Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. Report on a Randomized Treatment Study

II. Objectives and Design of Randomized Aneurysm Study

BY DONALD W. NIBBELINK, M.D.,* AND LLOYD A. KNOWLER, PH.D.†

Abstract: *II. Objectives and Design of Randomized Aneurysm Study*

■ Four selected treatments, namely, regulated bed rest, drug-induced hypotension, carotic ligation, and intracranial surgery, were randomly allocated with respect to location of th aneurysm and interval following last bleed. The objective of the Study was to answer the ques tion, "What mode of treatment offers a patient with a single ruptured intracranial aneurysn during the previous three months the highest probability of optimal results with respect to sur vival, residual neurological deficit, capacity for self-care, and gainful employment?" Variou treatments were suspended at specific intervals when a particular mode of therapy became in ferior to the others.

A group of 33 patients was disqualified after treatment was randomly allocated. Th numbers of protocols remaining for analysis within each treatment category were 202 fc regulated bed rest, 309 for drug-induced hypotension, 187 for carotid ligation, and 274 for ir tracranial surgery.

Additional Key Words
subarachnoid hemorrhage
ruptured aneurysm
sequential analysis
cooperative aneurysm stud
randomized stud

Introduction

□ Evaluation of surgical and nonsurgical treatment of ruptured intracranial aneurysms has been the primary objective of the Cooperative Aneurysm Study since 1958. Uncontrolled clinical variables have always made the development of a properly designed treatment study very difficult. For nonsurgically treated patients with a single aneurysm, a mortality of 38% was observed in the previous Cooperative Study[1] within 14 days following the last bleed, and 68% at the end of eight years; whereas mortality following intracranial operation was 30% during the interval from surgery to time of discharge. However, it was emphasized that "selective withdrawal of cases favorable for surgery is likely to affect the data and probability calculations based thereon, in the direction of making them more pessimistic than would be ol tained from a completely undistorted sample Because of theoretical and practical limitations "case matching" on a statistical basis, the prese Study was established so that selected treatments we randomly allocated with respect to location of tl aneurysm and interval from last bleed.

Objective

The principal objective of the Study was to provide answer to the question, "What designated mode treatment offers a patient with a single ruptured i tracranial aneurysm during the previous three mont the highest probability of optimal results with respe to survival, residual neurological deficit, and capaci for self-care and gainful employment?" The fo modes of treatment recommended for random alloc tion were: (1) regulated bed rest, (2) drug-induc hypotension with regulated bed rest, (3) ipsilate common carotid artery occlusion with bed rest, a (4) intracranial surgery. Definition of each treatm category will be defined with the forthcoming repor

*Department of Neurology, University Hospitals, and †Department of Mathematics and Actuarial Sciences, University of Iowa, Iowa City, Iowa 52242.

Reprint requests to: Aneurysm Registry, Department of Neurology, University of Iowa, Iowa City, Iowa 52242.

TABLE 1

Definition of Aneurysm Site

1. Internal carotid — a single aneurysm located on the internal carotid artery distal to its emergence from the cavernous sinus to its terminal bifurcation, and including those aneurysms at the junction of the posterior communicating artery with the internal carotid artery. Infundibular dilatations 2 mm in diameter or less were not included.
2. Middle cerebral — a single aneurysm on the middle cerebral artery and its branches.
3. Anterior cerebral-anterior communicating — a single aneurysm on the anterior cerebral artery and its branches, the anterior communicating artery, and its junction with the anterior cerebral artery.
4. Vertebral-basilar — a single aneurysm on the vertebral, basilar, posterior communicating-posterior cerebral artery junction; posterior cerebral artery, and all its branches.

The relative value of each treatment was expected to remain usefully represented so that the effects of various factors not directly related to a ruptured aneurysm or its treatment would tend to cancel out. In that sense, the Study was designated a "randomized study." To minimize the effects of any dissimilarities among participating centers, such variables as professional skill, hospital facilities, biological differences among racial groups, and economic class were balanced to assure that each individual center constituted, of itself, a small "randomized study."

Design of Randomization

The aneurysm sites chosen for this investigation were located on the internal carotid, middle cerebral, and anterior cerebral arteries, plus single aneurysms on the posterior portion of the circle of Willis (see table 1 for definition of each site). Intervals from last bleed to allocation of treatment were designated as follows: zero to seven days, eight to 21 days, and 22 to 92 days (table 2). A statistical method utilizing sequential analysis[2] was engaged to compare one treatment with another with respect to mortality at 30, 90, and 180 days following the last bleed. Additional analyses were performed on a yearly basis until five years following the bleed. The sequential plan was used in order to terminate the study as soon as feasible after a sufficient number of cases had been accumulated. Each treatment at each site and at each time interval was compared to each and every other treatment with respect to the principal objective of the study. Any evidence of inferiority comparing one treatment with another at a statistically significant level ($P = 0.05$) was immediately called to the attention of the participants. Mortality and morbidity were continuously monitored in order to assess those factors potentially deleterious in executing the treatment programs.

Within each interval following the last bleed, patients with a single aneurysm on the anterior portion of the circle of Willis were randomly allocated to one of four treatment categories (table 2). For those with an aneurysm on the posterior portion of the circle, only two alternatives were recommended: (1) regulated bed rest, and (2) intracranial surgery (table 3).

Each patient with subarachnoid hemorrhage underwent a prescribed protocol of clinical and laboratory evaluations. These included lumbar puncture with findings consistent with grossly bloody cerebrospinal fluid and xanthochromic supernatant,

TABLE 2

Stratification of Design for Randomization

Site:	1	Internal carotid
	2	Middle cerebral
	3	Anterior cerebral-anterior communicating
	4	Posterior circle
Interval:	1	0–7 days
	2	8–21 days
	3	22–92 days
		Interval from day of last bleed to date admitted to treatment study
Treatment:	1	Regulated bed rest
	2	Drug-induced hypotension with regulated bed rest
	3	Ipsilateral common carotid artery occlusion with regulated bed rest
	4	Intracranial surgery

TABLE 3

Designated Treatments for Each Aneurysm Site and Interval from Last Bleed

Site	Interval, days	Treatment*			
Internal carotid	0 – 7	1	2	3	4
	8 – 21	1	2	3	4
	22 – 92	1	2	3	4
Middle cerebral	0 – 7	1	2	3	4
	8 – 21	1	2	3	4
	22 – 92	1	2	3	4
Anterior cerebral-anterior communicating	0 – 7	1	2	3	4
	8 – 21	1	2	3	4
	22 – 92	1	2	3	4
Posterior circle	0 – 7	1			4
	8 – 21	1			4
	22 – 92	1			4

*See table 2 for definition of treatment.

TABLE 4

Intervals Various Treatments Were Suspended

Aneurysm site	Interval: From last bleed to randomization, days	Treatment: Beginning 6-15-63*	Treatment: Suspensions†	Treatment: 1-1-69 to 2-15-72
Internal carotid	0 – 7	1 2 3 4	B 2 3 B	X 2 3 X
	8 – 21	1 2 3 4	C 2 3 4	X 2 3 4
	22 – 92	1 2 3 4	C 2 3 4	X 2 3 4
Middle cerebral	0 – 7	1 2 3 4	D 2 3 4	X 2 3 4
	8 – 21	1 2 3 4	D 2 3 4	X 2 3 4
	22 – 92	1 2 3 4	D 2 3 4	X 2 3 4
Anterior cerebral	0 – 7	1 2 3 4	D 2 A 4	X 2 X 4
	8 – 21	1 2 3 4	D 2 A 4	X 2 X 4
	22 – 92	1 2 3 4	D 2 A 4	X 2 X 4
Posterior circle	0 – 7	1 4	C C	X X
	8 – 21	1 4	C C	X X
	22 – 92	1 4	C C	X X
Total		42		23

*Treatment designations:
Treatment: 1 = regulated bed rest
2 = drug-induced hypotension
3 = carotid ligation
4 = intracranial surgery

†Suspended treatments:
A 12-1-66
B 3-19-67
C 6-19-67
D 1-1-69

followed by angiographic visualization of the anterior and posterior cerebral circulations. Following visualization of a single aneurysm by cerebral angiography, and provided each patient was a candidate for any of the four treatment programs, the allocation of treatment was determined randomly, and the course of therapy instituted. Between June 15, 1963, and February 1, 1970, 1,005 protocols were presented to the Central Registry for analysis. A preliminary statistical analysis has been reported previously.[3]

During the Study, treatments were suspended in specific categories for various reasons. In the column designated "treatment suspensions" in table 4, ipsilateral common carotid ligation was discontinued in the group with an anterior cerebral-anterior communicating aneurysm on December 1, 1966 (A). This action followed a decision by the participants, and was *not* on the basis that carotid ligation was an inferior treatment. The rationale for the majority of participants at that time was the premise that ipsilateral common carotid ligation was ineffective in prevention of rebleeding in anterior communicating aneurysms. On March 19, 1967 (B, table 4), regulated bed rest and intracranial surgery were suspended for the internal carotid group because both treatment modes were significantly inferior to drug-induced hypotension (treatment 2) and carotid ligation (treatment 3). Regulated bed rest in the eight to 21-day interval and 22 to 92-day intervals was suspended later in the internal carotid group (June 19, 1967) following a statistically significant difference in mortality. Collection of single aneurysms on the posterior portion of the circle of Willis was also suspended on June 19, 1967. The number of cases was too few to have any statistical meaning. Later, on January 1, 1969, regulated bed rest was discontinued for all intervals in patients with an aneurysm located on the middle cerebral distribution and the anterior cerebral complex. For these reasons the number of cases for each site were not similar, especially with regard to the regulated bed rest and carotid ligation treatment categories.

Participating Institutions and Distribution of Cases

Fifteen institutions (table 5) began to submit protocols when the Study was initiated. One institution (Center 14) ceased participation after contributing one protocol (table 6) and a second institution (Center 22) submitted no more protocols after contributing 12 cases with the Central Registry. Centers 31, 32 and 33 began to contribute protocols after the Study was in progress.

Overseas participants collectively contributed 587 protocols (58.4% of 1,005). Without their high quality material, this Study could not have been completed. The remaining 418 protocols were from ten institutions in the United States. As noted in table 6, the variation in protocols from various centers was considerable. Center 20 submitted anterior cerebral anterior communicating aneurysms only per arrangement at the outset of the Study.

By random allocation, patients at each center

TABLE 5

Participating Investigators and Centers

NIH grant number	Investigators	Code no.	Centers
NB 04347	Mark L. Dyken, M.D. Robert L. Campbell, M.D.	(12)	Indiana University Medical Center, Indianapolis, Indiana
	Milton Ettinger, M.D.	(14)*	Minneapolis General Hospital, Minneapolis, Minnesota
NB 04373	A. L. Sahs, M.D. George Perret, M.D. Carl J. Graf, M.D. Herbert B. Locksley, M.D. Donald W. Nibbelink, M.D. Hiro Nishioka, M.D.* Lloyd A. Knowler, Ph.D.	(19)	University of Iowa, Iowa City, Iowa
	Mr. Wylie McKissock Mr. Lawrence Walsh Mr. Alan Richardson	(20)	Atkinson Morley's Hospital, London, England
	Paul Slosberg, M.D.	(22)*	Mt. Sinai Hospital of New York, New York, New York
NB 04345	Marshall B. Allen, Jr., M.D.	(24)	Medical College of Georgia, Augusta, Georgia
NB 04937	Albert Cook, M.D. Reza Khatib, M.D.	(25)	State University of New York, Downstate Medical Center, Brooklyn, New York
NB 04708	Hubert L. Rosomoff, M.D. Labe Scheinberg, M.D.	(26)	Albert Einstein College of Medicine, Bronx, New York
	Lars Leksell, M.D. R. Galera, M.D. Ladislau Steiner, M.D.	(27)	Karolinska Institute, Stockholm, Sweden
	Mr. Keith Bradley Mr. W. L. Elrick	(28)	University of Melbourne, Melbourne, Australia
NB 04343	Joseph Ransohoff, M.D. Clark Randt, M.D. Albert Goodgold, M.D.	(29)	New York University, New York, New York
	Erik Kågström, M.D. Nils Lundberg, M.D.	(30)	University of Lund, Lund, Sweden
NB 02413	Edwin B. Boldrey, M.D.	(31)	University of California Medical Center, San Francisco, California
NB 07135	Robert McLaurin, M.D. James Salmon, M.D.	(32)	University of Cincinnati, Cincinnati, Ohio
NB 07113	Orlando Andy, M.D. Robert R. Smith, M.D.	(33)	University of Mississippi, Jackson, Mississippi

*Ceased participation during investigation.

were designated to one of four treatment programs. The allocated treatment distribution for each center (table 7) reveals similar proportions. Total accumulations for each treatment were 214 for regulated bed rest, 315 for drug-induced hypotension, 191 for carotid ligation, and 281 for intracranial surgery.

TABLE 6

Distribution of Cases With Respect to Aneurysm Site for Each Participating Center

Center	Aneurysm site: Internal carotid	Middle cerebral	Anterior cerebral	Vertebral basilar	Total
12	21	10	20	0	51
14	0	0	0	1	1
19	30	18	25	2	75
20*	0	0	314	0	314
22	4	2	6	0	12
24	19	9	20	1	49
25	38	4	20	2	64
26	36	13	25	0	74
27*	27	22	37	5	91
28*	51	30	57	4	142
29	13	5	12	1	31
30*	8	10	22	0	40
31	5	1	13	0	19
32	7	0	7	0	14
33	9	4	15	0	28
Total	268	128	593	16	1,005

*Overseas participants.

TABLE 7

Distribution of Allocated Treatments for Each Participating Center

Center	Treatment allocations: Regulated bed rest	Drug-induced hypotension	Carotid ligation	Intracranial surgery	Total
12	10	17	8	16	51
14	0	0	0	1	1
19	15	23	18	19	75
20	77	97	46	94	314
22	6	4	1	1	12
24	9	13	10	17	49
25	11	21	16	16	64
26	14	21	19	16	70
27	20	29	13	29	91
28	27	49	32	34	142
29	8	6	9	8	31
30	10	11	7	12	40
31	3	5	3	8	19
32	1	5	4	4	14
33	3	14	5	6	28
Total	214	315	191	281	1,001
Allocated to special Study					4
					1,005

Within this group of 1,005 patients, 33 were disqualified (table 8). Disqualification signifies that following allocation of treatment, certain conditions or events arose which precluded the continuation of allocated therapy. These items (table 8) were similarly distributed among the four treatment categories. Subtracting these 33 patients leaves a total of 972 for analysis. The distribution for each aneurysm site and treatment allocation is represented in table 9.

The following reports will include a detailed analysis of all patients included in each treatment category. Each presentation will discuss factors primarily concerned with medical parameters followed later by the details of statistical analysis.

TABLE 8

Tabulation of Disqualified Cases

8	— Surgery required
7	— Previous hypotensive treatment
4	— Refused treatment
4	— Incorrect allocation of treatment
4	— Special study
3	— Multiple aneurysms found
1	— Extracranial aneurysm
1	— Refused hospitalization
1	— Uremia
33	Total disqualified

References

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TABLE 9

Distribution of Patients Allocated to Specified Therapy Program for Each Aneurysm Site

Aneurysm site	Treatment allocation: Regulated bed rest	Drug-induced hypotension	Carotid ligation	Intracranial surgery	Total
Internal carotid	37	82	88	50	257
Middle cerebral	23	35	27	38	123
Anterior cerebral-anterior communicating	135	192	72	180	579
Vertebral basilar	7	0	0	6	13
Total	202	309	187	274	972