Vitamin C Prophylaxis in Marine Recruits

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• **A prospective, randomized, double-blind study was carried out to determine whether vitamin C prophylaxis, 2.0 g/day, vs placebo prophylaxis would reduce the incidence or morbidity of the common cold and other respiratory illnesses in 674 marine recruits during an eight-week period. Whole-blood ascorbic acid levels measured six weeks after initiation of the study were significantly higher in the vitamin C group. There was no difference between the two groups in the incidence or duration of colds. The vitamin C group rated their colds as being less severe, but this was not reflected in different symptom complexes or in fewer sick-call visits or training days lost. This study and the literature do not support the prophylactic use of vitamin C to prevent the common cold.**

(*JAMA* 241:908-911, 1979)

EPIDEMICS of adenovirus, coxsackie virus, rhinovirus, and *Mycoplasma pneumonias* infections have been well documented in military recruits. Despite attempts to avert outbreaks of these infections through the use of adenovirus, influenza, and *M pneumoniae* vaccines, pneumonia and the common cold have continued to be an important cause of disability in this population.[1]

Since the publication of *Vitamin C and the Common Cold,*[2] considerable controversy has arisen about Pauling's claims that large doses of ascorbic acid could prevent the common cold.[3,4] Several studies[5-19] have been published in recent years, and clinical trials by Coulehan et al,[10] Miller et al,[14] and Wilson et al[17-19] have suggested that vitamin C may benefit school-aged girls more than school-aged boys. Further studies have shown that differences exist between the sexes in their metabolism of vitamin C. While some of the studies published in the past decade have shown an effect of vitamin C on the common cold,[5,7-10,15,17-19] no consistent, reproducible effect on the incidence, duration, or severity of colds has become evident.

Of the recent clinical trials of the effect of vitamin C on the common cold, only Sabiston and Radomski[15] studied military personnel. Their results indicate that a daily 1.0-g supplement of vitamin C substantially reduced the incidence of colds during Canadian northern military operations. To clarify the question of the efficacy of vitamin C in male military recruits, a randomized, double-blind study was undertaken to determine whether vitamin C prophylaxis, 2.0 g/day, could substantially reduce the incidence or morbidity of the common cold and other respiratory illnesses in this population.

MATERIALS AND METHODS

Subjects and Randomization.—The participants in the study were male marine recruits from 15 platoons who underwent 11 weeks of recruit training at the US Marine Corps Recruit Depot, Parris Island, SC, in October, November, and December 1974. Informed consent was obtained from 1,185 of 1,312 recruits who were asked to participate. Pill taking did not begin until the recruit's third week at Parris Island. By this time 321 volunteers had been removed from their original platoon by the US Marine Corps for further training or for discharge. An additional two recruits were excluded from the study because of a history of kidney stones, leaving 862 recruits who began taking the pills.

These 862 recruits were assigned randomly to either the vitamin C or placebo group from a list of consecutive numbers randomized in pairs. Randomization was carried out by individual recruits within each platoon.

Tablets and Protocol.—During each of the eight weeks of the study, each recruit received a new bottle of pills labeled with only his name, platoon number, and study number. The bottles were otherwise identical, and each contained 28 plain white tablets. The vitamin C tablets each contained 500 mg of ascorbic acid in the anhydrous form, and the placebo tablets were formulated from citric acid and were indistinguishable in appearance and taste from the vitamin C tablets. Each recruit was instructed to take two tablets each morning and two each evening, and pill taking was supervised and observed by the drill instructors in each platoon. Neither the recruits or drill instructors nor the physicians and corpsmen who treated the recruits were aware of which pill any individual recruit was taking. No attempt was made to alter the number of tablets ingested in response to the occurrence of cold symptoms.

Before the initiation of pill taking, each recruit received adenovirus 4 and influenza vaccines and either intramuscular penicillin G benzathine or oral erythromycin estolate streptococcal prophylaxis. Marine recruits are not permitted to bring or receive medications or vitamins from home; while at Parris Island, their only access to these items is from the medical dispensary.

Blood Studies.—One third of the recruits who had volunteered also had whole-blood ascorbic acid determinations, with every third recruit who had volunteered being selected from an alphabetic listing by platoon. The first blood-sample drawing took place during the recruit's first week at Parris Island, which was two weeks before the initiation of pill taking. The second blood drawing was done eight weeks later, which was during the sixth week of pill taking. These blood samples were drawn in the afternoon approximately eight to ten hours after the morning pills had been taken. The blood samples were frozen, and whole-blood ascorbic acid levels were subsequently determined by the 2,4-dinitrophenylhydrazine method.

Data Collection.—Four methods of data collection were employed: (1) weekly respiratory illness questionnaires, (2) surveillance of sick-call visits for respiratory

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The views expressed herein are those of the authors and do not necessarily reflect the views of the Navy Department or the naval service at large.

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illness, (3) review of health records for illness other than respiratory, and (4) efforts to determine the cause of all cases of pneumonia. In addition, two weeks before the initiation of pill taking, each recruit completed a questionnaire with regard to his age, race, home state, cold history, and past medical history.

During the eight-week study period, each recruit completed weekly questionnaires with respect to the previous week's cold history. The symptoms listed on this questionnaire were (1) fever or chills, (2) headache, (3) stuffy or runny nose, (4) sore throat, (5) dry or productive cough, (6) nausea or vomiting, (7) diarrhea, and (8) stomach pain. The duration and severity of each cold was also ascertained. The criterions necessary for a cold to be included as an episode were (1) the presence of either runny or stuffy nose, sore throat, or dry or productive cough, (2) at least two days of symptoms, and (3) at least three symptom-free days between episodes. The recruits were also asked to report weekly any suspected side effects and any lapses in pill taking. On the final questionnaire, the recruits were asked to state if they knew which pill they had been taking and how they knew.

There was active surveillance by corpsmen and physicians of all sick-call visits and training days lost from respiratory infections. Cultures and roentgenograms were obtained when indicated. Each recruit's sick-call visit was assigned to one of seven respiratory syndromes for which diagnostic criterions had been established. The seven categories included (1) uncomplicated upper respiratory infection, (2) streptococcal pharyngitis, (3) tonsillitis, (4) otitis externa or otitis media, (5) sinusitis, (6) bronchitis, and (7) pneumonia.

At the end of the eight-week study period, the health record of each recruit was reviewed to determine the number of sick-call visits and training days lost for reasons other than respiratory infections. Finally, in all recruits admitted to the medical ward of the Branch Dispensary with a diagnosis of pneumonia, an effort was made to establish the cause. Each of these recruits had throat, sputum, and blood cultures; sputum Gram's stains; WBC count; and acute and convalescent liters for influenza A and B, parainfluenza 1-3, adenovirus, rhinovirus, coxsackie B 1 to 6, respiratory syncytial virus, and *M pneumoniae.*

Statistical Analysis.—The statistical analysis employed was the χ^2 test except for the analysis of the whole-blood ascorbic acid levels in which the means were compared using the *t* statistic.

RESULTS

Subjects.—Of the 862 recruits who began taking the pills, 64 recruits (34, vitamin C; 30, placebo) were removed from their platoons by the US Marine Corps for further training or for discharge during the eight-week study period. An additional 123 recruits (64, vitamin C; 59, placebo) were excluded from the final analysis because they did not continue to take their pills for the eight-week study period. One additional recruit was eliminated from the vitamin C group because of recurrent urticaria related to taking the tablets. The remaining 674 recruits (331, vitamin C; 343, placebo) completed the eight-week protocol and are the subject of analysis. The number of recruits per platoon varied from 35 to 58.

There were no statistically significant differences between these two groups with respect to age; race; area of the country from which they came to Parris Island; previous cold history, including number, duration, or disability from colds; and previous medical history of respiratory-related illness, allergy, smoking, or vitamin intake (Table 1).

Table 1.—No. of Recruits With Specific Prestudy Characteristics

	Vitamin C	Placebo
No. of recruits	331	343
Mean age, yr	18.5	18.5
Race, %		
White	70	68
Black	28	32
Other	2	2
Previous medical history, %		
Sinusitis	11	8
Ear infection	26	25
Tonsillitis	31	24
Septic sore throat	25	20
Asthma	6	7
Bronchitis	7	7
Pneumonia	13	12
Allergy	27	24
Smoking	63	59
Vitamin intake	10	6
Geographic distribution, %		
Northeast	50	54
Southeast	34	32
Other	16	14
Previous cold history, %		
No. of colds per year		
0	1	1
1-2	41	36
3-4	38	40
>4	19	23
Duration of average cold (days)		
1-2	11	12
3-4	30	25
5-6	25	26
>6	34	37
Work days lost per year		
0	26	26
1-4	49	52
5-10	17	16
>10	8	6

Whole-Blood Ascorbic Acid Levels.—Two determinations of the mean whole-blood ascorbic acid levels of the 234 recruits (103, vitamin C; 131, placebo) were made. There was no significant difference in these levels between the two groups during their first week at Parris Island, 1.00±0.27 mg/dL for recruits taking vitamin C vs 0.98±0.32 mg/dL for recruits taking placebo. After six weeks of pill taking, the vitamin C group had significantly higher ascorbic acid levels (1.36±0.46 mg/dL) than the group taking placebo (0.91±0.28 mg/dL) ($P<.001$). The placebo group's ascorbic acid levels did not significantly change from the first determination.

Cold Data.—Data for the two groups with respect to incidence, duration, and severity of their colds as well as the number of sick-call visits and training days lost are presented in Table 2. The incidence of colds was almost identical in the two groups, with 90% of the recruits in both the vitamin C and placebo groups having at least one cold during the eight-week study period. There was also no statistically significant difference between the two groups with respect to the length of each cold or to the mean number of days with a cold per recruit.

Furthermore, when the incidence and duration of colds in the two groups were analyzed simultaneously, no significant differences were found. Sixty percent of the colds reported in each group lasted two to seven days; however, 14% of colds in the vitamin C group and 15% in the placebo group lasted longer than 21 days. If these colds lasting more than three weeks were eliminated from evaluation, there were still no significant differences between the two groups in the number or duration of their colds.

Each cold was rated by the recruits as being "mild," "average" "bad," or the "worst ever," and these four subjective classifications were given a numerical rating from 1 to 4. The colds in each group were generally less severe than average, but the colds in the vitamin C group were subjectively less severe ($P<.03$) than those in the, placebo group (Table 2). However, the vitamin C group had slightly more sick-call visits and training days lost from colds, but this

Table 2.—Cold Data

	Vitamin C	Placebo
No. of recruits	331	343
Incidence of colds		
Recruits with no colds, %	10	10
Mean colds per recruit	1.81	1.80
SEM	±0.065	±0.064
Duration of colds		
Mean No. of days per cold	11.2	11.5
Mean No. of days with a cold per recruit	20.3	20.7
SEM	±0.879	±0.842
Severity of colds	1.87*	1.97*
Sick-call visits per recruit		
For colds	0.31	0.29
For all medical problems	0.97	0.99
Training days lost per recruit		
From colds	0.19	0.17
From all medical problems	0.71	0.75

*From table comparing number of colds and severity rating, χ^2=27.8, 15 *df*, *P*<.03.

Table 3.—Classification of Colds by Symptoms

	Colds, No. (%)	
Symptom Complex	Vitamin C	Placebo
Uncomplicated cold		
Single symptom*	139 (23.1)	158 (25.5)
More than one symptom*	231 (38.6)	251 (40.6)
Total	370 (61.7)	409 (66.1)
Complicated cold		
Cold and toxic symptoms†	144 (24.0)	132 (21.3)
Cold and gastrointestinal (GI) symptoms‡	30 (5.0)	28 (4.2)
Cold and toxic and GI symptoms	56 (9.3)	52 (8.4)
Total	230 (38.3)	210 (33.9)

*Runny or stuffy nose, sore throat, or cough.
†Fever, chills, or headache.
‡Nausea, vomiting, diarrhea, stomach pain.

difference was not statistically significant (Table 2). In addition, when the colds were classified as uncomplicated or complicated by toxic or gastrointestinal (GI) symptoms, no significant differences were found between the two groups (Table 3).

Other Respiratory Infections.—The incidence of sinusitis, otitis externa, otitis media, tonsillitis, streptococcal pharyngitis, and bronchitis was sufficiently low in each group that no meaningful conclusion could be made of the effect of vitamin C on these infections. Pneumonia developed in eight recruits, and only one of these recruits was from the vitamin C group (P<.04). Each of these eight recruits had typical roentgenographic and physical signs of pneumonitis, although five recruits were febrile, and only four recruits had elevated WBC counts. Pneumococci were isolated from the sputum in three recruits and seen intracellularly on Gram's stain in two other recruits. Two of these recruits also had fourfold increases in parainfluenza titers. No other significant elevations of influenza, adenovirus, rhinovirus, coxsackievirus, respiratory syncytial virus, or *Mycoplasma* titers were noted. All of the blood cultures were negative, and each recruit responded clinically to either penicillin or erythromycin. Each of these recruits returned to his platoon after a mean Medical Dispensary stay of 4.4 days.

Side Effects.—Approximately 15% of the recruits in each group reported symptoms that they believed were due to the pills. The most commonly reported symptoms were tiredness, headache, urinary frequency, abdominal pain or cramps, diarrhea, and nausea. However, none of these symptoms was statistically more frequent in the vitamin C than in the placebo group. Urticaria developed in one recruit in the vitamin C group, which subsided when the pills were withheld and recurred when he resumed taking his pills. He was instructed to stop taking his pills and was excluded from the final analysis. No other adverse effects were noted by either the recruits or the physicians seeing them at sick call.

Which Pill?—When asked which pill they thought they were taking, 53% of the recruits in each group stated that they did not know. Of those who replied either vitamin C or placebo, the reasons given were that their health either was or was not better, that they did or did not have colds, or that the pills did or did not taste as they expected vitamin C might. Based on these reasons, 27% of the vitamin C group and 26% of the placebo group correctly stated which pill they were taking. Twenty percent of the vitamin C group and 21% of the placebo group guessed incorrectly and for the same reasons, and these differences were not statistically significant.

COMMENT

Acute respiratory disease in military recruits was described many years ago. The high incidence and relatively long duration of colds reported in this study confirm the fact that respiratory tract infections continue to be one of the most important causes of disability in this population. Ninety percent of the recruits reported at least one cold during the eight-week study period, which is a higher percentage than that reported by others.[5,7,9,10,15] The number of colds per recruit was 1.8 in eight weeks in this study, which is similar to that reported by Miller et al[14] but is two to three times the incidence reported by Anderson et al,[6,7] Charleston and Clegg,[8] and Clegg and MacDonald[9] and is five to six times the incidence reported by Wilson et al,[17-19] Karlowski et al,[13] and Coulehan et al.[10,11]

Although the colds in this study were reported to be of average severity, they tended to last longer than those reported in most studies.[5-8,10-13,15,17-19] If the colds lasting longer than 21 days had been eliminated from the analysis in this study, the mean cold duration would have been 7.1 days for each group, and only

Miller et al[14] report a comparable mean cold duration. The relatively high incidence and long duration of cold symptoms reported in this study can most likely be explained by the unique living conditions of military recruits compared with the other populations that have been studied.

The high incidence of viral, *Mycoplasma,* and bacterial pneumonia among marine recruits has been well documented.[1] This study showed a reduced incidence of pneumonia among the recruits receiving vitamin C. However, there were only eight recruits in whom pneumonia developed among the 674 recruits completing the study, and statistical analysis with so few cases might be misleading. No claim of a beneficial effect of vitamin C in preventing viral or bacterial pneumonia should be made on the basis of this study, although this certainly should be an area for further investigation.

Numerous reports of potential adverse reactions to large doses of ascorbic acid have appeared in the literature. The possible development of kidney stones, infertility, abnormal bone metabolism in children, withdrawal scurvy, intestinal obstruction, destruction of vitamin B_{12}, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency have been described. However, Dykes and Meier[4] and Korner and Weber,[20] who have reviewed the possible toxicity of high doses of vitamin C, agree that there is presently little evidence of any effect that is detrimental to health. No serious side effects were noted in this study, and complaints about the GI tract were equally frequent in the vitamin C and placebo groups.

Of the prospective, randomized, double-blind studies on the efficiency of vitamin C in preventing the common cold, few have included a question of the participants as to which pill they thought they were taking. In the study by Karlowski et al,[13] it became apparent that the majority of the participants knew which pill they were taking. In the present study, there was a slight trend toward guessing the correct group, but these differences were not statistically significant.

A number of studies have been published since 1970 in an effort to determine whether prophylactic or therapeutic high doses of vitamin C could reduce the incidence of or disability from the common cold. These studies have been carried out in Canada, England, Ireland, and the United States and have included children, adolescents, and adults. Anderson et al,[5] Coulehan et al,[10] and Sabiston and Radomski[15] have reported a substantial reduction in the percentage of study participants taking vitamin C who had no colds during the period studied. However, subsequent studies by Anderson et al[6,7] and Coulehan et al[9] did not confirm this find ing. The study of Clegg and MacDonald[9] showed a decreased incidence of colds in those volunteers who received D-isoascorbic acid, but not in those who received L-isoascorbic acid. The study by Charleston and Clegg[8] also showed a decreased incidence of colds in those receiving vitamin C, but this study was not double-blind and had relatively few subjects.

The only trend that has been present in the studies by Coulehan et al,[11] Miller et al,[14] and Wilson et al[17-19] is that school-aged girls seem to have benefited more from vitamin C than school-aged boys. This finding may be due to differences in the metabolism of vitamin C secondary to age and sex. However, in the second studies by Anderson et al[6] and Coulehan et al[11] and in those by Elwood et ai,[12] Karlowski et al,[13] Miller et al,[14] and Schwartz et al,[16] no statistically significant advantage for vitamin C in reducing the incidence, duration, or severity of the common cold was noted. In some of the studies that show statistically significant results, so many subcategories of prophylactic or therapeutic treatment groups and classifications of colds were done that it is not surprising that some significant differences were noted.

In the present study, no benefit was seen from the prophylactic consumption of 2.0 g of vitamin C in decreasing the incidence, duration, or disability from the common cold in marine recruits. Although Pauling and Wilson continue to recommend large doses of vitamin C for prevention of the common cold, Chalmers,[3] and Dykes and Meier,[4] and other experts do not believe that the literature supports this view. We also believe that at this time the prophylactic or therapeutic use of large doses of vitamin C to prevent the common cold is not warranted.

This study was supported in part by the Naval Medical Research and Development Command Project M-4305, Work Unit 5021.

Myron Brin, PhD, and Hoffmann-LaRoche Inc supplied the tablets. David Uddine, PhD, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md, performed the whole-blood ascorbic acid determinations. R. Clifton Bailey, PhD, Naval Medical Research Institute, National Naval Medical Center, assisted in statistical analysis.

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