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ular fibrillation, may produce syncope or ischemic cerebral infarcts,[3] especially in patients with coexistent carotid stenosis. These abnormalities were not present in the patient reported here.

We conclude that the association of MVP and MD is not a fortuitous one, and therefore should be sought in all patients with MD. Since the presence of MVP in patients with MD represents a potential source of neurologic problems, the symptomatic supportive treatment of these patients should include periodic cardiological evaluation and prophylaxis against infective endocarditis at the time of oral surgery. The use of antiplatelet agents should be considered in patients over 40 years of age with MVP.

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Problems in Design of Stroke Treatment Trials

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SUMMARY Critical evaluation of the literature was used to identify remediable flaws in the design of clinical trials of stroke treatment. Trials of dexamethasone, dextran, and glycerol were reviewed. Available studies have in common major weaknesses in case selection (failure to exclude arteriolar strokes due to hemorrhage or lacunar infarction), and failure to estimate required sample size. Problems of case selection can be avoided with computerized tomography; the sample size required to show superiority of active treatment over placebo can be estimated using standard formulas. Prognostic stratification is suggested as a method of overcoming problems of unbalanced allocation. Further studies with improved design are required to evaluate the prospects for medical limitation of cerebral infarct size.

THE studies leading to this presentation took the form of critical analysis of the literature, undertaken during the design of a controlled trial of stroke treatment. Serious problems in design were detected in many of the available studies. The purpose of this paper is to describe to clinicians who are in a position to design and implement future studies the weaknesses in design of earlier stroke treatment trials. The issues presented here deserve particular attention at this time, since trials of high-dose dexamethasone[1] and barbiturate coma[2] for the edema of cerebral infarction are undoubtedly being currently designed at this time.

The use of such treatments in the acute management of stroke is intended to minimize the extent of infarction resulting from occlusion of a given artery, and should be seen in the context of a comprehensive approach to stroke management (table 1). This ap-

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TABLE 1   *Goals of Medical Treatment of Stroke*

Diagnosis (detailed specific identification of etiology & pathogenesis)

Support (airway, ventillation, arrhythmias, blood pressure)

Minimization of the extent of infarction resulting from a vascular occlusion (acute care)

Minimization of the extent of disability resulting from a given amount of brain infarction (rehabilitation)

Prevention of recurrence

proach to the treatment of ischemic cerebral edema is analogous to the use of after-load reduction to minimize the extent of myocardial infarction after a coronary artery occlusion. The role of cerebral edema in the progression of cerebral infarction has been analyzed extensively in recent reviews.[3, 4]

A number of therapeutic agents have been tried to reverse ischemic cerebral edema; including dexamethasone, glycerol, and low molecular weight dextran.[5-15] Although these agents have been the subject of controlled trials, their role in treatment of stroke is not yet clear. The purpose of this study was to identify remediable errors in the methodology of such trials.

Only medical therapies were considered. Hyperventilation has received limited study,[16] while surgical treatment of ischemic cerebral edema remains anecdotal.[17] Eight studies were selected for analysis on the basis that they are well known, widely quoted, randomized prospective controlled trials. Some characteristics of these studies are shown in table 2.

Observations

Case Selection

Entry criteria for patients were too broad. In part, this may have been due to the inadequacy of clinical

methods for distinguishing between strokes due to occlusion of major cerebral vessels (such as the internal carotid artery and middle cerebral artery), strokes due to intracerebral hemorrhage, and those due to lacunar infarction. Patten et al.[6] included "all patients with the sudden onset of a focal neurologic deficit within 24 hours prior to admission . . ." (subarachnoid hemorrhage was excluded by sampling cerebrospinal fluid). It is clear that the outcome of a patient with occlusion of a given cerebral artery is determined by the extent of collateral circulation, and by the extent to which cerebral edema secondary to ischemia causes raised tissue pressure and thereby interferes with collateral circulation.[4] It is now recognized that pressure gradients exist within the cranial cavity, and that the area of edema secondary to infarction is associated with raised pressure.[18-21] Furthermore, it is known that because blood vessels in the ischemic area have lost the ability to autoregulate, flow is dependent on perfusion pressure.[22, 23] As the tissue pressure in the ischemic brain rises, the perfusion pressure in that ischemic area goes down. Thus, the very part of the brain which has been deprived of its autoregulation and is therefore dependent on perfusion pressure for its survival, has a gradual and progressive diminution of its perfusion as the cerebral swelling gets worse. A vicious circle is thus set up with edema causing increased tissue pressure, resulting in decreased perfusion pressure, increasing ischemia, and so on.[4] Oxbury et al.[24] observed that the rational treatment of cerebral hemorrhage would be different from the treatment for cerebral infarction, and that before computerized tomography became available, in many cases it was not possible to distinguish between cerebral hemorrhage and cerebral infarction. Thus, studies that were designed to measure the effects of treatment for cerebral infarction and edema, but were done

TABLE 2

Study	Reference #	Rx	#	Timing of Rx	Follow-up	Results
1. Patten et al 1972	(6)	Dexamethasone 10 mg Q6H vs placebo	31 (3H)*	24 hrs	17 days	$p < 0.02$ for severe group (15)
2. Bauer & Tellez 1973	(11)	Dexamethasone 12 mg, 4 mg Q8H vs placebo	54 (severe)	48 hrs	14 days	NS
3. Norris 1976	(9)	Dexamethasone 8 mg, 4 mg Q6 H	53	24 hrs	30 days	$p < 0.05$ (Dex. worse)
4. Matthew et al 1972	(7)	Glycerol 50 g IV daily vs placebo	62 (8H)	96 hrs	14 days	$p < 0.01$ for infarct cases (54)
5. Gilsanz et al 1975	(8)	Glycerol 50 mg daily vs Dex. 4 mg Q6H	68 (7H)	36 hrs	15 days	$p < 0.05$ improved patients
6. Gilroy et al 1969	(12)	Dextran 40 vs placebo	100	72 hrs	10 days	$p < 0.05$
7. W. B. Matthews et al 1976	(10)	Dextran 40 vs placebo	100	48 hrs	6 months	NS
8. Kaste et al 1976	(13)	Dexamethasone 10 mg, 5 mg Q6H	40	48 hrs	29 days	NS

*H = intracerebral hemorrhage

before the advent of computerized tomography, will inevitably have included a number of patients with cerebral hemorrhage, thus confounding the analysis of the results.[24] Studies done before the advent of computerized tomography cannot be faulted for failing to use the technique; however, since computerized tomography is now available, it will be possible to better evaluate all patients included in future treatment trials. Only patients with major vessel occlusion and hemisphere edema should be included in these studies. Therefore, patients with cerebral hemorrhage or with lacunar infarction in the internal capsule or brain stem, should be excluded.

Allocation of Subjects to Treatment Groups

Simple random allocation, especially in small studies, carries some risk of serious imbalance between study groups with respect to the initial severity of disease. This problem can be avoided by prognostic stratification. One method of accomplishing this is to assign an initial severity score at the time of patient allocation, and to randomize patients to treatment groups within previously defined levels of severity. An example of such an initial severity score, based on the observations of Oxbury et al.,[24] is given in table 2. Using such a scoring system, patients could be assigned to mild, moderate, and severe groups on the basis of previously defined ranges for their total score, and then randomized to treatment groups within each of those severity levels.

An alternative to prognostic stratification in the design stage of a study is to stratify on the basis of important prognostic factors at the analysis stage, using, for example, methods discussed by Peto et al.[25] However, as pointed out by Brown,[26] stratification at the design stage has the advantage of being more persuasive than post hoc statistical adjustment in convincing clinicians that the treatments were "fairly" compared. Moreover, no method of statistical adjustment can compensate for severe cases of imbalance in important prognostic factors.

Sample Size Estimates

None of the studies contained a formal discussion of sample size requirements. The number of patients studied ranged from 21 to 100, and only two of the studies included more than 70 patients. Since the outcome of patients with stroke is highly variable, the sample size aspect of design is crucial.

As an illustration, table 3 shows sample size estimates based on standard formulas[27] for a hypothetical trial comparing an experimental treatment (for example dexamethasone) with placebo. Case 3 in this table gives the number of patients required in each group to provide a .80 chance $(1-\beta)$ of showing a statistically significant difference at the .05 level (α), if the active treatment reduces mortality from 20% to 10%. This estimate of 198 subjects in each group, or a total of 396 subjects in the study, does not make an allowance for dropouts. It is important to realize how sensitive the sample size estimates are to small changes in expected outcomes. Case 4 shows that using the same α and β, but with the expected mortality in the placebo group being 15%, and the treatment effect reducing mortality by only a third, the sample size then required would be 688 subjects in each group. The comparison of Case 4 with Case 5 shows how sensitive the sample size requirements are to the level of the expected event rates.

Brown[26] has pointed out various approaches that are useful in effectively reducing the number of patients required for a clinical trial. One of these is to expand the definition of events counted as end point occurrences; for example, by using poor outcome and stroke death as a combined end point. Effective sample size requirements may also be reduced by recording the times at which end point events occur (rather than simply counting the number of end points), by extending the follow-up period of a trial, or, in some cases, by adopting a sequential approach to monitoring outcome.[28]

Studies with large numbers of patients, particularly when confined to patients with CT evidence of hemisphere edema from major vessel occlusion, would almost certainly have to be conducted as multicenter trials, which invariably involves many other complex issues. A good discussion of the problems particular to multicenter clinical trials may be found in a report of a recent seminar held in France.[29]

Time of Entry

Ischemic cerebral edema is at a maximum from 2 to 4 days following the ischemic event.[3] In the trials under discussion, patients were entered from 14 to 96 hours after the event (see table 2). Based on the timing of maximum cerebral edema, any medical therapy aimed at minimizing the amount of infarction should probably be initiated within 24 or 48 hours of the ischemic event.

TABLE 3   *Sample Size Estimates*

Case	1-β (probability of detecting a difference)	α (level of significance two-tailed)	Expected experimental mortality rate	Expected placebo mortality rate	Sample size (number in each group)
1	.95	.05	10%	20%	325
2	.90	.05	10%	20%	263
3	.80	.05	10%	20%	198
4	.80	.05	10%	15%	688
5	.80	.05	30%	45%	208

TABLE 4 *Initial Severity Score*

Modality	Description	Score	Weight	Weighted Score
1. Age	Yrs.			
	< 40	—0		
	40–50	—1		
	50–60	—2	× 5	
	60–70	—3		__ (Max 15)
2. Conscious Level				
	Normal	—0		
	Drowsy	—1		
	Obtunded	—2	× 10	
	Adaptive responses to pain	—3		
	Reflex responses to pain	—4		
	No limb movements to pain	—5		__ (Max 50)
3. Motor Power (*each* limb on affected side)				
	Normal	0		
	Minimal weakness	1		
	Moderate weakness	2	× 5	
	Slight movement only	3		
	Complete paralysis	4		__ (Max 40)
4. Gaze Palsy or Deviation				
	None	0		
	Palsy	1	× 10	
	Forced deviation	2		__ (Max 20)
			Total	__ (Max 125)

Duration of Follow-up

The final assessment of the patients in the studies reviewed was at one month or less in all but one study, and was within 17 days of the ischemic event in five of the eight studies. Clearly, such early assessments pertain only to the very acute events associated with vascular occlusion. If the aim of such therapy is not only to reduce mortality, but also to minimize the extent of infarction resulting from a given vascular occlusion, then the outcome measures should be extended to a much longer recovery period. For example, evaluation of outcomes could be carried out at intervals (e.g. 3 months) for at least one year after the ischemic event, in order to compare the degree of recovery in the treatment groups. As mentioned above, increasing the follow-up period in a study is also a method of reducing the total number of patients required for the trial.

Definition of Initial and Outcome Scores

There was some inefficiency in the scoring systems used to evaluate the outcome measures in the trials. One weakness was that the studies tended to use the same neurological scores to measure severity at entry as to measure outcomes. These neurological scores are largely based on traditional clinical examination, and place undue emphasis on features of the neurological examination that reflect details of the location of the ischemic event (such as language function), rather than reflecting the amount of brain involved in the lesion. It seems more useful to use two types of scores: an initial severity score based on the features of the neurological examination that predict a high mortality, and then separate outcome scores which reflect useful benefits of treatment. Such outcome scores should be weighted heavily towards placement (did the patient get home to his usual job, or did he require

constant attendance in a nursing home), and functional performance, in addition to details of the clinical neurological examination.[30, 31]

Oxbury et al.[24] showed that patients with a dense hemiplegia and impaired consciousness, with or without conjugate deviation of the eyes toward the infarcted hemisphere, suffered a mortality rate in excess of 40%; whereas patients without these features had a mortality rate of less than 12%. Table 4 gives an example of an initial severity score based on those features of the examination, and on age.

Examples of Alternative Scoring Systems

Appendix A presents examples, from the literature, of elements that might be included in functional outcome scores.[30, 31] An alternative to some of these scores would be the Barthel index.[30]

Discussion

Peck has observed that editorial requirements for statistical analysis of studies led in the early 1970's to virtual deification of what he called "the almighty 'P' value."[32] Unfortunately, a frequent result of the application of statistical tests to improperly designed trials is that the conclusions tend to be based solely on the outcome of the statistical test. Thus, Fisher's designation of $P \leq .05$ as "significant" has been distorted by many to the point that a decision as to the efficacy of a therapy depends on the P value obtained in a clinical trial. Such conclusions are totally unwarranted if the study was designed in such a way that it would not be possible to reach a meaningful conclusion; for example, if the sample size were much too small to show benefit of a treatment. This type of error, in which a negative result is wrongly accepted, is called the β-error and is particularly common.[33]

APPENDIX A *Outcome Scores*

I. Neurological

| Motor function: | Hand | 0 Normal
1 detectable impairment
2 marked impairment
3 useless | Arm | 0 normal
1 definite weakness
2 slight movement
3 paralyzed |

Gait:
0 normal
1 abnormal, no aids required
2 abnormal, aids required
3 unable to walk

Visual Field:
0 normal
1 inattention
2 hemianopia

Incontinence:
0 no
1 occasional — no drainage apparatus needed
2 frequent — drainage apparatus needed

II. Communication and Intellectual Adaptability

Communication ability
— Verbal and hearing
0 Independent
— No more than slight to moderate limitation in communication due to language barrier or verbal or hearing disorder.

1 Dependent
— Either no communication is possible or else a structured setting or interpreter is needed to facilitate communication due to a verbal or hearing or language barrier.

Intellectual and Emotional Adaptability
0 Independent
— Patient functions independently without impairment or only mild impairment in problem-solving, regard for others, perceptual-motor skills, judgment, reliability or self-esteem.

1 Dependent
— Patient is observed to function appreciably better with assistance, supervision, cuing, coaxing or structured environment due to above impairments or else impairments are too severe to be benefited by assistance.

III. Performance

Class I   No significant impairment
Fully independent acts of daily living (ADL), pursues usually avocational activities, and returns to previous living site and occupation without modification.

Class II   Mildly impaired
Semidependent (requiring some assistance) in ADL, and/or slight restriction of avocational activities, and/or able to return to previous occupation with some modification of the latter.

Class II   Moderately impaired
Semidependent (requiring lifting assistance) in ADL, and/or considerable restriction of avocational activities, and/or unable to return to previous occupation and must seek selective occupation.

Class IV   Severely impaired
Fully dependent in conduct of ADL, and/or unable to participate in avocational activities, and/or unable to carry out any occupation.

IV. Placement

Class A.   No limitation

Class B.   Mild limitation
Requires occasional supervision, and/or modified environment, and/or occasionally medical care.

Class C.   Moderate limitation
Requires much supervision, and/or physical assistance or outside helpers, and/or regularly available medical care.

Class D.   Severe limitation
Requires constant or nearly constant attendance and/or immediately available medical-nursing care.

V. Neuropsychological Testing

I.Q.

Memory score

Language score

Sensory score

Visual motor skill

Glantz[34] has estimated that almost half the articles published that use statistical methods use them incorrectly. This was true even for such a respected journal as Circulation.

This didactic presentation highlights the difficulties that clinicians have in designing, implementing, and analyzing clinical trials. Perhaps the most important lesson to be taken from it is that a statistical consultant should always be involved in the design of clinical trials. Too often it is impossible to "rescue" a poorly designed trial by analysis of the data in retrospect because of the kinds of problems discussed here.

Recent trials of stroke prevention (as opposed to stroke treatment) show evidence of extensive input from epidemiologists and statisticians at the design stage.[35, 36] Hopefully, such examples will carry over to treatment trials in future.

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