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Vitamin C as a Preventive Medicine against Common Colds in Children

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ABSTRACT. During 7 weeks in the spring of 1973 a double-blind pilot study on 172 children in the age group 8–9 was carried out to test the possible effect of 1 000 mg vitamin C daily as a prophylactic agent against common colds. During the autumn of 1973, a main study was carried out on 642 children of the same age. The investigations had the same pattern and lasted for 3 months. Both studies have been processed on the same principles. The results were somewhat divergent but, like previously published studies on children, seemed to indicate that the duration and severity of the colds were reduced while, on the other hand, the incidence remained unaltered or indeed increased. The total number of days of upper respiratory tract infection was smaller for the vitamin C group only in the pilot study (not in the main study). No proven biochemical effects were obtained. Preventive treatment of healthy children with vitamin C in large doses thus had no definitely proved effect against colds.

INTRODUCTION

Earlier studies (24, 25, 31) on the effects of vitamin C on common colds have led to varying conclusions. Since Linus Pauling stated that there was sufficient proof of the good effects of vitamin C against common colds (20, 21, 22), the interest in vitamin C's possible effects in this connection has again increased. Several researchers have thought that they could confirm an effect of vitamin C against upper respiratory tract infection at large doses (1, 2, 3, 6, 8, 12, 32, 33, 34, 35), while others have not found such an effect (4, 5, 26). The results have, however, been difficult to interpret, and further studies are called for (36, 37, 38). For that reason a study was carried out in 1973 on school children in Linköping on the questions: "Has vitamin C in large doses any preventive effect against common colds in children?", and "Is it possible to establish any biochemical effects from such administration?"

SUBJECTS AND METHODS

The investigation consisted of a pilot study and a main study. The *pilot study* took place over 7 weeks March–April 1973 at 2 schools in Linköping, situated in a district with many children and known to be high in frequency of infections. Ten classes in form 2–3 took part. Of 207 pupils asked, 172 took part from the start, and of those 158 completed the investigation (Table I). Then the *main study* was carried out during September–December 1973 along the same lines. Of 92 classes in forms 2–3 in Linköping which had not taken part in the pilot study, 50 were chosen at random. Of these 36 took part, while in the remaining 14 classes the teachers either would not or could not participate. The classes belonged to 15 schools spread all over Linköping. Of 719 pupils asked, 642 took part, and of those 615 completed the study (Table I). In both studies, permission was obtained from the school authorities, teachers and representatives of the health authorities. All school children and teachers were informed orally by the authors on the layout of the study and its aim. The children's parents were informed by letter and also had to give their written consent to the children's participation. The parents also gave information on any illnesses of their children such as allergies, asthma, diabetes mellitus, kidney disease and other illnesses. Information was also obtained on the number of siblings and the degree of daily contact with infants. Children from vegetarian families were excluded.

Every class was divided at random into two groups. Background variables were divided at random so that the groups became nearly identical (Table II). In one of the groups the children received daily a fizzy tablet which contained 1 000 mg vitamin C; in the other group the fizzy tablet looked and tasted the same but contained 30 mg vitamin C in the spring study and 10 mg in the autumn study. The fizzy tablets were handed out on school days by the teachers, dissolved in water and taken by all during one of the first lessons of the day. On other days, i.e. holidays, weekends and days off sick, the children's fizzy tablets were given in the home. The children were told (by

Table I. *Sex and age compositions of various vitamin C dosage groups*

	Pilot study March/April 1973 Vitamin C		Main study Sept./Dec. 1973 Vitamin C		Laboratory group Vitamin C	
	30 mg	1 000 mg	10 mg	1 000 mg	10 mg	1 000 mg
Total no.	78	80	311	304	78	83
Sex						
Males	42	41	155	161	36	41
Females	36	39	156	143	42	42
Year of birth						
1962	2	2				
1963	23	29	7	6	2	2
1964	53	49	174	174	58	64
1965			130	122	18	17
1966				2		
Average age at start	9.55	9.61	9.31	9.31	9.49	9.53

their parents as well) not to eat any other vitamin tablets containing vitamin C during the test.

Both studies were carried out totally double blind. Teachers and parents noted on special forms in parallel the occurrence of various cold symptoms, other illnesses and any absence from school (Table III). Some variables which were used in the pilot study gave so little information that they were not used in the main study. The teachers' notes were supplemented by those made by the parents, whereupon the information was collated, the code used decoded and the material processed statistically.[1] As the basis of the statistical processing the following firm definitions were made of the different infection variables which parents and teachers had noted:

(*a*) Cold symptoms from the nose (runny nose and/or sneezing and/or stuffed nose), sore throat and cough: The number of days with a cold were counted as a continuous period if they were noted down as symptom-free for up to a maximum period of 2 days at a time.

(*b*) Temperature from upper respiratory tract infection or from other illness, general symptoms (i.e. "feeling bad", "muscle ache", "heaviness in the head"): Only days noted as with symptoms were counted, i.e. the 2-day symptom-free were not counted.

(*c*) Upper respiratory tract infection: A continuous period, including up to 2 days symptom-free, showing the following symptoms: Runny nose, stuffed nose or sneezing + cough, sore throat, general symptoms, temperature or absence from school because of infection in upper respiratory tract.

(*d*) Active infection in upper respiratory tract: A continuous period, including up to 2 days symptom-free, during which at least 2 symptoms of upper respiratory tract infection (see above) have been noted occurring together. In a continuous upper respiratory tract infection, however, the occurrence of "active upper respiratory tract infection" is not counted as more than one period.

[1] Statistical calculations were carried out by Mr Lars Lindvall, Institute of Mathematics, Linköping University.

(*e*) Upper respiratory tract infection with general effect: The days counted under "Upper respiratory tract infection" (*c*) and also marked "general symptoms" and/or "temperature".

(*f*) Absence from school for other reasons: Absence from school is always considered to be "for other reasons" when that is so noted, regardless of whether symptoms of a cold were also present.

(*g*) Absence from school because of other illness: The number of days is given when according to the notes another illness was the reason for absence from school, e.g. measles even if symptoms of a cold were also noted.

(*h*) Absence from school because of upper respiratory tract infection: Marked days of absence during upper respiratory tract infection when no other illness or cause is given.

The main study was supplemented by certain biochemical studies. Of the 36 classes taking part 10, divided among 7 schools, were chosen at random. Of 212 pupils in those classes 161 (Table I) gave, with their own and their parents' agreement vein blood samples and urine samples taken on an empty stomach during the period 26 November–12 December 1973. The following were determined: haemoglobin, haematocrit, red cell count, MCV, MCH, MCHC, serum iron, transferrin, cholesterol, triglycerides, blood sugar, serum ascorbic acid, prealbumin, albumin, alpha$_1$antichymotrypsin, orosomucoid, alpha$_1$antitrypsin, haptoglobin, alpha$_2$macroglobulin, C3 (beta$_{1c}$), fibrinogen, IgG, IgA, IgM, IgE and haemopexin. Quantitative determination of C3 (beta$_{1c}$) and IgM was carried out with radial immunodiffusion according to Mancini et al. (17). IgE was determined with the Phadebas IgE test, Pharmacia 1971 (13, 23). Other proteins were determined by Laurell's electrophoresis method (15). The remaining analyses were made according to standard methods.

In 52 cases chosen at random the number of white cells was determined, and also the percentage of polymorphonuclear leucocytes, the ascorbic acid in the leucocytes, and the hexose monophosphate shunt activity

Table II. *Background variables for those who completed the study*

	Pilot study March/April 1973 Vitamin C		Main study Sept./Dec. 1973 Vitamin C		Laboratory group Vitamin C	
	30 mg	1 000 mg	10 mg	1 000 mg	10 mg	1 000 mg
No. of subjects with younger siblings	52	46	149	149	42	48
Daily contact with small children	56	51	179	175	42	48
Suffers from allergic disease or allergic conditions	2	1	21	16	2	3
Has previously had hay fever	0	0	10	7	1	2
Has previously had asthma or asthmatic bronchitis	1	4	14	14	1	1
Other illnesses	0	0	7	5	3	0

of the leucocytes, which were carried out at the Microbiological Institute of Linköping University according to a standard procedure (28).

Urine samples were analysed for the following: pH, protein, glucose. The sediment was examined for leucocyte count, clumped leucocytes, red cell count, epithelium, urates, oxalates, other salts, and cylinders.

RESULTS

Of the 172 children who started in the pilot study 14 dropped out. As reason 3 gave side effects (Table IV) and the others were excluded because of incomplete or interrupted noting down of symptoms because the children moved to another school or got tired of the medication. For the same reason, 27 children dropped out of the initial 642 in the main study, but only 2 because of side effects which were few and slight in type (Table IV).

In Table V the incidence and duration of the 3 variables which were judged to be the most interesting are shown: cold symptoms in the nose, infection in the upper respiratory tract and absence from school because of upper respiratory tract infection. The table shows that there was no difference between the groups in number which remained totally free from the various symptoms. With regard to the incidence of cold symptoms in the nose and upper respiratory tract infection respectively there were no significant differences either but perhaps a hint of a tendency towards an increased incidence in those who had taken 1 000 mg vitamin C. On the other hand, the duration of the symptoms was longer in the patients who had received placebo compared with the group who had 1 000 mg vitamin C. The severity of the infection which could be expected to be reflected somewhat in the absence from school because of upper respiratory tract infection, varied between the groups especially as to duration, which was longer among those who had the placebo.

The means and the variances are for the two groups, i.e. the placebo group (30 and 10 mg) as against the vitamin group (1 000 mg), while the *t*-value is based on dividing each class at random into two groups. The *t*-values are thus based on combined intraclass differences and intraclass variance. The two-tailed *P* values have been given, as it cannot be excluded that vitamin C may have a negative effect instead of a positive one.

Incidence and duration for all cold variables are reported graphically in Figs. 1–3. With regard to the frequency with which the subjects were entirely free from the various symptoms, the curves in both studies are almost identical for placebo and vitamin groups. The same applies to incidence, while there is a tendency towards longer duration for those receiving placebo. The difference was most marked in the pilot study, with regard to sore throat (variable 3) ($P<0.05$) and upper respiratory tract infection (variable 4) ($P<0.01$). A significant difference also appeared during the main study in the duration of "absence from school" (variable 10) ($P<0.05$). The pattern remains unchanged when, instead of comparing the entire 30 mg or 10 mg daily group with the 1 000 mg group, subgroups are analysed, such as boys, girls, children with no history of al-

Table III. *Variables recorded by parents and teachers*
× shows those who recorded the variable

Variable recorded	Pilot study		Main study	
	Parents	Teacher	Parents	Teacher
Runny nose, thin, watery	×	×	×	×
Runny nose, thick, stuffy (grey, grey-yellow, yellow-green)	×	×	×	×
Stuffed nose	×		×	
Sneezing	×		×	
Sore throat	×	×	×	×
Cough	×	×	×	×
Temperature	×	×	×	
"Feeling bad", muscle ache, "heavy in the head"	×		×	
Absence from school	×	×	×	×
Visit to doctor (when? For what?)	×		×	
Suspected side effects	×		×	
Cold sweat, "shivers"	×			
Staying in bed	×			
Ear infection	×			
Sinusitis	×			
Tonsillitis	×			
Bronchitis	×			
Pneumonia	×			
Medicines	×			
Other illnesses			×	
Other reason for absence from school			×	
Generally affected		×		×
Off P.T. (physical training)		×		
School work above/below usual level		×		

lergic diseases, or if one compares children with high and low vitamin C levels in serum or leucocytes.

There was a pronounced difference in serum ascorbic acid between those who received 10 mg and those who received 1 000 mg vitamin C daily (86.4±19.1 and 107.0±19.6 mg/dl, $P<0.001$), but on the other hand there was no difference in the leucocyte ascorbic acid levels (17.0±5.3 and 17.4±6.9). There was, however, a significant positive correla-

Table IV. *Suspected side effects recorded by parents or teacher*

Symptom	Pilot study				Main study				Total
	30 mg		1 000 mg		30 mg		1 000 mg		
	N	%	*N*	%	*N*	%	*N*	%	*N*
Stomach pains	2	2.6[b]	–	–	–	–	1	0.3	3
Skin rash	1	1.3	1	1.3	3	1.0[a]	4	1.3	9
Headache	–	–	1	1.3[a]	–	–	–	–	1
Diarrhoea	–	–	–	–	1	0.3	1	0.3	2
Nausea	–	–	–	–	–	–	3	1.9[a]	3
	3	3.8	2	2.5	4	1.3	9	3.0	18

[a] One subject withdrew.
[b] Two subjects withdrew because of side effects.

Table V. *Occurrence of certain cold variables in control group and vitamin C group*

	Totally free from symptoms			Incidence (no. of cases/person)		Duration (no. of days/period)		Incidence × duration (no. of days)	
	N	%	*t*	M±S.D.	*t*	M±S.D.	*t*	M±S.D.	*t*
Pilot study (30 mg, *N*=78; 1 000 mg, *N*=80)									
Cold symptoms from the nose									
30 mg	17	22	0.87	1.36±1.21	−1.59	7.61±8.07	1.82	9.00±9.80	0.46
1 000 mg	13	16		1.63±1.15		5.39±4.88		8.35±8.30	
Upper respiratory tract infection									
30 mg	34	44	0.68	0.71±0.72	−0.72	14.53±9.75	3.05**	9.50±11.49	1.65
1 000 mg	31	39		0.78±0.75		8.90±5.96		6.94±8.55	
Absence from school because of upper respiratory tract infection									
30 mg	54	69	−0.39	0.35±0.55	0.80	3.87±3.45	1.44	1.37±3.19	1.58
1 000 mg	58	73		0.28±0.45		2.68±1.88		0.74±1.55	
Main study (10 mg, *N*=311; 1 000 mg, *N*=304)									
Cold symptoms from the nose									
10 mg	53	17	0.37	2.00±1.80	−1.41	5.67±7.89	−0.67	12.05±15.87	−0.47
1 000 mg	49	16		2.16±1.63		6.04±5.47		12.53±14.00	
Upper respiratory tract infection									
10 mg	71	23	−0.35	1.28±1.03	−1.38	10.14±11.60	0.56	12.50±16.71	−0.66
1 000 mg	74	24		1.39±1.11		9.54±8.65		13.20±16.28	
Absence from school because of upper respiratory tract infection									
10 mg	146	47	0.04	0.72±0.82	−0.08	3.22±2.38	2.42*	2.61±6.95	1.48
1 000 mg	142	46		0.74±0.86		2.77±1.74		2.07±2.87	

*=$P<0.05$. **=$P<0.01$.

tion between the hexose monophosphate shunt activity in the leucocyte and the leucocyte ascorbic acid level. This will be further discussed in another connection.

With regard to all other laboratory variables mentioned on page 92, there were no significant differences between the placebo group and the vitamin group, nor was there any correlation between the serum ascorbic acid level and the other laboratory variables.

DISCUSSION

Many of the sources of error that can be found in studies of this type we have sought to avoid. We chose an age group in which honest cooperation can be expected from the children and where the interest in simulating symptoms can be expected to be fairly low. The classes were divided at random so that an epidemic of colds in one class would not distort the results and the teacher's judgement could not give a systematic error. Most subjects cannot be under daily medical supervision, and they must produce some type of daily report themselves, or by close relatives. In the present case, the teacher and parents complement each other by recording the symptoms. There was some check on whether the subjects took the tablets because the children were given them by their teacher and consumed them in his presence. A further check was provided by determination of ascorbic acid levels in

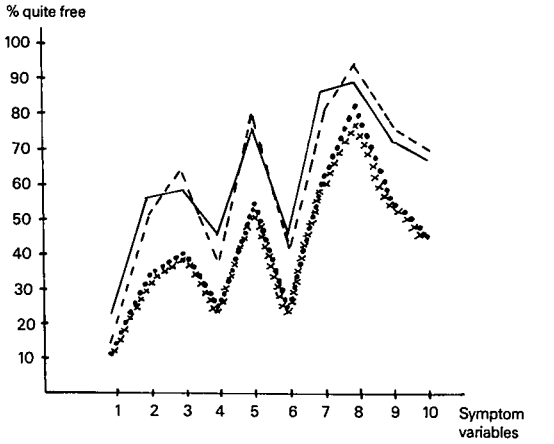

Fig. 1. Subjects indicated by the register as quite free from respiratory symptoms. —=Placebo (30 mg) pilot study; ---=vitamin C (1 000 mg) pilot study; ×××=placebo (10 mg) main study; · · ·=vitamin C (1 000 mg) main study.

Note: In Figs. 1–3 the following figures mean: 1, cold symptoms in nose; 2, cough; 3, sore throat; 4, upper respiratory tract infection; 5, upper respiratory tract infection with general effect; 6, active upper respiratory tract infection; 7, temperature because of upper respiratory tract infection; 8, temperature from other illness; 9, at home because of other illness; 10, at home because of upper respiratory tract infection.

serum and leucocytes in a group of children chosen at random. 1–2 g daily has been considered a suitable dose for an adult in similar studies (12, 34), and so 1 g daily for children of the age 9–10 was considered adequate, and at the same time that dose can be assumed to be totally atoxic (14, 16). The placebo tablets contained a small dose of vitamin C, as the aim of the study was to investigate whether large doses of vitamin C have any prophylactic effect against colds as compared with the low doses

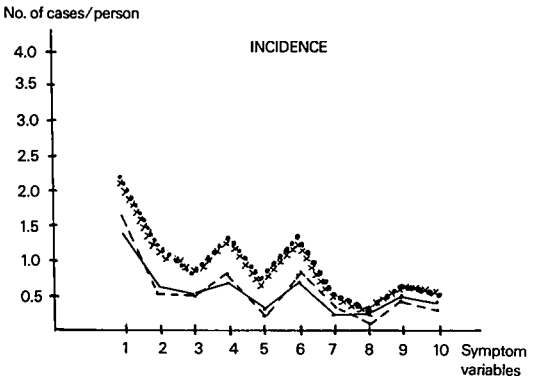

Fig. 2. No. of cases per person of each symptom. Symbols as in Fig. 1.

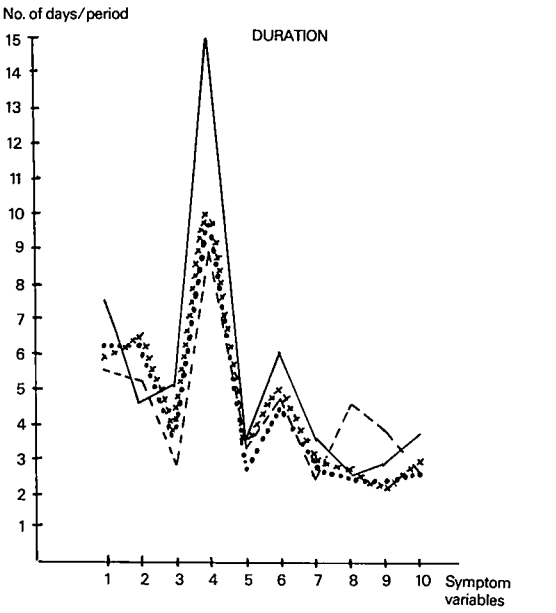

Fig. 3. Number of days per symptom period. Symbols as in Fig. 1.

which are considered to be the basic need. During the spring, 30 mg was considered to satisfy this basic need of vitamin C, while only 10 mg was in the placebo tablets in the autumn, when it could be assumed that the vitamin C content in Swedish food is adequate.

There is no generally accepted definition of "common cold". In this study certain definite criteria have been determined. Of those, certain variables, such as general effect, temperature and absence from school have been considered to reflect an increasing degree of severity. As the statistical calculations were made on a large number of variables and many groups were compared, it cannot be ruled out that certain statistically significant differences result from chance.

Several earlier studies (1, 2, 8, 33) suggest that the duration and also the severity insofar as that can be assessed, are slightly reduced, while the incidence either increases or remains unaltered. Thus Wilson et al. (33, 34, 35) found reduced severity and intensity, but on the other hand significantly increased incidence. In all groups compared in their studies, a tendency was found to increased incidence of upper respiratory tract infections, while girls who received 200 mg vitamin C daily had reduced severity and intensity, mainly in catarrh symptoms, as compared with placebo. Coulehan et

al. (8) did not find a reduced incidence either, but rather a reduced duration. The effect seemed mainly to be related to local catarrh symptoms, whereas Anderson et al. (1) found for adults that there was no detectable effect on catarrh symptoms but some on general symptoms, although these were not definitely related only to colds. This latter study is, however, not entirely comparable with others, as they in that study were investigating preventive and therapeutic effects at the same time. In a later study by Anderson et al. (2), the results indicated reduced severity but no differences in incidence or duration.

The results from our two studies are partly conflicting. The correlations are weak and the significances obtained may to some extent be a consequence of the fact that so many analyses are performed. However, in concordance with earlier studies the results suggest that the duration and severity of the colds may be reduced by vitamin C in large doses while the incidence remains unaltered or increases.

An improved curative power could possibly explain a shortened duration. Vitamin C is needed for wound healing (9, 30). The need for vitamin C increases under stress (27). There are studies which indicate that vitamin C improves fibrinoblast performance (11), reduces the risk of thrombosis (29) and possibly also improves leucocyte bactericidal activity (10, 12, 18).

Preventive treatment perhaps causes increased metabolism and excretion of ascorbic acid to such a degree that the tissue levels drop again after a while (36). In the present case, there was no difference in leucocyte vitamin C levels after 2 months' daily consumption of 10 mg and 1 000 mg vitamin C respectively. A therapeutically oriented investigation could possibly be preferable with the aim of being able quickly to increase the serum and tissue level of ascorbic acid at the beginning of an infection. It would be of special interest to study certain particularly infection-prone groups, such as those with allergies and diabetes, or groups with low levels of vitamin C in the body such as old people, alcoholics or newly operated upon patients.

From the laboratory point of view a statistically significant connection was noted between the amount of ascorbic acid in leucocytes and hexose monophosphate shunt activity, which is important for the bactericidal activity of the leucocytes, which confirms earlier findings in vitro (7, 10). We have not found any other biochemical effects from large doses of vitamin C measured with the variables we have examined. This will be commented upon in greater detail in another connection.

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