Proc. Nat. Acad. Sci. USA
Vol. 68, No. 11, pp. 2678-2681, November 1971

The Significance of the Evidence about Ascorbic Acid and the Common Cold

(vitamin C/double-blind studies/statistical significance)

LINUS PAULING

Department of Chemistry, Stanford University, Stanford, California 94305

Contributed by Linus Pauling, August 9, 1971

ABSTRACT **Only four independent double-blind studies have been reported of the effect of ascorbic acid regularly ingested in daily amounts more than 100 mg, in comparison with a placebo, in decreasing the incidence and integrated morbidity of the common cold for subjects exposed to cold viruses in the ordinary way and without colds when the test period began. A statistical analysis of these four studies leads to rejection of the null hypothesis that ascorbic acid has no more protective power than the placebo at the 99.86% level of confidence for the incidence of colds and the 99.9978% level of confidence for the integrated morbidity.**

For many years there has existed the popular belief that ascorbic acid has value in providing protection against the common cold and in ameliorating the manifestations of this viral disease. This popular belief has, however, not been generally shared by physicians, authorities on nutrition, and official bodies.

I was puzzled by the contraction between the popular belief and the official opinion, so I studied the published reports of controlled trials of ascorbic acid in relation to the common cold. On the basis of this study and of some general arguments about orthomolecular medicine (1) (the preservation of good health and the treatment of disease by varying the concentrations in the human body of substances that are normally present in the body and are required for health) and the process of molecular evolution (2), I reached the conclusion that ascorbic acid, taken in the proper amounts, decreases the incidence of colds and related infections, and also decreases the severity of individual colds. These arguments were presented in my book "Vitamin C and the Common Cold" (3). The evidence and arguments presented in this book were not convincing to some physicians and authorities on nutrition. Many statements contradicting my conclusions were made. Although my analysis of the published accounts of controlled studies in this field seems to me to be clear and straightforward, I have decided that, because of the importance of the question, it is desirable to publish a more detailed account of the evidence, including a more thorough statistical analysis of the controlled trials that have been performed. No statistical analysis of the body of evidence has previously been published.

THE NATURE OF THE STATISTICAL ANALYSIS

Each of the reports discussed in this paper describes a study of two groups of subjects selected at random from one population. The subjects in one group were administered the active substance (L-ascorbic acid, vitamin C) in certain amounts once or more every day, and those in the second group were administered an apparently identical inactive material, a placebo. The studies were double-blind, with neither the subjects nor the investigators knowing which subjects received the ascorbic acid and which received the placebo, that knowledge being kept by some other person until all of the information had been collected.

The question that I attempt to answer by analyzing the published reports is the following: Does the regular administration of ascorbic acid at a rate greater than 100 mg per day over a period of time beginning before the subjects have contracted a cold, and with the subjects exposed to cold viruses under ordinary living conditions, have an effect different from that of a placebo in decreasing the incidence and the severity of the common cold? A comparison with a placebo, with the subjects not knowing which group they are in, is essential because of the well-known "placebo effect" of even inactive medications.

The statistical methods used in the analysis are the conventional ones, for the most part Student's t-test or the calculation of χ^2 and then of the probability P(one-tailed) that the observed difference in effect of ascorbic acid and placebo (or a larger difference) would be obtained by chance alone in two groups taken at random from a uniform population if the null hypothesis of equal effectiveness of ascorbic acid and placebo were true. I have chosen to give P(one-tailed) rather than P(two-tailed) because no one contends that the placebo (usually citric acid) has a greater effect than ascorbic acid in preventing or ameliorating the common cold; the difference of opinion is between those people who state that ascorbic acid is no better than a placebo and those who say that it is better. Moreover, in none of the studies discussed did the investigators find a greater protective effect of the placebo than of ascorbic acid; in every study ascorbic acid is reported to provide greater protection than the placebo against the common cold, and the question to be answered is the level of confidence with which the reported results can be accepted and the null hypothesis of equal effectiveness of placebo and ascorbic acid can be rejected.

The following analysis includes every published double-blind study, whether statistically significant or not, of the comparative effects on the common cold of ascorbic acid and a placebo for two groups of subjects selected by some random process from a single population exposed to cold viruses in the ordinary way (contact with other people), with the ascorbic acid, in amounts over 100 mg per day, and placebo administered regularly over a period of time, beginning before colds were incurred. The common cold is considered to be the disease

or complex of diseases described by the investigators themselves as the common cold. Observations for other diseases are not included.

The results of the studies are usually reported in one or more of three aspects: first, the incidence of colds (number of colds per person in unit time, usually taken as the period of the study); second, the average severity of individual colds (as measured by days of illness per cold or number of days when symptoms were recorded); and third, the integrated morbidity (the product of the other two). In the following discussion I have assigned to each investigation a value of P for the incidence and a value for the integrated morbidity, based as reliably as possible on the reported observations, and then have combined the values for all of the published studies satisfying the criteria given above to obtain two values for the level of confidence at which the null hypothesis of equal effect of ascorbic acid and placebo is to be rejected. These two values, for incidence and for integrated morbidity, are of course not independent of one another.

THE WORK OF RITZEL

A study of the effect of 1 g of ascorbic acid per day was reported by G. Ritzel, a physician with the medical service of the School District of the City of Basel, Switzerland (4). The study was carried out in a ski resort with 279 skiers during two periods of 5–7 days. The conditions were such that the incidence of colds during these short periods was large enough (about 20%) to permit results with statistical significance to be obtained. The subjects were roughly of the same age and had similar nutrition during the period of study. The investigation was double-blind, with neither the participants nor the physicians having any knowledge about the distribution of the ascorbic-acid tablets and the placebo tablets. The tablets were distributed every morning and taken by the subjects under observation, so that the possibility of interchange of tablets was eliminated. The subjects were examined daily for symptoms of colds and other infections. The records were largely on the basis of subjective symptoms, partially supported by objective observations (measurement of body temperature, inspection of the respiratory organs, auscultation of the lungs, and so on). Persons who showed cold symptoms on the first day were excluded from the investigation.

After the completion of the investigation, a completely independent group of professional people was provided with the identification numbers for the ascorbic-acid tablets and placebo tablets, and this group performed the statistical evaluation of the observations.

The number of colds was 31 for the placebo group of 140 subjects and 17 for the ascorbic-acid group of 139 subjects. [The number of colds was not given explicitly in the paper. However, the number of days of illness for each of the two groups was given (80, 31), and the average number of days of illness per cold (2.6, 1.8). The only integral values for the number of colds allowed by these numbers are 31 for the placebo group and 17 for the ascorbic-acid group.] The incidence of colds is accordingly 0.221 per person for the placebo group and 0.122 for the ascorbic-acid group, a decrease of 45% for the ascorbic-acid group. The value of χ^2 is found to be 4.81, with P(one-tailed) < 0.015. This investigation accordingly shows with statistical significance that the null hypothesis that ascorbic acid has only the same effect as the placebo in decreasing the incidence of colds is to be rejected.

The group receiving ascorbic acid showed only 39% as many days of illness, per person, as the group receiving the placebo, and the number of individual symptoms per person was only 35% as great for the ascorbic-acid group as for the placebo group. The investigator states that the statistical evaluation of these differences by two-by-two tables gives a significant difference, $0.001 < P$(two-tailed) < 0.01. Each of these observations is a measure of the integrated morbidity. Information (values of standard deviation) permitting independent calculation of P is not given in the paper. I accept the value P(one-tailed) < 0.005 for the level of rejection of the null hypothesis with respect to the integrated morbidity.

THE WORK OF COWAN, DIEHL, AND BAKER

Another careful study of ascorbic acid and the common cold was reported by Cowan, Diehl, and Baker in 1942(5). The principal work was done during the winter "cold season" of 1939–1940. The subjects were all students in the University of Minnesota, who volunteered to participate in this study because they were particularly susceptible to colds. Persons whose difficulties seemed to be due primarily to chronic sinusitis or allergic rhinitis, as shown by examination of the nose and throat and consideration of symptoms of allergy, were excluded from the study. The subjects were assigned alternately and without selection to an experimental group and a control group. The subjects in the control group were treated exactly like those in the experimental group, except that they received a placebo instead of the ascorbic acid. The subjects were instructed to report to the Health Service whenever a cold developed, so that special report cards could be filled in by a physician. Dr. Cowan has informed me that the study was a double-blind one, with neither the subjects nor the physicians knowing which group a subject was in. Each subject was interviewed every 3 months in order to check the completeness of the reports.

The study was continued for 28 weeks. Of the 233 students initially in the ascorbic acid group, 183 received 200 mg per day throughout the period of 28 weeks, and 50 received 200 mg per day for 2 weeks, followed by 100 mg per day, except on inception of a cold, when an additional 400 mg per day for 2 days was administered. This group numbered 208 subjects at the completion of the study, 25 having dropped out. If the composition of the group remained unchanged, the average intake of ascorbic acid was 180 mg per day. The students in the control group initially numbered 194, of whom 155 completed the study. The reported average number of colds per person during the period of study was 2.2 ± 0.08 (SD 0.12) for the control group, and 1.9 ± 0.07 (SD 0.10) for the ascorbic acid group. The difference between the average number of colds in the control group and in the experimental group is given by the authors as one-third of a cold and also as 0.3 ± 0.11 (SD 0.16).

The authors state in their paper that "The actual difference between the two groups during the year of the study amounts to one-third of a cold per person. Statistical analysis of the data reveals that a difference as large as this would arise only three or four times in a hundred through chance alone. One may therefore consider this as probably a significant difference, and vitamin C supplement to the diet may therefore be judged to give a slight advantage in reducing the number of colds experienced."

Because the authors rounded off the numbers giving the actual numbers of colds per person, the difference is not

TABLE 1. *The weight of evidence for rejecting the null hypothesis of equal effectiveness of ascorbic acid and placebo*

Investigators	Daily intake of ascorbic acid, (mg)	Value of P(one-tailed) at which the null hypothesis is rejected	
		Incidence	Integrated morbidity
Ritzel	1000	0.015	0.005
Cowan, Diehl, and Baker	180	0.02	0.02
Wilson and Loh	200	0.025	0.025
Franz, Sands, and Heyl	205	0.44	0.008
χ^2 (8 df)		25.24	35.46
Combined P		0.0014	0.000022

known exactly. It is probably 0.33 or 0.34, which correspond (Student's t-test) to the values 0.04 or 0.03 for P(two-tailed), in agreement with the statement by the authors. This difference represents a decrease by 15% in the incidence of colds in the ascorbic-acid group as compared with the control group.

I accept the value P(one-tailed) < 0.02 for rejection of the null hypothesis with respect to the incidence of colds.

The average number of days lost from school per person in the placebo group was reported as 1.6, and in the ascorbic-acid group as 1.1, giving a decrease of 31% in integrated morbidity. Values of the standard deviation are not given in the paper. I accept as a conservative estimate of the level of rejection of the null hypothesis with respect to the integrated morbidity the same value, P(one-tailed) < 0.02, as with respect to incidence.

THE WORK OF WILSON AND LOH

Wilson and Loh (Department of Pharmacology, University of Dublin) have published a report of a double-blind study of subjects in a girls' boarding school during a winter period of 6 months (6). Of the 108 subjects, 57 received ascorbic acid (200 mg per day) and 46 received placebo tablets. The investigators state that ascorbic acid significantly reduced the incidence, duration, and severity of symptoms of colds, in comparison with the placebo. They do not give information permitting an independent statistical analysis to be carried out. I assume that their statement about significance has the usual meaning, P(two-tailed) < 0.05, and I accordingly assign the corresponding value $P < 0.025$ for rejection of the null hypothesis with respect to both incidence and integrated morbidity.

THE WORK OF FRANZ, SANDS, AND HEYL

A double-blind study of ascorbic acid and the common cold was carried out by Franz, Sands, and Heyl of Dartmouth Medical School during the 3-month period from February to May 1956, with 89 volunteer medical students and students and student nurses as subjects (7). The subjects were divided in a random way into four groups, three of 22 subjects and one of 23 subjects. One group received tablets containing ascorbic acid, the second ascorbic acid and a bioflavonoid (naringin), the third a placebo, and the fourth naringin only. The daily amount of ascorbic acid was 205 mg and that of the bioflavonoid was 1000 mg. Symptoms of colds were systematically recorded. The results for the bioflavonoid groups, with or without ascorbic acid, were the same as for the corresponding groups without bioflavonoid. The authors concluded that the administration of a bioflavonoid had effect neither on the incidence or the cure of colds nor on the ascorbic-acid concentration in the blood.

The incidence of colds in the ascorbic-acid group (with or without bioflavonoid) was 4.6% less than for the control group (placebo or bioflavonoid only), 14/44 versus 15/45, which corresponds to rejection of the null hypothesis at the level P(one-tailed) < 0.44. The only other results reported by the investigators is the incidence of serious colds (not cured or improved in 5 days), which I take as a measure of the integrated morbidity. This incidence was 1/44 for the ascorbic-acid group and 8/45 for the control group, significantly different ($\chi^2 = 5.88$, P(one-tailed) < 0.008). The authors state that this difference is statistically significant (0.05 level).

THE TOTAL EVIDENCE FOR THE EFFECTIVENESS OF ASCORBIC ACID

Each of these four double-blind studies of ascorbic acid has given the statistically significant result that the hypothesis that ascorbic acid administered in amounts over 100 mg per day to subjects who have not yet caught cold and are subjected to ordinary conditions of exposure to cold viruses show the same incidence and integrated morbidity of colds and related infections as placebo subjects is to be rejected, with one exception—the observation of Franz, Sands, and Heyl on incidence (Table 1). I now ask what the weight of the total body of evidence is.

There is no doubt that the four studies, carried out by different investigators in different places and at different times, are independent of one another. Moreover, these four studies constitute the entire set of published double-blind comparisons of ascorbic acid (more than 100 mg per day) and placebo administered to subjects who have not yet caught cold and are subjected to exposure to cold viruses in the ordinary way. We may, accordingly, combine the four values of P to obtain a measure of the significance of all of the evidence in rejecting the null hypothesis. Fisher's method (Table 1) leads to χ^2 (8 degrees of freedom) $= -2\Sigma \ln P_i = 25.24$, $P = 0.0014$ for incidence and 35.46, $P = 0.000022$ for integrated morbidity. I conclude that the evidence about incidence leads to rejection of the null hypothesis of equal effect of ascorbic acid and placebo at the 99.86% level of confidence and the evidence about integrated morbidity leads to rejection of the null hypothesis at the 99.9978% level of confidence.

THE AMOUNT OF PROTECTION

To within the experimental error, the effect of ascorbic acid, relative to that of the placebo, can be represented by exponential expressions: incidence of colds $= 1 - \exp(-0.60a)$; severity of individual colds $= 1 - \exp(-0.29a)$; integrated morbidity $= 1 - \exp(-0.99a)$, with a the intake of ascorbic acid in grams per day. The coefficients are fitted to the values reported by Ritzel. The equation gives integrated morbidity (relative to placebo) of 61% for an intake of 500 mg per day, 37% for 1 g per day, and 14% for 2 g per day. The values are, of course, expected to depend somewhat on the nature of the population and environment.

OTHER STUDIES

Dahlberg, Engel, and Rydin (8) did a double-blind study with an average daily intake of about 90 mg of ascorbic acid. They observed a decreased incidence of the common cold by 4%, not statistically significant. (Decrease in incidence of 6% is given

by the exponential expression.) Cowan, Diehl, and Baker (5) also performed a second double-blind study, with a daily intake of 50 mg for one group and 25 mg for another, and observed no difference in incidence (to ±2%) from the placebo group. (Decreases in incidence of 3% and 1.5%, respectively, are given by the exponential expression.) These are the only double-blind studies that have been done with small daily amounts of ascorbic acid. They were not designed in such a way as to provide results with statistical significance, which would have required about three times as many subjects as were used.

THE WORK OF WALKER, BYNOE, AND TYRRELL

The study by Walker, Bynoe, and Tyrrell (9) is often mentioned as having shown that ascorbic acid has no protective value against the common cold. Of the 91 subjects, 47 received 3 g of ascorbic acid per day for 3 days before inoculation with viruses (a mixture of rhinoviruses, influenza B virus, or B814 virus) and for 6 days after inoculation, and 44 subjects received a placebo. The incidence of colds was only 6% less for the ascorbic-acid group (18/47) than for the placebo group (18/44); this difference is not statistically significant. The investigators concluded that there is no evidence that the administration of ascorbic acid has any value in the prevention or treatment of colds produced by five known viruses. In fact, their study rejects with statistical significance ($P < 0.05$) a protective effect greater than 40%, but not a smaller effect, for subjects inoculated with viruses in the way used. The results of this study suggest that inoculation with viruses is not equivalent to ordinary exposure to viruses.

CONCLUSION

An analysis has been made of all published results of double-blind controlled studies of the effect of ascorbic acid in daily amounts over 100 mg on the incidence, severity, and integrated morbidity of the common cold in populations that receive the ascorbic acid (or a placebo) regularly, beginning before colds have been incurred, and with the subjects exposed to cold viruses in the ordinary way (contact with other people). The observations reject with high statistical significance the null hypothesis that under these conditions ascorbic acid has the same effect as a placebo. Ascorbic acid in a daily amount of 1000 mg is reported to decrease the incidence of colds by about 45% and the integrated morbidity by about 63%. These values are used in formulating exponential expressions for the amount of protection as a function of the intake of ascorbic acid. No controlled study under these conditions has given results rejecting with statistical significance the hypothesis that this amount of protective effect occurs. A smaller protective effect (not statistically significant) is reported when the colds are induced by inoculation with a virus suspension.

1. Pauling, Linus, *Science*, **160**, 265 (1968).
2. Pauling, Linus, *Proc. Nat. Acad. Sci. USA*, **67**, 1643 (1970).
3. Pauling, Linus, *Vitamin C and the Common Cold* (W. H. Freeman and Co., San Francisco, 1970).
4. Ritzel, G., *Helv. Med. Acta*, **28**, 63 (1961).
5. Cowan, D. W., H. S. Diehl, and A. B. Baker, *J. Amer. Med. Ass.*, **120**, 1267 (1942).
6. Wilson, C. W. M., and H. S. Loh, *Acta Allergol.*, **24**, 367 (1970).
7. Franz, W. L., G. W. Sands, and H. L. Heyl, *J. Amer. Med. Ass.*, **162**, 1224 (1956).
8. Dahlberg, G., A. Engel, and H. Rydin, *Acta Med. Scand.*, **119**, 540 (1944).
9. Walker, G. H., M. L. Bynoe, and D. A. J. Tyrrell, *Brit. Med. J.*, **1**, 603 (1967).