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REVIEW ARTICLE

Does Vitamin C Alleviate the Symptoms of the Common Cold? - A Review of Current Evidence

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Since 1971, 21 placebo-controlled studies have been made to establish whether vitamin C at a dosage of ≥ 1 g/day affects the common cold. These studies have not found any consistent evidence that vitamin C supplementation reduces the incidence of the common cold in the general population. Nevertheless, in each of the 21 studies, vitamin C reduced the duration of episodes and the severity of the symptoms of the common cold by an average of 23%. However, there have been large variations in the benefits observed, and clinical significance cannot be clearly inferred from the results. Still, the consistency of the results indicates that the role of vitamin C in the treatment of the common cold should be reconsidered.

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INTRODUCTION

There has been a long-standing controversy about whether vitamin C is effective against the common cold. From 4 placebo-controlled studies carried out before 1971, Pauling concluded that vitamin C reduces the incidence and severity of the common cold (1, 2). The greatest benefit was observed by Ritzel (3, 4), who used the largest dose (1 g/day). This led Pauling to propose such amounts for the prevention and treatment of the common cold. Pauling's claims were not generally accepted, yet they inspired a number of intervention studies to determine whether vitamin C has any actual effect.

In the present study the placebo-controlled studies published since 1971 in which at least 1 g/day of vitamin C has regularly been given to test subjects are briefly reviewed. If vitamin C has any effect on the incidence of, or morbidity due to, the common cold it should be observed most clearly in these studies. Moreover, these studies test whether Pauling's conclusions (1, 2) were correct, since none of the studies on which his claims were based are included.

MATERIALS AND METHODS

The literature was thoroughly searched to find all placebo-controlled studies published since 1971, in which at least 1 g/day of vitamin C had been regularly given to the study subjects. The search of the literature consisted of several database searches using various search strategies (SCISEARCH, EMBASE, MEDLINE) and inspection of the reference lists of all relevant articles and reviews. 18 publications (5-22) and 1 correction (23) were found, describing studies falling under the specifications of the search. Two other extensive literature searches of "vitamin C and the common cold" have also been carried out previously (21, 24). The studies found by this author are consistent with the studies found in the 2 other literature searches (21, 24).

The data shown in Fig. 1 are derived from 18 publications (5-22), 3 of which contain results with 2 vitamin groups (9, 10, 17). Thus, the total number of vitamin groups has been 21. For a concise summary of the original results, see Table I in ref. 25. The total number of subjects in the studies has been 6,600. All studies except 1 (6) were double-blind. Some of the placebo groups were given 10-70 mg/day of vitamin C to ensure that the effects of the larger doses were not due to alleviation of dietary deficiency (17, 19, 21). The group of twins living together in the study by Carr et al. (19) has not

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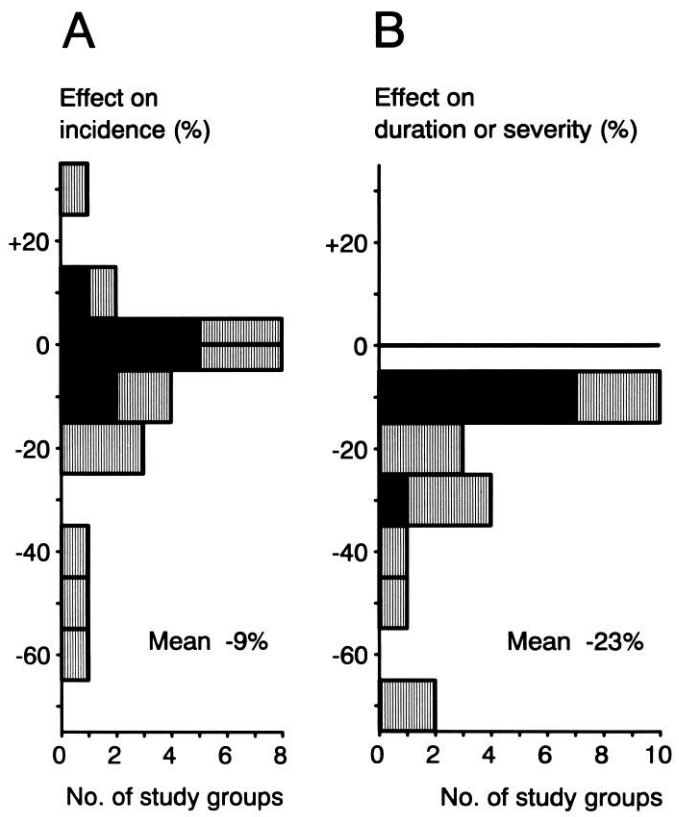

Fig. I. Effect of vitamin C on the common cold. (A) Relative effect on incidence. (B) Relative effect on the duration of episodes or on the severity of symptoms. A horizontal bar indicates the number of studies recording a relative change in the vitamin group which falls within the vertical region of the bar. Black bars indicate the studies in which at least 400 subjects have been used (test and control group combined). A horizontal line is added to visualize the level of the control group.

been included, for reasons previously discussed (25). The D-ascorbic acid group in the study by Clegg and Macdonald (12) is not included, even though a benefit from the D-isomer was observed, since the physiological form of vitamin C is L-ascorbic acid. Some studies have used several parameters to quantify the duration of the episode or the severity of the symptoms (25). As regards alternative outcome parameters, days off from work, absence from school, days in bed (5, 16, 17), general malaise and fever (11), and severity of symptoms (18) have been chosen as measures of morbidity due to the common cold for Fig. 1B.

The probability that the distribution of results in Fig. 1B was due to chance was calculated with the formula for binomial distribution. Provided that the vitamin C and placebo groups are well matched, and that vitamin C does not affect the common cold, a vitamin group has a 50% probability of showing an increase and a 50% probability of showing a decrease in morbidity, when compared with a placebo group. Consequently, the probability that all 21 groups, purely by chance, experienced a decrease in morbidity is $(0.5)^{21} = 0.0000005$. However, this is a very conservative estimate of the statistical significance of all the evidence, since several studies have found a statistically significant difference ($p < 0.05$) between vitamin and placebo groups (25). The probabilities of individual studies could be combined by using Fisher's method (26), but it would not be worthwhile, since the null hypothesis that vitamin C does not differ from placebo, can already be rejected by the simple binomial distribution analysis.

RESULTS AND DISCUSSION

No marked effect on incidence

Vitamin C has no marked effect on the incidence of the common cold (Fig. 1 A). The mean decrease in incidence has been –9%. 10 study groups out of 21 found a decrease in incidence (–7% and over), while 8 groups found no effect on incidence (range –3% to +2%) and 3 groups found an increase in incidence (+9% and over). Apart from 4 studies, all the results are quite symmetrically grouped around zero. Of the 4 outliers, 2 contained fewer than 25 subjects (16, 22), the third was poorly described and not published in a regular scientific forum (11), and the fourth was the only non-double-blind study of the entire group (6).

It is noteworthy that the studies with the largest numbers of subjects have not shown any consistent decrease in incidence (black bars in Fig. 1 A). If the results are weighted with the number of subjects used in each study, the mean change in incidence becomes quite insignificant (–4%). Thus, the studies do not support the practice of regular ingestion of vitamin C with the purpose of reducing the incidence of the common cold in the general population.

It is possible that vitamin C reduces the incidence of common cold in certain subgroups, but the intervention studies indicate that such subgroups may not be very large or numerous. Still, it is interesting that 2 studies which found a significant decrease in incidence were conducted using Canadian military troops undergoing Arctic exercises (11), and students at a ski school in the Swiss mountains (3), which may suggest that vitamin C has some effect on the common cold incidence under conditions of great stress.

Symptoms are alleviated

Each one of the 21 vitamin C groups showed a decrease in the duration or the severity of symptoms, of common cold episodes (Fig. 1B). The probability that, purely by chance, none of the vitamin groups would find an increase in morbidity is extremely small ($p = 0.0000005$). Hence, it is very unlikely that the pattern of results emerging was due to chance (Fig. 1B). Moreover, the possibility of a systematic bias seems to be excluded, since all studies, with the exception of a single one (6), were conducted with the double-blind method. Several of the individual studies, though not all of them, have observed a decrease in morbidity that has been statistically significant (5-8, 11, 17-20, 22). Accordingly, there is very strong evidence which indicates that vitamin C alleviates the symptoms of the common cold. The next question is to assess the magnitude of the benefit.

Estimation of the benefit

In most of the studies the decrease in morbidity has been between 5% and 35% (Fig. 1B). The mean decrease in duration or severity of the common cold has been 23%, which is not negligible, even though it does not promise total relief from symptoms. A large number of factors have varied between the studies: types of subject, geographical location and climate, types of respiratory viruses infecting the subjects, definition of disease and calculation of the duration and severity, etc. Furthermore, the intake of vitamin C in the control groups may be an important variable; in some of the studies the control subjects had received quite large doses of the vitamin in their diet (25). Thus, the large variation in the effects of vitamin C supplementation may depend on several factors and, consequently, certain subgroups may benefit much more than the calculated average.

Dose of vitamin C

What is the best dose of vitamin C for the treatment of the common cold? Most of the studies have used 1 g/day. Six study groups were given 2 g/day (7, 9, 10, 18, 20, 22) and 2 groups were given 3 g/day (8, 13). Anderson et al. gave 1 g/day regularly, but increased the dose to 4 g/day during a cold episode (5). The mean decrease in severity was 19% in studies that used 1 g/day of the vitamin, and 29% in studies that used 2-4 g/day of the vitamin during the cold episode (25). This difference suggests that maximal benefit is not obtained with 1 g/day of the vitamin, even though one must be cautious when comparing the quantitative results, since there are large experimental variations in the studies.

Some of the studies have contained 2 or 3 vitamin groups that were given different doses. In such studies the definition of disease and several other factors have been constant and therefore the results of the different vitamin groups are comparable. Karlowski et al. gave

1 group 3 g vitamin C/day regularly, a second group 3 g/day during the cold episode, and a third group 3 g/day regularly plus 3 g/day during a cold episode (i.e. 6 g/day during an episode). The average decrease in the duration of symptoms was 5% and 8% in the 3 g/day groups, and 17% in the 6 g/day group (13). Coulehan et al. gave 1 group of children 1 g/day and another group 2 g/day of the vitamin. The decrease in duration of the episode in these 2 groups was 12% and 29%, respectively (10). Anderson et al. compared the effect of 4 and 8 g/day when given, in several doses, only on the first day of illness. The larger dose was consistently more effective when 8 classes of symptoms were followed to determine the duration of the episodes (9). Thus, these three studies also suggest that the maximal benefit is not obtained with 1 g/day of the vitamin.

Certain physicians have treated their common cold patients with doses still larger than those used in the intervention studies (27, 28). Cathcart observed that patients with common cold infection can ingest over 30 g/day of vitamin C without getting diarrhea, in contrast to healthy subjects who get diarrhea with 4–15 g/day (28). Based on his observations, Cathcart has proposed that the best dose may be one that is slightly smaller than the dose that causes stomach problems. He suggests that the dose is first increased to a level that causes minor stomach ailments, in order to find the upper limit, and thereafter smaller doses are used for therapy (28).

Placebo effect does not explain the results

It has been suggested that the effect of vitamin C on the common cold could be due to the placebo effect (29). This suggestion was based on the study by Karlowski et al., in which the subjects who could correctly identify vitamin C reported, on average, greater benefit from the vitamin than those who could not identify it (13). In this study the placebo consisted of lactose, which could easily be distinguished from ascorbic acid by taste. However, it has been explicitly reported in a number of studies that the placebo tablets were indistinguishable from the vitamin C tablets (4, 5, 7, 9, 10, 12, 14, 15, 17-20). It is unlikely that the placebo effect could explain the benefits observed in these studies. Furthermore, provided that vitamin C does afford some benefit, it is probable that certain subjects can identify whether they get the vitamin or the placebo on the basis of the physiological effects. For example, Asfora initiated a double-blind study to test the effect of 6 g/day of vitamin C on the common cold, but subjects receiving the vitamin could be identified due to their clinical progress (30).

Physiological effects of vitamin C

The beneficial effects of vitamin C against the common cold may be caused by its antioxidant properties (25). Vitamin C is one of the major biological antioxidants (31). It appears that neutrophils play a significant role in producing the symptoms of the common cold (32); in an infection they release large amounts of oxidizing compounds that are toxic to other cells (33-35). Activation of neutrophils promotes an efficient consumption of extracellular vitamin C, which suggests that high concentrations of the vitamin may provide protection against the harmful effects of the oxidants released (36). Furthermore, a common cold episode causes a significant decrease in vitamin C concentration in leukocytes, and this decrease can be prevented by giving the subjects 6 g/day of the vitamin (37).

It is a common assumption that the only physiological role of vitamin C is to prevent scurvy. For example, the purpose of the nutritional recommendation for vitamin C (60 mg/day) is the prevention of deficiency (25, 38-42). However, the diet of our ancestors contained 0.4–2 g/day of vitamin C (40, 43, 44), which indicates that such amounts are not unfamiliar to human physiology, i.e. they are not pharmacological. Furthermore, the nutritional recommendations are based on the concept of 'nutrient need', which appears to lack a sound

biochemical basis (41, 42). Vitamin C is a cheap and safe nutrient; several of the suspected side effects of fairly large amounts are unfounded (40, 45, 46). For example, none of the intervention trials has revealed any significant side effects of the vitamin (3-22). Furthermore, in a recent epidemiological study the men who had been taking vitamin C supplements, on their own initiative, had a standardized mortality rate 30% lower than the control group (47). Accordingly, there are good reasons for reconsidering the potential role of vitamin C in the treatment of the common cold.

REFERENCES

1. Pauling L. The significance of the evidence about ascorbic acid and the common cold. Proc Natl Acad Sci USA 68: 2678-2681, 1971.
2. Pauling L. Ascorbic acid and the common cold. Am J Clin Nutr 24: 1294-1299, 1971.
3. Ritzel G. Critical analysis of the role of vitamin C in the treatment of the common cold [in German]. Helvetica Medica Acta 28: 63-68, 1961.
4. Ritzel G. Ascorbic acid and the common cold. JAMA 235: 1108, 1976.
5. Anderson TW, Reid DB, Beaton GH. Vitamin C and the common cold: a double-blind trial. Can Med Assoc J 107: 503-508, 1972.
6. Charleston SS, Clegg KM. Ascorbic acid and the common cold. Lancet 1: 1401-1402, 1972.
7. Elliott B. Ascorbic acid; efficacy in the prevention of symptoms of respiratory infection on a Polaris submarine. International Research Communications System/Medical Science 1(3): 12, 1973.
8. Schwartz AR, Togo Y, Hornick RB, Tominaga S, Gleckman RA. Evaluation of the efficacy of ascorbic acid in prophylaxis of induced rhinovirus 44 infection in man. J Infect Dis 128: 500-505, 1973.
9. Anderson TW, Suranyi G, Beaton GH. The effect on winter illness of large doses of vitamin C. Can Med Assoc J 111: 31-36, 1974.
10. Coulehan JL, Reisinger KS, Rogers KD, Bradley DW. Vitamin C prophylaxis in a boarding school. N Engl J Med 290: 6-10, 1974.
11. Sabiston BH, Radomski MW. Health problems and vitamin C in Canadian northern military operations. DCIEM Report no. 74-R-1012. Downsview, Ontario: Defence Research Board, 1974.
12. Clegg KM, Macdonald JM. L-ascorbic acid and D-isoascorbic acid in a common cold survey. Am J Clin Nutr 28: 973-976, 1975.
13. Karlowski TR, Chalmers TC, Frenkel LD, Kapikian AZ, Lewis TL, Lynch JM. Ascorbic acid for the common cold. A prophylactic and therapeutic trial. JAMA 231: 1038-1042, 1975.
14. Coulehan JL, Eberhard S, Kapner L, Taylor F, Rogers K, Garry P. Vitamin C and acute illness in Navajo schoolchildren. N Engl J Med 295: 973-977, 1976.
15. Elwood PC, Lee HP, Leger AS, Baird IM, Howard AN. A randomized controlled trial of vitamin C in the prevention and amelioration of the common cold. British Journal of Preventive and Social Medicine 30: 193-196, 1976.
16. Miller JZ, Nance WE, Norton JA, Wolen RL, Griffith RS, Rose RJ. Therapeutic effect of vitamin C. A co-twin control study. JAMA 237: 248-251, 1977.
17. Ludvigsson J, Hansson LO, Tibbling G. Vitamin C as a preventive medicine against common colds in children. Scand J Infect Dis 9: 91-98, 1977.
18. Pitt HA, Costrini AM. Vitamin C prophylaxis in marine recruits. JAMA 241: 908-911, 1979.
19. Carr AB, Einstein R, Lai LYC, Martin NG, Starmer GA. Vitamin C and the common cold: A second MZ co-twin control study. Acta Genet Med Gemellol (Roma) 30: 249-255, 1981.
20. Bancalari A, Seguel C, Neira F, Ruiz I, Calvo C. Prophylactic value of vitamin C in acute respiratory infections of schoolchildren [in Spanish]. Rev Med Chil 112: 871-876, 1984.
21. Briggs M. Vitamin C and infectious disease: a review of the literature and the results of a randomized, double-blind, prospective study over 8 years. In: Briggs MH, ed. Recent Vitamin Research. Boca Raton, Fla: CRC Press, 39-82, 1984.
22. Mink KA, Dick EC, Jennings LC, Inborn SL. Amelioration of rhinovirus colds by vitamin C (ascorbic acid) supplementation. Medical Virology 7: 356, 1988.
23. Anderson TW, Reid DB, Beaton GH. Vitamin C and the common cold (correction). Can Med Assoc J 108: 133, 1973.
24. Kleijnen J, Riet G, Knipschild PG. Vitamin C and the common cold [in Dutch]. Ned Tijdschr Geneeskd 133: 1532-1535, 1989.
25. Hemilä H. Vitamin C and the common cold. Br J Nutr 67: 3-16, 1992.

26. Fisher RA. Statistical Methods for Research Workers. 7th ed. London: Oliver and Boyd, 104-106, 1938.
27. Regnier E. The administration of large doses of ascorbic acid in the prevention and treatment of the common cold. Part II. Review of Allergy 22: 948-956, 1968.
28. Cathcart RF. Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy. Med Hypotheses 7: 1359-1376, 1981.
29. Chalmers TC. Effects of ascorbic acid on the common cold. An evaluation of the evidence. Am J Med 58: 532-536, 1975.
30. Asfora J. Vitamin C in high doses in the treatment of the common cold. Int J Vitam Nutr Res Suppl 16: 219-234, 1977.
31. Halliwell B, Gutteridge JMC. The antioxidants of human extracellular fluids. Arch Biochem Biophys 280: 1-8, 1990.
32. Turner RB. The role of neutrophils in the pathogenesis of rhinovirus infections. Pediatr Infect Dis J 9: 832-835, 1990.
33. Anderson BO, Brown JM, Harken AH. Mechanisms of neutrophil-mediated tissue injury. J Surg Res 51: 170-179, 1991.
34. Maeda H, Akaike T. Oxygen free radicals as pathogenic molecules in viral diseases. Proc Soc Exp Biol Med 198: 721-727, 1991.
35. Ward PA. Mechanisms of endothelial cell killing by H_2O_2 or products of activated neutrophils. Am J Med 91: Suppl 3C, 89S-94S, 1991.
36. Hemilä H, Roberts P, Wikström M. Activated polymorphonuclear leucocytes consume vitamin C. FEBS Lett 178: 25-30, 1984.
37. Hume R, Weyers E. Changes in leucocyte ascorbic acid during the common cold. Scott Med J 18: 3-7, 1973.
38. National Research Council. Recommended Dietary Allowances. 10th ed. Washington DC: National Academy Press, 115-124, 1989.
39. Levine M. New concepts in the biology and biochemistry of ascorbic acid. N Engl J Med 314: 892-902, 1986.
40. Pauling L. How to live longer and feel better. San Francisco: Freeman, 1986.
41. Hemilä H. Nutritional need versus optimal intake. Med Hypotheses 14: 135-139, 1984.
42. Hemilä H. Is there a biochemical basis for 'nutrient need'? Trends in Food Science and Technology 2: 73, 1991.
43. Pauling L. Evolution and the need for ascorbic acid. Proc Natl Acad Sci USA 67: 1643-1648, 1970.
44. Eaton SB, Konner M, Shostak M. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. Am J Med 84: 739-749, 1988.
45. Rivers JM. Safety of high-level vitamin C ingestion. Ann NY Acad Sci 498: 445-454, 1987.
46. Bendich A. Safety issues regarding the use of vitamin supplements. Ann NY Acad Sci 669: 300-312, 1992.
47. Enstrom JE, Kanim LE, Klein MA. Vitamin C intake and mortality among a sample of the United States population. Epidemiology 3: 194-202, 1992.