VITAMIN C AND ACUTE ILLNESS IN NAVAJO SCHOOLCHILDREN

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Abstract To evaluate earlier observations, including our own, showing usefulness of vitamin C for managing the common cold, we performed a double-blind trial of vitamin C versus placebo in 868 children. There was no difference in number becoming ill (133 versus 129), number of episodes (166 versus 159) or mean illness duration (5.5 versus 5.8 days) between the groups. Children receiving vitamin C had fewer throat cultures yielding β-hemolytic streptococcus (six versus 13, $P<0.10$), but no difference in overall complicated illness rate (24 versus 25). Plasma ascorbic acid levels were higher in the vitamin group 24 to 26 hours after supplementation (1.28 versus 1.04 mg per 100 ml, $P<0.01$). Children with high plasma ascorbic acid concentrations had longer mean illness (6.8 versus 4.0 days, $P<0.05$) than those with low levels. Vitamin C does not seem to be an effective prophylactic or therapeutic agent for upper respiratory illness. (N Engl J Med 295:973-977, 1976)

DURING a 14-week period in 1973, we conducted a double-blind study among Navajo schoolchildren to evaluate the effects of large vitamin C supplements on acute illness, respiratory and otherwise.[1] Although we noted no prophylactic influence, our findings suggested modest symptomatic benefit in that children taking 1 or 2 g of vitamin C daily had about 30 per cent fewer total days of morbidity from respiratory illness, and 26 per cent fewer symptom-days of cough or nasal complaints, than those taking a placebo. The clinical implications of such findings were, in themselves, questionable, especially so far as nonparametric statistical tests failed to show our results significantly different from chance alone. However, other recent work had indicated some influence of pharmacologic doses of vitamin C in ameliorating acute illness.[2,3] Consequently, we considered further study indicated to determine if use of vitamin C could prevent complications of the common cold, such as superinfections or otitis media, if certain symptoms or symptom complexes responded to vitamin C therapy and if, indeed, as our small sample had suggested,[1] higher blood ascorbic acid levels were correlated with fewer days of illness.

Thus, another investigation was designed to confirm, if possible, and expand these observations. The second trial, conducted in two Navajo boarding schools during early 1974, used supplements of 1 g ascorbic acid versus placebo tablets. In a preliminary analysis of classroom surveillance data, we found no significant difference in the reporting of a variety of symptoms between children taking vitamin C and those on placebo.[4] The present report completes the analysis of this second trial, with clinical illness experience, data on school absence and biochemical results.

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MATERIALS AND METHODS

Subjects

The study population included children enrolled at two boarding schools: Toyei, located at Steamboat, Arizona, and Greasewood, located at Lower Greasewood, Arizona. At each school, there was an Indian Health Service clinic and a physician, physician assistant or registered nurse available throughout each week. Parental permission forms were signed during the autumn of 1973. Permission to conduct this investigation was granted by the Indian Health Service, the Bureau of Indian Affairs and appropriate Navajo tribal authorities, including local school boards.

At the outset, 944 children were enrolled with parental consent, including 484 at Greasewood and 460 at Toyei, which constituted approximately 80 per cent of the total enrollment of both schools. These children ranged in age from six through 15 years and all lived at the schools, with the exception of 83 day students at Greasewood. The two schools had identical meal plans designed by an Indian Health Service nutritionist. These meals contained vitamin C in excess of minimum recommended daily requirements.

Materials and Procedures

Tablets manufactured for this study contained 500 mg of ascorbic acid in anhydrous form, and placebo tablets were formulated with citric acid to be identical in appearance and taste with ascorbic acid pills. This procedure was unlike our earlier clinical trial, in which study tablets were composed of sodium ascorbate and anhydrous ascorbic acid in an approximate ratio of 3:1.

Each child received tablets from his or her own bottle, identified only by study number. Individual treatments were assigned randomly by computer within groups of 20 consecutive numbers. People involved in data collection or tablet distribution had no access to treatment identification, although one of us (S.E.) retained a master key to use in case of adverse reactions.

The investigation took place from January through mid-May, 1974, at Greasewood School, a period of 18 weeks, whereas at Toyei, the study was 15 weeks in length. Children took 2 tablets daily (1 g for those on vitamin C), supervised by teachers at the beginning of the school day and drawn from the child's own bottle. On Fridays or before holidays, children were given individual packets for use on the weekend or holiday period, but there was no specific, consistent supervision outside the classroom. Those absent from school unexpectedly did not get tablets during their absence. Children were instructed to take the tablets whether they felt sick or well.

Data Collection

Three major types of observation were made in this study. A trained clerk conducted classroom surveillance in each school to ascertain the frequency of various symptoms. Children were simply asked if any of these symptoms were present on the day in question. The results of this part of the investigation were the subject of an earlier report.[4]

The second type of observation involved clinical episodes of ill-

ness seen at either of the clinics. An "episode" was defined as any illness for which a child sought or was referred for medical evaluation and treatment, preceded by at least seven symptom-free days. Written diagnostic criteria were established for four acute respiratory syndromes* (upper respiratory infection, pharyngitis, otitis media and lower respiratory infection). Other diagnostic categories included gastroenteritis, impetigo, conjunctivitis and "all other illness." After a diagnosis was made, the child was observed daily until symptoms subsided. A complete record of school absence for all children was kept at Greasewood School.

A third form of data assessment, involving biochemical determinations of plasma ascorbic acid levels on children at Toyei School, used the automated 2,6-dichlorophenol-indophenol technic described by Garry et al.[5] Blood samples were drawn at two times during the trial, on the fifth and ninth weeks, but on different children each time. Samples were obtained by venipuncture at different times after vitamin C (or placebo) ingestion, so that groups of values were obtained from one to two, three to six and 24 to 26 hours after the supplement was taken.

Results

Of the original 944 children participating, 76 (8 per cent) dropped out during the investigation. Twenty-one Greasewood students were eliminated from consideration because of high absenteeism (greater than one third of the total study days), but no children were dropped at Toyei for this reason since accurate records of attendance were unavailable. The remaining 55 children were removed from the program by parental request, because they officially left school or because they were simply unwilling to take the tablets. No children left the study because of observed adverse effects. This analysis includes only the experience of 868 children who completed the entire investigation.

Illness-episode data were collected beginning in the second study week. Overall, 263 children (30.3 per cent) reported to the clinic with 325 discrete illness episodes. Among those taking vitamin C (C group), 133 children had 166 episodes, whereas 129 children receiving placebo (P group) experienced 159 episodes. With correction for a three-week shorter trial period at Toyei, absolute incidence of illness was similar in the two schools. Proportionately, more females than males became ill (33.2 versus 27.6 per cent, chi-square = 3.73, with 1 degree of freedom, $P<0.10$), whereas the proportion of children ill 10 years of age and under was much the same as those over 10 (29.4 and 31.5 per cent).[6]

Table 1 shows total illness episodes according to treatment groups, sex and clinical category. Respiratory illness included all four defined clinical categories. Illnesses characterized primarily by gastrointestinal complaints were kept separate, since pharmacologic doses of ascorbic acid can cause abdominal discomfort and diarrhea. Vitamin C did not decrease the incidence of illness in any group, nor did it cause more gastrointestinal problems. "Complicated" respiratory episodes were defined as otitis media and lower respiratory infections. Overall, 25 of 98 respiratory episodes were complicated in the P group, and 24 of 98 in the C children. Throat cultures were performed in all cases in which there was a complaint of throat discomfort. There were 57 such cultures performed in each treatment group, six (11 per cent) of which were positive for β-hemolytic streptococcus in C children, and 13 (23 per cent) were positive in the P group (chi-square = 3.095, with 1 degree of freedom, $P<0.10$).

Fifty-five episodes (26 in P and 29 in C) either were caused by injuries or their durations not evaluated. However, in all other cases, children were seen daily by a nurse until symptoms resolved; date of onset of symptoms was ascertained from the clinical history. Table 2 shows distributions of illness duration according to age, sex and treatment groups. Mean duration of episodes in C children was 5.5 days (137 episodes) whereas that of P children was 5.8 days (133 episodes). Vitamin C supplements were not associated with a significant reduction in illness duration.

Although an accurate recording of days absent from class was available at Greasewood, it did not specify the reason for absence. There were no differences in distribution of days absent between overall P and C children, or other age and sex groups, but P male

Table 1. Types of Illness Episodes* According to Treatment Group and Sex.

Type of Episode	Vitamin C	Placebo	Totals
		no. of episodes	
Respiratory†:			
Boys	38 (213)§	43 (207)	81
Girls	60 (215)	55 (221)	115
Totals	98	98	196
Gastrointestinal:			
Boys	3	4	7
Girls	2	4	6
Totals	5	8	13
Other‡:			
Boys	18	21	39
Girls	34	21	55
Totals	52	42	94

*Total of 325 episodes, less 22 injuries.

†Includes upper respiratory infection, pharyngitis, otitis media & lower respiratory infection.

‡Includes all other diagnoses, except injuries.

§No. of children in treatment group.

Table 2. Distribution of Episode Duration According to Sex and Treatment Group.

Days Ill	Boys		Girls		Totals	
	Vitamin C	Placebo	Vitamin C	Placebo	Vitamin C	Placebo
0*	16	14	13	12	29	26
1 - 5	22	21	41	35	63	56
6 - 10	24	25	28	28	52	53
⩾11	8	13	14	11	22	24
Total episodes	70	73	96	86	166	159
Comparison of duration distribution (3 degrees of freedom)	chi-square=1.30†		chi-square=3.35†		chi-square=0.46†	

*Includes injuries & episodes for which accurate duration was not ascertained.

†Not significant.

*Available from the authors upon request.

children over 10 did have significantly fewer days absent (chi-square = 11.22, with 3 degrees of freedom, $P<0.05$).

Table 3 presents plasma ascorbic acid values according to age, sex, treatment group and hours after ingestion. Samples drawn at five weeks and nine weeks on different children were included together because there were no meaningful, consistent differences between subgroups. There were consistent elevations in plasma ascorbic acid in the C group at both one to two hours and three to six hours, with peak values at one to two hours, as compared to time-matched P children, although these increases were not significant in girls over 10. In girls a smaller difference remained at 24 to 26 hours, indicating improved tissue saturation in these C children. The mean plasma level overall at 24 to 26 hours in the C group was 1.28 mg per 100 ml (45 children), whereas the mean ascorbic acid value for all P students (156) was 1.04 mg per 100 ml ($t_0 = 4.45$, $P<0.01$).[6]

For each interval after ingestion, age and sex group, plasma ascorbic acid levels were arrayed from highest to lowest. Children with values in the upper third within each cell were combined with children whose values were in the upper third of all other cells in the same treatment group (C or P). Children with values in the middle or lower thirds were handled similarly. Absolute ascorbic acid levels could not be arrayed in a continuous distribution since the three separate times after ingestion were employed. This procedure provided a relative index of ascorbic acid status within each subgroup, and then lumped children on the basis of their relative standing in the subgroup. Table 4 shows the illness experience of children with low, middle and high ascorbic acid levels derived from this procedure.

Table 3. Plasma Ascorbic Acid (AA) Levels According to Age, Sex, Treatment Group and Time after Supplement Ingestion.

Hr after Ingestion	Vitamin C			Placebo			t_0*
	No.	Mean AA Level	±S.D.	No.	Mean AA Level	±S.D.	
		mg/100 ml			*mg/100 ml*		
Boys:							
Age ≤10 yr:							
1 - 2	10	2.78	0.44	4	0.90	0.13	8.17†
3 - 6	25	1.84	0.74	26	1.02	0.32	5.20†
24 - 26	10	1.31	0.43	14	1.25	0.34	0.36
Age >10 yr:							
1 - 2	6	2.47	0.45	1	0.70	—	—
3 - 6	10	1.54	0.87	11	0.95	0.13	2.23‡
24 - 26	14	1.24	0.46	9	0.98	0.20	1.57
Girls:							
≤10 yr:							
1 - 2	3	2.83	0.36	7	1.42	0.38	5.48†
3 - 6	37	1.85	0.67	31	1.02	0.27	6.43†
24 - 26	9	1.35	0.42	18	1.04	0.16	2.74†
>10 yr:							
1 - 2	4	1.59	0.93	3	0.84	0.23	1.35
3 - 6	13	1.50	0.66	16	1.11	0.41	1.92
24 - 26	12	1.26	0.36	16	0.89	0.22	3.41†

*Student t-statistic. †$P<0.01$. ‡$P<0.05$.

Table 4. Illness Experience According to Relative Plasma Ascorbic Acid (AA) and Vitamin C (C) or Placebo (P) Group.

AA Level	Vitamin C			Placebo		
	No. of Children	No. of Episodes	Mean Duration	No. of Children	No. of Episodes	Mean Duration
			days			*days*
Low:						
C (49)*	19	22	4.0†	14	20	5.6
P (51)						
Middle:						
C (55)	12	15	2.7†	17	18	4.5
P (54)						
High:						
C (49)	11	13	6.8†	9	10	4.4
P (51)						

*No. of children in group.

†Distributions of episode duration different (Kruskal–Wallis H test = 9.20, $P<0.05$); low vs middle, $z = 0.41$, not significant; low vs high, $z = -2.58$, $P<0.05$; middle vs high, $z = -2.75$, $P<0.05$.

There were no significant differences in number of children with episodes among relative ascorbic acid levels or between treatment groups. However, when we compared the distributions of illness duration using the nonparametric Kruskal–Wallis H test, we found low, middle and high ascorbic acid distributions to be different from one another in the C group only ($H = 9.20$, $P<0.05$).[7] Specifically, durations were longer in the children with high than in those with low or middle ascorbic acid levels (Dunn's statistic for multiple comparisons: low vs. high, $z = -2.58$, $P<0.05$; middle vs. high, $z = -2.75$, $P<0.05$).[7] This finding corresponds with the longer mean duration in the group with high ascorbic acid levels (6.8 days).

Discussion

In our first double-blind trial of vitamin C supplements, we concluded "there are enough data suggesting a beneficial influence of vitamin C on respiratory infections to warrant further investigation." This report, in conjunction with our previous analysis of surveillance data,[4] gives no evidence of prophylactic or therapeutic potential for 1 g of vitamin C supplements in Navajo schoolchildren. More specifically, we were unable to show that vitamin C prevents "complicated" respiratory infections, such as otitis media. Although children receiving vitamin C did have fewer positive throat cultures, the numbers were quite small, and not all those with respiratory episodes had cultures performed. We also found no support for the hypothesis that vitamin C preferentially ameliorates certain symptoms. In the earlier investigation, we noted catarrhal symptoms, such as cough and nasal discharge, to be most relieved,[1] an observation similar to the findings of Wilson,[3,8] but unlike those of Anderson et al.,[2,9] who reported the benefit of vitamin C to be greater with systemic or toxic symptoms, rather than "colds" per se. Finally, we were unable to demonstrate that higher plasma ascorbic acid levels are

associated with less respiratory illness, at least on a single, controlled determination.

How can the differences between our first and second investigations be explained? In the first place, some of the discrepancy may be only apparent and based on statistical artifact. Our conclusion that vitamin C supplements of 1 or 2 g ameliorate acute illness by decreasing duration was based on an analysis of symptoms reported in a systematic, though intermittent, classroom surveillance and an analysis of total "days of morbidity" in illness episodes. Difficulties with the first technic were previously discussed.[4] Regarding the second analysis, there were relatively few episodes observed (164, of which 75 were respiratory), and a nonparametric test of illness duration distribution showed no influence of vitamin C on duration. We went on, however, to analyze total "days of morbidity" using a chi-square test, but this procedure has been correctly criticized in that the units compared were not truly independent of one another.[10] The same criticism holds for our suggestion that children with higher whole-blood ascorbic acid values may have a more favorable illness experience.

On the other hand, a number of controlled, double-blind trials have indicated some reduction in severity of colds or "winter illness" with pharmacologic doses of vitamin C, and others have shown decreased incidence as well. Wilson recently summarized the evidence published through the end of 1974.[11] It is important, however, to examine the positive data in context, and to look at the negative data as well. The reported efficacy is generally modest, although statistically significant when extrapolated to large populations, and it deals with minor symptoms, generally self-reported, in self-limited illness. We agree with Chalmers, who, in reviewing the evidence, concluded that he did not consider "the very minor potential benefit that might result from taking ascorbic acid three times a day for life worth either the effort or the risk, no matter how slight the latter might be."[12]

The series of trials by Anderson et al. is most comprehensive, involving a variety of regimens and attempts at replication.[2,9,13] In the initial study, those receiving a 1-g prophylactic supplement of vitamin C and 4 g daily during the first three days of any illness, had 30 per cent fewer days of disability (confined indoors) than those on placebo.[2] Similar results were obtained in a third trial using much smaller doses, 500 mg per week and 1.0 to 1.5 g daily for three days during sickness; those on vitamin C had 25 per cent fewer days of disability.[9] Anderson believes,[9] in interpreting this sequence, tissue saturation with ascorbic acid does ameliorate "the burden of winter illness," but this saturation can be achieved with much lower supplements than those suggested by Pauling,[14] and is not restricted to colds per se in that systemic symptoms were more influenced in his trials than catarrhal symptoms. At 24 to 26 hours after ingestion in our study, the mean plasma ascorbic acid level in C children was 1.28 mg per 100 ml (45 children) — substantially higher than that of P children: 1.04 mg per 100 ml (156). This finding indicates that, as a group, children receiving supplements had improved "tissue saturation," although not at the steady-state maximal plasma ascorbic acid level, which is approximately 1.40 to 1.45 mg per 100 ml.[5] Thus, we did increase tissue saturation at a presumably base-line state, but did not reduce the burden of illness.

Navajo children have a high incidence of acute respiratory disease, and particularly otitis media, and we believed a boarding school, with its potential for epidemic transmission, would be an ideal setting to show therapeutic potential for a cold remedy. However, we observed many fewer illness episodes than Anderson,[2] for example. He noted 1.38 to 1.48 episodes per person in 12 weeks whereas we saw 0.34 episodes per child in 14 weeks, excluding the additional three weeks at Greasewood. The former, of course, were self-reported whereas ours involved medical referral and treatment. Our surveillance-data technic, relying on a single observation per child every two weeks, was much less sensitive than the log-book recordings used by Wilson,[3,8] Anderson[2,9,13] and most other investigators. Consequently, the data are not strictly comparable, but we believe our observations, at least so far as clinical episodes are concerned, showed more symptomatic though less frequent illness.

Lewin summarized the biochemistry of ascorbic acid, with particular emphasis on the potential effects of high intake.[15] The observation that leukocyte ascorbic acid levels decrease in colds and a number of other stress situations[16,17] in no way necessarily implies that "resaturation" will shorten or ameliorate the pathologic state. We believe the work of Žuškin et al.[18,19] suggests a more likely method in which high-dose vitamin C supplements may influence cold symptoms to a modest degree. They showed that aerosols of ascorbic acid can prevent or lessen histamine-induced bronchospasm in both human beings and laboratory animals. This effect was also evident on pulmonary-function testing of flax workers, many of whom were known to have byssinosis.[19] Little is known about the functional aspects of acute airway responses during upper respiratory infections. We believe, however, that an antihistaminic action of vitamin C could provide mild relief for symptoms such as nasal congestion and cough, particularly in atopic persons.

Thus, despite our earlier promising report,[1] we were unable to demonstrate a benefit of 1-g vitamin C supplements in Navajo children. It is clear that effects, if any, are so modest and inconsistent as to require large populations and detailed statistical analysis to make them apparent. We believe introducing daily supplements of 1,2 or more g per subject into a population system conceivably leads to change in response to acute illness observable in the system. It is not clear which of the many pharmacologic properties of ascorbic acid could be involved, but we suggest that an antihistaminic property may be relevant. In

any case, we do not believe that vitamin C has widespread usefulness as a cold remedy.

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PROGRESSION TO UREMIA AFTER REMISSION OF ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

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Abstract Whether or not poststreptococcal glomerulonephritis advances over the long term to uremia remains an unsettled issue. We documented ultimate progression to renal failure in six patients who were observed at onset with the typical clinical and morphologic features of acute nephritis after proved beta-hemolytic streptococcal infection. Within one year, renal function returned essentially to normal in all, as the proliferative changes in glomeruli subsided. Subsequently, increasing renal failure developed in these patients over periods ranging from two to 12 years, during which all were hypertensive. As the renal disease progressed, glomeruli showed increasing sclerosis in the absence of proliferation, and fibrohyaline thickening of renal arterioles appeared. (N Engl J Med 295:977-981, 1976)

WE recently reported our long-term observations on the course of poststreptococcal glomerulonephritis in 126 patients who were followed from onset.[1] Except for nine who pursued an unrelenting course and progressed to terminal uremia within six months, all underwent clinical and morphologic remission during the first year. Still, on long-term follow-up study, by clinical and histologic criteria and by precise evaluation of renal function, features of irreversible renal damage were demonstrable in more than half the 60 patients who were under observation two to 15 years from onset.

The question arises whether persistent features of renal disease years after subsidence of acute poststreptococcal glomerulonephritis represent only the end result of glomerular damage inflicted at onset or whether a mechanism exists for continuing glomerular damage. We present here the clinical and morphologic features of six patients (of the original 126) who have been observed to advance to renal failure or uremia on continued follow-up over periods ranging from two to 12 years after remission of the initial manifestations. The course taken by these patients demonstrates that progressive disease does, in fact, occur in poststreptococcal glomerulonephritis after subsidence of the early proliferative changes.

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Methods

The six patients, four men and two women 28 to 47 years of age, were studied at onset of poststreptococcal glomerulonephritis on the Medical Wards of Bellevue Hospital and the Manhattan Veterans Administration Hospital and subsequently in the Hypertension and Nephritis Clinic of Bellevue Hospital. Their initial manifestations were typical of acute glomerulonephritis, and all had serologic evidence of an antecedent Group A beta-hemolytic streptococcal infection.

Renal-biopsy specimens were studied by light, immunofluorescence and electron microscopy as previously described.[1]

Glomerular lesions were evaluated histologically for diffuse proliferation according to the following grading system: Grade 0, normal cellularity in all glomeruli; Grade I, increased nuclei in some or all mesangial regions; Grade II, mesangial-cell proliferation and mild endothelial-cell proliferation, with occlusion of occasional peripheral capillary lumens; Grade III, mesangial-cell and endothelial-cell proliferation occluding up to 50 per cent of capillary lumens; Grade IV, proliferation of mesangial and endothelial cells, with occlusion of most capillary lumens, with or without occasional small