Vitamin C and Infectious Diseases

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Introduction

Early in this century several authors suggested that vitamin C intake may have beneficial effects on the incidence and severity of various infections. Two exhaustive bibliographical searches of the old literature on vitamin C and infections have been published. One of them was overenthusiastic [1] in its interpretation of the findings, whereas the other was overly pessimistic [2]; neither offered any statistical analysis of the available data. However, a quantitative analysis of controlled studies has been published recently [3]. The mechanisms whereby vitamin C affects the immune system are poorly understood, although there are reports indicating that it affects the functions of phagocytes, the proliferation of T lymphocytes, the production of interferon, and the replication of viruses [3-5].

Infections in Animals

Most mammals synthesize vitamin C in their liver [6]. The guinea pig is one of the rare species that has lost this capability and thus provides a good experimental model for studies examining its effects. Vitamin C intake affects the susceptibility of guinea pigs to infections by bacteria and other microorganisms [3,7-31].

Primates also lack the ability to synthesize vitamin C [6]. Albert Sabin found that many rhesus monkeys on a vitamin C-deficient diet succumbed to spontaneous infections, chiefly pneumonia and enterocolitis, while those administered vitamin C remained well [32]. In marmosets, vitamin C supplementation decreased morbidity and mortality due to parainfluenza infection [33].

Mice, rats, and rabbits synthesize vitamin C in their livers and thus cannot be used to study the effects of vitamin C deficiency, but the effects of supple-

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mentation can be studied in these species. Vitamin C decreased the morbidity and mortality of animals infected with several different kinds of microorganisms [3, 34-38]. Furthermore, it has been commented that humans, monkeys, and the guinea pig are susceptible to both the human and bovine tubercle bacillus, whereas mice, rats and dogs, which synthesize vitamin C, are resistant to them [39].

Infections in Humans

The Common Cold

The effect of vitamin C on the common cold has been extensively studied, primarily because of the wide publicity provoked in the early 1970s by Linus Pauling [40, 41]. Pauling did not carry out any experimental work himself, but based his conclusions on published data. So far, over 60 interventional studies examining this issue have been published [42], The effect of vitamin C on the common cold has been a controversial issue largely because of conflicting results. Nevertheless, important consistencies in the results can be seen on careful analysis.

Incidence of the Common Cold

There is strong evidence that large-dose vitamin C supplementation has no effect on the number of common cold episodes in ordinary people in Western countries. None of the six largest trials found any significant effect, and when their results were combined, no difference was seen between vitamin C and placebo groups [43], In these trials there were over 3500 subjects and over 5000 common cold episodes in all.

Nevertheless, a number of small-scale trials have found a significantly lower number of colds in a group supplemented with vitamin C and it is possible that some of these positive results are explained by the use of different kinds of subjects or by other differences in experimental conditions when compared to the six largest trials.

It was suggested that subjects under acute heavy physical stress forms one group in which vitamin C supplementation may be beneficial. In three placebo-controlled trials, the number of cold episodes was decreased on average by 50% in the vitamin C groups [44]. In a fourth study, vitamin C also decreased common cold incidence significantly but the control group was not administered a placebo [45].

Furthermore, it is possible that some of the positive results on cold incidence are not due to the high vitamin C dose per se, but rather to the correction of marginal deficiency. In the UK, the dietary vitamin C intake is particularly low among the Western countries, and in four trials in British men vitamin C decreased the incidence of the common cold on average by 30% [43]. One of the

UK trials used a low vitamin C dose, 80 mg/day, implying that the benefit was due to correcting marginal deficiency [43,46],

Some further studies have also observed preventive benefits from vitamin C on common cold incidence [40, 41, 47]. Nevertheless, the six largest trials show that subpopulations in Western countries potentially benefiting from regular vitamin C supplementation are rather restricted [43],

Severity of Common Cold Episodes

Placebo-controlled trials have shown that vitamin C alleviates the symptoms and shortens the duration of the common cold. However, there has been great divergence in the results, some studies reporting only a 5% decrease, while a few have reported an up to 50% decrease in the duration or severity of colds among the vitamin C group [47-51].

There is some evidence of variation in the size of the benefit between subgroups. Vitamin C may be more beneficial in subjects with a low dietary intake of the vitamin and in adults in regular contact with children [3]. Studies in children also tend to reveal greater benefit than studies in adults and studies using larger doses tend to reveal greater benefit [51]. Karlowski et al. [52] found that 6 g/day produced approximately twice as great a benefit as 3 g/day, implying dose dependency in the >1 g/day region [51,53].

Essentially all published trials have examined the effect of regular vitamin C supplementation. However, if the goal is to alleviate the symptoms of cold episodes, it appears more rational to administer vitamin C therapeutically, starting immediately after the first symptoms, but few such trials have been carried out [48, 51]. Promptness may be important in such therapeutic supplementation. Asfora [54] found great benefit from vitamin C (6 g/day for 5 days) when treatment was initiated within 24 h of the onset of common cold symptoms. The benefit was considerably less when initiated 24-48 h after onset, and no benefit was seen with still later initiation of treatment.

Pneumonia

In one of his last texts Albert Szent-Györgyi mentions a personal experience [55]: "Last year I collected a rather unfortunate personal experience. I broke down with pneumonia which I could not shake off for months, until I discovered that the quantities of ascorbic acid which I took (one gram daily) had become insufficient at my age (84 years). When I went up from one gram to eight, my troubles were over."

There are numerous other suggestions that vitamin C may have therapeutic benefits in pneumonia patients [56-65]. However, we are aware of only one randomized trial pertinent to this issue [66], carried out in the UK with elderly hospital patients with pneumonia *(n* = 17) and acute bronchitis *(n* = 40). Therapeutic vitamin C (0.2 g/day) caused a statistically significant decrease in a score of respiratory symptoms in those patients who were most severely ill when admitted to

hospital, and a decrease bordering on statistical significance in all patients. Furthermore, there were six deaths among the patients, all due to respiratory infection; five in the placebo group, but only one in the vitamin C group [66].

Vitamin C intake can also have preventive effects on pneumonia. Three studies have reported the number of pneumonia cases in vitamin C and control groups [67-69], each of these studies finding at least an 80% lower incidence of pneumonia in the vitamin C group and the difference being statistically significant in each case [70]. The latest of these studies was a double-blind, placebo-controlled trial with marine recruits in the USA [69]. In contrast, placebo was not used in the two older studies [67, 68]. Dietary vitamin C intake was low in the older studies [67, 68] and the benefit of higher vitamin C intake may be explained by the correction of marginal deficiency. However, in the latest trial [69] dietary intake was rather high, and the effect thus seems to be due to the large dose per se (2 g/day). In this respect, these studies do not yield a simple biological explanation of the observed benefits.

Other Infections

There is limited and fragmentary data on the possible effects of vitamin C on other infections, yet the available data strongly suggest that the effects are not restricted to the common cold and pneumonia [1-39, 71]. Findings of three particularly interesting trials are shown in Table 1.

Glazebrook and Thomson [67] studied schoolboys in an institution in the UK. A placebo was not used, but vitamin C was added to food in the kitchen and it is unlikely that a placebo effect would have occurred in the dining hall. No difference was seen in tonsillitis incidence between the study groups. However, prominent differences between the control and vitamin C groups were seen among the subjects who contracted tonsillitis. In the vitamin group fewer tonsillitis patients were referred to hospital and their average stay at the hospital was shorter (Table 1). A further interesting finding in this trial was the absence of pneumonia and rheumatic fever in the vitamin group. This trial shows that vitamin C may have quite variable effects on different infectious disease endpoints. It is similarly noteworthy that Pitt and Costrini [69] found no effect on common cold incidence but an 85% decrease in pneumonia incidence in the vitamin C group [43, 70]. Glazebrook and Thomson estimated that the dietary vitamin C intake of schoolboys was only 10-15 mg/day [67]. It is thus possible that the observed benefits are due to the correction of marginal deficiency. Consequently, even if we assume that their results reflect genuine biological effects, great care must be exercised when extrapolating such findings to other population groups.

Ritzel [72, 73] carried out a double-blind, placebo-controlled trial with schoolchildren in a skiing camp in Switzerland, which belongs to the group of studies with subjects under acute heavy physical stress [44]. He observed a substantial decrease in the number of pharyngitis, laryngitis, and tonsillitis episodes, and in the number of bronchitis episodes in the vitamin C group

(Table 1). The trial was small and these decreases were not significant statistically, but they are consistent with the observed effect on common cold incidence. A substantial difference between the groups in the occurrence of other symptoms was also reported (Table 1).

Table 1. Vitamin C and infectious diseases

Study (vitamin C dose)	Number	Study group: Vitamin C	Study group: Control	Decrease	*p* Value[a] (one-tail)
Glazebrook and Thomson 1942 [67] (0.05-0.3 g/day)	Subjects	335	1100		
	Common cold	72	286	17%	0.047
	Tonsillitis	29	94	0%	0.5
	Admitted to hospital	18	83	30%	0.002
	Days in hospital	10.1	16.7	40%	0.013
	Pneumonia	0	17	100%	0.005
	Rheumatic fever	0	16	100%	0.007
Ritzel 1961 [41, 72, 73] (1 g/day)	Subjects	139	140		
	Common cold	17	31	45%	0.015
	Pharyngitis, laryngitis and tonsillitis	7	14	50%	0.062
	Bronchitis	8	13	38%	0.14
	Other symptoms[b]	8	21	62%	–[b]
	Total days of illness[c]	9	48	81%	
Terezhalmy et al. 1978 [74] (0.6 g/day)	Subjects	19	10		
	Herpes labialis				
	Days of pain	1.7	3.5	51%	<0.001
	Days before healing	4.2	9.7	57%	<0.001
(0.6-1.0 g/day)	Subjects	38	10		
	Herpes labialis				
	Patients with vesicle formation	14	10	63%	<0.001

[a] With continuous data, *p* value was calculated using the *t*-test, and with dichotomous data the mid-*p* value was calculated [3].

[b] Muscle ache, headache, abdominal pain, vomiting, diarrhea, general malaise. *p* Value not calculated since the outcome is highly heterogeneous.

[c] Days of illness per group for other symptoms.

Terezhalmy et al. [74] carried out a double-blind, placebo-controlled trial with subjects with recurrent herpes labialis. The duration of pain and the percentage of subjects with vesicle formation were both significantly reduced by vitamin C (Table 1). No meaningful difference was seen between 0.6 and 1.0 g/day doses, suggesting that saturation was reached at 0.6 g/day or lower. A further interesting finding in this trial was that prompt initiation of treatment within 24 h was more beneficial than later initiation [3, 74], consistent with Asfora's findings with the common cold [54]. Bioflavonoids were given along with vitamin C and it is unknown to what extent they are responsible for the differences between the study groups.

A number of authors have suggested that vitamin C may be beneficial in patients with tuberculosis [1, 3, 75-84] and for preventing and treating viral hepatitis [1, 3, 64, 65, 71, 85-91], With all the evidence indicating that vitamin C has nonspecific effects on the immune system and on various infections [3-39], it seems clear that these old reports should not be disregarded without further carefully designed trials. Vitamin C has been suggested as having beneficial effects on still further infections, but they are not commented on here [1-3, 7, 64,65,92-98].

Problems in Interpreting the Vitamin C Studies

Szent-Gyorgyi stated that "as to ascorbic acid, right from the beginning I felt that the medical profession misled the public. If you don't take ascorbic acid with your food you get scurvy, so the medical profession said that if you don't get scurvy you are all right. I think that this is a very grave error. Scurvy is not the first sign of the deficiency but a premortal syndrome, and for full health you need much more [71,99]."

This oversimplified view vividly described by Szent-Györgyi in separate instances [1, 100-103] is still prevalent. It recently was shown that three highly influential reviews [104-106] concluding that vitamin C is not efficacious against the common cold misrepresented data from the original publications and analyzed the data improperly [107, 108]. Furthermore, the authors of the most influential common cold trial, which was carried out at the National Institutes of Health in the USA [52], concluded that the apparent benefit from vitamin C was actually caused by the placebo effect. However, the placebo effect was recently shown to be an erroneous explanation of these findings [53]. It is noteworthy that two of these biased papers [52, 104, 109] were authored by Thomas Chalmers who was a highly influential pioneer of randomized trials [110]. It seems that the biased analysis of data in the four important papers [52, 104-106] is largely explained by uncritical adherence to the concept that the physiological purpose of vitamin C is merely to prevent scurvy [3,108, 111].

There are many more problems in interpreting the vitamin C studies [3, 108]. A particular difficulty arises from the fundamental difference between vitamin C and ordinary drugs such as antibiotics. It is possible to select a control

group which has no intake of an ordinary drug, making the interpretation of results reasonably simple. It is impossible, however, to select control subjects who have no vitamin C intake and no vitamin C in their body. Consequently, all intervention studies with vitamin C compare two different intake levels. The lower level arising from diet has not usually been estimated at all, making the comparison between studies and the generalization of findings problematic issues.

One important problem that has hampered acceptance of the notion that vitamin C supplementation can produce benefits is concern for safety. For example, in a recent review Victor Herbert [112] stated that vitamin C may lower plasma vitamin 612 levels and reduce insulin production. However, speculation that vitamin C breaks down vitamin 612 was shown to be false over two decades ago [71, 113-115], and speculation that vitamin C reduces insulin production was based on a single study from the year 1946 with alloxan treated rats; however, the original authors explicitly stated that vitamin C alone had no effect on their rats [115]. The safety of vitamin C is of no real concern [65, 71, 100,115-117]. In his reminiscences Pauling [118] recalled that the reason he sat down and wrote the bestselling book reviewing the evidence that vitamin C is beneficial against the common cold [40] was an acrimonious exchange of letters with Herbert who authored the biased review claiming that vitamin C is harmful [112,115].

Some people such as Szent-Györgyi [1, 55, 99-103], Pauling [40, 41, 71, 99], and Stone [1] were able to see that the physiological role of vitamin C is not limited to the prevention of scurvy. Nevertheless, they were overly enthusiastic when extrapolating the reported benefits of higher doses to the general population in Western countries [3,43,47, 51]. For example, they did not properly consider the possibility that the reported benefits of high doses were due to the correction of marginal deficiency, in which case their conclusions from the published findings would probably have been more moderate.

The Need for Further Trials

Paul Knipschild [119] describes how a colleague once asked him to help set up a preventive trial on vitamin C and the common cold. However, before undertaking a new trial he decided first to carry out a systematic review of the issue to see what was previously known and this led to a thorough and useful bibliography on the subject [42].

Judging by published reports, many other workers did not take a proper look at the literature to formulate relevant questions for their own trials. Consequently, many published trials teach us little, if anything. For example, in 1975 it was reported that 6 g/day of vitamin C caused twice as great a benefit as 3 g/day, and therapeutic supplementation was found to be more efficacious than regular supplementation [51-53]. Nevertheless, after 1975 only one paper has reported a therapeutic trial administering 6 g/day [54]. Strangely enough, in this double-blind, placebo-controlled trial patients receiving vitamin C could be

identified by their clinical progress, which led to the breakdown of blindness in the trial [54], Since 1975 several trials have examined the effect of a regular 1 g/day dose [48-51], which seems largely a waste of time and resources considering the data published before those trials.

According to the available evidence, there is no sound reason to research the effects of regular vitamin C supplementation on the incidence of infections in Western countries, except in carefully selected population groups. Regular supplementation trials are recommended in populations with low vitamin C intakes combined with a particular problem with infections. Such conditions are common in the developing countries.

Therapeutic trials on various infections are encouraged, irrespective of the nutritional background of the patients, although the greatest benefits may be anticipated with patients initially having an unsatisfactory diet. Different doses and different supplementation protocols should be compared in such trials. In planning such therapeutic trials, the reports by physicians who have been using vitamin C in their clinical practice may provide useful information on appropriate doses and on the possible ways of administering the vitamin.

Conclusions

In the first part of this century numerous reports were published, concluding that vitamin C has effects on various infections. Szent-Györgyi himself believed at the end of the 1930s that "vitamins, if properly understood and applied, will help us reduce human suffering to an extent which the most fantastic mind would fail to imagine [99]." In those days Szent-Györgyi was shocked by the lack of biological insight and by the lack of interest in the basic problems on the part of the leading clinicians [103].

The role of vitamin C in preventing and treating infections was not dismissed because of large-scale controlled trials showing that the vitamin is ineffective. There seem to be two particular reasons why the early reports were disregarded. Antibiotics were introduced in the middle of this century. They have specific effects on bacteria and are therefore much more rational drugs for patients with specified infections than vitamin C. The second reason seems to be the strong adherence to the notion that vitamin C is just for preventing scurvy. Evidently it was unreasonable to consider that a substance participating in collagen synthesis might have effects on infections. However, the biochemistry of vitamin C is complex and not at all limited to collagen metabolism. Numerous reports have shown that vitamin C has effects on the immune system [3-5]. Vitamin C is not a specific agent against any particular infection but possibly has moderate effects on general resistance to infections. Much more work is needed to discover the practical importance of vitamin C in preventing and treating infections.

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The state of the art in disease prevention sixty years after the Nobel Prize

Springer

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