

Ascorbic Acid for the Common Cold

A Prophylactic and Therapeutic Trial

Thomas R. Karlowski, MD; Thomas C. Chalmers, MD; Lawrence D. Frenkel, MD;
Albert Z. Kapikian, MD; Thomas L. Lewis, MD; John M. Lyrtch, MD

• Three hundred eleven employees of the National Institutes of Health volunteered to take 1 gm of ascorbic acid or lactose placebo in capsules three times a day for nine months. At the onset of a cold, the volunteers were given an additional 3 gm daily of either a placebo or ascorbic acid. One hundred ninety volunteers completed the study. Dropouts were defined as those who missed at least one month of drug ingestion. They represented 44% of the placebo group and 34% of those taking ascorbic acid. Analysis of these data showed that ascorbic acid had at best only a minor influence on the duration and severity of colds, and that the effects demonstrated might be explained equally well by a break in the double blind.

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ASCORBIC acid has been repeatedly recommended as a prophylactic and therapeutic agent for the common cold, and a large number of studies of its efficacy in this use have been carried out.¹ Nevertheless, a careful review of the literature has failed to re-

See also p 1073.

veal a long-term prospective double-blind trial with high doses of ascorbic acid that was designed to measure as well as distinguish between the prophylactic and therapeutic effects of the agent. We undertook a study in an effort to fill this void.

From the Clinical Center (Drs. Karlowski, Chalmers, Frenkel, Lewis, and Lynch) and the National Institute of Allergy and Infectious Diseases (Dr. Kapikian), National Institutes of Health, Bethesda, Md. Dr. Chalmers is now with the Mount Sinai Medical Center and School of Medicine of the City University of New York, New York. Dr. Karlowski is now in private practice in Waterloo, Iowa. Dr. Frenkel is now in private practice in Washington, DC.

Reprint requests to Mount Sinai Medical Center, Fifth Ave and 100th St, New York, NY 10029 (Dr. Chalmers).

METHODS

A random sample of 2,500 National Institutes of Health employees received a questionnaire asking about the number of colds they had experienced during the previous 12 months and whether they were interested in joining a study of the effectiveness of ascorbic acid in preventing and ameliorating the common cold. Nearly 600 persons returned questionnaires, and 473 of these persons were considered by the Employee Health Service for entrance into the study. A preliminary history and physical examination were then carried out on these employees.

Volunteers were excluded from joining the study if they fulfilled any one of the following criteria: (1) history of diabetes, gout, renal stones, or respiratory symptoms of probable allergic origin, (2) women who were pregnant, suspected of being pregnant, or anticipated pregnancy in the following year, (3) those taking orally administered anticoagulants or medications that produce side effects involving the respiratory system, (4)

those unwilling or unable to refrain from taking vitamin preparations containing ascorbic acid, and (5) those found to have an elevated blood uric acid level.

Of the initial 473 potential volunteers, 323 were admitted to the study and given a prescription for the study drug. Twelve persons dropped out of the study before taking an appreciable number of capsules and were eliminated from further consideration. Thus, 311 employees were classified as having been admitted to the study.

Randomization

An unrestricted randomization was used. The numbers 0,1,2,3 were generated from pseudorandom sequence by the usual method on a CDC 3100 computer. The first 70 identification numbers were assigned to the volunteers who reported that they had experienced four or more colds during the previous year; the remaining 241 numbers were assigned to volunteers reporting fewer than four colds. The treatment groups are described in Table 1.

Treatment Groups

The maintenance dose of study drug was two capsules taken three times a day with meals. When a volunteer had a cold, the dose was doubled (supplemental drug was recommended: two additional capsules three times a day). Each test capsule contained 500 mg of ascorbic acid, 180 mg of spray-dried lactose, and 5 mg of magnesium stearate. Each placebo

capsule contained 645 mg of lactose and 5 mg of magnesium stearate. Validity of the randomization was checked by comparing the frequency of the following characteristics in the four groups and the two combinations: age (less than 35, 35 to 55, and more than 55 years), sex, race, number of cigarettes smoked daily (zero, one to ten, more than ten), history of nonrespiratory allergy, and previous regular intake of vitamins. The only significant ($P < .05$) discrepancy was in the distribution of a history of allergy between group 0 and groups 2 and 3. Similar comparisons were carried out for each combination of the six characteristics, for example, age and sex, age and race. No differences significant at the .05 level were found.

The study drug was dispensed by the pharmacy in bottles of 200. Volunteers were asked to return at monthly intervals with their bottles for refills of their prescription. At this time, they were interviewed for symptoms of side effects, and a check was made on the capsules remaining in their bottle to ascertain how carefully they were taking their study drug. Distribution of the capsules actually ingested by the volunteers was very similar for the ascorbic acid and placebo groups and indicated reasonable compliance with the prescribed study. Of the volunteers who completed the study, 99% took at least four of their six capsules per day, and 87% took at least five capsules per day.

If a cold developed, the volunteers were instructed to return to have their symptoms and clinical observations recorded and to receive supplemental study drug to be taken for the first five days of their colds. A routine throat culture was obtained and the volunteers were encouraged to have nasal washings and blood titers for viral isolation and identification performed. The volunteers were seen three times a week for the duration of their colds. Symptoms were recorded daily and observations were made and recorded for each return visit. Twenty different but interrelated symptoms were graded on a 0 to 3+ scale. The number of days home from work was also recorded. The end of the common cold was defined as that point in time when the individual

Treatment Group	Daily Dose	
	Maintenance	Supplemental
0	Placebo	Placebo
1	Placebo	Ascorbic acid, 3 gm
2	Ascorbic acid, 3 gm	Placebo
3	Ascorbic acid, 3 gm	Ascorbic acid, 3 gm

Actual Drug	Suspected Drug		Do Not Know	Total
	Ascorbic Acid	Placebo		
Prophylactic				
Ascorbic acid	40*	12*	49	101
Placebo	11*	39*	39	69
Total	51	51	88	190
Supplemental (therapeutic)				
Ascorbic acid	20†	11†	39	70
Placebo	10†	12†	40	62
Total	30	23	79	132

* $\chi^2=28.6$; $P < .001$.

† $\chi^2=1.8$; $P < .25$.

Group	No. of Colds	No. of Persons	Average No. of Colds per Person	
Completed study				
0	65	46	1.41	} 1.36
1	56	43	1.30	
2	52	44	1.18	
3	76	57	1.33	} 1.27
Total	249	190	1.31	
Did not complete study				
0 and 1	27	69	0.82*	
2 and 3	25	52	1.07*	

*Prorated to a nine-month basis.

being monitored failed to fulfill the criteria as described in the definition outlined in the next section.

Treatment Failures

In this study, an individual was defined as having a common cold if he complained of the acute onset of at least two symptoms indicative of conditions in either of the following categories: (1) sneezing, nasal congestion, rhinorrhea, and postnasal drip, or (2) laryngitis, pharyngitis, dysphagia, and bronchitis.

Selected for analysis were the number of colds per person, in total and according to various prerandomization characteristics, mean duration of colds and time at home, and summation of severity scores. Since most of the distributions were quite skewed, limiting the usefulness of a compari-

son of means, the Wilcoxon test for shift was employed. In the case of severity of symptoms, the scores were ranked according to magnitude, and the Wilcoxon two-sample test applied. The value of the Wilcoxon test was then converted to a standard normal deviate.

Estimates of the numbers required for the study were based on the estimated number of colds to be expected, on the basis of previous experience. It was calculated that if 100 volunteers were assigned to the maintenance ascorbic acid group and the same number to the placebo group, there would be a 95% chance that a 30% reduction in colds among the treated volunteers would be detected, provided that such reduction in fact exists. An extra 100 patients were admitted to allow for dropouts.

It was assumed that there was no need to try to detect a reduction of less than 30% because in the possible application of the study results to the general population, less than a 30% reduction would not be worth the trouble involved in taking two capsules three times a day.

Cessation of Study

It was decided to continue the study for a period of one year, provided that (1) the dropout rates from the group treated with ascorbic acid and the placebo group did not become significantly different (the level of

significance was to be taken at .15); (2) the number of persons under study did not fall below 200; (3) at six months from the beginning of study, the number of colds in the ascorbic acid-treated group was not significantly greater than the number in the placebo group (level of significance, .05). In the event that one of these situations occurred, the study would be stopped.

It was stopped nine months after the last subjects had entered, when the number remaining dropped below 200 and it was apparent that more of the dropouts were in the placebo group ($P=.10$).

Maintenance of Double Blind

Early in the study, we discovered that some of the volunteers had tasted the contents of their capsules and professed to know whether they were taking the ascorbic acid or the placebo. The magnitude of the problem was not realized until completion of the study, when a questionnaire was submitted to each of the participants asking them to guess which substance they had been taking. The results of the questionnaire (Table 2) made it mandatory to perform the analyses both in toto as well as according to the participants' impres-

sion as to what they were taking. The data in the tables indicate that there was more tasting of the prophylactic capsules than of the therapeutic ones.

RESULTS

Average Cold Rates

Table 3 shows the number of colds per person among those who did and did not complete the study. Those receiving ascorbic acid prophylactically had 1.27 colds in nine months and those receiving a placebo, 1.36 ($P>.50$). Knowledge of the medication ingested did not appreciably change the numbers of colds per person (Table 4), except that those who guessed wrong had an interesting distribution of colds. The frequency of colds by month is indicated in Table 5. There was some increase in the winter months and a sharp drop-off in the spring, when the study was terminated. Not much ascorbic acid effect is apparent in the monthly rates. Also, no differences significant at the .05 level occurred in the average number of colds per person according to the previously determined characteristics: age, sex, race, number of cigarettes smoked daily, history of allergy, or previous vitamins.

Volunteers taking placebo had colds of a mean duration of 7.14 days, while those taking 3 gm of ascorbic acid (groups 2 and 3) had colds of a mean duration of 6.59 days and those taking 6 gm had colds of a mean duration of 5.92 days. Thus, each 3-gm increment of ascorbic acid would appear to shorten the mean duration of a cold by approximately half a day. However, these differences were eliminated by taking into account the correct guesses of medication ingested (Table 6).

Analyzing the severity of the 20 recorded symptoms of a cold in each treatment group and the association between knowledge of capsule content and severity presented a complicated statistical problem (Table 7). Each symptom on each day of the cold had been graded 0 to 3, depending on whether it was absent, mild, moderate, or severe. The total score for each symptom was obtained by adding the digits for all colds, and this sum was divided by the number of colds to give the average score per volunteer. For

Table 4.—Distribution of Colds According to Knowledge of Capsule Contents

Treatment	No. of Colds Per Person		Total
	0-1	≥2	
Placebo			
Knew	19	20	39
Did not know	19	20	39
Guessed wrong	9	2	11
Subtotal	47	42	89
Ascorbic acid			
Knew	25	15	40
Did not know	36	13	49
Guessed wrong	4	8	12
Subtotal	65	36	101
Total	112	78	190

Table 5.—Average No. of Colds per Person by Month, According to Treatment

Month	Ascorbic Acid			Placebo		
	Completed Study	Did Not Complete Study	Combined	Completed Study	Did Not Complete Study	Combined
1. September	0.139	0.140	0.139	0.135	0.118	0.127
2. October	0.099	0.152	0.116	0.191	0.044	0.127
3. November	0.119	0.065	0.106	0.146	0.109	0.133
4. December	0.139	0.080	0.127	0.146	0.057	0.121
5. January	0.168	0.130	0.161	0.191	0.172	0.186
6. February	0.208	0.153	0.202	0.202	0.095	0.182
7. March	0.198	0.200	0.198	0.169	0.056	0.150
8. April	0.129	0	0.121	0.124	0.111	0.122
9. May	0.069	0	0.065	0.056	0	0.054

Table 6.—Mean Duration of Colds: Completed Study

Group	No. of Colds	Duration, Days	"Blinded" Subjects		"Unblinded" Subjects	
			No. of Colds	Duration, Days	No. of Colds	Duration, Days
0	65	7.1	30	6.3	16	8.6
1	56	6.5	18	6.7	15	4.7
2	52	6.7	14	6.4	8	7.0
3	76	5.9	30	6.5	13	4.8

each of 20 symptoms, the distributions of clinical scores among the two groups of subjects were compared by ranking the scores according to magnitude and applying the Wilcoxon two-sample test. The value of the Wilcoxon test was then converted to a standard normal deviate (Z statistic). When the effects of therapeutic ascorbic acid were examined (columns 2 and 3 of Table 7), no trends in the shifts were encountered, so these were combined for comparisons of the prophylactic ascorbic acid and placebo (column 4). Here there was a distinct tendency for the ascorbic acid volunteers to have less severe symptoms. (A positive Z statistic indicates that those scores of the groups designated first in the column tended to be higher than the scores of the groups designated second, and vice versa for a negative statistic.) In only two of the 20 symptoms did the shift favor the placebo, and four of the 18 symptoms whose shift favored ascorbic acid were significant, two at the .05 and two at the .01 levels.

The effects of knowledge on the clinical score (columns 5 and 6) were assessed by comparing again the respective E statistics. This was done by finding the difference between the Z statistics and then dividing by $\sqrt{2}$. Positive values of the resulting statistics (column 7) are in keeping with the tendency of subjects who know they are getting placebo to rate the severity of their symptoms higher than those subjects on placebo without knowing it, and the opposite tendency in the subjects receiving ascorbic acid with and without knowledge. Fifteen of the 20 and all nine of the symptoms complained of by more than 50% of the subjects are positive Z figures in column 7, strongly indicating an association between severity of symptoms and correct guessing of the medication received. The difference in symptoms between the placebo and ascorbic acid groups was lessened when the symptoms of those who did not know what they were taking were analyzed separately (column 6 of Table 7). The placebo is favored in an additional four symptoms, and now none of the differences favoring ascorbic acid is significant.

Table 7.—Comparison of Distributions of Clinical Scores of Symptoms, Based on Average Score per Volunteer

Symptom	Subjects With Zero Scores, %	Z-Statistic					Difference*
		Group 0 vs Group 1	Group 2 vs Group 3	Groups 0 and 1 vs Groups 2 and 3			
		Total	Knew	Did Not Know			
Sneezing	22	-1.10	0.14	-1.43	-0.02	-1.51	1.05
Stopped-up nose	15	-1.59	0.43	1.05	1.12	0.79	0.23
Runny nose, watery	16	-1.41	-0.24	0.09	0.83	-0.51	0.95
Runny nose, thick	77	0.57	0.83	-2.06†	-1.82	-0.21	-1.14
Postnasal drip	19	0.58	-1.31	2.21†	2.89‡	0.55	1.65
Sore throat	20	0.11	-0.43	1.31	1.31	-0.67	1.40
Pain on swallowing	51	0.29	-0.38	2.63‡	2.83‡	0.90	1.36
Hoarseness	30	-0.73	-0.64	2.79‡	2.35†	1.46	0.63
Cough, dry	39	0.36	-0.60	1.99†	1.86	0.74	0.79
Cough, productive	58	-1.00	-0.29	1.09	0.96	1.02	-0.04
Chest pain	73	-0.40	-0.24	1.14	0.16	1.30	-0.81
Headache	41	0.37	-1.14	0.79	1.12	0.79	0.23
Eyes tearing	66	1.55	0.01	0.14	0.41	-0.04	0.32
Earache	81	0.16	0.42	1.88	1.44	1.10	0.24
Loss of appetite	72	1.70	-0.03	1.52	0.66	1.54	-0.62
Feverishness	55	2.13†	0.24	0.18	0.02	-0.18	0.14
Chills	67	0.59	-0.76	0.22	1.25	0.13	0.79
Night sweats	80	1.54	0.64	1.20	1.21	0.75	0.33
General aches and pains	59	0.13	-0.39	1.55	0.71	0.73	-0.01
Feel below par	9	0.34	0.39	1.59	2.38†	0.58	1.27
Stay at home	54	-0.46	0.04	0.14	0.07	0.03	0.03

*Values in previous two columns divided by $\sqrt{2}$.
 † $P < .05$.
 ‡ $P < .01$.

Viral Studies

Only 20% of the volunteers had complete virus isolation studies. A virus was isolated or a serologic response demonstrated in 15 of the 39 volunteers (33%, an infection rate consistent with previous studies in civilian adults). Although the virus infection rate in the prophylactic placebo groups combined was higher than that in the ascorbic acid groups combined, the difference was not statistically significant.

Side Effects

No important side effects could be determined in either the placebo or ascorbic acid groups. A battery of laboratory tests that included measurements of the albumin-globulin ratio, alkaline phosphatase, total bilirubin, calcium, cholesterol, glucose, lactic acid dehydrogenase, phosphorus, serum glutamic oxaloacetic transaminase, urea nitrogen, and uric acid in 20 randomly selected volunteers failed to reveal any difference be-

tween the ascorbic acid and placebo groups.

COMMENT

This study was designed during the summer and rushed into operation to take advantage of the rise in upper respiratory infections expected to occur in the fall. There was no time to design, test, and have manufactured a placebo that would be indistinguishable from ascorbic acid. It did not occur to the investigators that a substantial number of the volunteers, presumably fully informed about the purpose of the study and the importance of the double blind, would not be able to resist indefinitely the temptation to learn which medication they were taking. In retrospect, this phenomenon is understandable in any study that continues for as long as nine months. The increasing placebo-ascorbic acid disproportion in dropout rates made the investigators suspicious that the study might not be completely blind, and this was confirmed by the data from the routine

end-of-study questionnaire, an essential ingredient of all clinical trials.

The Power of Suggestion

Depending on one's point of view, it is either an unfortunate or fortunate aspect of the study. It would have been gratifying to have performed a flawless clinical trial; on the other hand, it has turned out to be a unique opportunity to gain some insight into the importance of perfect blinding in trials with subjective endpoints. An association between severity and duration of symptoms and knowledge of the medication taken seems to have been clearly established.

Most pertinent then are the following questions: Did the participants who had less severe and shorter colds than formerly guess correctly that they were receiving ascorbic acid because they expected it to be effective, while those who had more severe colds assumed that they must be taking the placebo? Or did those who knew they were taking ascorbic acid or placebo because they had tasted their capsules have less or more severe colds as a result of suggestion? In an attempt to determine which might be the appropriate explanation, those who guessed correctly and confessed to tasting were compared with those who did not admit to tasting but did guess correctly, possibly by chance. Unfortunately, the numbers were too small to draw definite conclusions, and, in addition, the possibility remains that a number may have tasted and not confessed to having done so.

In any event, the effects of ascorbic acid on the number of colds seem to be nil (an average of 0.11 colds per person per year), and the effects on severity, although statistically significant if tests are allowable when the blinding has been broken, are clinically insignificant. In view of the absence of any information on possible toxicity if the medication is taken in such high doses over a period of years, it does not seem worthwhile to take two capsules or tablets three times a day for the rest of one's life to achieve such a small and equivocal benefit. Furthermore, recent studies in animals show that ascorbic acid

mobilizes calcium from bone,² and this could be a disastrous long-term side effect, albeit difficult to prove, in people with a tendency to osteoporosis, and other side effects of long-term administration are possible.³ No study of these has ever been conducted.

Small Effect in Other Studies

This study is in conformity with the rest of the better clinical trials of prophylaxis.⁴ A review of nine reasonably well-controlled trials in 3,940 volunteers has shown an average difference in number of colds per person per year of 0.09 ± 0.06 (1 SE), and in duration of 0.11 ± 0.24 days, both favoring ascorbic acid. The only other study that included a questionnaire at the end did not reveal any breaking of the blind.⁵ A study among Navajo Indian children⁶ did not include a questionnaire, but school children might not be expected to break the blind purposely. However, observations of the colds were made by the children's teachers, and the latter might have had an irresistible curiosity about the nature of the pills ingested. In this study, there was little effect on number of colds, and the statistically significant severity effect was not found in the older boys.

The two challenge experiments^{7,8} revealed no influence on number of colds, but in one there was slight but significant effect on the severity score. No information was available on breaking of the blind.

Some corroborative data suggest a possible mechanism for an effect on severity of colds, if such exists. A drop in white blood cell ascorbic acid with onset of a cold has been demonstrated,⁹ and an antihistamine-like action of ascorbic acid has been shown in some volunteers¹⁰ and patients.¹¹

Caveats

Several caveats are necessary with regard to interpretation of the present study. Viral culture data were not obtained on enough of the colds to be sure that a significant effect on a particular viral infection was not being missed. The volunteers were all healthy and it is possible that serious late effects of colds might be pre-

vented by ascorbic acid, especially in the elderly or infirm, who might be consuming a subnormal amount in their food.

Finally, there are two claims made by ascorbic acid advocates that have not been tested in this trial. Many people are convinced of their ability to abort a cold by taking ascorbic acid at the first sign and repeating the dose every few hours for a day or two. The therapeutic increment in this study was begun after delays of 1 to 24 hours. Obviously, an increased awareness could lead to many false impressions that a cold is starting, and there would result a false impression that ascorbic acid had prevented it. Now, a competent trial by the British General Practitioner Clinical Trials Group has shown no suggestion of an early ascorbic acid effect.¹² We know of no attempt to study whether or not herpes labialis is aborted by the early ingestion of large doses of ascorbic acid.

Denfiis A. George, MD, George M. Shaffer, MD, Nancy Mullen, RN, and Helen Auth, RT, assisted with this study.

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