Methodological Issues in Studying Treatment Effects in Patients with Cerebrovascular Disease

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Evaluation of the neuropsychological effects of surgical treatment on cerebrovascular disease is beset by numerous methodological difficulties. These include problems specific to this patient population as well as others inherent in all retrospective studies. Five such problems are described: 1) nonrandomized subject selection; 2) dropout from follow-up; 3) natural history of cerebrovascular disease; 4) effects of hospitalization; and 5) the role of practice effects. This paper examines these methodological problems for their impact on our knowledge and proposes alternative research directions to address their shortcomings.

Evaluating the neuropsychological effects of intervention for cerebrovascular disease has been complicated by methodological problems. Some of these problems are unique to the study of patients with cerebrovascular disease, while others relate to follow-up studies in general.

Five problems are of particular concern: 1) nonrandomized subject selection; 2) dropout from follow-up; 3) natural history of cerebrovascular disease; 4) effects of hospitalization; and 5) the role of practice effects.

These five problems are related to two general methodological issues, namely, the choice of experimental design and the use and selection of control groups.

Specific Methodological Problems

1. Nonrandomized subject selection

The usual philosophy of medical and surgical case management determines that a specific set of symptoms will receive specific treatment. Thus, patients with cerebrovascular disease who receive surgical treatment are selected systematically rather than randomly. While there is not a broad consensus as to specific indications for medical or surgical management, these considerations cause bias in subject selection.

Nonrandomization of surgical candidates creates an obvious interpretational problem: one cannot say whether the natural history of surgical patients differs from that of the nonsurgical patient in terms of neuropsychological functioning. For example, assume that patients who are not surgical candidates will improve after their hospitalization just on the basis of natural recovery. Further, assume that surgical candidates do not improve without surgery, but with surgery they do improve. In this case, comparison of the surgical and nonsurgical groups would lead us to conclude that surgery had no effect. Thus, potential differences in the natural history of these two patient groups may obscure valid relationships in the data or suggest the presence of a relationship where none exists.

The random assignment of surgically acceptable patients to surgery and nonsurgery groups is commonly used in national collaborative studies to evaluate the effectiveness of various treatment regimens. Unfortunately, the national collaborative study of carotid endarterectomy (CE) did not include systematic neuropsychological evaluation (1). The ongoing multicenter study of extracranial/intracranial (EC-IC) arterial bypass surgery suffers from the same shortcoming. While psychologists may have access to randomized patients at individual centers, there is no central coordination of this effort, and detailed, uniform neuropsychological testing is not part of the international protocol. For this reason, no truly randomized study of the effect of these procedures on higher cognitive functioning is likely to be carried out.

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Thus, it is quite possible that treatment effects may be confounded with natural recovery. This issue is further complicated because individual patients vary considerably in their ability to recover from a stroke. In the long term, the natural history of cerebrovascular disease takes a downhill course. Accordingly, some researchers have concluded that if surgery halts this progression, the patient has benefited (2). While this argument has some validity, one must specify the time span over which progressive deterioration is to be expected in order to define the parameters for interpreting lack of change as a gain.

The natural history of cerebrovascular disease is complicated further by the differing natural outcomes of stroke and transient ischemic attacks (TIA). While TIA patients have been shown to be mildly impaired on neuropsychological testing (3), they are not so severely affected as stroke patients. Since reconstructive cerebrovascular surgery may produce different effects in patients with a different level of impairment, it may be useful to compare results of treatment among patients who differ widely in this respect.

2. Posttreatment dropout

Posttreatment dropout, which confronts all longitudinal studies, is a particularly salient issue in research on cerebrovascular disease. Two major sources of dropout are mortality and withdrawal from participation.

Postsurgical mortality creates particular difficulty in interpreting studies in which patients have been systematically assigned to either an experimental or a control group. All reported studies of the neuropsychological effects of the treatment of cerebrovascular disease fall in this class, and it is difficult, if not impossible, to make comparisons between the two groups.

The second source of dropout is voluntary withdrawal from the study. In general, patients who undergo CE and EC-IC bypass surgery are old and not healthy. Before surgery they may agree to participate in a spirit of cooperation with the care team. However, postoperatively these patients may be reluctant to undergo a rigorous day of testing, and the problem worsens as the postoperative interval lengthens. Voluntary withdrawal also occurs frequently when patients are dissatisfied with any aspect of the care they received during their hospital stay.

Three specific recommendations to reduce voluntary withdrawal have one common aim: to personalize the relationship between the study staff and the patient. First, there should be as much contact as possible between the patient and the staff. Be willing to listen to and deal with the fears and frustrations of the patient during the preoperative hospitalization. Second, keep in touch. For long-term test follow-up, telephone interviews at three- to four-month intervals will help to maintain contact. Third, be flexible. When patients must rely on others for transportation, weekend testing may be necessary. When the trip to the hospital is too taxing, home visits are required for follow-up testing. Even with these procedures, dropout cannot be eliminated altogether. Consequently, all investigators must report their dropout rates so that the effect of this problem on an individual study can be assessed.

3. The natural history of cerebrovascular disease

Cerebrovascular disease typically progresses in a non-linear manner. Symptoms are most prominent immediately after an acute cerebrovascular event, while some recovery of function generally follows the acute phase. Thus, it is quite possible that treatment effects may be confounded with natural recovery. This issue is further complicated because individual patients vary considerably in their ability to recover from a stroke. In the long term, the natural history of cerebrovascular disease takes a downhill course. Accordingly, some researchers have concluded that if surgery halts this progression, the patient has benefited (2). While this argument has some validity, one must specify the time span over which progressive deterioration is to be expected in order to define the parameters for interpreting lack of change as a gain.

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4. Effects of hospitalization

It has long been suspected that hospitalization may have a depressing effect on test scores; anxiety, novel surroundings, and loss of control over activities have all been suggested as contributory factors (4). If hospitalization does depress test scores, any score increases found during outpatient postoperative visits may simply reflect release from this artificial influence. This phenomenon is not a problem for studies using control patients who are also hospitalized for evaluation, but it is a problem for studies which do not (5). Some evidence suggests that preoperative anxiety is not a major factor affecting the performance of cerebrovascular disease patients on neuropsychological tests (6). Anxiety levels have been assessed through administration of the State Trait Anxiety Index (7). Kelly and his colleagues (6) reported significant reductions in anxiety level from the pre- to the postoperative evaluation. While this observation appears to support the preoperative anxiety theory, such is not the case. Although the differences are statistically significant, the actual mean scores for both preoperative and postoperative tests fall within a few points of each other; and both are well below the mean (35-40th percentile) of the normal college undergraduate standardization sample. The effects of generalized arousal on test performance are best described by an inverted U-shaped curve. That is, both high and low arousal levels have a deleterious effect on performance, while moderate arousal improves performance. Clearly, measured levels of preoperative anxiety cannot reasonably be construed to have had a deleterious effect on neuropsychological test performance.

5. Practice effects on test scores

Much has been written about the effects of practice on postoperative score changes in cerebral revasculariz-
tion patients. Some authors have even suggested that all the observed score changes are best explained as the result of practice (5). This is a critical methodological issue for evaluating endarterectomy and vascular bypass effects, because much early research did not include control groups and provided no way to assess the effects of retesting. Many studies have in fact disclosed that mean increases in the Wechsler Adult Intelligence Scale (WAIS) scores are in the range generally attributed to practice.

Matarazzo and his co-workers (5) reported that the magnitude of WAIS IQ changes in their CE patients did not differ from that found in several neurologically intact groups. They concluded that CE had no specific effect on WAIS IQ scores. However, available test-retest data suggest that their conclusion may have been premature. To evaluate the results of CE requires comparison with neuropsychologically impaired patients rather than with the neurologically intact groups used by Matarazzo. In fact, patients with neurological impairment are marked by their failure to demonstrate a practice effect (8).

In a recent study of seizure patients, Seidenberg (9) found that those patients who achieved the best seizure control with medication demonstrated WAIS practice effects, while those patients who had greater neurologic impairment achieved only minor decreases in seizure frequency and did not show practice effects on testing. Although this observation suggests a relationship between impairment and practice, brain damaged patients cannot be expected to show the same practice effects as normal individuals. An inverse correlation between neurologic impairment and practice effects has also been shown by Spielberger (7).

In test-retest research, two major errors can be made in the treatment of practice effects. The first is failure to consider practice effects at all, and studies which do not employ control groups exemplify this approach. The second is failure to recognize that practice effects may differ markedly from group to group. Hence, to control for practice effect, not just any control group will do: only non-operated patients with equivalent functional impairment would comprise an appropriate control group.

**General Methodological Issues**

These five specific problems relate to two interrelated general methodological issues: experimental design and the use of appropriate controls. The use and selection of control groups has proven to be problematic. Many studies have omitted control groups entirely, while others have used inadequate controls, such as healthy young adults. Although they contribute limited information about the effect, such studies of cerebrovascular surgery do not provide an opportunity for comparisons among alternative therapeutic options. Without a randomized sample of surgically and nonsurgically treated patients with cerebrovascular disease, one control group must be employed so that factors such as type, duration and degree of deficit, natural course of the disease, the influence of hospitalization, and practice effects can be evaluated.

Closely related is the issue of choice of experimental design. Because research in this field has relied on only two basic research designs, practice effects have been confused with treatment effects in many studies. One experimental design employs a simple one group, pretest-posttest comparison, and the basic datum is the difference between the two tests. As the name implies, the subjects are tested before and after the experimental manipulation, in this case surgery. This design permits no estimation of the effects of practice on the observed postoperative improvements. The second study design employs a nonequivalent control group (10). In these studies, surgical patients are compared both pre- and postoperatively with a nonneurological/general medical patient group. This design controls for practice effects only to the extent that the comparison and experimental groups have the same potential to improve with practice. Thus, if patients with symptomatic cerebrovascular disease are less likely to show practice-related score increases. Similarly, preexisting, between-group differences in other covariates, such as the natural course of disease, will be confounded with treatment effects.

It is essential that we develop new experimental designs. A nonrandomized version of the Solomon four-group design (10) is one good possibility. In this design, the surgical and control patients are randomly divided into posttest only and pretest-posttest groups. Creating these four groups permits comparisons which are controlled for factors such as history, recovery, practice, regression effects, and mortality. Without such studies, our knowledge about the effects of these factors will remain speculative.

Beyond the problem of experimental design, such important issues as the interaction of test-retest interval and the natural history of cerebrovascular disease must be considered. Two- or three-month follow-up intervals are not long enough to evaluate issues of the basic quality of life, yet few reports describe results as long as one or two years after surgery (11).
All of these methodological issues limit our ability to interpret research findings in the field. Only a few authors have attempted to implement controlled research designs (5,12). Some investigators report neuropsychological improvements after vascular surgery (12,13), but others have not (5). Some authors stress practice effects (5), others do not (2). This diversity highlights the need for careful attention to these methodological issues. However, the weight of evidence does suggest that some patients improve in these neuropsychological functions after surgery. Similarly, some surgical patients do not show improved neuropsychological function. Regrettably, we cannot differentiate these patients a priori, but with more rigorous experimental methods we hope to make that differentiation in the future.

References