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An early parallel group trial in cardiology

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The 1948 report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction[1] describes a clinical trial sponsored jointly by the American Heart Association and the US Public Health Service. The idea that anticoagulation might be useful in coronary thrombosis had been around for a few years. It was based on the use of heparin in animal experiments, but it was thought that heparin would be too dangerous in humans. The development of dicoumarol seemed to present an opportunity to test the theory and to develop a useful new therapy.

Patients were to be selected for anticoagulant or conventional therapy according to the date of their admission to hospital: patients admitted on odd dates were to receive anticoagulants (heparin for 48 h and then dicoumarol for 30 days), while those admitted on even dates were to receive (undefined) 'conventional therapy', without anticoagulants.

The report does not include a clear definition of myocardial infarction, nor does it specify either an endpoint (the results being presented more as a series of observations) or an intended length of follow-up (results at six weeks are given). It had been planned to study about 1000 patients with acute myocardial infarction, but the results were reported after only 800 patients had been followed to completion, implying that the accumulating results had been monitored, for the authors judged that the addition of the last 200 cases was unlikely to alter the conclusions.

The death rate among patients allocated to anticoagulation was 15% compared with 24% among those in the control group, a statistically significant difference (the authors explain in a footnote that this term meant that on the basis of chance alone, differences such as this would occur less than 1 in 100 occasions). Thromboembolic 'complications' (myocardial infarction, stroke and venous thrombosis) were also lower among those allocated to anticoagulants than among controls, albeit at the cost of an increased risk of bleeding (12% compared with 6%).

To what extent were these differences in favour of anticoagulants a reflection of the effects of the drugs? The paper describes the two treatment groups as showing a 'striking similarity' in terms of age, history of previous infarction, and estimated severity of the admission event and tables suggest that this was so. The authors do not seem to have been concerned that the imbalance in the sizes of the anticoagulant and control groups (432 and 368 patients, respectively) may have reflected allocation bias, although they comment that 12% of the control patients received anticoagulants 'because of pressure on the part of the family or a private physician' (mentioning in a footnote that 'this factor became intensified as the study progressed').

Six years after the report was published, reference was made to the study in one of the conferences on therapy organised by the Department of Pharmacology and Medicine of Cornell University Medical College and New York Hospital, one of the participating centres in the anticoagulant study.[2] In this study allocation had been open, whereas in the multi-centre studies done under the aegis of the Medical Research Council allocation bias had been controlled by concealing the allocation schedules from the participants.[3,4] The discussions on the other side of the Atlantic – led by Dr Harry Gold in particular – emphasised the value of using placebos to promote adherence to allocated treatment.

One of the participants in the conference on 'How to evaluate a new drug' asked whether placebos are needed when comparing non-subjective outcomes like mortality rates in treated and untreated patients. In response, Dr William Foley commented as follows:

> I would like to make a point here in regard to mortality statistics as related to our study on dicumarol in coronary thrombosis. We placed most dependence on the course of mortality rates. The design of the study called for the alternate case method of treated and untreated cases in the sixteen hospitals. We were a bit troubled, however, by the fact that in some instances this plan for the selection of cases was

> disturbed. Here was a new drug supposed to be helpful for a disease which carried a high mortality. The word soon got around among the patients in the hospitals and among the families that certain patients were receiving the drug and others were not. In many instances great pressure was brought to bear to see that certain cases would receive it. It raised some question in our minds as to how far one might properly go in judging the value of a method of therapy by the mortally statistics.

In support of the use of active and placebo treatments to overcome this problem, Dr Gold commented: 'This is just one more illustration of the importance of seeing to it that there are no untreated cases in a study of a new drug or treatment'.

It seems likely that discussion among the local medical communities about the expected value of anticoagulants may indeed have resulted in allocation bias in the study reported by Wright et al.[1] The need for early treatment of myocardial infarction had not been recognised at that time (resuscitation from ventricular fibrillation was still several years in the future) and family doctors may well have kept their patients at home for a day if their attack occurred on an even date, to ensure that they would receive the 'best' treatment. We now know – although they did not know it then – that a group with delayed admission will have a lower fatality rate.

The paper by Wright et al.[1] concludes that 'anticoagulant therapy should be used in all cases of coronary thrombosis with myocardial infarction unless a definite contraindication exists'. Given the likely effects of allocation bias on the results – which appear to have set the pattern for American medicine – was this recommendation justified? The report by Wright et al.[1] was published in the same year as the Medical Research Council trial of streptomycin in the treatment of pulmonary tuberculosis,[4] in which treatment was allocated at random using a system of sealed envelopes held in the trial coordinating centre (it was considered unethical to use placebo injections, but assessment of the lung X-rays was done by people who were blind to patient allocation). Another early Medical Research Council trial – of antihistamines for treating the common cold – was blinded by giving patients in the control group a small dose of phenobarbitone, so that both groups would suffer the same amount of drowsiness. But it was not until 1959 that the Medical Research Council published a report of a randomized, double-blind trial in cardiology, assessing the effects of anticoagulation after myocardial infarction.[5] And nearly 30 years after the study reported by Wright et al.,[1] the topic addressed in one of the first reports of a meta-analysis of clinical data concluded that anticoagulants had a favourable effect during the hospital phase of acute myocardial infarction.[6]

Anticoagulants continue to have a major role in the prevention of thrombo-embolism in atrial fibrillation and in patients with prosthetic heart valves; however, they are no longer used routinely for myocardial infarction, for which there are now so many other treatments – thrombolysis, aspirin, more modern and more powerful anti-platelet agents, and interventions such as coronary angioplasty. Even though anticoagulants may have been largely set aside, the main lesson from the early, American anticoagulant study is the importance of avoiding allocation bias by preventing foreknowledge of treatment allocations among those involved in entering patients in clinical trials.

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