHg in vitamin C group and from 154.1 ± 4.9 to 149.1 ± 4.9 mmHg in placebo-treated group. Mean D_{BP} decreased from 95.7±1.4 to 91.4±1.7 mmHg in vitamin C group and from 96.2±1.6 to 94±1.6 mmHg in the other group at 8 weeks, there was significant difference in the decrease of S_{BP} (P< 0.05) and D_{BP} (P<0.001) between two groups and there was no significant difference in mean systolic and diastolic blood pressures between males and females in vitamin C group (Table 2).

Table II. The mean systolic and diastolic blood pressure measurements according to sex in vitamin C-treated group at base line and 8 weeks.

	Male (n=8)		Female (n=13)	
Blood pressure (mmHg)	0 weeks	8 weeks	0 weeks	8 weeks
S_{BP}	152.4 (5.5)	143 (6.1)	153.5 (4.8)	146.2 (5.7)
D_{BP}	95.6 (1.7)	91.1 (2.2)	95.8 (1.2)	91.6 (1.5)

Values are mean (SEM) mmHg

In vitamin C group, plasma ascorbic acid concentration significantly increased from 8.8 ± 3 umol/L at baseline to 32.3 ± 12 umol/L at 8 weeks, (P< 0.0001) but in the

* CI: Confidence Interval

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placebo-treated group, it changed from 13.8 ± 6 umol/L at baseline to 9.01 ± 4.1 umol/L at 8 weeks (Table 3).

Table III. Plasma ascorbic acid concentrations (umol/L) in the vitamin C-treated and placebo-treated groups at baseline, 1, 2, 4 and 8 weeks.

Group	0 weeks	1 weeks	2 weeks	4 weeks	8 weeks
Vit. C (n=21)	8.8 (3)	13.3 (5.3)	17.2 (7.3)	22.4 (11.5)	32.3 (12)
Placebo (n=21)	13.8 (6)	11.1 (6)	11.6 (5)	9.8 (3.8)	9.01 (4.1)

Values are mean (SEM)

Discussion

Hypertension is an important risk factor for cardiovascular disease including myocardial infarction and stroke. It is a multifactorial disease in which nutrition has an important role.

It has been recently proved that dietary antioxidants such as vitamin C and E, selenium, carotenoids has an important role on blood pressure.[1]

Noradrenergic vascular hyper-responsiveness is a hallmark of essential hypertension. This response is due to enhanced inactivation of nitric oxide realized by oxygen free radicals specifically produced by norepinephrine. Antioxidant therapy can restrain the effect of sympathetic nervous system on vascular tissue through increased nitric oxide availability in hypertensives. In addition, it can reduce cardiovascular morbidity and mortality.[6] Giuseppe showed that vascular endothelial response to sympathetic neurotransmitters and angiotensin-II is impaired in hypertensives and it is corrected by ascorbic acid injection.[6]

McCarron and Salonen also observed that blood pressure is inversely related to plasma vitamin C level.[9,12]

Ghosh and other investigators concluded that high intake of vitamin C in elderly patients could have useful effects on lowering blood pressure.[5,2]

Fotherby determined the effect of vitamin C on ambulatory blood pressure and showed that vitamin C supplementation only affected daytime not night-time or clinic blood pressure in both placebo and vitamin C groups. Daytime ambulatory blood pressure in vitamin C group showed a small but significant fall in S_{BP} (2.0 ± 5.2 mmHg; 95% CI 0-3.9 mmHg) but not in D_{BP}.[4] But in present study, significant fall in both clinic systolic (9.1 mmHg; 95% CI 6.3-9.95) and diastolic (4.3 mmHg; 95% CI 4.1-4.5) blood pressure occurred, therefore, vitamin C had better effect on lowering blood pressure in the present study than Fotherby's study. These differences may be related to age or plasma vitamin C level. Fotherby's subjects were older (60-80 years old) and also had higher base line plasma vitamin C level (49 ± 14 umol/L).

In the present study decrease in both systolic and diastolic blood pressure of placebo-group can be due to placebo effect and more decrease in blood pressure in vitamin C group also related to significant increase of plasma ascorbic acid level due to regular intake of vitamin C tablets.

Bates showed that the decrease in S_{BP} for a 50 umol/L increase in plasma vitamin C was 7 mmHg.[1] But in the present study the decrease in SBP and DBP for 10 umol/L increase in plasma vitamin C were 3.25 and 1.5 mmHg, respectively. Therefore in present study decrease in blood pressure was higher than Bates' study. This difference may be due to age, race and dietary habits.

Bates' subjects were older than our subjects (>65 vs. 35-50 years old). We selected the middle-aged patients with mild primary hypertension and therefore cardiovascular problems were less. It is possible that older patients with higher blood pressure respond better to vitamin C treatment.

Various studies show that vitamin C effect on vascular tissue depends on endothelium.[6,16] Vitamin C improves abnormal endothelium better than intact endothelium. Therefore it is recommended to examine this hypothesis on older

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patients with higher blood pressure by adding vitamin C to classic antihypertensive agents. In the present study, lower plasma vitamin-C level at base line than normal range (23-84 umol/L)[13] shows that all people especially hypertensives must use higher amounts of vitamin C as part of a healthy diet rich in fruits and vegetables.

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