Vitamin C and Common Cold Incidence: A Review of Studies with Subjects Under Heavy Physical Stress

H. Hemilä
Department of Public Health, University of Helsinki, Finland

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Several studies have observed an increased risk of respiratory infections in subjects doing heavy physical exercise. Vitamin C has been shown to affect some parts of the immune system, and accordingly it seems biologically conceivable that it could have effects on the increased incidence of respiratory infections caused by heavy physical stress. In this report the results of three placebo-controlled studies that have examined the effect of vitamin C supplementation on common cold incidence in subjects under acute physical stress are analyzed. In one study the subjects were school-children at a skiing camp in the Swiss Alps, in another they were military troops training in Northern Canada, and in the third they were participants in a 90 km running race. In each of the three studies a considerable reduction in common cold incidence in the group supplemented with vitamin C (0.6-1.0 g/day) was found. The pooled rate ratio (RR) of common cold infections in the studies was 0.50 (95 % CI: 0.35-0.69) in favour of vitamin C groups. Accordingly, the results of the three studies suggest that vitamin C supplementation may be beneficial for some of the subjects doing heavy exercise who have problems with frequent upper respiratory infections.

• Key words: Vitamin C, ascorbic acid, common cold, upper respiratory infection, physical stress, sports, exercises, viruses

Introduction

Several studies have suggested that there is an increased risk of respiratory infections in subjects doing heavy exercise (9, 12,17,21,25,30). It is not well known what the physiological basis of this increased susceptibility is (9,17), but decrease in the proliferative responses of T-lymphocytes (8,9,13,17), depression of the immune system by corticosteroids produced under physical stress (9,17), or harm done to the immune system cells by oxygen radicals generated during heavy exercise (41) are among the possible explanations.

Vitamin C has been reported to increase the proliferative responses in T-lymphocytes (2,18,23,26,38), to prevent the defects in neutrophils caused by corticosteroids (5,27,36), and it is also a major biological antioxidant (15). Thus vitamin C possibly could aid the immune system in subjects under heavy physical stress. It is also noteworthy that the highest concentrations of vitamin C in the body are found in the adrenal glands and adrenal vitamin C is rapidly depleted by various forms of stress (20); however, the role of vitamin C in the adrenal glands is not well understood. Moreover, in several laboratory animals vitamin C has increased resistance to low temperature (6,39), further suggesting some role for the vitamin in stress responses.

Placebo-controlled studies have shown that vitamin C ($\geq$ 1 g/day) decreases the severity of common cold episodes (15,16). In contrast, vitamin C has not consistently affected the common cold incidence, although a few studies have reported a significant decrease (15,16,28). The largest studies have not found any marked effect on the incidence of colds (3,15,16,22, 32). Nevertheless, it is possible that vitamin C affects common cold incidence in certain limited groups of people. The purpose of the present work was to assess the evidence from intervention studies as to whether vitamin C supplementation affects the incidence of the common cold in subjects under heavy physical stress.

Methods

Selection of studies

The literature on vitamin C-common cold studies has been thoroughly surveyed earlier (16,19), and an exhaustive list of studies published prior to 1989 has been published (19). The previous searches were supplemented by MEDLINE and SCISEARCH searches to identify vitamin C-common cold intervention studies published since 1988. For the present work, studies were selected in which the subjects were under heavy physical stress, and four randomized placebo-controlled double-blind studies were identified (refs. 31,32,34,37; Table 1). One study falling within the selection criterion did not employ placebo tablets (4). No further vitamin C-common cold studies

Table 1 The effect of vitamin C on the common cold incidence in subjects under acute heavy physical stress.

Study (ref.)	Vitamin C dose (g/day)	Duration of study (weeks)	Vitamin C group: No. of subjects	Vitamin C group: No. infected	Vitamin C group: Proportion sick (p_C)	Placebo group: No. of subjects	Placebo group: No. infected	Placebo group: Proportion sick (p_P)	RR (p_C/p_P)	95 % CI
Ritzel 1963 (28, 34, 35)	1	1	139	17	0.12	140	31	0.22	0.55	0.32–0.95
Sabiston & Radomski 1974 (37)	1	2	56	6	0.11	56	14	0.25	0.43	0.18–1.04
Peters et al. 1993 (31)	0.6	2	43	14	0.33	41	28	0.68	0.48	0.30–0.77
								RR_{pool}:	0.50 p = 0.00003	0.35–0.69

done with subjects under comparable heavy physical stress were located. The remaining studies have typically been carried out with subjects not exposed to considerable physical stress (15,16), e.g. adults at regular work (3) or children at school (22).

Statistical methods

In Table 1 the proportion of subjects catching a common cold infection during the study (p) was calculated from the published results (p_c for the vitamin C group and p_p for the placebo group). The 95 % confidence interval (95 % CI) for the rate ratio ($RR = p_C/p_P$) found in each study was calculated with the normal distribution approximation of the binomial distribution (1).

In Table 1 the pooled RR and the 95 % CI were derived by averaging the individual logarithm values ln(RR) using the inverses of variances var(ln(RR)) as the weights, with the formulae:

$$\ln(RR_{pool}) = \frac{\sum \ln(RR_i)/\mathrm{var}(\ln(RR_i))}{\sum 1/\mathrm{var}(\ln(RR_i))}$$

$$\mathrm{var}(\ln(RR_{pool})) = \frac{1}{\sum 1/\mathrm{var}(\ln(RR_i))}$$

$$95\ \%\ \text{CI limits: } RR_{Up,Low} = RR_{pool} \times \exp\{\pm 1.96 \sqrt{\mathrm{var}(\ln(RR_{pool}))}\}.$$

The p-value corresponding to the pooled estimate (Table 1) was derived from the standard normal deviate:

$$z = \ln(RR_{pool}) / \sqrt{\mathrm{var}(\ln(RR_{pool}))}.$$

Dichotomous data were analyzed with Fisher's exact test. The 1-tailed p-value was calculated since the question being considered in the present analysis is whether vitamin C decreases the incidence or not; there is no theoretical or experimental reason to assume that higher vitamin C intake would increase the incidence of the common cold or pneumonia.

Results

So far three randomized placebo-controlled double-blind studies have been carried out to test whether vitamin C has an effect on the incidence (i.e. the occurrence of new cases over time) of common cold infections in subjects under acute heavy physical stress (Table 1). Each of these studies lasted for a few weeks only and there was at most one episode per subject. Ritzel (28,34,35) conducted his study with school-children in a skiing camp in the Swiss Alps. Sabiston and Radomski (37) did theirs with troops on a military exercise during the winter in Northern Canada. Thus both of these studies used subjects under acute physical stress in a cold environment. The study by Peters et al. (31) was carried out with subjects participating in a long-distance running race (90km) in South Africa. The subjects in this third study were thus also under acute heavy physical stress, although they were not enduring a cold environment.

Each of these three studies with subjects under acute heavy stress found a considerable decrease in common cold incidence with vitamin C supplementation (Table 1). Furthermore, the three studies form a fairly homogeneous group as regards the type of stress, and their results may consequently be pooled together. Doing so yields a combined RR of 0.50 for common cold infections in the vitamin C groups (Table 1). The probability that the differences between the vitamin C and placebo groups are caused purely by chance is very small (p = 0.00003).

The three studies in Table 1 were all placebo-controlled, but there is a further study with subjects under acute physical stress but without using placebo tablets (4). Bessel-Lorck (4) carried out a study with school-children in a skiing camp in the Bavarian woods, and administered 1 g/day of vitamin C during a nine day period to the study group. There were 9 cases of common cold among 20 control subjects but only 1 case among 26 subjects given vitamin C. It is unlikely that the difference in incidence in favour of the vitamin C group is caused purely by chance (RR = 0.09, p = 0.001). However, as the control group was not administered placebo, there may have been biases between the study groups. Nevertheless, the result of the study is consistent with the placebo-controlled studies of Table 1. The results from all four studies with subjects under acute heavy physical stress identified in the literature have thus reported a decrease in common cold incidence in the group supplemented with vitamin C (4,31,34,37).

One study was identified in which the experimental conditions are quite close to those in the studies in Table 1. Pitt and Costrini carried out a randomized double-blind study with military recruits in a training camp in South Carolina (32). They administered 2 g/day of vitamin C to the study group, but there was no difference (0%) in common cold incidence when compared to the placebo group. There were over 1200 common cold episodes in the study (32), i.e. over ten times the total number of episodes in the three studies in Table 1, and thus this study has great weight as regards the possible role of vitamin C in subjects under heavy stress. Nevertheless, there are several noteworthy differences between the Pitt and Costrini study and the three studies of Table 1. Pitt and Costini's subjects were under a regular training program, the study lasted for 2 months and, furthermore, the tablet administration did not begin until their third week at the training camp (32). In contrast, the subjects of the studies in Table 1 were under acute and unusual stress and the studies lasted for just few weeks. The body may adapt more efficiently to regular stress than to acute stress and accordingly experimental differences may well explain the difference in results between the studies of Table 1 and the Pitt and Costrini study. Moreover, the subjects of the Sabiston and Radomski study, which is closest to the Pitt and Costrini study, were training in a cold climate during the special arctic exercise, and were thus under much heavier stress. Nevertheless, even though Pitt and Costrini found no decrease in common cold incidence, they found a considerable decrease in the incidence of pneumonia in the vitamin C group (32). There were 7 cases of pneumonia among the placebo subjects, but only 1 case among the subjects receiving vitamin C ($p = 0.04$), suggesting that vitamin C supplementation possibly did have some effects on susceptibility to infections in the Pitt and Costrini study.

Discussion

In early 1970's Pauling concluded from previously published studies that vitamin C supplementation decreases the incidence of the common cold (28). However, the majority of studies carried out thereafter have not found that regular vitamin C supplementation (> 1 g/day) has any marked effect on common cold incidence, indicating that the vitamin has no particular preventive effect against colds in the general population of Western countries (3,15,16,22). Nevertheless, a few studies have reported a significant decrease in cold incidence with vitamin C supplementation. When a large number of studies are carried out it is probable that some studies find great benefit purely by chance, and therefore individual studies deviating from the great majority must be evaluated cautiously. On the other hand, it is also possible that vitamin C has some real effect on susceptibility to colds, but that the effects are quantitatively important only in limited groups of the general population, and this was the basic assumption in the present work.

Heavy physical stress was used as the criterion to select studies for the present analysis. Three placebo-controlled studies with subjects under acute heavy physical stress were identified, each of these studies having found a considerable decrease in common cold incidence in the vitamin C group (Table 1). A comparable result was obtained in a fourth study which did not employ placebo (4). However, a study by Pitt and Costrini with military recruits found no decrease in common cold incidence with vitamin C supplementation, although their subjects were under considerable stress during the study (32). The experimental conditions in the latter study differ significantly from the conditions in the three studies in Table 1, which may explain the conflicting results.

The amount of stress from physical exercise does not divide people into two well-defined groups, the variable having a continuous distribution instead. Also, the effect of supplementation apparently depends on the initial dietary vitamin C intake. We may accordingly conclude that the estimated 50 % decrease in the common cold incidence (Table 1) is a crude estimate of the maximal benefit for subjects under acute heavy stress, and that there is evidently a gradual decrease in the benefit from supplemental vitamin C both as the amount of stress decreases and as the dietary vitamin C intake increases.

Even though the studies in Table 1 indicate that vitamin C intake is associated with the incidence of the common cold, the actual interpretation of the results is not obvious, for example due to the lack of any knowledge on the dose-response relationship. The observed difference in the study groups may be caused by a rather low vitamin C intake in the control group ("marginal deficiency"), or by the high dose in the vitamin group. In the former case a much smaller dose of supplement might produce a similar benefit, whereas in the latter case the dose probably must be of the magnitude used in the studies (0.6 -1.0 g/day) to obtain the maximal benefit. Sabiston and Radomski (37) estimated that the food rations contained approximately 40 mg/day of vitamin C, which is lower than the recommendation in the USA (60 mg/day; ref. 24), but higher than in the UK (30 mg/day; ref. 40). They found that the whole-blood vitamin C level was increased 100 -150 % by vitamin C (1 g/day) supplementation (37). Pitt and Costrini (32) found a much lower increase (50%) with a larger vitamin C dose (2 g/day). In healthy people plasma vitamin C level is saturated with doses much below 1 g/day (10). Thus the vitamin C levels were apparently much lower in the control group of Sabiston and Radomski than that of Pitt and Costrini, and this represents a further noteworthy difference between the two studies. Ritzel did not estimate the dietary intake of his subjects (34), but it seems probable that the intake was rather low at the skiing camp in the Swiss Alps. Thus, in the studies by Ritzel and by Sabiston and Radomski it cannot be determined whether the benefit from supplementation was due to "the correction of marginal deficiency" or the high supplementary doses. Peters et al. (32) evaluated the dietary vitamin C intake and found it was on average 0.5 g/day in their subjects, i.e. close to 10 times the RDA recommendation (60 mg/day; ref. 24). It seems then that in Peters' study the effect was not caused by the correction of marginal deficiency, but rather by the high dose of supplemental vitamin C *per se* (0.6 g/day).

The suggestion that vitamin C may decrease common cold incidence particularly in subjects under acute heavy stress is not a novel one. Peters et al. (31) were explicitly interested in whether vitamin C supplementation is beneficial for long-distance runners and, in fact, they did a parallel study with subjects not participating in the race which showed that vitamin C did not decrease common cold incidence in the latter group (31). The present analysis indicates that Peters' result with the long distance runners was not just a statistical artifact among the large number of studies that have been carried out so far, as three other studies with quite similar experimental conditions have also found a comparable decrease in common cold incidence from vitamin C supplementation (4,34,37).

Large-scale studies have shown that vitamin C supplements (≥ 1 g/day) do not prevent common cold infections in ordinary people (3,15,16,22). Nevertheless, if vitamin C intake has effects on common cold incidence even in limited groups of people it may be of practical interest as the common cold is a frequent complaint. Furthermore, the issue is also important more generally as regards nutritional recommendations. The goal of nutritional recommendations is to prevent overt scurvy and for that purpose the recommendation of 30-60 mg/day provides a good margin of safety. However, these recommendations are not based either on clinical or epidemiological studies suggesting that 30 or 60 mg/day is an optimal dose for human beings in the long term, or on biochemical studies suggesting that such doses would saturate the numerous vitamin C dependent reactions (7,11,14,15,20,24,29,33). The studies analyzed in this paper suggest that there may be groups of people who benefit from doses larger than those officially recommended.

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References

[1] Ahlbom A.: Biostatistics for Epidemiologists. London, Lewis Publishers, 1993.
[2] Anderson R., Smit M. J., Joone G. K., van Staden A. M.: Vitamin C and cellular immune functions. *Ann NY Acad Sci* 587: 34-48, 1990.
[3] Anderson T. W., Reid D. B. W., Beaton G. H.: Vitamin C and the common cold: a double-blind trial. *Can Med Assoc J* 107: 503-508, 1972.
[4] Bessel-Lorck C: Common cold prophylaxis in young people at a ski-camp (in German). *Medizinische* 44: 2126-2127, 1959.
[5] Chretien J. H., Garagusi V. F.: Correction of corticosteroid-induced defects of polymorphonuclear neutrophil function by ascorbic acid. *J Reticuloendothel Soc* 14: 280-286, 1973.
[6] Dugal L. P.: Vitamin C in relation to cold temperature tolerance. *Ann NY Acad Sci* 92: 307-317, 1961.
[7] Englard S., Seifter S.: The biochemical functions of ascorbic acid. Annu Rev Nutr 6: 365-406, 1986.
[8] Eskola J., Ruuskanen O., Soppi E., Viljanen M. K., Jarvinen M., Toivonen H., Kouvalainen K.: Effect of sport stress on lymphocyte transformation and antibody formation. *Clin Exp Immunol* 32: 339-345, 1978.
[9] Fitzgerald L.: Overtraining increases the susceptibility to infection. *Int J Sports Med* 12: S5-S8, 1991.
[10] Garry P. J., Vanderjagt D. J., Hunt W. C.: Ascorbic acid intakes and plasma levels in healthy elderly. *Ann NY Acad Sci* 498: 90-99, 1987.
[11] Ginter E.: Ascorbic acid in cholesterol metabolism and in detoxification of xenobiotic substances: problem of optimum vitamin C intake. *Nutrition* 5: 369-374, 1989.
[12] Heath G. W., Ford E. S., Craven T. E., Macera C. A., Jackson K. L., Pate R. R.: Exercise and the incidence of upper respiratory tract infections. *Med Sci Sports Exerc* 23: 152-157, 1991.
[13] Hedfors E., Holm G., Ohnell B.: Variations on blood lymphocytes during work studied by cell surface markers, DNA synthesis and cytotoxicity. *Clin Exp Immunol* 24: 328-335, 1976.
[14] Hemilä H.: A re-evaluation of nutritional goals - not just deficiency counts. *Med Hypotheses* 20: 17-27, 1986.
[15] Hemilä H.: Vitamin C and the common cold. *Br J Nutr* 67: 3-16, 1992.
[16] Hemilä H.: Does vitamin C alleviate the symptoms of the common cold? - A review of current evidence. *Scand J Infect Dis* 26: 1-6, 1994.
[17] Keast D., Cameron K., Morton A. R.: Exercise and the immune response. *Sports Med* 5: 248-267, 1988.
[18] Kennes B., Dumont I., Brohee D., Hubert C., Neve P.: Effect of vitamin C supplements on cell-mediated immunity in old people. *Gerontology* 29: 305-310, 1983.
[19] Kleijnen J., Riet G., Knipschild P. G.: Vitamin C and the common cold; a review of the megadose literature (in Dutch). *Ned Tijdschr Geneeskd* 133: 1532-1535, 1989.
[20] Levine M., Morita K.: Ascorbic acid in endocrine systems. *Vitam Horm 42: 1-64*, 1985.
[21] Linde F.: Running and upper respiratory tract infections. *Scand J Sports Sci* 9: 21-23, 1987.
[22] Ludvigsson J., Hansson L. O., Tibbling G.: Vitamin C as a preventive medicine against common colds in children. *Scand J Infect Dis* 9: 91-98, 1977.
[23] Manzella J. P., Roberts N. J.: Human macrophage and lymphocyte responses to mitogen stimulation after exposure to influenza virus, ascorbic acid, and hyperthermia. *J Immunol* 123: 1940-1944, 1979.
[24] National Research Council. Recommended Dietary Allowances. 10th ed. Washington D.C., National Academy Press, 1989, pp 115-124.
[25] Nieman D. C., Johanssen L. M., Lee J. W., Arabatzis K.: Infectious episodes in runners before and after the Los Angeles marathon. J Sports Med Phys Fitness 30: 316-328, 1990.
[26] Oh C., Nakano K.: Reversal by ascorbic acid of suppression by endogenous histamine of rat lymphocyte blastogenesis. *J Nutr* 118: 639-644, 1988 .
[27] Olson G. E., Polk H. C.: *In vitro* effect of ascorbic acid on corticosteroid-caused neutrophil dysfunction. *J Reticuloendothel Soc* 22: 109-112, 1977.
[28] Pauling L: The significance of the evidence about ascorbic acid and the common cold. *Proc Natl Acad Sci USA* 68: 2678-2681, 1971.
[29] Pauling L: Are recommended daily allowances for vitamin C adequate? *Proc Natl Acad Sci* USA 71: 4442-4446, 1974.
[30] Peters E. M., Bateman E. D.: Ultramarathon running and upper respiratory tract infections. *S Afr Med J* 64: 582-584, 1983.
[31] Peters E. M., Goetzsche J. M., Grobbelaar B., Noakes T. D.: Vitamin C supplementation reduces the incidence of postrace symptoms of upper-respiratory-tract infection in ultramarathon runners. *Am J Clin Nutr* 57: 170-174, 1993.
[32] Pitt H. A., Costrini A. M.: Vitamin C prophylaxis in marine recruits. *JAMA* 241: 908-911, 1979.
[33] Reynolds R. D.: Vitamin supplements: current controversies. *J Am Coll Nutr* 13: 118-126, 1994.
[34] Ritzel G.: Critical analysis of the role of vitamin C in the prophylaxis and treatment of the common cold (in German). *Helv Med Acta* 28: 63-68, 1961.
[35] Ritzel G.: Ascorbic acid and the common cold (letter). *JAMA* 235: 1108, 1976.
[36] Roth J. A., Kaeberle M. L.: *In vivo* effect of ascorbic acid on neutrophil function in healthy and dexamethasone-treated cattle. *Am J Vet Res* 46: 2434-2436, 1985.
[37] Sabiston B. H., Radomski M. W.: Health Problems and Vitamin C in Canadian Northern Military Operations. *DCIEM Report No. 74-R-1012.* Downsview, Ontario, Defence Research Board, 1974.
[38] Siegel B. V., Morton J. I.: Vitamin C and the immune response. *Experientia* 33: 393-395, 1977.

39 Spillert C. R., Hollinshead M. B., Lazaro E. J.: Protective effects of ascorbic acid on murine frostbite. *Ann NY Acad Sci* 498: 517-518, 1987.
40 Trichopoulou A., Vassilakou T.: Recommended dietary intakes in the European community member states. *Eur J Clin Nutr* 44 (Suppl 2): 51-126, 1990.
41 Witt E. H., Reznick A. Z., Viguie C. A., Starke-Reed P., Packer L: Exercise, oxidative damage and effects of antioxidant manipu-- lation. *J Nutr* 122: 766-773, 1992.

Corresponding Author

Dr. Harri Hemilä, PhD
Department of Public Health
P.O. Box 41
Mannerheimintie 172
FIN-00014 University of Helsinki
Finland