A CONTROLLED CLINICAL TRIAL OF ASCORBIC ACID 
FOR THE COMMON COLD

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Vitamin C has been a popular medication for preventing the common cold and reducing the severity of cold symptoms for many years. Professor Pauling’s recent book on the subject has led to even further use of vitamin C in even larger doses. This study was performed to look for a difference in the frequency and severity of colds in a generally healthy, middle-class, medically aware population of employees at the National Institutes of Health. High doses of vitamin C were used for both prevention and treatment; virus isolations were attempted in an effort to relate viral types to vitamin C response; and the study was continued for a nine-month period in an attempt to examine seasonal variations of viruses and colds. The study was conducted so that nurses, physicians, and volunteers did not know who received placebo and who received ascorbic acid. Only the consulting statistician and the pharmacist could relate patient code numbers to medication received. Progress was monitored by a research committee not connected with the day-to-day activities.

METHODS

A random sample of 2,500 of 12,000 NIH employees were sent a questionnaire explaining the study, requesting information on the number of colds in the past 12 months, and offering an opportunity to participate in a study of the effectiveness of vitamin C in the prevention and treatment of the common cold. Of nearly 600 respondents (23%), 473 volunteers were selected for history and physical examination based on their ability to participate in the study for a full year. Further exclusions were made because of a history of gout; diabetes; renal stones; allergic respiratory symptoms; definite, suspected, or anticipated pregnancy; oral anticoagulant therapy; medications with respiratory side effects; elevated blood uric acid, and unwillingness or inability to stop taking ascorbic acid vitamin preparations. These exclusions reduced the study population to 323, of whom 12 dropped out of the study after taking only a few capsules. Thus, 311 employees of the initial random sample of 2,500 constituted the study group.

The 311 people were randomly assigned to four groups based on the type of maintenance and treatment drug received. Group 1 received placebo for both maintenance and therapy during a cold. Group 2 received placebo maintenance but ascorbic acid for colds. Group 3 received ascorbic maintenance
and placebo for colds, and Group 4 received ascorbic acid for both maintenance and therapy. Maintenance therapy was two capsules three times a day. Treatment for colds was an additional two capsules three times a day. Each test capsule contained 500 mg of ascorbic acid, 180 mg of lactose, and 5 mg of magnesium stearate. The placebo contained 645 mg of lactose and 5 mg of magnesium stearate. Thus, the study patients received 0 or 3 g per day of ascorbic acid with an additional 0 or 3 g per day during colds. Volunteers were interviewed monthly for side effects and unreported cold symptoms, and a check was made on the number of capsules remaining in their bottle and the next month's supply of capsules given. The next month's supply was dispensed by the pharmacy in accordance with the double-blind study protocol so that neither physician nor patient knew the medication received. Only the pharmacist and the statistician knew which patient was to receive which drug. Most patients who completed the study took the capsules as directed: 99% took at least four of six capsules per day and 87% at least five per day.

If a cold developed, the volunteers returned for a clinical assessment and were given supplemental capsules to be taken for the first five days of the cold. Throat cultures were done routinely; blood samples and nasal washings for virus identification were obtained if possible. Volunteers returned three times weekly for the duration of the cold and 20 symptoms were recorded throughout on a scale of 0 to 3. The number of days home from work was also recorded. A cold was defined as acute at the onset of two or more symptoms in the following categories: (1) sneezing, nasal congestion, rhinorrhea, postnasal drip; and (2) laryngitis, pharyngitis, dysphagia, bronchitis.

The following variables were selected for analysis: 1) number of colds per person, 2) mean duration of colds, 3) time at home, and 4) summation of symptom severity scores. The comparison of means was not useful since these distributions were quite skewed, so the Wilcoxon test for shift was used instead. For severity of symptoms, the scores were rated according to magnitude and the Wilcoxon two-sample test used. The value of the Wilcoxon test was then converted to a standard normal deviation.

The number of study subjects to include was based on the estimated number of colds to be expected. If 100 volunteers were assigned to each of the ascorbic acid and vitamin C groups, then there was a 95% chance that a 30% reduction in colds among the treated volunteers would be detected, if such a difference existed. It was further decided to continue the study for one year unless (a) the dropout rates for the vitamin C and placebo groups differed significantly (p = 0.15); (b) the number under study became less than 200; or (c) the number of colds in the vitamin C group was significantly greater than in the placebo group at six months (p = 0.05). The study was stopped at nine months, when the number of study subjects dropped below 200 and more dropouts were in the placebo group (p = 0.10).

As the study progressed, more and more subjects indicated that they knew the kind of medication received, although the physicians still did not know. A final questionnaire asking subjects to guess their maintenance and treatment medications showed a high degree of correct guessing. Therefore the data analysis was performed both as originally planned and again taking the subject's impression of his medication into consideration.
RESULTS

TABLE 1 shows the number of persons completing the study, the number of
colds, and the average number of colds per person for each of the four groups.
When the two treatment groups are combined there is a slight increase in the
average number of colds for a nine-month period in the placebo group. (1.36
vs. 1.27, p>0.50). The cold duration averaged 7.14 days for the placebo
group, 6.59 days for those taking 3 grams of vitamin C per day either as
maintenance or placebo, and 5.92 days for those in the 6-gram vitamin C group,
suggesting that each three groups of vitamin C might shorten a cold by one half
day. Ascorbic acid subjects had milder symptoms in 18 of 20 categories, with
5 being statistically significant. Average number of colds was not related to
age, sex, race, number of cigarettes smoked daily, history of allergy, or previous
vitamin usage.

During the study an increasing number of subjects claimed to know whether
they were receiving vitamin C or placebo, although the nurses and physicians
following them remained unaware of the maintenance drug used. The results
of a final questionnaire asking subjects to guess which drug they were taking
are shown in TABLE 2. Those individuals willing to guess had a high probability
of guessing correctly, both for placebo and vitamin C (p < 0.001). TABLE 3
compares correct and incorrect guessing based on whether a subject admitted
to tasting the capsule contents, suggesting that taste was a very important factor
in determining what medication a person received (p < 0.001). Further analysis
(TABLE 4) showed that among those individuals who did not taste their capsules,
correct guessing of medication received was associated with the total number
of colds on ascorbic acid versus placebo (p < 0.01), but not with the number
of people who did or did not have colds. In particular, for those individuals
who received placebo and did not taste their capsules (TABLE 5), guessing
placebo was more common in those who had colds, compared with those who
did not (p < 0.05). A similar relationship was not found for those receiving
ascorbic acid. In addition, the group on placebo who thought they were on
ascorbic acid had significantly fewer colds than the group on ascorbic acid who
thought they were on placebo (p < 0.05).

TABLE 6 shows the average duration of colds by suspected medication for
each treatment group. Individuals who did not know the medication received
had colds of essentially the same duration. Individuals who guessed correctly
as to medication received, on the average had longer colds if on placebo and
shorter colds if on ascorbic acid.

The analysis of 20 cold symptoms with and without the effect of knowledge
of capsule contents was a complicated statistical problem. Each symptom was
graded from 0 to 3 for each day of the cold. The average score for each symp-
tom for each volunteer was obtained by adding the scores for each cold and
dividing by the number of colds. There were thus 20 symptom distributions to
be compared among the four prophylactic-therapeutic categories. Comparisons
were done by ranking the scores for each symptom and using the Wilcoxon two-
sample test. Therapeutic ascorbic acid did not affect the severity of any
symptoms, so groups were combined to compare the prophylactic ascorbic acid
with placebo. Here, subjects receiving ascorbic acid tended to have less severe
symptoms (18 of 20 symptoms, with 2 at the 0.05 level and 2 at the 0.01 level).
However, when the analysis was repeated separately for those who knew the
<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Persons Completing Study</th>
<th>Total Number of Colds</th>
<th>Mean Number of Colds per Person</th>
<th>Mean ± Standard Error</th>
<th>Duration of Colds (days)</th>
<th>Mean ± Standard Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (P.P.)</td>
<td>45</td>
<td>56</td>
<td>1.4 ± 0.19</td>
<td>7.14 ± 0.46</td>
<td>6.46 ± 0.39</td>
<td>6.71 ± 0.53</td>
</tr>
<tr>
<td>Placebo (A.P.)</td>
<td>43</td>
<td>56</td>
<td>1.3 ± 0.18</td>
<td>6.46 ± 0.39</td>
<td>6.71 ± 0.53</td>
<td>6.09 ± 0.40</td>
</tr>
<tr>
<td>Ascorbic acid (P.A.)</td>
<td>44</td>
<td>52</td>
<td>1.1 ± 0.16</td>
<td>6.63 ± 0.36</td>
<td>6.71 ± 0.53</td>
<td>5.92 ± 0.40</td>
</tr>
<tr>
<td>Ascorbic acid (A.A.)</td>
<td>57</td>
<td>76</td>
<td>1.3 ± 0.15</td>
<td>6.46 ± 0.39</td>
<td>6.71 ± 0.53</td>
<td>6.09 ± 0.40</td>
</tr>
</tbody>
</table>

* ± One standard error.
**TABLE 2**
RESULTS OF QUESTIONNAIRE ON MAINTENANCE DRUG *

<table>
<thead>
<tr>
<th>Actual Drug</th>
<th>Suspected Drug</th>
<th></th>
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<th></th>
<th></th>
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<tr>
<td></td>
<td>Ascorbic Acid</td>
<td>Placebo</td>
<td>Unknown</td>
<td>Total</td>
<td></td>
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<tr>
<td>Ascorbic acid</td>
<td>40</td>
<td>12</td>
<td>49</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
<td>39</td>
<td>39</td>
<td>89</td>
<td></td>
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<tr>
<td>Total</td>
<td>51</td>
<td>51</td>
<td>88</td>
<td>190</td>
<td></td>
</tr>
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</table>

* $X^2 = 28.6, p < 0.001$.

**TABLE 3**
EFFECT OF TASTING CAPSULE ON GUESS *

<table>
<thead>
<tr>
<th>Tasted</th>
<th>Correct</th>
<th>Incorrect</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>55</td>
<td>9</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>No</td>
<td>24</td>
<td>14</td>
<td>76</td>
<td>114</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>23</td>
<td>88</td>
<td>190</td>
</tr>
</tbody>
</table>

* $X^2 = 57.4, p < 0.001$.

**TABLE 4**
COMPARISON OF SUSPECTED MEDICATION WITH NUMBER OF Colds FOR THOSE NOT TASTING CAPSULES *

<table>
<thead>
<tr>
<th>Number of Colds</th>
<th>Correct</th>
<th>Incorrect</th>
<th>Unknown</th>
<th>Total</th>
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<tr>
<td>Ascorbic acid</td>
<td>10</td>
<td>7</td>
<td>47</td>
<td>64</td>
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<td>Placebo</td>
<td>33</td>
<td>5</td>
<td>46</td>
<td>84</td>
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* $X^2 = 10.1, p < 0.01$.

**TABLE 5**
COMPARISON OF SUSPECTED MEDICATION WITH NUMBER OF INDIVIDUALS HAVING Colds *

<table>
<thead>
<tr>
<th>Received Placebo—Medication Not Tasted Guessed</th>
<th>Number of Individuals</th>
<th>Ascorbic Acid</th>
<th>Placebo</th>
<th>Unknown</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>With colds</td>
<td>3</td>
<td>15</td>
<td>21</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Without colds</td>
<td>6</td>
<td>2</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

* $X^2 = 8.1, p < 0.05$. 
medication received and those who did not, no effect of ascorbic acid in ameliorating symptoms was detected. Furthermore, there was a strong indication that knowledge of the medication received influenced the severity of symptoms, with the placebo group showing more severe symptoms on the average than the ascorbic acid group.

No side effects were noted in either the placebo or the ascorbic acid groups. No ascorbic acid toxicity was found among the following laboratory tests: albumin, globulin, alkaline phosphatase, total bilirubin, calcium, cholesterol, glucose, lactic acid, lactic acid dehydrogenase, alanine amino transferase, urea nitrogen, and uric acid.

Data on virus isolation was not meaningful, as only 39 volunteers participated in the virus-isolation portion of the study.

### TABLE 6

<table>
<thead>
<tr>
<th>Group *</th>
<th>Total Number</th>
<th>Total Duration</th>
<th>Medication Not Suspected Number</th>
<th>Medication Not Suspected Duration</th>
<th>Medication Suspected Number</th>
<th>Medication Suspected Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.P.</td>
<td>65</td>
<td>7.1</td>
<td>30</td>
<td>6.3</td>
<td>16</td>
<td>8.6</td>
</tr>
<tr>
<td>P.A.</td>
<td>56</td>
<td>6.5</td>
<td>18</td>
<td>6.7</td>
<td>15</td>
<td>4.7</td>
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<tr>
<td>A.P.</td>
<td>52</td>
<td>6.7</td>
<td>14</td>
<td>6.4</td>
<td>8</td>
<td>7.0</td>
</tr>
<tr>
<td>A.A.</td>
<td>76</td>
<td>5.9</td>
<td>30</td>
<td>6.5</td>
<td>13</td>
<td>4.8</td>
</tr>
</tbody>
</table>

* Groups as in Table 1.

### DISCUSSION

Perhaps the most interesting aspect of this study is the analysis of the effect of knowledge of medication received on the duration and severity of cold symptoms. This study was begun on short notice to take advantage of the fall "cold season." The lactose placebo selected could easily be distinguished from ascorbic acid by tasting the capsule contents. Little thought was given to possible tasting of capsules, in part because of the rush to start and in part because of the generally well-educated, well-motivated, medically sophisticated group of volunteers. In fact, our volunteers were quite curious and tasted capsules frequently. The volunteer population dropped from 311 to 192 over a nine-month period, with a gradually increasing dropout rate in the placebo group (p=0.10). This was our first clue that the patients knew which study drug they received even though the medical staff did not. An end-of-study questionnaire confirmed our impression that a significant number of subjects knew which medication they were receiving.

While we were disappointed that the study was no longer double-blind for 42% of the volunteers, the analysis of the data for the entire population and separately based on knowledge or lack of knowledge of treatment received, illustrated some of the problems of performing controlled clinical studies and the effect of knowledge of treatment on outcome.
In this study we have shown an association between knowledge of the medication received and the duration and severity of colds, with the ascorbic acid group showing the favorable response compared with placebo. No differences in response were noted if the medication received was not suspected. However, we cannot definitely conclude that the knowledge of medication received is the explanation, since those participants who by chance had fewer colds may have therefore guessed ascorbic acid as their medication and conversely for the placebo group. It is true that tasting the capsule was a highly reliable guide to medication received (p < 0.001). However, among those not tasting the capsules, correct guessing was associated with the number of colds for both the ascorbic acid and placebo groups (p < 0.01) and with the number of individuals having colds for the placebo group. To further determine if volunteers guessed their medication because of the duration and severity of their colds or because duration and severity responses were modified by knowledge of the medication received, we compared the number of colds detected during the study with the number each volunteer claimed to have had in the previous year. Unfortunately, volunteers uniformly overestimated their cold rates compared with the rates found in our study. As a result, the cause-and-effect relationship between correct guessing of medication and duration and severity of symptoms is not entirely clear. Definite knowledge, acquired by tasting the capsule contents, was associated with shorter, milder colds for the ascorbic acid group and the converse for the placebo group.

While this study needs to be interpreted cautiously because many subjects knew the medication received, our results on frequency, duration, and severity of colds are consistent with those of well-controlled studies in that ascorbic acid had at best a small effect. In addition, there is strong evidence in our data that the effects of ascorbic acid on duration of colds and severity of symptoms are the result of suggestion; however, we cannot entirely rule out some small effect due to the ascorbic acid itself. In any case, our experience with a large population of well-motivated volunteers was that taking two capsules three times a day was too much bother for the possible small benefit received.

REFERENCES


DISCUSSION

DR. K. E. SCHAEFER: I am not sure what diseases are meant by "the cold." What is the NIH's definition of a cold?

DR. LEWIS: It is defined as an acute onset of two or more symptoms in either of the following groups: (1) sneezing, nasal congestion rhinorrhea and postnasal drip; or (2) laryngitis, pharyngitis, dysphagia, and bronchitis. We would like to exclude from the study individuals with respiratory kinds of allergies, because of possible confusion. We did not want to have to distinguish hayfever and the like from upper respiratory viral infections, which is what we were trying to study.

DR. SCHAEFER: So you presumed that you were dealing with an infectious virus. Did anybody study whether or not these colds were due to rhinoviruses, adeno-, influenza, and so forth?

DR. LEWIS: One of the original design criteria was to study the viral agents. However, we attempted to study it by obtaining nasal washings from patients when they came in for colds, and we discovered that this discouraged them from returning.

QUESTION: Have you estimated the basal vitamin C intake of the subjects?

DR. LEWIS: We tried to do that in two ways. We did get initial blood specimens for ascorbic acid as well as some specimens later on in the study, but these were not handled in the right fashion. In the lab, white cells were not removed, the serum was not frozen properly, and so forth. Subjects taking vitamins were initially excluded from the study population. We continued to ask subjects if they were taking any vitamins, and it is hoped that they were excluded if they took vitamin-C-containing preparation. We really have no better estimate of actual basal measurements.
# CONTENTS

## Part I. Metabolism of Ascorbic Acid

<table>
<thead>
<tr>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction: Overview of Ascorbic Acid Metabolism. By J. J. Burns</td>
<td>5</td>
</tr>
<tr>
<td>Biosynthesis and Metabolism of Ascorbic Acid in Plants. By Frank A. Loewus, George Wagner, and Joan C. Yang</td>
<td>7</td>
</tr>
<tr>
<td>Chemistry and Metabolism of Ascorbic Acid and Ascorbate Sulfate. By B. M. Tolbert, M. Downing, R. W. Carlson, M. K. Knight, and E. M. Baker</td>
<td>48</td>
</tr>
<tr>
<td>Liquid Chromatographic Analysis of Ascorbate and Ascorbate-2-Sulfate. By William N. Bigler and Dennis M. Kelly</td>
<td>70</td>
</tr>
<tr>
<td>Utilization of Ascorbic Acid in Fish. By J. E. Halver, R. R. Smith, B. M. Tolbert, and E. M. Baker</td>
<td>81</td>
</tr>
<tr>
<td>Distribution of Ascorbic Acid, Metabolites and Analogues in Man and Animals. By Dietrich Hornig</td>
<td>103</td>
</tr>
</tbody>
</table>

* This series of papers is the result of the Second Conference on Vitamin C, sponsored by The New York Academy of Sciences and the Institute of Human Nutrition, College of Physicians and Surgeons, Columbia University, and held on October 9-12, 1974 in New York, New York.
Part VI. Ascorbic Acid and Respiratory Illness

Large-Scale Trials of Vitamin C. By TERENCE W. ANDERSON .................. 498
A Controlled Clinical Trial of Ascorbic Acid for the Common Cold. By THOMAS L. LEWIS, THOMAS R. KARLOWSKI, ALBERT Z. KAPIKIAN, JOHN M. LYNCH, GEORGE W. SHAFFER, DENNIS A. GEORGE, AND THOMAS C. CHALMERS ......................................................................................................... 505
Safety Considerations with High Ascorbic Acid Dosage. By LEWIS A. HARNESS 523
Ascorbic Acid Function and Metabolism During Colds. By C. W. M. WILSON 529