random number table used for randomization.

No scope to test tastes of tablets - recipients were handed tablet (by blinded monitor) and watched taking them.

AMELIORATION OF RHINOVIRUS COLDS BY VITAMIN C (ASCORBIC ACID) SUPPLEMENTATION

L C Jennings*, E C Dick, K A Mink and S L Inhorn.

Canterbury Health Laboratories, Christchurch, New Zealand* and University of Wisconsin, Madison, Wisconsin, USA

ABSTRACT

The efficacy of Vitamin C (Vit C) supplementation in preventing or ameliorating common colds in open populations has been controversial. Therefore Vit C efficacy was evaluated in a controlled human volunteer model wherein virus is transmitted naturally. In each of three double-blind trials, rhinovirus type 16 (RV16) susceptible males (recipients) were supplemented with Vit C (2.0 - 2.5g daily, n = 8) and interacted with eight RV16 infected volunteers (donors) for one week. Interaction primarily included playing poker and sharing sleeping quarters. Recipients' colds were then thoroughly characterised. Vit C recipients (n=24) had markedly fewer symptoms (p=0.002 to 0.022) and signs (p=0.020) than placebo recipients (n = 24). These findings correlated with Vit C recipients' substantially higher serum Vit C levels (mean ± SD = 2.10 ± 0.27 vs 0.47 ± 0.15mg/100ml). However, there was no significant difference in incidence of total infection between Vit C (19/24) and placebo (22/24) recipients nor in virus shedding and serologic response to RV16. Thus, Vit C supplementation significantly moderated cold severity but did not prevent infection.

INTRODUCTION

The effectiveness of Vit C supplementation in ameliorating or preventing common colds is a subject of controversy. Confusion is due to the difficulty in controlling a number of variables in previous trials. We have developed a human volunteer model whereby laboratory-induced colds caused by a single rhinovirus (RV) serotype can be naturally transmitted to others at a predictable rate over a one-week period. This system allows nearly complete control over a small study population. In a series of three trials, we used this model to evaluate the effect of Vit C supplementation upon naturally transmitted RV16 colds.

MATERIALS AND METHODS

In each of three, randomized double-blind trials, 16 adult male volunteers (recipients) free of neutralizing antibody to rhinovirus type 16 (RV16) were given, under direct supervision, tablets containing either Vit C 2.0 - 2.5g daily; (n=8) or placebo (n=8). The recipients were dosed for 3.5 weeks and then housed for 7 days with eight men (donors) with laboratory-induced RV16 colds. During this week, the donors and recipients engaged in a variety of supervised interactions as well as sleeping, eating and studying in the same room. Vit C and placebo tablets were continued over the interaction period and the following two weeks.

Colds in the recipients were detected by several methods. Hourly symptom diaries, in which a number of symptoms and signs were graded from 0 (absent) to 3 (severe) were kept by each recipient throughout the waking hours of the interaction period and the subsequent two weeks.

A daily total symptom score (TSS) as well as a cumulative (TSS) for the entire study was then computed. In addition, during the interaction period all volunteers were closely monitored 24 hours a day (except when at class) for clinical signs (coughs, sneezes and nose-blows) and a combined sign score (CSS) computed (lowest 3, highest 48).

Infection was detected by virus culture and titration of daily nasal washings taken during the interaction and the two-week post-interaction periods, and by RV16 seroconversion.

Vitamin C levels in serum were monitored weekly throughout each experiment, including three times during the interaction period.

RESULTS

Vit C Supplementation

Recipients were given 2.0 - 2.5g Vit C daily.
Vit C mean 2.10 ± 0.27mg/100ml, n = 24, placebo mean 0.47 ± 0.15mg/100ml, n = 24 (p<0.001 over 3 trials).

Symptom Scores

Vit C recipients had significantly lower symptom scores than those of recipients (Figure 1a & b).

- 95.8% (23/24) Vit C recipient colds were subclinical to mild (score 0-6), while:
  70.8% (17/24) placebo recipient colds were moderate to severe (Fig 1a).
- Vit C recipients also had significantly lower cumulative Total Symptom Scores; reflecting diminished symptom severity over entire course of their illness (Fig 1b).

Sign Scores

Frequency of clinical signs was consistently lower in Vit C recipients (Table 1).

- Significantly fewer cough episodes in Vit C vs placebo (p = 0.044, n=48).
- Sneezes and noseblows were lower, but not significantly.

Combined sign scores were significantly lower in Vit C recipients (p=0.020, n=48) (Figure 2).

- Placebo recipients had higher CSS's (11 placebo vs 5 Vit C, score > 33).
- Vit C recipients had lower CSS's (13 Vit C vs 5 placebo, score ≤ 20).

Virology

Virologic measurements of illness were not significantly affected by Vit C (Table 2)

- Incidence of laboratory confirmed infections was lower in Vit C (79.2%, 19/24) vs placebo recipients (91.7%, 22/24) $X^2 = 0.67$, 1d.f., p=0.420.
- Quantity and duration of virus shedding, and number of days to first virus shedding similar (data not shown).

Treatment Blinding

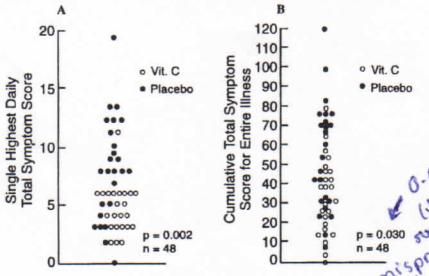
Treatment blinding among study recipients was maintained (Table 3).

- The number of subjects correctly guessing which treatment they recieved was not statistically significant.
- During 24 day pre-interaction dosing (16/24 vs 10/24) $X^2 = 0.771$, 1d.f; p =0.39.
- Also true for back-up recipients (7/12 vs 5/9).

CONCLUSIONS

- Vit C supplementation significantly decreased the severity of symptoms and signs of naturally transmitted RV16 colds.
- Vit C supplementation did not prevent infection with RV16.
- A comprehensive questionnaire revealed that recipients' perception of their treatment was based on guessing.
- Findings support role of Vit C in modifying the typical symptoms and signs of the common cold.

Figure 1:
Ranking of: (a) single highest daily TSS and (b) cumulative TSS's of Vitamin C and placebo recipients in three trials.



0.022? (Jennings suggested misprint during presentation)

Figure 2:
Combined Sign Scores of Vitamin C and placebo recipients in 3 trials

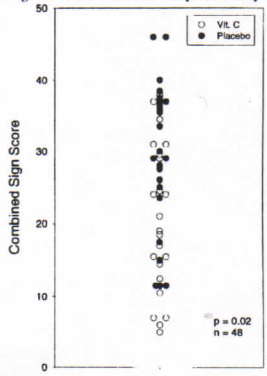


Table 1
Total episodes of cough, sneezes and noseblows in recipients of Vitamin C versus placebo in 3 trials

	Cough Episodes		Sneezes		Noseblows	
	Vitamin C (n=8)	Placebo (n=8)	Vitamin C (n=8)	Placebo (n=8)	Vitamin C (n=8)	Placebo (n=8)
Study 1	188 p=0.013*	522	28 p=0.804	46	54 p=0.234	83
Study 2	291 p=0.646	653	35 p=1.00	37	124 p=0.339	216
Study 3	659 p=0.442	812	19 p=0.130	55	61 p=0.176	196
Totals (24 Vit.C versus 24 placebo recipients)	1136 p=0.044*	1987	82 p=0.260	137	230 p=0.086	497

a. Statistical significance determined by two-tail Wilcoxon Rank Sum Test.
b. Statistical significance on combined results determined by "Fisher method of adding the logarithms of P-values."

Table 2
The number and etiology of respiratory infections in recipients of Vitamin C vs placebo in 3 trials

	Vitamin C				Placebo			
	Total no. of recipients	RV16 infection only	Other* virus infection	Total infections	Total no. of recipients	RV16 infection only	Other* virus infection	Total infections
Study 1	8	6	0	6	8	7	0	7
Study 2	8	6	1*	7	8	6	1*	7
Study 3	8	5	1*	6	8	5	3*	8
Totals	24	17	2	19†	24	18	4	22

a. Virus other than rhinovirus type 16 (RV16) isolated, alone or together with RV16.
b. Acid labile, presumed RV (non RV16) isolated.
c. Acid labile, presumed RV (non-RV16) and RV16 isolated.
d. Acid labile, presumed RV (non-RV16) isolated.
e. Subject 1: Acid labile, presumed RV (non-RV16) and RV16 isolated.
Subject 2: Respiratory syncytial virus and RV 16 isolated.
Subject 3: Acid labile, presumed RV (non-RV16) isolated.
f. The difference between Vitamin C and placebo recipients in total infections was not statistically significant (X^2=0.67, 1 d.f., p=0.420)

Table 3
Number of recipients of Vitamin C or placebo correctly guessing their treatment

	Study recipients					
	Pre-interaction* questionnaire		Post-study* questionnaire		Back-up recipient questionnaire*	
	Placebo (n=8)	Vitamin C (n=8)	Placebo (n=8)	Vitamin C (n=8)	Placebo	Vitamin C
Study 1	N.D.*	N.D.	4	7	3 (n=5)	3 (n=5)
Study 2	N.D.	N.D.	3	4	N.D.	N.D.
Study 3	2	5	3	5	2 (n=4)	4 (n=7)
Totals	2.8*	5.8	10.24	16.24†	5.9	7.12

a. Questionnaire administered to recipients immediately before interaction period.
b. Questionnaire administered to recipients immediately after study which asked which treatment recipients thought they received prior to the interaction period.
c. Questionnaire administered to a pool of recipients who served as back-ups to the study recipients and who were treated identically, but not used in the study.
d. Not done.
e. Most recipients indicated that their perception of the treatment received Vitamin C versus placebo was based on guessing. Furthermore, all claimed that there was nothing unusual about the pills taken.
f. This proportion is not statistically significant X^2 = 0.771, 1d.f, p = 0.39