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Letters to the Editor

Erroneous calculation of sample size in a vitamin C and atrial fibrillation trial

Antonic et al. reported the findings of a randomized trial on vitamin C and atrial fibrillation (AF) [1]. They wrote that “the sample size estimation was based on the assumption that the incidence of AF after CABG lies at about 25% and that the administration of ascorbic acid would result in a 20% decrease of AF. With a power of 80%, beta error of 0.2 and alpha of 0.05, about 50 patients were required in each group” [1]. This sample size calculation does not seem to be correct. The calculation can be easily checked, since there are sample size calculators available on the web [2,3].

Antonic et al. assumed that the proportion of patients who suffer from AF is 25% in the non-treated group and that vitamin C would decrease that rate by 20%, which leads to AF incidence of 20% (=0.80*25%) in the vitamin C group. With these assumed proportions, 25% and 20%, and also the assumed beta and alpha levels, the sample size calculators give 1092–1134 patients per group as adequate sample sizes, depending on the details of the calculation [2,3]. Thus, the published calculation that 50 patients in each group is sufficient seems to be incorrect.

Antonic et al. apparently assumed in their calculation that the effect of vitamin C was an 80% decrease in the AF rate, which is complementary to the published assumption of 20% effect (100% – 20% = 80%). Assuming that the AF rate is 25% in the non-treated group and 5% (=0.20*25%) in the vitamin C group leads to sample sizes of 47–59 patients per group [2,3]. Thus, the sample sizes actually calculated by the authors seem to be based on an assumption that vitamin C might decrease AF incidence by 80%, and not by the published assumption of a 20% decrease [1].

Furthermore, those authors observed 7 cases of AF among 52 vitamin C patients and 10 cases of AF among 53 control patients [1]. This leads to a risk ratio (RR) 0.713 that corresponds to 29.7% lower incidence of AF in the vitamin C group. This difference is greater than the 20% effect that was the basis for the sample size calculation by the authors [1], yet the difference was not statistically significant because the number of patients was so small.

Based on a 2014 meta-analysis that included 565 participants [4], and on a 2016 meta-analysis that included 1037 participants [5], there is strong evidence that vitamin C decreases the average risk of AF after cardiac surgery. Therefore, more research on vitamin C and AF is warranted to understand the practical importance of vitamin C and to find out the optimal protocol for its administration. Unfortunately the number of patients in the Antonic et al. trial was so small, and the 95% confidence interval around the observed RR = 0.713 is so wide, that it does not provide substantial additional information of the effects of vitamin C.

References


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Author’s reply

The authors are aware of the relatively small study sample size and this problem has also been addressed in the ‘Discussion’ section of the article.

Our interest to investigate the effects of vitamin C on postoperative atrial fibrillation (AF) was triggered by a study by Eslami et al. [1] and the following editorial commentary by Wilson [2]. In this study, Eslami reports on a strong effect of vitamin C on postoperative incidence of AF in coronary artery bypass graft (CABG) patients. The incidence of AF in the group of patients receiving perioperative vitamin C was only 4% compared to 26% in the control group (p = 0.002). This represents an absolute reduction of 22%. Considering these results (an absolute reduction of about 20%), a power of 80%, a beta error of 0.20 and alpha of 0.05, the sample size calculation results in about 50 patients per study group.

Most authors of previously published controlled prospective randomized trials studying the effect of vitamin C on postoperative AF after CABG have used a study sample, which is in size similar to ours (a total of 105 patients): Eslami 100 patients [1], Bjordahl