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A Study of Vitamin C Levels in the Aged and Subsequent Mortality

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Although the role of vitamin C in the prevention of scurvy has been known for more than 2 centuries, it is only in recent years that deficiency has been suspected to play a part in the aetiology of other clinical conditions such as wound healing, in anaemia [1, 2] and with less certainty in the collagen diseases [3], in lowered resistance to infection and in the multiple pathological conditions found in the aged. Beyond this, it has been postulated that low vitamin C levels may aggravate physical and mental disorders in the aged and may be a contributory factor to the lethargy, generalised aches and pains, skin disorders and blood vessel fragility commonly found in the aged [4, 8].

Dietary intake of vitamin C in old people has been found to be low by many observers. This is true of those in hospital and welfare accommodation as well as of those living at home. In those living at home income appears to be the main determining factor in this nutritional defect [5, 16]. In the institutional group the fault lies mainly in methods of preparation of food [6].

Mean plasma and buffy layer levels of vitamin C have been found to be lower in the elderly than in the younger age groups [7], lower in winter than in summer [9], in smokers than in non-smokers [7, 10] and lower in men than in women [7, 11].

Attempts have been made to assess the effects of vitamin C supplements on morbidity in the aged. Blood levels can undoubtedly be raised by oral administration of ascorbic acid [12], but the effects on such conditions as senile purpura and sublingual petechial has been found to be negligible. Brocklehusrt *et al.* [4] have carried out a

controlled clinical trial on 80 long-stay patients suffering mainly from cerebrovascular degeneration, stroke and arteriosclerotic dementia. The object was to discover whether low vitamin levels were associated with clinical signs. Unfortunately multiple vitamin therapy was used and it is difficult to attribute the clinical improvement seen in the actively-treated group to one specific vitamin. The principal clinical manifestations attributed to vitamin deficiency were cheilosis, angular stomatitis, glossitis and follicular hyperkeratosis of the skin. Bedsores apparently healed more rapidly in the treated groups. At the end of the trial 9 out of 29 untreated patients showed bedsores while only 2 out of 33 treated patients were similarly affected.

The recommended daily intake of vitamin C for adults is 30 mg in this country [17] and 60 mg in the United States of America [18]. O'SULLIVAN *et al.* [5] in Cork have found that a considerable proportion of elderly subjects receive less than this. Similar results have been found in this country [13, 16]. The question has, however, been raised as to whether the minimum recommended is too low.

STONE [14] has pointed out that the primates including man and also the guinea pig are almost alone in lacking the liver enzyme L-Gulonolactone oxidase which enables most mammals to synthesise ascorbic acid from glucose. Man, therefore, is one of the few mammals dependent on exogenous sources of ascorbic acid for survival. Over the centuries his physiology has adapted to very low intakes of vitamin C. He obtains milligrams from food while the synthesis of an equivalent sized mammal is measured in grams. The concept of ascorbic acid as a vitamin has led investigators to regard low dose levels as appropriate whereas the genetic defect concept encourages compensating for the *in vivo* production paralleled in mammals.

The investigation recorded in this paper was undertaken to determine vitamin C levels in old people admitted to an acute geriatric unit in 1968.

Those involved were a random selection from patients admitted during the period May to December, 1968. The sample is representative of total admissions for that period. This is proved by the almost identical age distribution, sex ratio, and mortality rate in the 2 groups. Sex ratio on all new admissions was male: female 31.5–68.5 with a 4-week mortality rate of 31%. In the sample the similar percentage figures were male: female 31.4–68.6 with a 4-week mortality of 30%. They were also evenly matched as regards age distribution. In the

Table I

	Under 60	61–70	71–80	81–90	Over 90
Number of patients	3	19	68	59	10
Mean vitamin C $\mu g/10^8$ WBC	20.0	28.1	22.6	20.1	24.0

sample 137 of 159 patients (86.2%) were over 70. The corresponding figure for total admissions (534 patients) for the same period was 446 (85.4%).

On admission vitamin C was estimated on early morning samples of venous blood by the method of DENSON and BOWERS [15]. This is a 'buffy layer' estimation which involves both leucocytes and platelets but is generally expressed in terms of 10^8/WBC and this method of expressing results is followed throughout in this paper. The mean leucocyte vitamin C level taking all 159 patients in the sample was 22.2 $\mu g/10^8$ WBC. The mean for the males was 20.0 μg (50 cases) and that for the females 23.3 μg (109 cases). There were no consistent significant differences between the mean vitamin C levels of the different age groups.

The vast majority (128) had levels between 10 and 40 $\mu g/10^8$ WBC. No significant difference was found between those living alone or with spouse or with relatives. An attempt was made to correlate vitamin C levels with intake and, as expected, a high proportion of those with a 'poor' dietetic history showed rather low vitamin C levels but dietetic history being notoriously difficult no great significance is attached to this finding.

Of the 159 patients, 50 were admitted to the psycho-geriatric wards, i.e., some form of psychiatric disturbance was one of the presenting features of the illness. The mean vitamin C level for this group was almost the same (22.9 μg) as that for the total sample.

Since vitamin C values are expressed in terms of 10^8 leucocytes it seems relevant to find out whether the leucocyte count had any direct bearing on vitamin C levels. No significant relationship was found. The group showing the lowest levels of vitamin C, i.e., below 10 $\mu g/10^8$ WBC had a mean WBC at 10,210 and the group having the highest, i.e., above 40 $\mu g/10^8$ WBC, a mean WBC at 9,007/cm^3.

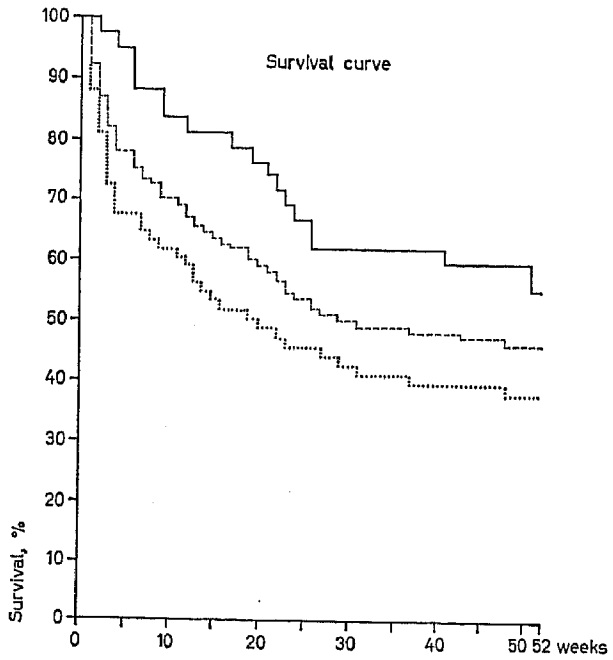

Fig. 1. Survival curve in 109 female patients (– – –). 41 patients with vitamin C above 25 $\mu g/10^8$ cells (——). 68 patients with vitamin C below 25 $\mu g/10^8$ cells (....).

The patients in this series were studied with regard to their ultimate fate, i.e., death or survival. The most interesting finding to emerge was that there was a significant relationship between leucocyte vitamin C levels on admission to hospital and expectation of life.

The striking finding here is the difference between the low (below 12 μg) and the high (over 25 μg) groups which is significant at the 1-per cent level $\chi^2=10.36$.

In a slightly different manner survival may be studied by including the whole group and by looking at the outcome in males and females separately with the aid of survival curves. In this case the natural division between the high and low vitamin groups is found to be 25 μg. This method makes maximal use of the statistical information available.

The graph sets out unbiased estimates of the survival curves for the high (>25 μg) and the low (<25 μg) vitamin C levels in the female patients. It is calculated by working out each week the death rate among those known to be surviving each week of the trial and does

Table II. Mortality at 4 weeks following admission

Mean vitamine C level	Below 12 μg	12–18.5 μg	18.6–25 μg	Over 25 μg
Number of sample	32	38	40	49
Number of deaths	14	14	10	5
Mortality as % of samples	47	37	25	10

not involve any assumption about the statistical distribution of the survival time of these patients. Using a test devised by PETO and PETO [19] the difference between the curves of the high and low vitamin C groups is significant at the 1-per cent level.

The data about the male patients has to be analysed separately because of differences between the 2 sexes in vitamin C level and mortality. The survival curve again showed a higher early mortality for the lower vitamin C group. However, the number of male patients with vitamin C levels above 25 μg was very small and the differences were far from statistically significant.

Discussion

One possible explanation of the association of low vitamin C levels with high mortality is that these levels are a manifestation of the general severity of the patients illness or of some special clinical features. The case records of the high and low vitamin groups (over 25 μg and under 12 μg) have, therefore, been examined and clinical features of the 2 groups compared. Cerebrovascular disease was about equal, 44% in the low group, 39% in the high. Congestive heart failure was a feature in greater or less degree of 8 cases (25%) in the low group and 11 cases (25%) in the high. There were actually more cases of cancer (including leukaemia) in the high vitamin C group (9 in 49 cases, 18%) than in the low (3 in 32 cases, 9%), but the numbers involved are too small to be significant. The mean vitamin C level of all cancer cases was marginally higher (25 μg) than that for the whole group (22.2 μg).

The low vitamin group (under 12 μg) included 5 who had sustained fractures within 12 months prior to admission (16%). There was no tohisry of recent fractures in the high vitamingro up (over 25 μg). In

view of the probable role of vitamin C in the manufacture of collagen tissue this finding deserves further investigation. There were 9 cases of diabetes in the high vitamin group (18%) as compared with 2 cases in the low (6%). This finding is presumably related to the higher vitamin content of the diabetic diet prior to admission.

Infective illness was so generalised in both groups that it is difficult to draw comparative conclusions. There was a higher incidence of detected urinary infection in the high vitamin group (>25 μg) than in the low (<12 μg) but this is probably related to the longer survival time, with consequent greater opportunity for investigation. Rather more respiratory infection was noted in the low group. Some of this was terminal in patients who died within a few days of admission.

The overall impression gained from a study of the case records is that there was surprisingly little difference in the clinical features of the 2 groups, but that the overall severity of the illness appeared to be somewhat greater in the low group than in the high.

Conclusion

This investigation strongly suggests that low vitamin C levels in old people admitted to geriatric hospitals are associated with an increased mortality particularly within 4 weeks of admission. It would not appear that this increase is explained by the association of such levels with any specific clinical features of the patients illness. It, therefore, seems necessary to decide whether raising the blood levels of vitamin C in such patients will materially affect the outcome. It is, of course, well known that these levels can readily be raised by the administration of ascorbic acid.

The further investigation which has now been commenced is designed to determine the effect of oral administration of a daily dose of 200 mg of ascorbic acid to a similar group of patients to that involved in this pilot survey.

This trial which commenced in February, 1970, and to which 400 patients have to date been admitted, is double blind. No patient or any member of the medical staff or nursing staff who is involved in assessing or treating patients knows which patient is having vitamin C and which placebo. Results of vitamin C estimations are not seen by the medical or nursing staff but are forewarded to the Department of

Applied Statistics of Reading University, whose staff guide the conduct of the trial and assist with the analysis of the results.

In a group of patients of such advanced age and with a high incidence of multiple pathological features, in whom the expectation of life is very short, it is probable that a prolonged trial with involvement of a large number of patients will be necessary before a conclusive answer can be obtained as to the effect of vitamin C administration. Such an investigation, however, seems justified not only in view of its possible application to the treatment of hospital patients but to the possibility of its wider application to the prophylactic care of old people. We are not aware of any similar trial designed primarily to test the effect of vitamin C administration on subsequent mortality.

When completed this trial will be the subject of a further publication.

Summary

In a survey of 159 patients admitted to an acute geriatric unit in 1968, it was found that those with low vitamin C levels (<12 $\mu g/10^8$ WBC) had a significantly higher mortality within 4 weeks of admission than those with a high level (>25 $\mu g/10^8$ WBC).

Possible reasons for this finding are discussed.

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