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A Collaborative Clinical Trial on Trial

COLLABORATIVE STUDIES have very high morbidity rates (deviation from the protocol) and very high mortality rates (total lack of success) because some investigators find it difficult to comply with the protocol. Sylvester *et al.* amplify on this problem in their recent critique of the impact of protocol deviation on the success of cooperative trials in cancer therapy.¹ The multi-center study of dantrolene's efficacy in the treatment of malignant hyperthermia published in this issue of *ANESTHESIOLOGY*² is certainly no exception to this conformity problem. The study is in the preterminal morbid state (questionable success): four out of 21 cases of malignant hyperthermia were not treated according to protocol. But this collaborative dantrolene study must be kept alive because the message it whispers (uncontrolled biases sap its strength) is very important clinically; and should it die, it is unlikely that another collaborative study would be attempted.

Could we have expected a more robust study which would have better protocol conformity? It is doubtful that any collaborative study of a very low incident problem could be expected to fare better. Collaborative studies require pilot work in every involved institution to test and clarify the protocol, to train personnel involved in the execution, and to sharpen the focus on reporting and analyses. Unfortunately, the low incidence and high severity of malignant hyperthermia mitigated against the luxury of even one pilot case in each hospital and virtually assured that this multi-institutional study would

have potentially fatal nonconformity problems. The investigators are to be complimented for their ability to keep this whispering oracle alive.

What are the biases that weaken the study's claim that patients treated with dantrolene plus symptomatic therapy have significantly lower mortality rates than those treated with symptomatic therapy alone? What are the implications of these uncontrolled biases and how might they have been controlled?

Hospitals and investigators were not selected randomly; it is fairly certain that many volunteered to participate in this study. Was this high level of interest in malignant hyperthermia a factor in determining the results? If so, how would it bias the data? One could speculate that physicians with a keen interest in malignant hyperthermia would be more skilled at diagnosing less severe cases of that disease. Milder cases would be more likely to have spontaneous remissions, or they would be more likely to recover reasonably quickly with aggressive symptomatic therapy which did not include dantrolene. In this nonrandomized study dantrolene was given to everyone diagnosed as suffering from malignant hyperthermia, and those milder cases which would have survived without the use of dantrolene are counted as dantrolene cures. The authors attempted to correct or minimize this bias by eliminating six cases classified *a posteriori* as questionable malignant hyperthermia. The results would have been more convincing had the authors required blindness for this *a posteriori* categorization of patients according to their severity of malignant hyperthermia. Blinding theoretically could have been achieved by eliminating the knowledge of dantrolene treatment

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and patient outcome from the data submitted to the expert reviewers.

Some study hospitals may have had greater capabilities to respond to emergencies than others and, therefore, provided more efficient and effective therapy and better salvage than other hospitals. In this cooperative trial, such cases may be sequestered among the eleven bonafide malignant hyperthermia cases treated according to protocol, and are counted as dantrolene cures. It is difficult to estimate the impact of this bias on the results. In the reported study, four patients with definite malignant hyperthermia were not treated according to protocol and could not be entered into the analysis. Whatever the reason for excluding them from the protocol, their omission from the analysis could falsely elevate the percentage incidence of successfully treated cases.

Most of these biases could have been cancelled out (not eliminated) simply by doing a double-blind randomized trial of dantrolene and placebo in a set of randomly selected institutions. The randomized trial is only one of several design options which were available to the planners.

In designing a study of this type, the choices of assignment of treatments to patients and the analytic strategy range from the most ideal—a randomized clinical trial—to the least desirable—an open assessment of efficacy, using existing historical mortality estimates for comparison. The decision against use of a randomized clinical trial may have been made “reluctantly,” as is commonly and unfortunately the case, for so-called ethical considerations. Another design—utilizing matched controls—would have circumvented the ethical problems

by treating all cases of malignant hyperthermia with dantrolene and would have fortified our confidence in the statistical analysis by using carefully matched non-dantrolene cases with known outcomes for control. Unfortunately, many of the above-mentioned biases are not circumvented in matched cohort studies. The decision to perform a nonrandomized study using historical mortality estimates for comparison may have been warranted for ethical reasons. And the perception that there was little hope of matching cases in a credible way probably fortified this decision. Unfortunately, the adopted design automatically lowers one's confidence in the results because of the uncontrolled bias in patient selection and treatment and the lack of confidence in historical control data.

In spite of the crippling deviations from the protocol by cooperating institutions, and in spite of potentially devastating biases in patient selection, this study's rich data had to be disseminated widely and the editors are to be complimented for their intrepid decision to publish.

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