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Vitamin C Mega Dose vs. Standard Dose in Smokers with Subclinical Hypovitaminosis C, A Controlled Randomised Clinical Trial – a short review.

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Abstract

Smoking induces oxidative stress, which has been demonstrated to lower plasma Vitamin C levels. Adult smokers in Bogota, Colombia were randomly recruited into 2 groups, a megadose Vitamin C group (Day 1, 15g IV, Day 2, 15g IV, One gram orally for 2 weeks after) and a standard Vitamin C dose group (Day 1, 100mg IV, Day 2 100mg IV). The study was double blinded. Urine Vitamin C, haemoglobin and haematocrit were measured pre and post intervention in both groups. Results: At the end of the study Haematocrit and Haemoglobin levels were lowered significantly in the megadose group. C-LDL was not significantly different between the groups. Urine Vitamin C was raised in both groups.

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Introduction

This is a brief overview of the full trial conducted by Salom et al in Bogota, Colombia in 2007. It does not contain details about randomization, masking, bias, statistical analysis and a full history of the trial which is presented in Spanish in the full original document. Rather it is an overview of some of the key aspects of the trial, with a summary of the results and a short discussion.

It is a well known fact that smokers present plasma and leukocyte concentrations of Vitamin C substantially lower than those of the ones who do not smoke.[1] The traditional explanation that used to be given to this phenomenon, was the alteration of eating habits of smokers, which reduces Vitamin C contribution.[1]

Nowadays it is known that smokers have a higher Vitamin C metabolism and, therefore, greater requirements of it than nonsmokers .[2] Another important consideration is that smokers have somewhat reduced Vitamin C absorption. These facts contribute to lower plasma and leukocyte levels of Vitamin C, which means that smokers run a higher risk of suffering from a marginal deficiency of Vitamin C.

The metabolic turnover of vitamin C starts to saturate itself towards 40-50 mg of metabolites per day amongst nonsmokers, and towards 70-90 mg per day of metabolites amongst smokers. In order to achieve these limits, a total turnover of 60 mg of Vitamin C per day is required amongst the nonsmokers, and of 90 mg of Vitamin C per day amongst smokers.[3] It is important to mention that plasma concentration is a better measure of Vitamin C status[4], however in Colombia no routine testing of plasma Vitamin C levels is conducted by local pathology groups or Universities. On account of this, for the purpose of this study, the level of Vitamin C will be measured in urine by testing with C-Strips®.[5]

Smoking is a great risk factor for the development of arteriosclerosis associated with coronary disease and peripheral vascular disease. The abnormal endothelial function, the increase in adhesiveness of monocytes and the oxidative damage, are the three mechanisms that contribute to the development of arteriosclerosis. Some researches suggest that supplementation with antioxidant vitamins, mainly Vitamin C, can help modulate these reactions[6]. In the past, it was believed that the diseases associated to smoking were caused by the oxidative damage to the lipoproteins. This is due to the fact that increased levels of products of lipid peroxide were found in the urine of smokers. Nevertheless, in later studies[7], the evidence suggests that abnormal endothelial function - a condition usually associated to chronic smoking - could be involved in the pathogenesis of arteriosclerosis. A study of smokers in 1996[8] reported improvement in endothelial function, with Vitamin C. It is also known that smoking increases adhesiveness of monocytes and decreases plasma levels of Vitamin C. The capacity of monocytes for adhering to the endothelium is a crucial step in the etiology of arteriosclerosis. A previous trial in smokers using 2 grams of Vitamin C a day during ten days restored the plasma levels of Vitamin C and diminished adhesion of monocytes to the values found in nonsmokers[9].

The multiple antioxidant mechanisms of ascorbate through intracellular sweeping of free radicals, the blocking of lipid peroxide and of establishing hemodynamic control, have been demonstrated in the smoking individual[3]. This effect is possible if an intravenous megadose is used - by contrast with the standard dose[10]. When reviewing the databases Pub Med, Cochrane, Proquest, Ovid, Ebsco and Hinary, we did not find specific studies on the effect of megadose Vitamin C in the treatment of hypovitaminosis C in smokers or its action on hematocrit and hemoglobin, which are increased in smokers.

Our intention with this study is to generate valuable data that may provide useful medical evidence and data for deciding whether or not to include megadose Vitamin C in treatment guides for the smoker. This study is a

randomized, controlled, double-blind, clinical trial of Vitamin C administered to patients who are smokers. The study is designed to test whether a megadose of Vitamin C diminishes the harmful effects of marginal Vitamin C deficiency in smokers, compared to a standard dose control.

Definitions

Considering the doses of Vitamin C used in various published studies and cases, the demonstrated safety of Vitamin C, and the opinion of the experts in Australia, our "megadose" criteria has been standardised for this study to 30g of Vitamin C (intravenously), and the'standard dose' to 200mg (intravenously).

Study population

Adult smokers, in the city of Bogotá, who fulfill the inclusion and exclusion criteria defined below.

Inclusion criteria

- Signing written agreement
- Not being in hospital
- Being over 18 years old
- Being smoker of more than 10 cigarettes a day
- Having smoked in a continuous way for at least 1 year
- Both genders
- Having subclinical hypovitaminosis C

Exclusion criteria

- Having personal record of anemia of any type (In order to rule out these participants, Hto and Hb will be taken before the intervention)
- Having personal record of urolithiasis and / or hyperuricemia (calculi)
- Having renal problems of any kind
- Pregnancy and lactation
- Woman at reproductive age, having active sexual life, who is not planning contraception with a reliable contraceptive during the period of implementation, and observation of this study and / or that may be positive for pregnancy test (in order to rule out a possible pregnancy, a test will be carried out before the intervention of this present study)
- Suffering from acute pathologies of any type
- Use of any Vitamin C 24 hours before the application.

In order to calculate the size of the study population, 2 procedures were used. Initially, software from the Universidad Javeriana was used to determine the size of the sample, and later on, the formula of Studies for the evaluation of differences was used. A sample of 46 randomly assigned patients was chosen - assigned to these groups: 27 patients in the megadose group and 19 patients in the standard dose (control) group.

The random assignment to the two groups was carried out by way of the use of the EPITABLE, Simple / Random List Program.

On enrolment in the study participants are given a questionnaire designed to evaluate the condition of the individual who was admitted to the study.

Materials and methods

Sodium Ascorbate 30g in 100mL (Biological Therapies, Melbourne, Australia), Vitamin C capsules (1g) and visually identical placebo capsules were used in the study.

The administration of the medications was blinded so that the administering doctor or the patient did not know which medication was being given.

Laboratory investigations included urine Vitamin C, Haematocrit, Haemoglobin, C-LDL, C-HDL. Systolic and diastolic blood pressures were measured.

DAY 1 Questionnaire is completed by both groups.

- Group A (experimental), or MEGADOSE: Pretest urine and blood samples were collected for baseline blood (FBE and lipids) and urine (Vitamin C) values. Patients are now infused with megadose intravenous Vitamin C (IVC) according to the following protocol: to 250 cc of 0.9% saline is added 15g of Vitamin C in 50 cc. Infusion is over 20 minutes during which time the patient is given 1 or 2 glasses of water.
- Group B (control), or Low Dose: Pretest urine and blood samples were collected for baseline blood (FBE and lipids) and urine (Vitamin C) values. Patients are now infused with low dose IVC according to the following protocol: to 250 cc of saline 0,9% is added 100 mg of Vitamin C. Once again infusion time is 20 minutes during which time the patient is given 1 or 2 glasses of water.

DAY 2

- Group A (experimental), or MEGADOSE: After 24 hours a further 15g of Vitamin C is administered intravenously using the same protocol as Day 1. At this stage the patient will now have received 30 grams of Vitamin C intravenously over 2 days.
- The patient is now given a bottle with 15 one gram Vitamin C capsules. Patients in this group are to take one capsule per day for a further 15 days. The patient is not informed on the amount of grams he / she is taking.
- Group B (control), or Low Dose: After 24 hours a further 100mg of Vitamin C is administered intravenously using the same protocol as Day 1. At this stage the patient will now have received 200mg of Vitamin C intravenously over 2 days.
- The patient is now given a bottle with 15 placebo capsules (identical in size and appearance to the test capsules). Patients in this group are to take one capsule per day for a further 15 days. The patient is not informed on the amount of grams he / she is taking.

DAY 17

- Group A (experimental), or MEGADOSE: In 15 days from the second dose (17th day), the patient returns and urine and blood samples collected. The questionnaire has to be repeated. The physician evaluates the patient anew. The intervention is ended
- Group B (control), or Low Dose: In 15 days from the second dose (17th day), the patient returns and urine and blood samples collected. The questionnaire has to be repeated. The physician evaluates the patient anew. The intervention is ended.

RESULTS: From 54 patients who fulfilled inclusion criteria 4 were excluded for not accomplishing inclusion criteria, randomizing 30 patients from the megadose group and 20 from the standard dose group. After the 17 days, 4 patients did not show up for the blood tests (8%), 3 (10%) from megadose group and

Table 1 Patients Characteristics at the beginning of the trial for both groups

Characteristic	GDE n = 19	GMD n = 27	p
Age	50 + 8.69	47.19 + 12.18	0.393
Male (%)	8 (42.1)	14 (51.85)	0.515
Systolic Blood Pressure**	122.11 + 10.85	120.04 + 11.85	0.520
Diastolic Blood Pressure**	78 + 4.91	75.37 + 7.59	0.157
Weight	65.53 + 9.34	70.85 + 14.46	0.166
Body Mass Index (BMI)	24.64 + 3.35	25.98 + 5.00	0.313
C-LDL**	115.47 + 32.01	128 + 41.14	0.422
C-HDL**	50.21 + 9.68	46.7 + 12.54	0.191
Haematocrit	48.72 + 2.34	48.84 + 3.97	0.904
Hemoglobin**	16.36 + 1.02	16.52 + 1.59	0.366

* GDE: Standard Dose Group & GMD: Megadose Group.

** Characteristic not distributed normally. Homogeneity was analyzed with non parametric statistics Mann Whitney test

1 (5%) from standard dose group.

In order to guarantee comparability of the 2 groups, homogeneity statistical analysis was completed, with parametric and non parametric tests according to each variable distribution.

No adverse events were reported during the trial.

From the results we want to highlight that in the Vitamin C megadose group there are statistically significant differences between measurements before intervention and the measurement of day 17 in urinary Vitamin C, blood hemoglobin and blood Hematocrit; whilst in standard dose group, there are significant differences only in urinary vitamin C.

In order to establish differences before and after the intervention, an analysis with Wilcoxon test for vitamin C level, Hemoglobin and C-LDL in the urine, T Test for related samples of Haematocrit were done.

Table 2 Comparison before and after GDE and GMD intervention

Variable/Group	GDE n = 19	GMD n = 27
Vitamin C in Urine	Z -3.3563 p = 0.000	Z -4.542 p = 0.000
Haematocrit	T 1.364 p = 0.189	T 3.732 p = 0.001
Hemoglobin	Z -0.260 p = 0.795	Z -2.416 p = 0.016
C-LDL	Z-0.201 p = 0.840	Z -0.432 p = 0.666

In the megadose group, actual haematocrit (p = 0.0001) and haemoglobin (p = 0.016) have decreased significantly vs. the standard dose group. (The p value means that the original hypothesis that these values should have decreased is probably true)

Discussion

This present study demonstrated statistically significant changes ($p<0.05$) in concentrations of Vitamin C in urine (indirect measure of the plasma concentrations) in standard dose and megadose groups, measured before the intervention and on day 17 after the first IV dose. This change was significantly superior ($p>0.05$) in the megadose group. In the standard dose group, the measure changed from 26.79 ± 13.76 before the intervention to 39 ± 19.74 mg / 10 ml on day 17. In the megadose group we found a change of 21.85 ± 11.9 to 71 ± 20.6 mg / 10 ml after the intervention. These results have not previously been reported in the literature for smokers, which makes this study a first approximation of this phenomenon.

The change in urinary concentrations of Vitamin C in the standard dose group before and after the intervention on day 17 of the study (group that received the standard dose and oral placebo) is statistically significant, which makes us think that there is a lasting effect, with time, of Vitamin C - even with low dose IV. This raises the plasma level for more than two weeks, which has previously been documented . Nevertheless, this has to be confirmed with additional studies. The concentrations of hemoglobin and haematocrit found to be increased above normal levels in both groups at the start, were returned to normal only in the megadose Vitamin C group - statistically significant differences in haemoglobin and haematocrit were found ($p=0.002$ and $p= 0.016$ respectively) only in the megadose Vitamin C group.

The return to normal of Haemoglobin and Haematocrit in the megadose group suggests that megadose Vitamin C treatment in smokers improves tissue oxygenation.

The strengths of this study include:

- the size of the sample n = 46, superior to previous studies on effectiveness of Vitamin C and smoking (n = 27) iii
- It is about a random clinical double-blind study in patients who are smokers, homogeneous in variables such as: age, sex, weight, and the BMI, with an additional control of intake of food rich in Vitamin C by standardized dietary recommendations given to participants.

A weakness of the study could be considered to be the determination of the levels of Vitamin C by using urine test strips, an indirect measure of the plasma levels. The ideal method is the measurement of Vitamin C in leukocytes, (Jacob et al., 1987) 28, which is not feasible in Colombia.

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References supplied on request and available on <www.acnem.org>