Vitamin C prophylaxis for posttransfusion hepatitis

Dear Sir:

The paper by Knodell et al. (1) with the above title has the subtitle “lack of effect in a controlled trial.” This subtitle misrepresents their observations, apparently because of a misunderstanding about biostatistics. The investigators observed a protective effect, which, however, was not statistically significant at the usually accepted level. The failure to reject with statistical significance the null hypothesis that the treatment (vitamin C prophylaxis) has no greater effect than the placebo cannot correctly be described as showing “lack of effect in a controlled trial.”

The clinical data in Table 1 are from Tables 2 and 4 of Knodell et al. It is seen that better than the placebo patients in that fewer of them showed hepatitis symptoms or signs or developed chronic liver disease, and those who developed hepatitis had a longer mean incubation period and lower mean SGPT levels. The number developing icterus was the same. In no respect were the placebo patients better off than the vitamin C patients.

Knodell et al. point out that in none of these comparisons was the apparent benefit of the vitamin C statistically significant at the usually accepted level, p (one-tailed) \( \leq 0.05 \). This fact may be attributed in part to their having studied too small a population. If they in essentially every respect the vitamin C patients fared better than the placebo patients. The fractional number developing hepatitis was 29% less, even though the mean number of units of blood received by the vitamin C patients was 29% greater than that for the placebo patients. The risk may be taken as proportional to the number of units of blood received; with this factor considered, the amount of protection afforded by the vitamin C administered (3.2 g/day) is calculated to be 45%. The mean units of blood received by the patients who developed hepatitis was 36% greater for those who were given vitamin C than for those who were given the placebo, again indicating that vitamin C has a protective effect.

Moreover, the vitamin C patients had studied nine times as many patients (as was done by Morishige and Murata (2)) with the same incidence of posttransfusion hepatitis, hepatitis signs and symptoms, and chronic liver disease, the protective effects of vitamin C would have been statistically significant.

Whereas the incidence of posttransfusion hepatitis in the placebo subjects of Knodell et al., 9.4%, is not much different from the value 7.1% (12 in 170) reported by Morishige and Murata for patients who received little or no vitamin C (1.5 g/day or less), there is a great difference between the corresponding values for the vitamin C patients, 6.7 and 0.2% (three in 1367), respectively. This difference may be attributed to the difference in the amount of vitamin C. Knodell et al. ad-
ministered 3.2 g of ascorbic acid for 16 days, whereas Morishige and Murata administered a median of 10 g/day for a much longer time, usually 6 months (Reference 2 and 3; and F. Morishige and A. Murata, personal communication). Knodell et al. stopped the administration of vitamin C 2 wk after surgery, whereas hepatitis developed 5 to 10 wk after surgery. It is possible that the rebound effect when the vitamin C was stopped contributed to the incidence of the viral infection in their vitamin C patients.

The toxicity of vitamin C is very low, its side effects are minimal, it is easily administered orally, and it is required for the healing of surgical wounds. It seems to benefit surgical patients even at the intake 3.2 g/day for 16 days (Knodell et al.) and to prevent hepatitis nearly completely at a larger and continued intake (Morishige and Murata). The report by Knodell et al. should not be cited as a reason for not giving vitamin C to surgical patients.

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References

Reply to letter by Pauling

Dear Sir:

Dr. Pauling’s fervor for vitamin C ingestion as prophylaxis against a variety of medical diseases is well known, and it will be difficult to convince him that our data (1) do not support a positive role for vitamin C in the prevention of posttransfusion hepatitis (PTH). However, I offer the following responses to the points raised in his letter.

We initially estimated the sample size required for our study using a predicted hepatitis attack rate of 20% in the placebo population and 5% in the vitamin C treatment group. This estimate of vitamin C efficacy is conservative in the light of the efficacy of vitamin C in preventing PTH claimed by Murata (2). Ninety-three patients were needed in each group to give a 90% probability of detecting a significance difference at the p < 0.05 level. We fulfilled the requirements of these prestudy power calculations and there is little reason to reject the null hypothesis for our study results as Dr. Pauling suggests. In regard to the number of patients assessed, Dr. Pauling makes the claim that, had we assessed 1245 patients as studied by Murata (2), statistical significance would have been achieved. If the number of patients assessed in our study was increased 8-fold to 1400 and the same incidence of hepatitis maintained in both groups, the protective effect of vitamin prophylaxis is still not statistically significant at the p < 0.05 level using \chi^2 analysis. More importantly, the assumption that the hepatitis attack rate would remain constant in the two groups throughout the next 1200 accessions is not logical or statistically valid.

We disagree with Dr. Pauling’s claim that vitamin C patients fared better than placebo patients. Differences between the two groups in the number of blood products received are not statistically significant nor are differences in incubation period. While more patients in the placebo group had clinical symptoms of hepatitis than in the vitamin C group, this is not necessarily bad. Many investigators believe that subclinical, asymptomatic attacks of acute hepatitis are more likely to progress to chronic hepatitis than acute hepatitis characterized by clinical illness (3, 4). Only four of the acute hepatitis patients in the vitamin C treatment group were followed for suffi-