

Vitamin C and acute respiratory infections

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SUMMARY

So far over 60 studies have examined the effects of vitamin C on the common cold. No effect on common cold incidence was observed in the six largest studies, indicating that vitamin C has no preventive effects in normally nourished subjects in the Western countries. There are, however, smaller studies reporting benefit. In three trials of subjects under heavy acute physical stress, common cold incidence decreased by on average 50%, and in four trials of British males common cold incidence decreased by on average 30% in the vitamin C groups. The dietary vitamin C intake in the UK is low, and consequently the benefit may be due to the correction of marginal deficiency, rather than high vitamin doses. Regular vitamin C supplementation (≥ 1 g/day) has quite consistently reduced the duration of colds, but the size of the benefit has varied greatly. In the four largest studies the duration

of colds was reduced only by 5%. In two of these studies, however, absence from school and work was reduced by 14–21% per episode, which may have practical importance. Three controlled studies recorded a reduction of at least 80% in the incidence of pneumonia in the vitamin C group, and one randomised trial reported substantial treatment benefit from vitamin C in elderly UK patients hospitalized with pneumonia or bronchitis. It seems that the preventive effects of supplementation are mainly limited to subjects with low dietary vitamin C intake, but therapeutic effects may occur in wider population groups. Further carefully designed trials are needed to explore the effects of vitamin C.

KEY WORDS: ascorbic acid; the common cold; pneumonia; tonsillitis; tuberculosis

EARLY THIS CENTURY several authors suggested that vitamin C intake may affect the incidence and severity of the common cold and other respiratory infections.¹⁻⁷ The effects of vitamin C on the immune system are not well understood, but there is a large number of reports indicating that vitamin C may affect the functions of phagocytes, the proliferation of T-lymphocytes, and the production of interferon.⁸⁻¹² Still, the precise immunological mechanisms whereby vitamin C may affect respiratory infections are not clear. The present authors have been involved separately in systematic overviews of the large body of published literature on these matters,¹⁰⁻¹⁸ and we here offer a joint assessment of where we consider this issue now stands.

THE COMMON COLD

The effect of vitamin C on the common cold has been extensively studied following the wide publicity on the issue engendered in the early 1970s by Linus Pauling.¹⁹ So far over 60 intervention studies have been carried out to examine the effect of vitamin C on simple upper respiratory infections.²⁰ While divergence

both in the design and in the results of these studies has hampered their interpretation, certain conclusions can be drawn from a careful overview of all of the published studies.

Incidence of the common cold

The published studies indicate that regular high dose vitamin C supplementation does not reduce the number of cold episodes in normally nourished subjects in Western countries. When the results of the six largest randomised trials were pooled,¹⁷ the rate ratio (RR) of the cold episodes between the vitamin C (≥ 1 g/day) and placebo groups was found to be 0.99 (95% confidence interval [CI] 0.93–1.04). These six trials included over 3500 subjects and over 5000 common cold episodes in all.

Nevertheless, a number of smaller studies have found a significantly lower incidence of colds in a group supplemented with vitamin C, and it is likely that some of these positive results are explained by special circumstances. Subjects under heavy acute physical stress appear to form one of the groups in which vitamin C supplementation reduces cold incidence.¹⁸ In three placebo-controlled trials of such

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subjects, a pooled estimate of the RR was calculated to be 0.50 (95% CI 0.35–0.69) in favour of the vitamin C groups.¹⁸

It is also possible that some of the studies reporting reduced cold incidence were correcting a marginal nutritional deficiency in the study population. The dietary vitamin C intake in the UK is low by comparison with other Western countries, and the recommended dietary intake there is the lowest in Western Europe.¹⁷ Four controlled studies with British men found a lower incidence of common colds in vitamin C groups than in the control groups (pooled RR = 0.70, 95% CI 0.60–0.81).¹⁷ One of these UK trials used a low dose of vitamin C, 80 mg/day, directly implying that the benefit seen in these trials was due to correcting marginal deficiency and not due to particularly high supplement doses.^{17,21} In populations that are marginally nourished, therefore, it seems that further prophylaxis studies would be justified.

Duration and severity of the common cold

Placebo-controlled studies testing the effects of regular vitamin C supplementation (≥ 1 g/day) have quite consistently found that the duration or severity of colds is reduced in the vitamin C group. Here again, there has been great variation in the results, with some studies reporting slight effects, while a few studies have reported differences of up to 50% in favour of the vitamin C group.^{11–16}

The results of the four largest trials are shown in Table 1, illustrating the spread of results when different outcome measures of severity are chosen. These trials found slight effects on the duration of colds, but a more marked and statistically significant benefit in outcomes that measure severity either directly or indirectly as absence from school or work. No effect on duration, but a moderate effect on common cold severity, was also found in a study in which experimental subjects were infected with rhinovirus.²⁷ Overall, firm evidence

demonstrates a moderate effect on severity and duration, whether large doses of vitamin C are given as regular supplements throughout the winter months, or in a therapeutic dosage at the time of the onset of cold symptoms. Further work is needed to clarify the optimum dosage strategy for treating colds.

PNEUMONIA

Studies with guinea pigs and other animals have found that vitamin C modifies susceptibility to various bacterial infections, including pneumococcal infections.^{10,28–33} Furthermore, in a study with rhesus monkeys, five cases of pneumonia were observed in a group of 25 monkeys on a diet deficient in vitamin C, while no cases occurred among 21 control animals administered vitamin C,³⁴ suggesting that in primates vitamin C intake may affect susceptibility to pneumonia.

Three intervention studies with human subjects have reported the number of pneumonia cases in two groups which differed in their vitamin C intake.^{25,35,36} Each of these three studies found a reduction of at least 80% in the incidence of pneumonia in the group supplemented with the vitamin, with all differences being statistically significant.²⁶ In the two older studies,^{35,36} baseline dietary vitamin C intake was low, so the benefit of supplementation may be due to correction of the marginal deficiency. However, in the latest and most rigorously conducted of these pneumonia trials,²⁵ the dietary intake was not low. In two studies the subjects were military recruits,^{25,36} and thus these two studies share physical stress as a feature common with one of the groups in which vitamin C decreased common cold incidence.¹⁸

A number of studies on human subjects have reported decreased levels of vitamin C in plasma, white blood cells, and in urine during various bacterial infections, which is not caused by poor diet alone, but at least partly a consequence of physiological

Table 1 Effect of regular vitamin C supplementation on common cold duration and severity in four major trials

Trial Subjects, country	Total number of		Outcome (per episode)	Outcome (days)			P (1-tail)
	Subjects	Episodes		Vitamin C group	Placebo group	Relative difference	
Anderson et al. 1972 ²² Adults, Canada	818	1170	Duration of colds	3.96	4.18	–5%	0.15
			Confined to house	1.04	1.32	–21%	0.008
Elwood et al. 1976 ²³ Women, UK	688	1317	Duration of colds	5.97	6.38	–6%	0.11
Ludvigsson et al. 1977 ²⁴ Schoolchildren, Sweden	615	1279	Duration of nasal symptoms	6.04	5.67	+7%	0.75
		821	Duration of colds	9.54	10.14	–6%	0.29
		449	Absence from school	2.77	3.22	–14%	0.008
Pitt and Costrini 1979 ²⁵ Marine recruits, USA	674	1219	Duration of colds	11.2	11.5	–3%	
			Severity of colds*	1.87	1.97	–5%	0.012
			Pneumonia cases†	1	7	–85%	0.022

Notes: All four trials were randomized, placebo-controlled and double blind, and their duration was 2–3 months. Elwood et al.²³ and Ludvigsson et al.²⁴ gave 1 g/day, and Pitt and Costrini²⁵ gave 2 g/day of vitamin C to their study subjects every day of the study. Anderson et al.²² gave 1 g/day regularly and 4 g/day during common cold episodes. The P values were re-calculated from the data available.

* Severity was measured on a scale of 1 to 4.

† The number of pneumonia cases in the two study groups; the P value is the mid-P value.²⁶

changes produced by the infections.^{10,37} In patients with pneumonia, reduced vitamin C levels in blood^{37,38} and urine³⁹ have been reported. While in the older literature vitamin C has been suggested as hastening convalescence from pneumonia,^{3-7,33,35} we are aware of only one controlled trial pertinent to this issue.³⁸ The subjects in this randomised double-blind placebo-controlled trial were a mixture of hospital patients in the UK with pneumonia ($n = 17$) and acute exacerbation of chronic bronchitis ($n = 40$), with an average age of 80 years. Therapeutic vitamin C (0.2 g/day) significantly decreased the score of respiratory symptoms in patients who were most severely affected when admitted to hospital, and a decrease bordering on statistical significance was seen in all patients.³⁸ Furthermore, of the six deaths among the patients during the trial, all due to respiratory infections, five of them were in the placebo group ($n = 29$), but only one in the vitamin C group ($n = 28$). This is another area where more work is needed. The possibility that therapeutic supplements could reduce death rates from serious respiratory infections in marginally nourished and well nourished populations warrants further careful trials.

OTHER RESPIRATORY INFECTIONS

Beside the common cold and pneumonia there are limited and fragmentary data on the possible effect of vitamin C on clinical outcomes of other respiratory infections, some of which suggest that vitamin C may be important.^{10,33} Vitamin C decreased the duration of rhinotracheitis in cats,⁴⁰ and in chickens it increased resistance to bronchitis.⁴¹ Higher vitamin C levels were associated with a considerably lower prevalence of hemolytic streptococci in the tonsils of children in both an observational⁴² and an intervention study.⁴³ In guinea pigs low vitamin C intake along with infection by hemolytic streptococci caused pathological changes resembling the lesions of rheumatic fever.^{32,44-46}

In a controlled study carried out on schoolboys in the UK in the early 1940s, vitamin C administration (0.05–0.3 g/day) had no effect on the incidence of tonsillitis.³⁵ However, marked differences between the study groups were seen among the subjects who actually contracted tonsillitis. In the vitamin C group significantly fewer tonsillitis patients (–30%) were referred to hospital, and among these the average stay in hospital was significantly shorter (–40%) compared to the control group.^{10,33,35} A further interesting finding, indirectly pertinent to tonsillitis, was a significant decrease in the incidence of rheumatic fever (–100%) in the vitamin C group.³³ The dietary vitamin C intake of the schoolboys in this study was particularly low, 15 mg/day.³⁵ Consequently, even if we assume that these results reflect genuine biological effects, great care must be exercised when extrapolating the findings to other population groups, since the

benefits observed may be due to the correction of marginal deficiency.

In two uncontrolled studies on subjects with neutrophil dysfunctions and repeated respiratory tract infections, vitamin C administration was associated with clinical benefit which paralleled improvements in neutrophil functions.^{47,48}

In guinea pigs low vitamin C intake has been associated with increased susceptibility to tuberculosis infections.^{10,33,49-51} Decreased plasma and urine vitamin C levels have been observed in tuberculosis patients,^{10,37,52-56} and in the older literature there are reports suggesting therapeutic benefit of vitamin C to tuberculosis patients.^{10,33,57-60} Furthermore, two early studies found that a higher vitamin C intake⁶¹ and a higher vitamin C concentration in plasma⁶² were associated with an incidence of tuberculosis that was over 80% lower in the group with higher vitamin C levels.¹⁰ The relevance of all these observations remains to be seen.

THE NEED FOR FURTHER STUDIES

The benefits observed in several of the published studies are substantial, encouraging further studies on the role of vitamin C on acute respiratory infections. Vitamin C can be given regularly or therapeutically, both modes of supplementation having different rationales and being of interest in different circumstances.

Studies on regular supplementation are primarily indicated in populations with marginal vitamin C intakes in their diet combined with a significant problem of respiratory infections. Accordingly, such studies should be carried out in developing countries, and among certain indigenous populations of developed countries such as Australian aboriginal children. Regular supplementation studies on respiratory infections are not recommended in Western countries except with carefully selected population groups.

Therapeutic trials are justified irrespective of the nutritional background of the patients. Various doses and supplementation protocols should be compared to evaluate more precisely the therapeutic effects of vitamin C on established respiratory infections.

Despite the large number of controlled trials aimed at the elucidation of preventive and therapeutic effects on the common cold, a recurrent feature has been a rather simplistic approach to the measurements of outcome, which in most of the published trials does not extend beyond the assessment of incidence and duration of symptoms. A more robust and consistent approach to the subjective assessment of severity has been used in some common cold studies.^{63,64} A typical scoring system is shown in Table 2.

In view of the uncertainties encountered in interpreting a number of earlier studies, future trials should pay particular attention to placebo indistinguishability, randomisation methodology, prealloca-

Table 2 Severity scoring system for daily self reports by subjects in common cold trials

	0	1	2	3
Cough	Nil	Mild	Troublesome and/or significant clear sputum	Incapacitating cough and/or purulent sputum
Nasal symptoms	Nil	Mild discharge, stuffiness, sneezing	Heavy, clear discharge and/or stuffiness	Yellow or green nasal discharge
Throat symptoms	Nil	Mild sore throat only	Moderate sore throat and/or hoarseness	Severe sore throat
Systemic symptoms	Nil	Some aches and/or slight fever	Definite elevation of temperature, moderate aches, headache	Severely incapacitated by general symptoms

A scoring system of this kind permits the patients' assessment of the severity of cold symptoms to be analysed by day, symptom, and episode, and could produce a total severity score for each episode which reflects both duration and severity of symptoms.

tion concealment, and to blinding with respect to patient and observer outcome assessment. These issues have often not been explicitly reported in the earlier papers. There is also an obvious need to control for potential confounding factors,^{10,22} such as prior respiratory infection history, exposure to young children, intake of fruit and fruit juices, and physical stress in the analysis of outcomes.

One of the particular problems which bedevils the interpretation of the vitamin C trials is the fundamental difference between vitamin C and ordinary drugs, such as antibiotics. It is possible to select a control group that has no intake of an ordinary drug, rendering the interpretation of results relatively simple. It is impossible, however, to select control subjects who have no vitamin C intake, and no vitamin C in their system. Accordingly, all vitamin C studies compare two different intake levels, the lower level obtained from the diet usually not being estimated at all, hampering the comparison of different studies and the generalization of their results. Consequently, efforts should be made to estimate the nature and extent of dietary intake, at least crudely, in future studies. There is also a need to distinguish nutrient replacement in marginally deficient population groups from the effects of particularly high doses.

CONCLUDING COMMENTS

From the studies published so far it is evident that in large doses vitamin C has distinct but modest therapeutic effects on the severity and duration of the common cold, even in well nourished populations. There are also possible benefits in the prevention of acute respiratory infections, especially in populations that are malnourished or physically stressed.

It is our view that three widely cited reviews⁶⁵⁻⁶⁷ concluding that vitamin C had little if any effect on the common cold did not accurately represent data from the original publications. For example, data inconsis-

tent with the original study reports were presented, several highly relevant findings were overlooked, and data were analysed inappropriately.^{12,68} Furthermore, the authors of the most influential trial so far⁶⁹ concluded that the difference between the vitamin C and placebo groups was paradoxically caused by the placebo effect. The placebo effect interpretation of the results was, however, recently shown to be erroneous, indicating that the observed benefit was indeed caused by the physiological effects of the vitamin.⁷⁰

The size and scope of the world respiratory infection problem highlights the need for rigorous trials which can further clarify the nature of both the prophylactic effects of vitamin C in high risk populations, and therapeutic effects in wider population groups.

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R É S U M É

Jusqu'ici plus de 60 études se sont attachées aux effets de la vitamine C sur le rhume. On n'a pas observé d'effet sur l'incidence du rhume dans les six études les plus importantes, ce qui indique que la vitamine C n'a pas d'effet préventif chez les sujets normalement nourris dans les pays occidentaux. On a toutefois fait état d'avantages dans de plus petites études. Dans trois essais portant sur des sujets soumis à un stress physique aigu violent, l'incidence du rhume a diminué d'environ 50% et dans quatre essais chez des hommes en Grande Bretagne, l'incidence du rhume a diminué en moyenne de 30% dans les groupes prenant de la vitamine C. L'utilisation alimentaire de vitamine C est basse en Grande Bretagne, et par conséquent l'avantage pourrait être dû à la correction d'une déficience limite plutôt qu'à des doses élevées de vitamine. La prise régulière d'un supplément vitaminique C (≥ 1 g/jour) a réduit de manière importante la durée des rhumes, mais l'importance de cet avantage a varié considérablement.

Dans les quatre études les plus importantes, la durée des rhumes n'a diminué que d'environ 5%. Dans deux de ces études toutefois, l'absentéisme à l'école et au travail a diminué de 14 à 21% par épisode, ce qui pourrait avoir une importance pratique. Trois études contrôlées ont signalé au moins 80% de réduction de l'incidence de la pneumonie dans le groupe prenant la vitamine C et un essai randomisé a fait état d'un avantage substantiel du traitement chez des patients âgés de Grande Bretagne hospitalisés en raison d'une pneumonie ou d'une bronchite. Il semble que les effets préventifs de l'administration complémentaire de vitamine C se limitent principalement aux sujets qui ont de faibles absorptions alimentaires de vitamine C, mais des effets thérapeutiques pourraient se produire dans des groupes de population plus larges. Il est nécessaire d'entreprendre des essais soigneusement élaborés pour explorer les effets de la vitamine C.

R E S U M E N

Más de 60 estudios han examinado los efectos de la vitamina C sobre el resfrío común. No se ha observado ningún efecto en la incidencia del resfrío común en los 6 estudios más grandes, en los que se ha visto que la vitamina C no tiene efectos preventivos en las personas bien nutridas de los países occidentales. Existen, sin embargo, estudios pequeños que refieren beneficios. En tres ensayos de individuos sometidos a estrés físicos agudos, la incidencia del resfrío común disminuyó en un 50% y en cuatro ensayos de varones ingleses la incidencia del resfrío común descendió en un 30% en el grupo con vitamina C. En el Reino Unido la ingesta alimentaria de vitamina C es baja y por lo tanto el beneficio puede atribuirse a la corrección de una deficiencia marginal más que a dosis altas de vitaminas. El suplemento regular de vitamina C (≥ 1 g/día) ha reducido francamente la duración de los resfríos, pero la magnitud del beneficio

varía grandemente. En los cuatro estudios más importantes la duración de los resfríos disminuyó sólo en el 5%. En dos de estos estudios, sin embargo, las ausencias escolares y laborales disminuyeron entre 14 y 21% por episodio, hecho que tiene importancia práctica. Tres estudios controlados refirieron por lo menos una reducción del 80% en la incidencia de neumonías en el grupo con vitamina C y un ensayo aleatorio mostró beneficios terapéuticos sustanciales de la vitamina C en pacientes ingleses ancianos hospitalizados por neumonía o bronquitis. Parece que los efectos preventivos de la suplementación están limitados a personas con ingestas bajas de vitamina C, pero los efectos terapéuticos pueden observarse en grupos de población más amplios. Son necesarios ensayos posteriores más cuidadosamente diseñados para explorar los efectos de la vitamina C.