Vitamin C supplementation and common cold symptoms: factors affecting the magnitude of the benefit

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Summary Placebo-controlled trials have shown that vitamin C supplementation decreases the duration and severity of common cold infections. However, the magnitude of the benefit has substantially varied, hampering conclusions about the clinical significance of the vitamin. In this paper, 23 studies with regular vitamin C supplementation (>1 g/day) were analyzed to find out factors that may explain some part of the variation in the results. It was found that on average, vitamin C produces greater benefit for children than for adults. The dose may also affect the magnitude of the benefit, there being on average greater benefit from ≥2 g/day compared to 1 g/day of the vitamin. In five studies with adults administered 1 g/day of vitamin C, the median decrease in cold duration was only 6%, whereas in two studies with children administered 2 g/day the median decrease was four times higher, 26%. The trials analyzed in this work used regular vitamin C supplementation, but it is conceivable that therapeutic supplementation starting early at the onset of the cold episode could produce comparable benefits. Since few trials have examined the effects of therapeutic supplementation and their results have been variable, further therapeutic trials are required to examine the role of vitamin C in the treatment of colds.

INTRODUCTION

In placebo-controlled studies, regular vitamin C supplementation (≥1 g/day) has consistently decreased morbidity due to the common cold (1-8). While the biochemical basis of this effect is not well understood, vitamin C does have diverse effects on the immune system (3,5,9).

Since the magnitude of the benefit has varied substantially in the controlled trials, the clinical significance of vitamin C in common cold therapy remains an open question. The purpose of the present work was to investigate whether factors can be identified to explain some part of the variation in the results of the controlled trials. The particular questions addressed in the present analysis were whether dose-dependency can be seen in high vitamin C doses, and whether the effect depends on the characteristics of subjects.

METHODS

Since the literature on vitamin C common cold studies has previously been thoroughly surveyed (4,10,11), the older literature was not searched anew. The previous searches were extended by MEDLINE searches to identify newer vitamin C-common cold trials. All placebo-controlled studies using regular vitamin C supplementation with ≥1 g/day of the vitamin were selected for the present quantitative analysis (12-31), and the results are shown in Table 1. Regular supplementation refers here to initiating supplementation with healthy people and continuing over the occurring common cold episodes. For a concise summary of the original results, see ref. 3. The Anderson 1974 study (17) with adults is excluded from Table 1, since there is evidence of biased distribution of subjects in the eight study groups (5,17). The Carson 1975 study (20) with adults administered 1 g/day is excluded, since the authors were interested solely in the possibility of there being an effect on the incidence of colds, and not on the severity of symptoms, so that appropriate data are not available. The results of the Karlowski 1975 study (22,32) were recently reanalyzed

Table 1 The effect of regular vitamin C supplementation (≥1 g/day) on common cold severity and duration

Study (Ref.)	No. episodes in vitamin C group	Dose (g/day)	Relative effect (%)	Outcome
Adults				
1 g/day during the cold episode				
Clegg & Macdonald 1975 (21)	68	1	−5.3	Duration of symptoms
Briggs 1984 (30)	125	1	−6.1	Duration of symptoms
Elwood et al 1976 (24)	627	1	−6.4	Duration of symptoms
Clegg & Macdonald 1975 (21)	51	1[a]	−7.9	Duration of symptoms
Charleston & Clegg 1972 (14)	44[b]	1	−17	Duration of symptoms
Total no. episodes:	915	1	−6.9	Mean
			−6.4	Median
≥2 g/day during the cold episode				
Karlowski et al 1975 (7,22,32)	52	3	−6.0	Duration of symptoms
Karlowski et al 1975 (7,22,32)	76	3 + 3[c]	−17	Duration of symptoms
Anderson et al 1972 (13)	561	1 + 3[c]	−21	Days confined to house
			(−5.3)	Duration of symptoms
Schwartz et al 1973 (16)	11[d]	3	−30	Severity of symptoms[e]
Mink et al 1988 (31)	4[d]	2	−50	Severity of symptoms
Total no. episodes:	704	4.1	−20	Mean
			−21	Median
Schoolchildren				
1 g/day during the cold episode				
Carr et al 1981 (28)	94[f]	1	+ 6.3	Severity of symptoms
			(+ 0.7)	Duration of symptoms
Coulehan et al 1976 (23)	98	1	−5.2	Duration of symptoms
Coulehan et al 1974 (18)	19	1	−12	Duration of symptoms
Ludvigsson et al 1977 (26)	225	1	−14	Absence from school
			(−5.9)	Duration of symptoms
Miller et al 1977 (25)	53	1	−20	Days in bed
			(−7.2)	Duration of symptoms
Ritzel 1961 (1,2,12,33)	17	1	−29	Duration of symptoms
Ludvigsson et al 1977 (26)	22	1	−31	Absence from school
			(−39)	Duration of symptoms
Carr et al 1981 (28)	57[g]	1	−35	Severity of symptoms
			(−35)	Duration of symptoms
Total no. episodes:	585	1	−13	Mean
			−17	Median
≥2 g/day during the cold episode				
Bancalari et al 1984 (29)	38	2	−24	Duration of symptoms
Coulehan et al 1974 (18)	16	2	−29	Duration of symptoms
Total no. episodes:	54	2	−26	Mean
			−26	Median
Military recruits				
Pitt & Costrini 1979 (27)	600	2	−5.1	Severity of symptoms
			(−2.6)	Duration of symptoms
Sabiston & Radomski 1974 (19)	6	1	−67	Duration of constitutional symptoms[h]
			(−25)	Duration of nasal symptoms
Elliott 1973 (15)	37[i]	2	−72	Days to sore throats
			(−69)	Days of productive coughs

Notes: The mean Relative Effect and the mean dose were calculated using the number of episodes in the vitamin C group as the weight. The differences in outcomes indicated by parentheses are not included in the calculations.
[a] 1 g/day of D-isoascorbic acid;
[b] Single-blind study (all the other studies in the table are double-blind studies);
[c] At the onset of a cold episode an additional 3 g/day was given for 3-5 days; in the present analysis, 4 and 6 g/day are regarded as the doses corresponding to the observed effects.
[d] Induced rhinovirus infection;
[e] Severity of symptoms on the 4th day of infection;
[f] Twins living together
[g] Twins living apart;
[h] Constitutional symptoms: headache, chills and fever, general malaise, nausea or vomiting;
[i] The explicit number of colds was not reported; the number of subjects in the vitamin C group is 37.

Group	Vitamin C (g/day)	*c*	No. of episodes	Duration of episodes (days)		
				Mean	SE	Var
0	0	1	65	7.14	0.46	13.75
1	3	0	56	6.46	0.39	8.52
2	3	0	52	6.71	0.53	14.61
3	6	−1	76	5.92	0.40	12.16
			249			

Analysis of variance for trend

	DF	SS	MS	F	P
Between groups	3	54.4			
linear	1	52.1	52.1	4.25	0.040
non-linear	2	2.3	1.1	0.093	0.91
Within groups	245	3005.7	12.3		
Total	248	3060.1			

Notes: *c* indicates the contrast used in the calculation of the linear trend. Variance (Var) was calculated from the standard error (SE) and the number of episodes (32). Group 1 was administered vitamin C for 5 days during colds, whereas group 2 was administered vitamin C each day during the study. Group 3 received vitamin C both ways.

(7), and the linear trend in their results has been analyzed in this work (Table 2) with the analysis of variance (34). All the studies with children used schoolchildren as subjects. The total number of subjects in the studies in Table 1 was over 6100. All studies except one (14) were double-blind. Some of the placebo groups were given 10–70mg/day of vitamin C to ensure that the effects of the larger dose were not due to the alleviation of a true dietary deficiency (25,26,28,30). The Relative Effect on the severity of common cold episodes in the vitamin C groups relative to the placebo groups was calculated for each study as the difference between the outcomes in the vitamin C and placebo group divided by the outcome in the placebo group (Table 1). Pooled confidence intervals for the four groups were not calculated since in several studies standard error and standard deviation were not reported. The discussion of therapeutic trials is also restricted to studies that employed ≥1 g/day of vitamin C (22,35-40).

THE COMMON COLD STUDIES

To estimate the magnitude of the benefit of vitamin C supplementation on common cold symptoms, all placebo-controlled trials with regular supplementation (≥1 g/day) were searched. The Relative Effect of vitamin C on the severity of cold episodes for each outcome was calculated (Table 1). In some studies, 2-3 outcome parameters were measured to quantify the duration or severity of episodes, the results on different parameters occasionally differing considerably. For the present analysis, we selected the outcome seemingly most important for the patient, such as days of absence from work or school, or days in bed,

when several parameters were measured in the study. Nevertheless, in such cases the effect on the duration of symptoms is still shown in parenthesis in Table 1.

In order to analyze the dose-dependency of vitamin C intake, the trials were divided into those using 1 g/day and those using ≥2 g/day. Furthermore, as the weight and/or age of the subjects can modify the effect of a fixed dose, the studies with children were concurrently separated from the studies with adults (Table 1). Finally, because three of the adult trials used military recruits who are highly atypical representatives of the general adult population, these three trials were segregated from the other adult studies (Table 1).

The mean Relative Effect was calculated for the four groups of trials in Table 1, excluding the soldier trials, using the number of episodes in the vitamin C group as the weight, thereby giving more precise results greater weight in calculating the mean (Table 1). The resultant mean Relative Effect values have been plotted in Figure 1 as a function of vitamin C dose. Assuming that the mean Relative Effect is a valid estimate for each of the four groups, the results suggest that larger doses (≥2 g/day) produce a greater benefit than small doses (1 g/day) for both adults and children.

The assumption that the dose-dependency is linear allows crude extrapolation of doses that could possibly decrease the severity of cold episodes by half (Fig. 1). For children and adults respectively 3.9 and 10 g/day of vitamin C would yield Relative Effect = –50%. However, in the case of children there are only two rather small trials in the high dosage group, and there is a great variation in the results of the low dosage trials (Table 1). In the case of adults, two trials with high dosages used
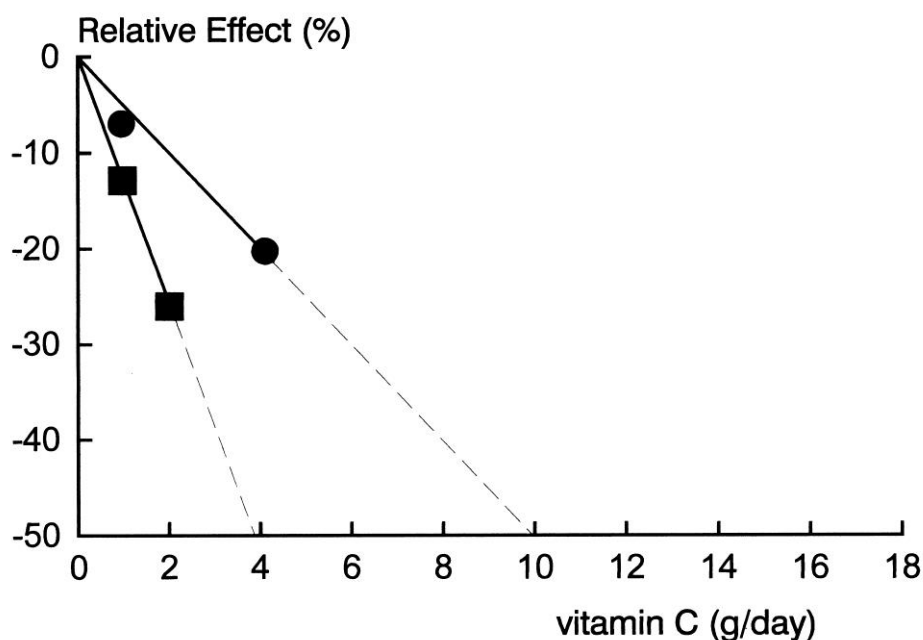
Relative Effect (%)

Fig. 1 The effect of vitamin C dosage on the severity of common cold episodes. The mean Relative Effect on severity values for schoolchildren (■) and adults (●) was taken from Table 1. Linear regression analysis was used to extrapolate the dose producing Relative Effect = -50%. The regression lines were forced through Relative Effect = 0% at 0 g/day of vitamin C since such a dose must equal placebo.

induced rhinovirus infection (16,31), and one trial found a great divergence in two different outcomes (13). The evidence for dose-dependency is thus not strong in Figure 1. Still, as children on average weigh considerably less than adults, the difference between them is also consistent with the notion that a higher dose per unit of weight produces a greater benefit at the dosage levels studied so far.

Several factors have varied between the trials, such as the characteristics of subjects, the types of infecting viruses, the geographic location, etc. The dietary vitamin C intake by the control group may also affect the differences between the vitamin and placebo groups, but the dietary intake has not been estimated at all in most trials. The definition of outcome has varied greatly and in several trials there has been a smaller effect on the duration but a larger effect on the severity of colds (13,19,25-27). Such factors, along with random variation, can explain a large part of the differences between the results, hampering the comparison of the studies.

In two trials (18,22) different vitamin C doses were given to separate groups within the same study. Because of the similarity of subjects and the constant outcome definition across the study groups, these two trials are more pertinent to the question of dose-dependency than the comparison of means of dissimilar studies. Karlowski et al (22) examined the effect of 3 and 6 g/day of vitamin

C on adults, and Coulehan et al (18) examined the effect of 1 and 2 g/day on children (Fig. 2). Extrapolation from the results of Coulehan et al suggests that 3.5 g/day would decrease the duration of cold episodes by half, consistent with the estimate derived from all studies with children.

Karlowski et al's results suggest that 18 g/day would decrease the duration of episodes by half (Fig. 2). Finally, Karlowski et al reported the standard errors of the mean duration of episodes for their four study groups (Table 2). The linear trend in their study groups can consequently be analyzed by the analysis of variance. The linear trend explains a significant part of the differences between the groups, whereas the remaining non-linear differences are easily explained by random variation (Table 2). The results of the Karlowski study are the most unambiguous evidence so far indicating that there is dose dependency in the >1 g/day region.

Three of the adult trials used military recruits as subjects, and there is extreme variation in their results. Two of these trials (15,19) found the greatest benefit among all the 1 g/day and ≥2 g/day studies, whereas the third (27) found the smallest benefit among all the ≥2 g/day studies (Table 1). The trials reporting the great benefit were carried out in a special exercise during the wintertime in northern Canada (19) and with the crew on a submarine (15). The Pitt and Costrini study reporting
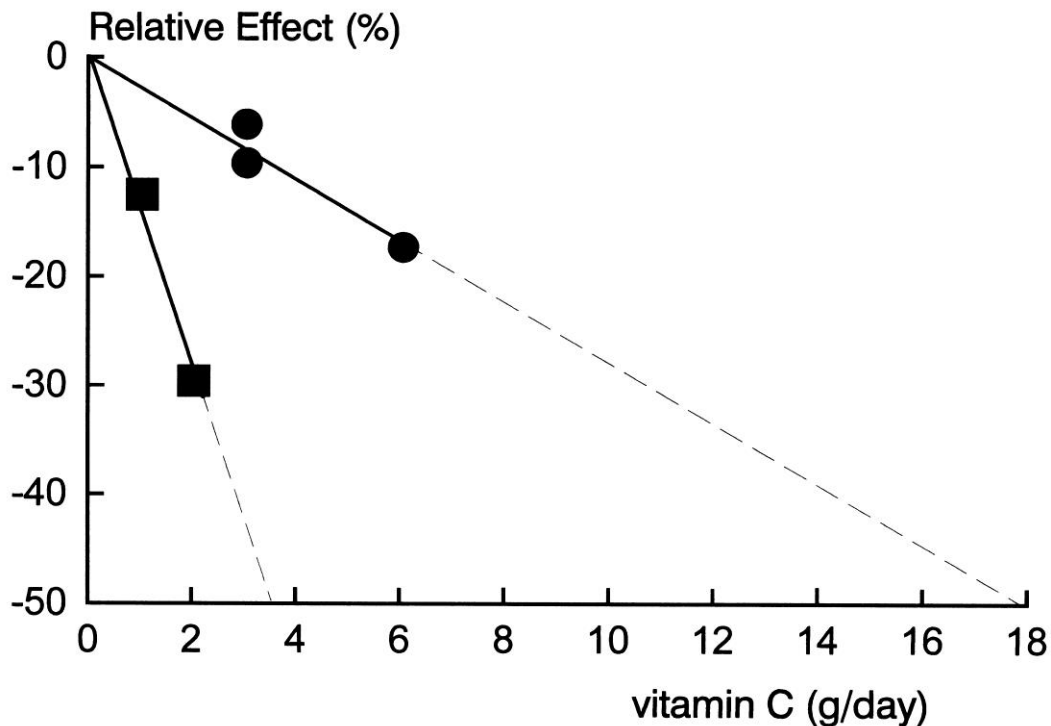
Fig. 2 The effect of vitamin C dosage on the duration of common cold episodes in the Coulehan 1974 and Kariowski 1975 trials. The Relative Effect on severity values are taken from Table 1 for the Coulehan 1974 study (■) and the Karlowski study (●). Kariowski et al (22,32) also had a therapeutic group which was administered 3 g/day of vitamin C for 5 days during cold episodes and for this group Relative Effect = −9.5% (Table 2). In this figure, it is assumed that there is no meaningful difference between the regular and therapeutic supplementation and therefore the Kariowski results are plotted on the basis of total vitamin C dosage during the cold episodes (c.f. Table 2).

the minor benefit was carried out in a training camp in South Carolina (27). In the latter trial, the subjects were on average sick 36% (20/56) of the study days (27,41). The subjects have usually been sick less than 10% of the study days (3), as in the large-scale trial with adults by Anderson et al (13), where it was 7% (6/90). Because of the exceptional conditions in the Pitt and Costrini study it is not clear to what extent their results can be generalized to other circumstances. Thus, the substantially greater benefit found in the other two trials with military recruits (15,19) might be caused by differences in the experimental conditions. It is possible that specific circumstances for example in accommodation (41) and in training conditions are important factors affecting the role of vitamin C in military recruits.

DISCUSSION

The effect of vitamin C on the common cold has been studied quite extensively since the early 1970s when Linus Pauling, a dual Nobel laureate, wrote a popular book on the topic suggesting that, in gram doses, the vitamin would substantially decrease morbidity due to the common cold (1). Although in further trials the benefit was not as great as Pauling had concluded from the early studies, the duration and severity of common cold has consistently been lower in vitamin C groups indicating a physiological effect (Table 1).

In his quantitative analysis, Pauling (2) based his estimation of benefit on a single trial carried out by Günther Ritzel in the early 1960s with schoolboys in a skiing camp in the Swiss Alps (12,33). However, the conditions at a skiing camp are highly exceptional and later studies with children have mostly found smaller effects (Table 1). Moreover, Pauling did not restrict his estimate to children, and it appears that the extrapolation of Ritzel's results to adults was among the reasons for the great discrepancy between Pauling's quantitative conclusions (2) and the effects seen in later studies carried out largely with adults (Table 1; see also ref. 8).

The magnitude of the benefit from vitamin C supplementation is an important issue in evaluating the clinical significance of the vitamin in common cold therapy, even though it is unrealistic to assume that a single estimate of benefit would be valid for all subjects. A major problem in the comparison of the studies is the great variation in the outcomes between trials. For example, in the control group of Miller's study (25) the mean duration of 'days in bed' was 1.0, whereas in Ludvigsson's control group (26) the mean duration of 'symptoms present' was 14 days. Since it is obvious that such outcomes and their arithmetical differences between vitamin C and placebo

groups are not comparable between different studies, the present analysis was based on the relative effect on outcomes, which are more comparable between studies. Although severity and duration may appear to be independent outcome parameters, the duration may largely be considered as a way of estimating the severity of episodes. This is most evident in the case of days of absence from school or work, or days in bed, which clearly depend on the severity of symptoms.

The published trials indicate that the effect of a given vitamin C dose is on average greater for children than for adults (Table 1, Fig. 1). This difference may be largely due to the smaller weight of children, i.e. a greater dose per unit of weight, but it is possible that there also are age-dependent physiological differences. Furthermore, there is evidence of dose-dependency in both children and adults (Figs 1 & 2, Table 2). Accordingly, even though the median decrease in duration by 1 g/day can be considered clinically insignificant in adults (–6%; Table 1), this may be an underestimate of the potential benefits of higher doses, particularly when given to children. For children the median decrease with 2 g/day of vitamin C was four times higher (–26%). Finally, as the results of the trials are mean values for a group of children, it is obvious that vitamin C is much more (and much less) beneficial for some individual children than is suggested by the result of a single study, or by the median of a group of studies.

It is noteworthy in Table 1 that only 22% (639/2901) of all cold episodes were observed in studies with children and the 2 g/day studies with children cover only 2% (54/2901) of all episodes. Thus, if a weighted general mean is calculated for all results in Table 1, there is heavy domination by the adult studies, which have mostly found only a slight benefit. Consequently, such a general estimate would completely hide the possibility of there being a worthwhile benefit in children.

In two studies with children, the vitamin C level in plasma (18) and urine (25) increased in subjects given a placebo (sic!) suggesting that tablets were exchanged by playful children. In this respect, the study by Carr et al (28) is interesting inasmuch as a marked benefit was observed in twins living apart, but no benefit in twins living together (Table 1), who apparently exchanged the tablets to a great extent - not so easy for twins living apart. It is thus possible that some of the published results underestimate the true physiological effects because of technical shortcomings in the studies.

Linear extrapolation suggests that 4 g/day can on average reduce the severity of cold episodes by half in children, and 10-18 g/day may produce a similar effect in adults (Figs 1 & 2). Obviously, these estimates are imprecise and should be interpreted highly cautiously, but it seems probable that the doses used in the placebo-controlled trials (≤2 g/day for children; ≤6 g/day for adults) have not been large enough to demonstrate the maximum effect of vitamin C supplementation (Figs 1 & 2). Several physicians have used vitamin C in the treatment of the common cold (42-50). Bee (47) proposed 10-15g/day for treating colds, and Cathcart (48,49) suggested that the optimum dose may be over 30 g/day. It is noteworthy that extrapolation with the data from the adult studies yields estimates crudely of the same magnitude (Figs 1 & 2).

The quantitative analysis in the present work was based on studies using regular vitamin C supplementation, and it is important to consider whether the resultant estimates may be extrapolated to therapeutic doses administered after an episode occurs. This is an important question, since regular supplementation is more costly and cumbersome. Although vitamin C is safe even when consumed at high levels of intake for long periods of time (51-54), any potential harm is even less with short-term supplementation during common cold episodes.

Two research groups compared the effect of therapeutic and regular vitamin C supplementation on colds. Karlowski et al (22) and Anderson et al (13,35) found that the estimates derived from regular supplementation do not overestimate the benefit of a 5-day therapeutic regime (7), suggesting that the estimates in Figure 1 may crudely apply to appropriate therapeutic supplementation. A few other trials have examined the role of therapeutic regimes, some reporting benefit from vitamin C (36-38), while some others found no effect (37-40).

In therapeutic trials, there are additional sources of technical variation when compared to regular supplementation studies. In the latter type of study, the vitamin is given over the entire cold episode. In the therapeutic trials, however, both a delay in the initiation of the treatment, and an inappropriately short treatment period might decrease the benefit. The former effect was observed in one of the therapeutic trials (36), and the latter effect may explain the inefficacy of vitamin C in three therapeutic trials in which supplementation lasted for only 2-3 days while the mean duration of cold episodes was 5-8 days (37-39). Finally, it is noteworthy that none of the published therapeutic trials used children as subjects, whereas the regular supplementation studies have on average found a considerably greater benefit for children (Table 1, Fig. 1). Vitamin C is a cheap substance and safe even in large doses (51-54). It would seem worthwhile to carry out well-planned therapeutic trials to obtain better quantitative estimates of the optimum doses and maximum therapeutic effects, and to better understand the potential differences between various groups of people. It also seems worthwhile to consider carefully the most relevant outcomes, as the effect on severity has often been greater than the effect on duration of symptoms.

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