Clinical Trial Methodology in Stroke

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On March 6 and 7, 1989, 28 researchers with expertise in cerebrovascular disease, clinical trial methodology, and biostatistics met at the Priory of Corsendonk, Belgium, to exchange views on the problems in design of clinical trials in stroke. The symposium was organized and chaired by Drs. W. Amery (Beerse, Belgium), M.-G. Bousser (Paris, France), F. Clifford Rose (London, UK), J.I.S. Robertson (Hong Kong), and J. van Gijn (Utrecht, Netherlands). Trials in ischemic or hemorrhagic stroke were addressed as were those in stroke prevention. The presentations are summarized below.

General Methodology

Dr. A. Donner (London, Canada) reviewed standards in the design and analysis of clinical trials. He reviewed 18 randomized clinical treatment trials published since 1986 for 10 methodologic criteria. Recently reported studies are fairly attentive toward issues such as blindness, consideration of prognostic factors, eligibility criteria, and patient attrition. However, many studies do not describe the methods used for statistical analysis of data, methods of randomization, or policies for handling deviations in the treatment protocol. Most clinical trials in question do not describe the sample size calculations used to justify the number of patients entered, which is the area of greatest concern and which should be addressed in future treatment trials. Future clinical trials in stroke should also use confidence intervals to demonstrate treatment responses.

Dr. P. Smets (Brussels, Belgium) outlined options for the design of future clinical trials in stroke. The decision for the type of trial will affect many critical aspects of design and interpretation including patient selection, follow-up, treatment regimen, and end points. An explanatory trial is a highly selective study that restricts recruitment to those patients most likely to demonstrate a response to test efficacy of an intervention. A pragmatic trial recruits a broader spectrum of patients who are closer to those seen in clinical practice and is better for testing the usefulness of a therapy.

Dr. F. Yatsu (Houston, Texas) commented on the potential value of modern neuroimaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain for trials of therapeutic interventions in stroke. At present, CT is the most useful neuroimaging tool to aid in the determination of eligibility and response to therapy. In particular, CT is an important baseline test in delineating ischemic from hemorrhagic stroke. MRI may prove to be superior to CT. Conceivably, localized magnetic resonance spectroscopy (MRS), positron emission tomography (PET), or single-photon emission tomography (SPECT), which can provide information on regional blood flow and cerebral metabolism, may replace CT.

Dr. L. Candelise (Milan, Italy) emphasized that the key to success in a large multicenter clinical trial in stroke is to keep the protocol simple. The aim of a study should be simply explained. Protocols should be kept simple because detailed forms are often time-consuming, methodology becomes inaccurate, and an excessive number of variables increases interobserver variability and reduces reproducibility. Simplicity also facilitates understanding of definitions and increases the likelihood of recruiting an adequate number of patients to test the usefulness of a treatment. Excessive exclusion criteria should be avoided since they may lead to biased selection and poor generalizability of results. Only those outcome events relevant to the hypotheses being tested should be included. If the principle of simplicity is observed, the findings of a multicenter study become more credible.

Dr. M.J.G. Harrison (London, UK) discussed the ethical constraints of clinical trials in stroke. The ethics of a clinical trial are no more than extensions of the normal moral responsibilities of a physician. Physicians should accept the high moral obligations to test treatments critically rather than prescribing therapy with the support of only convention or wishful thinking. Since the efficacy of aspirin has already been established in the prevention of stroke, new treatments should be tested against aspirin and not placebo. Placebo is acceptable in studies in acute stroke treatment because there is no established therapy. Stopping rules should be sufficiently
flexible so as to not expose patients receiving ineffective treatments to unnecessary risks when a trial becomes conclusive at any early stage. The Nuremberg Code and the Declaration of Helsinki provide important models of ethical conduct.

**Ischemic Stroke**

A major problem of randomized controlled clinical trials in ischemic stroke, namely the very large number of patients required to obtain statistically significant results, was discussed by Dr. K.J. Fullerton (Lurgan, Armagh, UK). Careful patient selection, limiting the study to a well-defined population, or alternatively, stratification of entrants in terms of prognostic factors may reduce the large numbers required. Factors that predict outcome include those not related to the stroke itself (age, cardiovascular disease), those that indicate persons at greater risk of ischemia (hyperglycemia, blood hyperviscosity), or those that indicate the size or severity of brain damage (level of consciousness). Complex neurologic scores are rather arbitrary. Multivariate statistical techniques are appropriate for randomized trials since such techniques allow the selection of factors that independently predict other interrelated measures.

Dr. T.J. Steiner (London, UK) noted that clinical trials in stroke can test either efficacy or usefulness of an intervention. An effective drug might not be useful because of side effects or other factors. Patient selection is of paramount importance in a clinical trial. Patients with other severe illnesses, severe disability, or an inability to cooperate should be excluded. Reasonable age limits are 40 and 85 years. Patients with very mild or extremely severe neurologic deficits should be excluded because usefulness of treatment will be difficult to test in such patients. The maximal delay from the onset of stroke until the entry into a trial should be 24-48 hours. If very strict entry criteria are used, approximately 10% of all screened patients will likely be enrolled in the trial, whereas if more pragmatic criteria are applied, investigators can expect to recruit approximately 17% of screened patients.

Many clinical trials in stroke have used scoring systems that are presented with little or no information as to validity and reliability. Dr. R. Adams (Augusta, Georgia) emphasized the importance of using a scale that has good interobserver and intraobserver reproducibility. Features that should preferentially be used in rating patients with ischemic stroke are level of consciousness, extremity motor power, gaze paresis, visual field deficits, speech, and language. A combined stroke score in which specific neurologic deficits are weighted may be of limited usefulness. Investigators may wish to measure response of treatment by evaluating one neurologic variable. Pretrial instruction of investigators on the components of the neurologic assessment scale is extremely important. Neurologic score is more useful in defining the patient population than in determining response to therapy.

Dr. J.M. Orgogozo (Bordeaux, France) presented data comparing outcome criteria including mortality, activities of daily living, neurologic scores, quality of life, length of stay, and cost of illness. The judicious use of such criteria combined with patient samples of sufficient size and with adequate duration of observation should, in his view, make it possible to demonstrate effects of a therapeutic intervention.

Dr. D.T. Wade (Oxford, UK) reviewed the methods of measuring quality of life among survivors of acute stroke. Future clinical trials should use measures based on a model developed for the World Health Organization. Investigators should focus on component items that may contribute to quality of life, that is, disabilities and handicaps. An outcome score should measure overall disabilities rather than be a composite score of neurologic deficits. The Barthel Index has undergone sufficient validity and reliability testing to be used as an outcome measure in stroke treatment trials.

**Hemorrhagic Stroke**

Dr. N. Poungvarin (Bangkok, Thailand) and Dr. J.M. Rice Edwards (London, UK) outlined methodologic features of clinical trials in intraparenchymal and subarachnoid hemorrhage. Dr. Poungvarin stressed the importance of prognostic factors and eligibility criteria in entering patients into trials of treatment for intracerebral hemorrhage. Dr. Rice Edwards emphasized that in trials of agents given to prevent cerebral ischemia with patient outcome as the end point, it usually is necessary to randomize more than 500 cases; these should include all patients with subarachnoid hemorrhage, not just those with aneurysmal rupture. The matter of timing of aneurysmal surgery is still not resolved and justifies a large randomized study. The revised rating scale of the World Federation of Neurological Surgeons, which is based on the Glasgow Coma Scale, should be used in future trials.

The timing and duration of therapeutic measures in trials of treatments for aneurysmal subarachnoid hemorrhage were discussed by Dr. N.F. Kassell (Charlottesville, Virginia). The two major complications of subarachnoid hemorrhage are rebleeding, which peaks ≤24 hours after the ictus and reaches a cumulative risk of 20% at 10 days, and vasospasm, which peaks at 7-9 days and resolves by 14-20 days. Trials of measures to prevent rebleeding should restrict entry to patients seen ≤3 days after the ictus, whereas studies of therapies to prevent vasospasm can enter patients seen ≤7 days after ictus.

The importance of both continuous clinical observation and serial CT scanning in treatment trials for subarachnoid hemorrhage was discussed by Dr. J. van Gijn (Utrecht, The Netherlands). CT is the confirmatory diagnostic study of choice for sub-
arachnoid hemorrhage and for rebleeding. Examination of the cerebrospinal fluid to document rebleeding is often unreliable. CT can also document important complications such as hydrocephalus or brain infarction. The clinical course of sudden neurologic deterioration is not sufficiently specific to make the diagnosis of rebleeding without confirmation by CT, nor is gradual deterioration of the neurologic condition specific for vasospasm; CT should be done to help eliminate other conditions such as hydrocephalus.

Problems in the design of clinical trials in subarachnoid hemorrhage that will allow for the determination of statistically meaningful conclusions were reviewed by Dr. H.P. Adams (Iowa City, Iowa). Statistical aspects of a trial cannot be evaluated in isolation. Any future trial should address the following issues: 1) the hypothesis tested, 2) the organization of the trial, 3) patient characteristics, 4) entry criteria, 5) treatment regimen, 6) monitoring response to treatment, 7) sample size calculations, and 8) statistical methods used. Because most future trials in subarachnoid hemorrhage will be aimed at prevention of either rebleeding or vasospasm, recruitment should be restricted to patients most at risk for these complications, that is, those with ruptured aneurysms.

**Stroke Prevention**

Dr. H.H. Kornhuber (Ulm, FRG) discussed the importance of management of risk factors for atherosclerosis in any long-term stroke prevention trial. Of particular importance is control of hypertension, which may be related to obesity or alcohol consumption. Cessation of alcohol consumption followed by weight reduction may lead to declines in blood pressure and a lowered risk of stroke. Future clinical trials in stroke prophylaxis should include management recommendations that discourage alcohol consumption.

Dr. C. Warlow (Edinburgh, UK) reviewed the importance of ongoing studies of the efficacy of carotid endarterectomy in preventing stroke in symptomatic persons who have presented with either a transient ischemic attack or a minor ischemic stroke and who have stenosis of the ipsilateral internal carotid artery. From an ethical point of view, carotid endarterectomy should be evaluated in a large, well-designed, randomized trial. Because even at maximum efficacy carotid endarterectomy will prevent only 3% of all strokes, efforts should also be invested in the identification and control of common risk factors for vascular disease.

The causal relation between atrial fibrillation and cerebral ischemic episodes was examined by Dr. P.J. Koudstaal (Rotterdam, The Netherlands). Several multicenter trials are now evaluating the primary or secondary stroke protective actions of anticoagulants or aspirin in patients with atrial fibrillation. Many patients will be required since event rates in untreated patients are low. Because atrial fibrillation is found in a variety of circumstances with reference to age, atrial size, extracranial arterial disease, and cardiac function, a sufficient number of patients in each category should be randomized to permit subgroup analyses. Standardizing prothrombin times between centers, independent of reagents and laboratory methods, can be achieved if calibrated thromboplastins are used.

The proceedings of this symposium edited by W.K. Amery, M-G. Bousser, and F. Clifford Rose will be published by Bailliere Tindall, London, UK.
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