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The clinical and Biochemical Effects of Vitamin C Supplementation in Short-stay Hospitalized Geriatric Patients

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Summary:

1. A double-blind placebo trial has been undertaken on 199 elderly patients admitted to an "acute" geriatric assessment ward. Clinical and biochemical assessment was made on admission (0) and at 2, 4, 8, 16 and 24 weeks (after admission). Ninety-four patients were supplemented with vitamin C (200 mg per day) and 105 had placebo tablets. Biochemical assessment included estimations of plasma and leucocyte (buffy layer) vitamin C, plasma folate, vitamin B₁₂, cortisol and total white cell count.

2. Plasma and leucocyte vitamin C levels remained low for several weeks in a substantial proportion of the non-supplemented patients, whereas low levels were virtually eliminated in the supplemented group.

3. The results from this study suggest that the leucocyte vitamin C levels may give some indication of prognosis in this category of patients (ie. "acute" geriatric admissions) as evidenced by:

i) the significantly higher mortality rate during the trial period of patients who started with low initial leucocyte vitamin C levels compared with those starting with higher levels, despite similar mean initial "severity of illness scores" between the two groups.

ii) the marked trend, amongst placebo subjects, for those commencing the study with higher leucocyte vitamin C levels to fare better, in terms of progression to "well", than those starting with low levels.

4. Amongst subjects starting with low leucocyte vitamin C levels, there was a trend for "vitamin C" subjects to have fared better by 8 weeks than "placebo" subjects. This again occurred despite similar mean initial "severity scores" between the two groups.

5. Amongst subjects diagnosed with respiratory infections there was some tendency for supplemented patients to fare better than unsupplemented patients.

6. Low leucocyte vitamin C levels, on admission, appear to be predictive of poor subsequent prognosis in elderly hospitalised patients. Results from this trial suggest that supplementation with a moderate dose of vitamin C may improve this prognosis and larger trials with greater numbers appear to be merited to confirm or deny this hypothesis.

Introduction

Low plasma and leucocyte vitamin C levels are common in institutionalized elderly people in the United Kingdom [ANDREWS *et al.*, 1966; BROCKLEHURST *et al.*, 1968; BATES *et al.*, 1972; VIR, 1976; SCHORAH *et al.*, 1981]. The significance of low vitamin C status in man remains a matter of controversy as pointed out in a recent review of the subject [SCHORAH, 1981]. However relatively few vitamin C supplementation trials have been performed on hospitalized patients. One of the largest of these trials [WILSON *et al.*, 1973] reported that in vitamin C supplemented patients, there was a lower four-week mortality rate in patients whose leucocyte levels responded to the supplementation than in those who did not; also that low vitamin C levels in the female were associated with an increased four-week mortality risk but that vitamin C supplementation of 200 mg daily did not significantly influence this mortality. Another study [SCHORAH *et al.*, 1981] reported some clinical benefit of vitamin C supplementation over a 2-month period in long-stay hospitalized elderly patients who had initially very low blood levels.

The trial described in this paper was an attempt to investigate whether vitamin C supplementation had any effect not just on mortality risk but on the rate of clinical progress to well of elderly in-patients monitored at regular intervals up to 24 weeks after admission.

Patients and Methods

A double-blind trial was performed over a period of 16 months in order to assess whether there would be any clinical or biochemical response to Vitamin C supplementation in 199 subjects (101 females, 98 males) admitted to a geriatric assessment ward.

Clinical and biochemical assessment was carried out on admission (0) and at 2, 4, 8, 16 and 24 weeks (after admission). Patients who improved and left hospital were followed up by out-patient appointments.

On admission, the condition of each patient was assessed by one clinician (GA) as "less severe" (LS), "moderately severe" (MS) or "very severe" (VS) in relation particularly to physical illness. A blood sample was taken and analysed at each interval for plasma vitamin C, and buffy layer vitamin C by the method of DENSON and BOWERS [1961]. Full blood counts were also performed at each interval, and at 0 and 4 weeks analyses were carried out for folic acid, vitamin B₁₂ and cortisol.

The six groups of patients, stratified according to sex and severity of illness, were randomized to receive either placebo or 200 mg vitamin C for the duration of the study. However, only 6 out of the 199 patients were categorised initially as "very severe" and thus most fell into the categories "moderately severe" (112 patients) or "less severe" (81 patients). Supplementation was started after the initial blood sample had been taken.

The results have been analysed using a modified version of "survival analysis", a statistical technique which has been described previously [PETO *et al*, 1977]. The technique has been adapted such that the "terminal event" has been taken as a progression to clinical assessment category "well". The cumulative probability of progressing to "well" by the various time intervals has been calculated both overall and in various sub-groups. This method of analysis attempts to correct for "missing values" which in this case refers to occasions when a patient's interval assessment of illness severity was not performed, for unknown reasons, *ie.* when a patient is lost to follow-up but not because he or she has died. Therefore it allows not only for those who are lost to follow-up during the trial and for the rest of the trial but also for those who are lost during, but return before the end of the trial.

Results and Discussion

a) Main Clinical and Biochemical Findings

Table I shows the numbers of patients who commenced the trial, died, went missing or progressed to well during the trial. The results are shown for supplemented and unsupplemented patients.

Tab. I: Overall numbers (percentages) of patients who started the trial, died, were lost to follow-up or progressed to "well" by the end of the trial.

| | No starting the trial | No (%) who died | No (%) who were lost follow-up | No (%) who progressed to assessment category "well" |
|---|-----------------------|-----------------|--------------------------------|---|
| C | 94 | 33 (35.1) | 25 (26.6) | 34 (36.2) |
| P | 105 | 28 (26.7) | 34 (32.4) | 39 (37.1) |

C = supplemented patients (males and females combined)

P = unsupplemented patients (placebo)

Table II shows the commonest diagnoses of the patients admitted onto the trial and the figures given for a particular disease coding include any patient who had that coding whether it was recorded as the primary, secondary or tertiary diagnoses. The single most common reason for admission was for respiratory infections affecting about one-quarter of the subjects on the trial.

Table III shows the mean plasma and leucocyte (buffy layer) vitamin C levels at each interval and demonstrate a clear response in the supplemented group by the 2

Tab. II: Commonest diagnoses of the patients on the trial

| Diagnosis | ICD* coding | Total No. of patients with this diagnosis | "Vitamin C" patients with this diagnosis | "Placebo" patients with this diagnosis |
|---|-------------|---|--|--|
| Respiratory infections | A89-93 | 58 | 29 | 29 |
| Heart disease (Ischaemic and other forms) | A83-84 | 35 | 14 | 21 |
| Cerebrovascular disease | A84 | 43 | 23 | 20 |
| Arthritis and spondylitis | A121 | 32 | 21 | 11 |
| Cancer (various forms) | A45-60 | 19 | 8 | 11 |

* WHO International Classification of Diseases

week interval and for the duration of the trial. They show that *mean* initial levels were not particularly low. However there was a wide spread of values and about one-third of the subjects on the trial had low plasma (less than 0.3 mg/100 ml) and leucocyte (less than 15 μ g/10⁸WBC) levels of vitamin C on admission; and whereas in the supplemented subjects these low levels were largely eliminated by week 2, there were still low levels in about one-quarter of the placebo subjects by the same interval (Table IV).

Tab. III: Mean plasma and leucocyte vitamin C levels for all subjects $m \pm s.e.$

| Interval | Vitamin C | | Placebo | | |
|--|-----------|------|---------|------|----|
| | m | s.e. | m | s.e. | |
| Plasma (mg/100 ml) | | | | | |
| 0 weeks | 0.61 | 0.07 | 0.53 | 0.06 | 98 |
| 2 weeks | 1.53 | 0.13 | 0.62 | 0.08 | 74 |
| 4 weeks | 1.50 | 0.12 | 0.68 | 0.09 | 64 |
| 8 weeks | 1.31 | 0.11 | 0.45 | 0.05 | 54 |
| 16 weeks | 1.20 | 0.10 | 0.57 | 0.09 | 44 |
| 24 weeks | 1.21 | 0.12 | 0.43 | 0.05 | 41 |
| Leucocyte (μg/10⁸WBC) | | | | | |
| 0 weeks | 35.3 | 2.9 | 30.7 | 2.8 | 93 |
| 2 weeks | 52.0 | 4.6 | 34.3 | 3.2 | 70 |
| 4 weeks | 58.7 | 4.8 | 34.0 | 3.5 | 60 |
| 8 weeks | 52.1 | 4.4 | 37.0 | 3.7 | 48 |
| 16 weeks | 62.1 | 4.9 | 37.6 | 4.6 | 46 |
| 24 weeks | 59.2 | 4.3 | 36.5 | 4.5 | 37 |

n = number of analyses

Tables IV, V and VI show that there was some persistence of these low levels in unsupplemented subjects, particularly in individuals who had low initial levels.

Tab. IV: Percentage of total remaining subjects analysed to have low leucocyte levels ($< 15 \mu\text{g}/10^9\text{WBC}$) and/or low plasma levels ($< 0.3 \text{ mg}/100 \text{ ml}$) of vitamin C at the various intervals.

| | | Assessment Interval (weeks) | | | | | |
|-----------------------|--------------------------|-----------------------------|---------|---------|---------|---------|---------|
| | | 0 | 2 | 4 | 8 | 16 | 24 |
| Vitamin C Subjects | % with $\text{Le} < 15$ | 27 (88) | 6 (62) | 3 (58) | 5 (43) | 0 (36) | 7 (27) |
| | % with $\text{Pl} < 0.3$ | 37 (86) | 2 (65) | 2 (60) | 4 (51) | 3 (38) | 6 (33) |
| Placebo Subjects | % with $\text{Le} < 15$ | 31 (94) | 26 (70) | 11 (61) | 17 (48) | 7 (46) | 19 (37) |
| | % with $\text{Pl} < 0.3$ | 33 (98) | 24 (74) | 30 (64) | 37 (54) | 27 (44) | 27 (41) |

NB Numbers in brackets refer to numbers of analyses

Tab. V: Number (%) of analysed cases at low ($\text{Le} < 15$) or higher ($\text{Le} > 15$) leucocyte levels at 2 and 4 weeks in relation to initial (wk 0) level

| | | n | 2 weeks | | 4 weeks | |
|--------------------|---|----|---------|---------|---------|----------|
| | | | < 15 | > 15 | < 15 | > 15 |
| $\text{Le} < 15$ C | | 24 | 1 (6) | 16 (94) | 0 (0) | 14 (100) |
| | P | 27 | 9 (47) | 10 (53) | 6 (38) | 10 (62) |
| $\text{Le} > 15$ C | | 64 | 3 (7) | 39 (93) | 2 (5) | 39 (95) |
| | P | 67 | 8 (17) | 39 (83) | 1 (2) | 42 (98) |

Tab. VI: Number (%) of analysed cases at low ($\text{Pl} < 0.3$) or higher ($\text{Pl} > 0.3$) leucocyte levels at 2 and 4 weeks in relation to initial (wk 0) level

| | | n | 2 weeks | | 4 weeks | |
|---------------------|---|----|---------|----------|---------|----------|
| | | | < 0.3 | > 0.3 | < 0.3 | > 0.3 |
| $\text{Pl} < 0.3$ C | | 36 | 1 (4) | 26 (96) | 0 (0) | 24 (100) |
| | P | 37 | 7 (26) | 20 (74) | 10 (45) | 12 (55) |
| $\text{Pl} > 0.3$ C | | 50 | 0 (0) | 34 (100) | 0 (0) | 31 (100) |
| | P | 59 | 9 (22) | 31 (78) | 9 (25) | 27 (75) |

With regard to clinical progress, significantly more patients who were initially categorised as "moderately severe" died during the 24-week trial period than of the "less severe" patients (Table VII). There was a slight tendency for "less severe" patients to fare better up to 4 weeks in terms of progression to well than for "moderately severe" patients but this was not statistically significant and therefore, in retrospect, categorisation proved to have been somewhat crude and mainly in terms of the assessed survival prospects.

Tab. VII: Numbers of patients who died during the trial period (vitamin C/placebo groups combined): comparison of "MS" and "LS" categories

| | Number who died | Number who survived |
|----|-----------------|---------------------|
| MS | 39 | 73 |
| LS | 18 | 63 |

$\chi^2 = 3.01$ (Adjusted value using Yates' continuity correction)
 $p < 0.10$

However one comparison which it was felt might prove interesting with regard to clinical progress was that between subjects starting the trial with low blood vitamin C levels (as previously defined) and those with higher initial levels. Appropriate analysis of the figures did indeed reveal interesting results.

There was a significantly higher mortality rate ($p < 0.05$) during the trial period of those with initially low leucocyte levels compared with those with higher levels, regardless of supplementation (Table VIII). The most obvious explanation of this would appear to be that those with low initial levels were more severely ill and therefore would be expected to have a higher mortality risk; and that the low leucocyte levels were merely the result and a reflection of their severity of illness as suggested by the study of WILSON *et al.* [1973]. However the mean illness "severity scores" were very similar between "low" and "higher" level subjects (Table IX), a finding which is somewhat surprising and which throws doubt on the above explanation. These results suggest that leucocyte vitamin C level may have some value as an indicator of subsequent mortality risk in acute elderly admissions.

Tab. VIII: Numbers of patients who died during the trial period (vitamin C/placebo groups combined): comparison of those with low initial (wk 0) leucocyte vitamin C levels ($< 15\mu\text{g}/10^9\text{WBC}$) with those having higher initial levels (> 15)

| | Number who died | Number who survived |
|-----------|-----------------|---------------------|
| Le 0 < 15 | 23 | 28 |
| Le 0 > 15 | 36 | 95 |

$\chi^2 = 4.43$ (Adjusted)
 $p < 0.05$

With regard to progression to "well", Table X summarises the main findings of interest. First, with regard to the overall figures (all patients, males and females combined, since separating the figures according to sex yielded similar results), there was a marginal tendency for "placebo" subjects to fare better than "vitamin C" subjects but this was nowhere near statistical significance at any of the time intervals

(including weeks 16 and 24). However the comparison of "low" and "higher" initial leucocyte level subjects is interesting, since whilst this shows very similar progression profiles amongst "low" and "higher" supplemented subjects there is a considerable divergence amongst unsupplemented subjects, *ie.* there is a marked tendency for placebo "low" subjects to fare worse than placebo "higher" subjects and this achieves marginal statistical significance at week 8. (The tendency continues at weeks 16 and 24 also.)

| | Le0 > 15 ($\mu\text{g}/10^6\text{WBC}$) | | Le0 < 15 | |
|-----------|---|----|----------|----|
| | sv | n | sv | n |
| Vitamin C | 3.64 | 64 | 3.67 | 24 |
| Placebo | 3.63 | 67 | 3.63 | 27 |

Scoring system: well (out-patients) = 1
 well (in-patients) = 2
 less severe = 3
 moderately severe = 4
 very severe = 5

Tab. X: Percentage probability of patients progressing to "well" by weeks 2, 4 and 8 for various groups of patients

| Assessment interval Group | | N | week 2 P % | week 4 P % | week 8 P % |
|---------------------------|---|-----|------------|------------|------------|
| All patients | C | 94 | 12.6 | 30.3 | 42.3 |
| | P | 105 | 17.8 | 40.7 | 46.0 |
| Le < 15 | C | 24 | 8.5 | 29.4 | 41.7 |
| | P | 27 | 15.7 | 31.0 | 31.0* |
| Le > 15 | C | 64 | 15.1 | 29.1 | 40.5 |
| | P | 67 | 21.1 | 48.4 | 53.0* |
| "Respiratory" | C | 29 | 14.6 | 41.7 | 48.2 |
| | P | 29 | 7.6 | 29.1 | 40.9 |

Key:

N = number of patients starting the trial

P % = percentage probability of progressing to "well" by the interval named (corrected for "missing" assessments)

C = "vitamin C" patients

P = "placebo" patients

Le0 < 15 and Le0 > 15 = as in Table IV

"Respiratory" = patients who had an initial diagnosis including respiratory infections)

* $\chi^2 = 3.68$ $p < 0.1$ ($\chi^2_{.05} = 3.84$)

The next question is whether supplementation improves the progress of the "low" subjects. The figures in Table X (*ie.* for $Le0 < 15$) show no dramatic effect but there is some tendency for supplemented subjects to have fared better by week 8. The difference at this interval is not statistically significant but this does not preclude the possibility that it might become so with larger numbers of subjects. Some evidence already exists to support this hypothesis [SCHORAH *et al.*, 1981].

Grouping the subjects on the trial by type of disease (as per Table 2) showed a tendency, though not significant, for patients with respiratory infections to fare better up to 8 weeks. Within each of the other major diagnoses (as per Table II) progress of supplemented and unsupplemented subjects were very similar

b) Other Biochemical Findings

With regard to other biochemical findings, Tables XI, XII and XIII show the main results. Correlation between plasma and leucocyte vitamin C contents is good when comparing *means* of various population groups but less good for individuals within a group, particularly during disease [BASU and SCHORAH, 1982]. Hence the weakness of the positive correlations found in this study (Table XI) are not surprising. More work is necessary to elucidate the relative distribution and movement of vitamin C between various white blood cell fractions, plasma and the tissues both in health and disease.

Tab. XI: Correlation coefficients (r) for plasma v leucocyte vitamin C levels for all subjects (vitamin C and placebo groups combined)

| | 0 | 2 | 4 | 8 | 16 | 24 weeks |
|-----|-------|-------|-------|-------|-------|----------|
| r | 0.116 | 0.305 | 0.225 | 0.209 | 0.537 | 0.367 |
| n | 169 | 124 | 109 | 86 | 73 | 55 |
| p < | 0.1 | 0.001 | 0.01 | 0.05 | 0.001 | 0.01 |

Tab. XII: Mean plasma folate, vitamin B₁₂ and cortisol levels for all subjects $m \pm s.e.$

| | 0 weeks | | | 4 weeks | | | | | | | | |
|----------------------------|-----------|------|----|---------|------|----|-----------|------|----|---------|------|------|
| | Vitamin C | | n | Placebo | | n | Vitamin C | | n | Placebo | | |
| m | s.e. | m | | s.e. | m | | s.e. | m | | s.e. | m | s.e. |
| Folate ($\mu\text{g/l}$) | 4.87 | 0.31 | 77 | 5.38 | 0.41 | 80 | 5.48 | 0.50 | 55 | 5.56 | 0.74 | 58 |
| B ₁₂ (ng/l) | 450 | 37 | 73 | 343 | 28 | 77 | 464 | 46 | 51 | 417 | 42 | 56 |
| Cortisol (nmol/l) | 627 | 29 | 76 | 634 | 22 | 73 | 471 | 25 | 53 | 486 | 29 | 55 |

n = Number of analyses

Tab. XIII: Mean plasma folate, vitamin B₁₂ and cortisol levels: comparison of patients with low initial leucocyte vitamin C levels (Le0 < 15 µg/18thWBC) with those having higher initial levels (Le0 > 15)

| | | 0 weeks | | | 4 weeks | | |
|----------|---|----------------|---------------------------|------------------|----------------|---------------------------|----------|
| | | Folate ng/l | B ₁₂ nmol/l | Cortisol µg/l | Folate ng/l | B ₁₂ nmol/l | Cortisol |
| Le0 < 15 | C | 4.63 | 518 | 676 | 5.48 | 374 | 490 |
| | P | 3.93 | 289 | 651 | 3.59 | 391 | 569 |
| Le0 > 15 | C | 5.09 | 426 | 620 | 5.50 | 494 | 544 |
| | P | 5.99 | 355 | 621 | 6.34 | 440 | 456 |

With regard to plasma folate and vitamin B₁₂, levels rose somewhat from 0 to 4 weeks in both vitamin C and placebo subjects (Table XII) and there were no significant differences between the two groups when looking at the overall figures. Mean cortisol levels declined considerably from 0 to 4 weeks and by similar amounts in both groups, presumably partly as a result of a general decline in mean severity of illness.

Grouping the subjects into "low" and "higher" initial leucocyte vitamin C levels (Table XIII) show some interesting results with regard to plasma folate. The "low" subjects have somewhat lower initial folate levels than the "higher" subjects which rise somewhat amongst the supplemented "low" subjects but not amongst the unsupplemented "low" subjects (of whom in fact, 57 % and 31 % had low folate levels at weeks 0 and 4 respectively, *ie.* less than 3.0 µg/l). This suggests a) that vitamin C supplementation may have some influence on folate status in subjects with low vitamin C status and b) that low vitamin C and folate status occur together. With regard to a) this is consistent with the known role of ascorbic acid in maintaining folate in the active reduced form, tetrahydrofolic acid which is otherwise more susceptible to being rapidly oxidised to folic acid (pteroyl monoglutamate) and excreted in the urine. With regard to b) the fact that many unsupplemented individuals who started the trial with low leucocyte levels remained at low levels suggests that either (i) their food intake was generally poor (including that of fruit and vegetables) or (ii) that the content of vitamin C in the vegetables eaten was low due to excessive cooking and/or keeping hot. In either case folate status of the subjects would then also be low since vegetables are a major source of both nutrients and both nutrients are similarly susceptible to oxidative loss during overheating of food. However, in this study, explanation (i) seems more likely since overall *mean* blood vitamin levels of the placebo subjects during the trial was not low; but it does suggest that supplementation of low vitamin C status patients with vitamin C and perhaps other nutrients, including folate, may be prudent.

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