J Neurosurg 69:15–23, 1988

High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury

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In a five-center study, 73 patients with severe head injury and elevated intracranial pressure (ICP) were randomly assigned to receive either a regimen that included high-dose pentobarbital or one that was otherwise similar but did not include pentobarbital. The results indicated a 2:1 benefit for those treated with the drug with regard to ICP control. When patients were stratified by prerandomization cardiac complications, the advantage increased to 4:1. A multiple logistic model considering treatment and selected baseline variables indicated a significant positive treatment effect of barbiturates, a significant effect of time from injury to randomization, and an interaction of treatment with cardiovascular complications. However, of 925 patients potentially eligible for randomization, only 12% met ICP randomization criteria. The results support the hypothesis that high-dose pentobarbital is an effective adjunctive therapy, but that it is indicated in only a small subset of patients with severe head injury.

Key Words · **head injury** · **increased intracranial pressure** · **barbiturate**

Present management of severe head injury relies on a combination of therapies, many of which are directed to prevent elevated intracranial pressure (ICP) or to normalize ICP once elevation has occurred. Management should evolve by adding new drugs or procedures to existing therapies when there is reason to believe that they would be effective. This five-center randomized clinical trial tested the hypothesis that the addition of high doses of pentobarbital will improve the ability to control ICP when compared with a standardized rigorously applied combination of conventional therapies. The control of ICP was chosen as the primary outcome criterion rather than mortality because the study design then avoided the ethical problem of not allowing the use of barbiturates in the control arm even when ICP reached presumably lethal levels. Although the use of high-dose barbiturates was and is controversial, there is clinical and laboratory evidence indicating a therapeutic effect.[2,3,18,19] However, any design that permits cross-over confounds interpretation of the mortality data. Before proceeding, then, two issues will be addressed: 1) is control of ICP an important outcome criterion? and 2) was it appropriate to study high-dose barbiturate therapy in the context of a complex multicentered randomized clinical trial?

Is ICP an important outcome criterion? All clinical studies of head injury that include data about ICP and its relationship to outcome report an association of elevated ICP with increased mortality and chronic morbidity.[1,4,9,14–16] In 1977, Miller and his coworkers[14] reported that, of 48 patients treated in the hospitals of the Medical College of Virginia, those who had severe head injuries but normal ICP had a 14% risk of dying while those whose ICP rose above 20 mm Hg had four times the chance of dying. Four years later, data from the same center but from a larger series of patients (207) indicated similar odds; 46% of the sample had elevated ICP as defined (> 20 mm Hg).[16] Eisenberg, *et al.*,[4] reviewing data from the Pilot Phase of the National Institute of Neurological and Communicative Disease and Stroke (NINCDS) National Traumatic Coma Data Bank identified 398 patients who had continuous monitoring of ICP during the acute period. In these patients ICP was a statistically significant predictor of outcome as graded by the Glasgow Outcome Scale (GOS),[8] and was independent of the severity of injury as indexed by the Glasgow Coma Scale (GCS).[23] These reports indicate an important association between outcome and ICP or, more specifically, ICP that is either normal or responds to therapy versus ICP not responsive to therapy.

While a critical ICP level has not been definitely identified, it is probably not only the degree of elevation but persistence that is important. Furthermore, there are indications that the critical level may be lower than had been previously suspected. Of particular interest in this regard is the study of Saul and Ducker[20] comparing two populations of severely head-injured patients, one (127 cases) in which efforts were made to control ICP at or below 25 mm Hg and the other (106 cases) in which ICP was manipulated to fall at or below 15 mm Hg. Although the two groups were studied sequentially, the methods of management were otherwise identical, giving credence to the interpretation that control of ICP to within the lower range is beneficial. However, the plausible interpretation that ICP or its response to therapy is not the critical factor but that ICP and outcome are both predetermined by the pathology resulting from impact must be considered in view of our study design. This interpretation is not supported by what is known of delayed herniation and secondary brain-stem injury and the relation between cerebral perfusion pressure and cerebral blood flow. Particularly relevant to our study design is the report by Marshall, *et al.*,[10] indicating that herniation can occur at pressures only slightly above normal.

Why study high-dose barbiturate therapy in a multicentered randomized clinical trial? More than 20 years ago, Ishii[7] proposed that high-dose barbiturates might be useful in the control of ICP. The first published series of head-injured patients receiving this therapy was reported by Marshall, *et al.*,[12] who found that barbiturates reduced elevated ICP in 75% of 25 patients who were declared refractory to a rigorous regime of ICP management which included mannitol administration and hyperventilation. In a follow-up report considering a larger series of 45 head-injured patients with intractable ICP, 36 responded to high-dose barbiturates of whom eight died and two were declared vegetative; of the nine nonresponders, eight died and one was vegetative.[19] A similar nonrandomized study was reported by Rea and Rockswold.[18] They identified 27 patients with severe head injury and intractable ICP. Fifteen of the 27 responded (five died and two were vegetative) compared with nine deaths and one vegetative outcome in the 12 nonresponders. These data indicated that there is a therapeutic effect of high-dose barbiturates and that failure to control ICP leads to death. In spite of this, the need for a randomized trial seemed clear.[13]

Our multicentered randomized clinical trial started in 1982. During the course of the study, the results of two other randomized trials were reported; the Richmond study analyzed data from 53 patients[26] and the Toronto study 59 patients.[21] In both studies the patients were given barbiturates prophylactically. In fact, in one (the Toronto study) barbiturates were given instead of mannitol. Neither study disclosed a beneficial effect of barbiturates. These results contrast with the results reported from our study where high-dose barbiturates were given only after elevated ICP was observed to be refractory to conventional management.

Clinical Material and Methods

The five centers that participated in this trial constituted the National Institutes of Health-supported Comprehensive Central Nervous System Trauma Centers: Albert Einstein College of Medicine, New York; Baylor College of Medicine, Houston; University of California at San Diego; University of Texas Health Science Center, Houston; and University of Texas Medical Branch, Galveston (see Appendix). The study was coordinated and monitored by investigators from the University of Texas School of Public Health, Houston, and from the NINCDS Division of Stroke and Trauma. Patients with severe head injury (postresuscitation GCS scores ≤ 7) and between the ages of 15 and 50 years were considered potential candidates. Pregnant patients or patients with a GCS score of 3 or nonreactive pupils were excluded. Eligible patients were intubated and computerized tomography (CT) scans were made as soon after stabilization as possible. Mass lesions, intracranial hematomas, and/or surgically accessible cerebral contusions (> 25 cc) were promptly evacuated. An ICP monitoring device (a ventriculostomy when possible) was inserted and ICP was continuously monitored and recorded. Elevations greater than 15 mm Hg were treated according to a rigorously applied sequence of therapies that was standardized across the centers and included hyperventilation, muscle paralysis, sedation, mannitol, and ventricular drainage (when possible). Despite the use of mannitol, there was a concerted effort to prevent dehydration. The state of the patient's hydration was monitored by a Swan Ganz or central venous pressure catheter. The effective dose of mannitol was determined by monitoring serum osmolarity. All patients were given dexamethasone because at least at the onset of the study there was still some question of its efficacy and, more importantly, patients frequently were given large doses prior to admission to a study hospital. It was then easier to control for a possible effect by giving a high dose to all patients. We believe that this management plan constituted the best conventional therapy; its specifics are outlined in greater detail in Fig. 1 ("conventional therapy").

Our strategy was to test the effect of high-dose pentobarbital by adding it to this conventional therapy only when pressure elevations (as specified below) were observed, indicating that the conventional therapy was not adequate for the control of ICP. Half of the patients were randomized to the barbiturate arm (pentobarbital was given in addition to continuing the "conventional therapy"), while the other half were continued on "conventional therapy" only. Pentobarbital was given in loading and maintenance doses as specified in Fig. 1 ("barbiturate therapy"). Serum pentobarbital levels were measured at regular intervals (four, 12, and 24 hours, and then every 24 hours) with the goal of maintaining serum concentrations in the range of 3 to 4 mg%. Patients were randomized (fixed block size) by center according to the last available GCS score (4 to

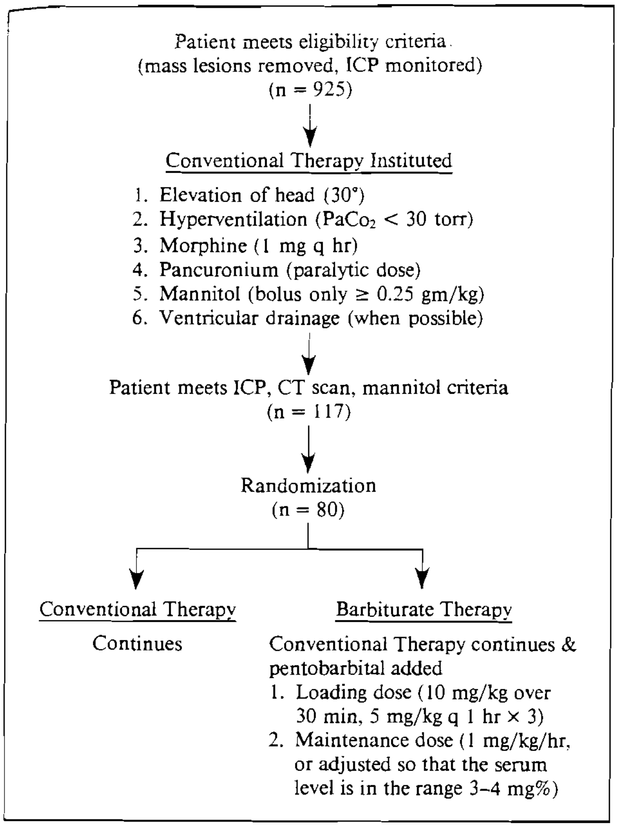

FIG. 1. Schema of study design with details of "conventional therapy" and "barbiturate therapy." ICP = intracranial pressure; CT = computerized tomography; n = number of cases.

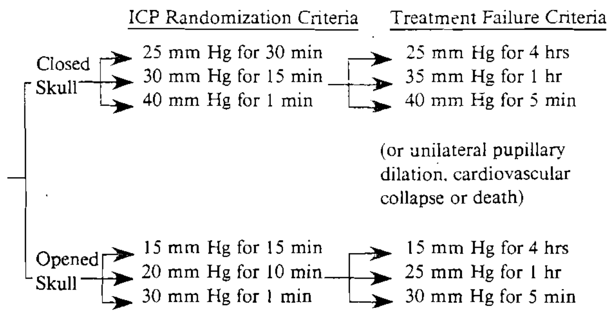

FIG. 2. Criteria for intracranial pressure (ICP) randomization and treatment failure. Eight patients were in the opened skull subgroup. "Opened skull" indicates craniectomy > 25 sq cm with the dura left open. A patient could not be considered a barbiturate treatment failure unless the full loading dose had been given or unless, in the event of cardiovascular compromise, as high a dose as could be tolerated had been administered.

7) using sealed opaque envelopes. Patients whose last available GCS score was 3, 8, or greater were excluded from this study, based on the reasoning that patients whose GCS score was 8 or greater were unlikely to respond to continued conventional therapy, and those whose GCS score was 3 were unlikely to respond regardless of further modifications of their therapy. The study design specified that the conventional therapy had to have been maximally applied before a patient could be considered as meeting randomization criteria. In addition, a CT scan was required within 24 hours before random assignment and all accessible mass lesions must have been removed. Furthermore, the patient had to have been given mannitol, 1 mg/kg, within 1 hour prior to assignment to a group or have a serum osmolarity of at least 315 mOsm. Patients were randomly assigned to a treatment group only if the responsible family member signed an informed consent. Regardless of which treatment group patients were randomly assigned to, an attempt was made to prevent and treat hypotension with cautious volume loading, and if treatment with vasopressors was necessary, dopamine was usually used. Randomization criteria were based on ICP levels and time of persistence. Different ICP criteria were used when a patient had a large craniectomy (> 25 sq cm) and the dura was left open ("skull opened"), since it was considered that in this group herniation may occur with less severe pressure elevations. Every effort, however, was made to close the dura and replace the bone flap, and only eight patients were entered according to these criteria (also see Table 6). The randomization criteria for both groups, "skull closed" and "skull opened," are detailed in Fig. 2.

With regard to the primary outcome criteria, there were only two possibilities: 1) "treatment success" was declared when a patient's ICP fell below 20 mm Hg (15 mm Hg for those classified as "skull opened") and remained below that level continuously for 48 hours; 2) "treatment failure" was declared when ICP became uncontrollable as specified in Fig. 2 or the patient developed a unilateral dilated pupil or cardiovascular collapse, or died. Furthermore, patients in the barbiturate arm could not be considered a treatment failure unless they were given the loading dosage or as high a dose as could be tolerated. Even though most patients in the conventional therapy arm had been treated according to the protocol for hours and some even for days prior to random assignment, we reviewed all cases declared conventional therapy failures that were recorded within $3\frac{1}{2}$ hours of assignment to a group ($3\frac{1}{2}$ hours is the time required for barbiturate loading): all continued to have elevated ICP or died during that interval. Thus, the $3\frac{1}{2}$-hour grace period did not result in an advantage for the barbiturate arm. Patients randomly assigned to the conventional therapy arm and declared a treatment failure could be crossed over to the barbiturate arm at the physician's discretion but, regardless of their subsequent response, were still designated as conventional treatment failures. When patients who were given pentobarbital had their ICP controlled (< 20 mm Hg for 48 hours), the drug was discontinued on a tapering dose schedule over 3 days. If during this time their ICP rose again to levels specified for randomization (Fig. 2), a second loading dose was given and high-dose pentobarbital therapy was continued until the patient was either ultimately declared a treatment success (at 48 hours after the last dose) or a treatment failure. Other outcomes observed were survival and GOS score at 30 days and 6 months. Demographic data, CT findings, and ICP profile as well as complications, treatment, and other pertinent clinical information were abstracted and recorded on forms developed for the National Traumatic Coma Data Bank.[11]

Based on estimates of success for head-injury management routines (10% to 20%), the study was designed to detect a minimum of a threefold improvement in the control of ICP with adjunct barbiturate therapy with at least 90% power at the 5% level of significance. The sample size required for this specification is 60 cases per treatment group. However, only two-thirds of the target sample size was achieved. This reduced the statistical power of the design to 75% for detection of a threefold improvement, and gave less than 50% power to detect a twofold improvement in ICP control.

The statistical significance of treatment effects was determined by fitting a logistic multiple regression model[25] to the binary dependent variables of treatment outcome (success/failure), using treatment and selected baseline variables as explanatory (independent) variables. Analysis proceeded by first fitting by maximum likelihood the logistic model to all of the indicated variables and then eliminating variables determined to be not significantly prognostic by the backward elimination method.[6] The statistical significance of the regression coefficients of the final model was judged by: z-statistic = parameter estimate/standard error, which follows a standard normal distribution under the null hypothesis that the parameter being tested is 0. The goodness of fit of the logistic regression model was tested by the chi-square test of Tsiatis.[24] All statistical computations were done using SAS Institute software (Version 5, 1985).

Results

During the study period from December, 1982, to December, 1985, 925 patients were admitted to the study hospitals for treatment of severe head injury (GCS score ≤ 7). According to the previously listed criteria, 116 (12.5%) were identified as eligible for entry into the clinical trial. Informed consent was received from 80 of these patients. Of the 80 patients randomly assigned to the two treatment groups, seven were withdrawn from the study (five from the conventional treatment arm and two from the barbiturate arm) because they did not meet all prerandomization study requirements. Patients were excluded for the following reasons: 1) barbiturates were given prior to randomization; 2) an operable mass lesion was detected after randomization, but was probably present before randomization (no CT scan within 24 hours of randomization); 3) ICP was below the randomization criteria; and 4) the patient did not receive the prescribed prerandomization conventional therapy (Fig. 1). Of the remaining 73 patients, 36 were randomly assigned to the conventional treatment arm and 37 to the barbiturate treatment arm.

The frequency and distribution of the major demographic and clinical variables for the treatment groups are shown in Table 1. The two groups are comparable in sex, race, age, and cause of injury. Similarly, the frequency of prior hospital admission (as opposed to direct admission from the scene of the injury), as well as the median time to arrival at the study hospital and the average time from injury to randomization, are similar for the two treatment groups. Table 2 lists the

TABLE 1

*Characteristics of patients by treatment group**

Characteristic	Conventional Treatment	Barbiturate Treatment
no. of cases	36	37
mean age (yrs)	24.3 ± 6.3	25.3 ± 8.0
male sex	33 (91.7%)	29 (78.4%)
race: white	29 (80.6%)	33 (89.2%)
cause of injury		
motor-vehicle accident	28 (77.8%)	30 (81.8%)
fall or fight	2 (5.6%)	4 (10.8%)
other	6 (16.7%)	3 (8.1%)
direct admission	18 (50.0%)	21 (56.8%)
admission time after injury		
median (hrs)	1.5	1.4
range (hrs)	0.2–27.2	0.5–97.3
mean time to randomization after injury (hrs)	89.0 ± 70.1	83.3 ± 72.5

* Means are given ± standard deviation.

TABLE 2

Diagnoses and computerized tomography (CT) findings for patients by treatment group

Characteristic	Conventional Treatment		Barbiturate Treatment	
	No.	Percent	No.	Percent
no. of cases	36		37	
primary diagnosis				
cortical contusion	7	19.4	7	18.9
diffuse injury	10	27.8	14	37.8
intracerebral hematoma	8	22.2	3	8.1
subdural hematoma	4	11.1	8	21.6
epidural hematoma	5	13.9	1	2.7
gunshot wound	2	5.6	2	5.4
midline shift on CT scan				
none	12	33.3	18	48.6
1–5 mm	6	16.7	10	27.0
6–10 mm	10	27.8	5	13.5
> 10 mm	5	13.9	2	5.4
status unknown	2	5.6	2	5.4
brain-stem cisterns				
normal	9	25.0	11	29.7
abnormal	18	50.0	25	67.6
status unknown	9	25.0	1	2.7

primary diagnoses and important CT scan findings for the two treatment groups. Subdural hematoma, an important predictor of a poor outcome,[1,5,17] appeared twice as frequently in the barbiturate arm. However, this was offset by the relative frequency of other mass lesions in the conventional arm, such as epidural hematoma which does not have a favorable outcome in comatose patients.[22] Gunshot wounds appeared infrequently and two patients with this cause of injury fell in each treatment arm. In contrast to the frequency of the primary diagnosis of subdural hematoma in the barbiturate arm, severe midline shift (> 5 mm) was seen on CT scans more frequently in the conventional arm. Normal brain-stem cisterns were approximately equally distributed between the two treatment groups (Table 2). On arrival at the study hospitals, approximately half of the patients showed a best motor response of "none" or "extensor," and slightly less than half showed no pupillary reactivity. The distributions of GCS scores and pupillary reactivity at the time of random assignment to a treatment group are shown in Table 3.

TABLE 3

*GCS score and pupillary reaction of study patients at time of randomization by treatment group**

Characteristic	Conventional Treatment		Barbiturate Treatment	
	No.	Percent	No.	Percent
no. of cases	36		37	
GCS score				
4	10	27.8	13	35.1
5	8	22.2	10	27.0
6	12	33.3	11	29.7
7	6	16.7	3	8.1
pupillary reactivity				
no reaction	11	30.6	11	29.7
one reactive	3	8.3	6	16.2
both reactive	22	61.1	19	51.4
unknown	0	0	1	2.7

* GCS = Glasgow Coma Scale.

TABLE 4

Prerandomization complications of patients by treatment group

Characteristic	Conventional Treatment		Barbiturate Treatment	
	No.	Percent	No.	Percent
no. of cases	36		37	
complications				
cardiovascular	14	38.9	17	46.0
pneumonia	11	30.6	6	16.2
pulmonary (other)	9	25.0	9	24.3
electrolyte imbalance	12	33.3	11	29.7
infection	3	8.3	0	0
complication frequency				
no complications	9	25.0	12	32.4
1–2 complications	22	61.1	20	54.0
3–4 complications	5	13.9	5	13.5

Of particular interest for their potential prognostic value were the frequency and distribution of complications prior to randomization. Table 4 gives the prerandomization frequency of complications of cardiovascular and pulmonary origin, electrolyte imbalance, and non-central nervous system infections for the two treatment arms and the distribution of all complications among patients. Prerandomization cardiac complications showed a possible important interaction with therapy, and is discussed below.

Table 5 lists the frequency and distribution for each for the randomization criteria for both treatment arms and also according to whether the skull was closed or opened. The mean ICP at the time of randomization was virtually identical to both treatment groups as was the frequency of each randomization criterion, neither arm having an apparent advantage due to the degree of duration of elevated ICP.

Analysis of the 73 patients randomly assigned to the two treatment groups showed that the chance of ICP control in patients with ICP refractory to conventional management was nearly double (ratio 1.94, $p = 0.12$) for those patients randomized to the barbiturate arm (Table 6). This finding is further analyzed for its consistency with the prognostic factors listed in Table 7. The factors examined are GCS scores at randomization, time from injury to randomization, and the occurrence of prerandomization cardiovascular complications. The approximate twofold therapeutic advantage of high-dose pentobarbital over continued nonbarbiturate ICP management was seen among patients randomized at combined GCS scores of 4/5 and 6/7, respectively,

TABLE 5

*Frequency of ICP randomization criteria and ICP distribution at randomization**

Characteristic	Conventional Treatment		Barbiturate Treatment	
	No.	%	No.	%
no. of cases	36		37	
closed skull				
ICP = 25 mm Hg (30 min)	13	40.6	13	39.4
ICP = 30 mm Hg (15 min)	7	21.9	8	24.2
ICP = 40 mm Hg (1 min)	12	37.5	12	36.4
opened skull				
ICP = 15 mm Hg (15 min)	1	25.0	1	25.0
ICP = 20 mm Hg (10 min)	0	0	1	25.0
ICP = 30 mm Hg (1 min)	3	75.0	2	50.0
ICP distribution (mm Hg)				
minimum ICP	20		20	
first quartile	28.5		30	
median	34.5		34	
third quartile	43		42	
maximum ICP	85		61	
mean ICP	38.0 ± 14.22		35.2 ± 8.12	

* ICP = intracranial pressure; closed skull = no craniotomy or craniotomy with skull and dura closed; Opened skull = craniotomy > 25 sq cm with dura opened. Mean ICP is given ± standard deviation.

TABLE 6

Control of intracranial pressure (ICP) in study patients by treatment group

Control of ICP	Conventional Treatment	Barbiturate Treatment	Total
yes	6	12	18
no	30	25	55
total cases	36	37	73
% controlled	16.7	32.4*	24.7

* Difference statistically significant (p = 0.12).

TABLE 7

Incidence of intracranial pressure control by treatment and prognostic factors

Factor	Barbiturate Treatment	Conventional Treatment	Ratio*
no. of cases	37	36	
Glasgow Coma Scale score			
4 & 5	7/23 (30%)	3/18 (17%)	1.83
6 & 7	5/14 (36%)	3/18 (17%)	2.14
time to randomization			
< median time (52 hrs)	3/21 (14%)	1/16 (6%)	2.28
> median time (52 hrs)	9/16 (56%)	5/20 (25%)	2.25
cardiovascular complication			
absent	8/20 (40%)	2/22 (9%)	4.40
present	4/17 (24%)	4/14 (29%)	0.82

* Ratio of the barbiturate group to the conventional treatment group.

TABLE 8

Maximum likelihood fit of a binary logistic regression model to treatment and prognostic factors on 73 patients

Factor*	Logistic Coefficient	Standard Error	Ratio	Significance
full model				
intercept	−6.6400	2.329	−2.85	0.01
treatment	2.179	0.951	2.29	0.02
CV complication	1.589	1.024	1.55	0.12
treatment × CV complication	−2.164	1.289	−1.168	0.09
GCS score				
5	−1.304	0.896	−1.46	0.15
6	−0.518	0.761	0.68	0.50
7	0.061	1.056	0.06	0.95
ICP at randomization	0.021	0.035	0.60	0.54
log (time)	0.895	0.354	2.53	0.01
reduced model				
intercept	−5.734	1.764	3.25	0.01
treatment (x_1)	2.011	0.909	2.21	0.03
CV complication (x_2)	1.355	0.977	1.39	0.16
treatment × CV complication (x_3)	−2.042	1.244	−1.64	0.10
log (time)	0.796	0.347	2.29	0.02

* CV = cardiovascular; GCS = Glasgow Coma Scale; ICP = intracranial pressure. For explanation of full model and reduced model see text.

and among patients classified by the median time from injury to randomization. Examination of time to randomization demonstrated an interesting but not unexpected relationship to treatment success. The median injury to randomization time for the entire group of 73 patients was 52 hours. Those patients assigned to a treatment group earlier than 52 hours after injury (patients with the most acutely elevated ICP) had only one-quarter the chance of responding to either therapy compared with those allotted to a group later than 52 hours. The ratio of barbiturate therapy success to conventional therapy success (2:1), however, was the same for both time epochs (Table 7).

Considering events antecedent to randomization for their possible association with treatment success, the occurrence of cardiac complications seemed, on the basis of published reports,[21,26] the most likely to be of clinical importance. When the data are stratified by the presence or absence of a cardiovascular complication (Table 7), the advantage of barbiturate therapy in the group without complications (42 patients) increased to fourfold while in the group with a prerandomization cardiovascular complication both treatments had a similar chance (24% vs. 29%) of success. Of those patients with a reported prerandomization cardiovascular complication, 20 or approximately two-thirds were found to be so grouped because of prerandomization hypotension (systolic blood pressure < 90 mm Hg for 30 minutes and/or required vasopressors), seven were hypertensive (systolic blood pressure > 160 mm Hg for 30 minutes and/or used antihypertensive drugs), and four experienced both hypo- and hypertension prior to randomization. Although the numbers of cases are too small to definitely qualify any one of these categories as the unique reason for treatment failure, the incidence ratio (barbiturate:conventional therapy success) for those only hypotensive was 1.70:1, while for the group with compromised cardiovascular systems as a whole the ratio was 0.82:1.

Since prognostic factors are interrelated, a more complex statistical model was used to analyze treatment effects jointly with the baseline risk factors in Table 7. A multiple logistic regression model was used to relate the binary response variable, Y, of ICP control (Y = 1 = success, 0 = failure) to treatment, cardiovascular complication and its interaction with treatment, GCS score at randomization, randomization ICP, and the logarithm of time from injury to randomization. The results are presented in Table 8 for the full logistic model including all variables and the reduced model obtained by backward selection of variables, excluding variables not significant at the 20% level. In both the full and reduced logistic models, the largest z-statistics are associated with a significant positive treatment effect due to barbiturate therapy (p = 0.03) and a small but positive statistically significant (p = 0.02) effect of time from injury to randomization. The other covariates in the reduced model (cardiovascular complication and its interaction with treatment) are not significant at the 5% level although the associated p values are all less than 0.16. The negative logistic regression coefficient (−2.042) associated with the interaction of cardiovascular complications with treatment quantifies its large negative effect on the probability of barbiturate treatment success. The coefficients of the reduced logistic model imply that, in the absence of cardiovascular complications and over a time period (for example, extending from 24 hours through 76 hours following injury), adjunctive barbiturate therapy was five to six times more likely to control elevated ICP than was continued conventional nonbarbiturate therapy; however, in the presence of a compromised cardiovascular system neither therapy dominated. When the data from all 80 randomized cases (including the seven cases that did not meet all prerandomization study requirements) were analyzed for treatment effects, the ratio of the incidence of barbiturate to conventional successful ICP control was 1.4:1. When the logistic model as described above was fit to the 80 cases, the results were virtually unchanged. The 80-case logistic model revealed a significant positive treatment effect due to barbiturate therapy ($p = 0.04$), a small but significant effect of time from injury to randomization ($p = 0.01$), and a negative interaction of treatment and cardiovascular complications ($p = 0.10$).

In patients included in the barbiturate arm, vigorous attempts were made to maintain serum pentobarbital levels in the range of 3 to 5 mg%. However, despite our efforts this was not possible in all patients. In some cases the maintenance dosage had to be decreased because of difficulty in treating postrandomization hypotension. At declaration of more "treatment failure" (25 cases), eight had levels below 3.0 mg% and four of those were at or below 2.0 mg%.

The data were examined to determine if prerandomization hypotension was frequently associated with postrandomization hypotension, particularly for patients in the barbiturate arm and how much difference postrandomization hypotension made with regard to the likelihood of treatment success. For these analyses postrandomization hypotension was defined as hypotension severe enough to require treatment with vasopressors (dopamine, in almost all cases). Table 9 gives the postrandomization use of dopamine (or other vasopressor) by treatment arm and the presence or absence of prerandomization hypotension. There was a modest increase in the requirement for dopamine in patients receiving barbiturates (10% vs. 13%), regardless of prerandomization hypotension. Overall, the incidence of postrandomization hypotension was 62% (23 cases) in the 37 barbiturate-treatment cases, and 50% (18 cases) in the 36 conventional-treatment cases. Using this definition of postrandomization hypotension (vasopressors required), the incidence ratio (barbiturate success/conventional success) was slightly less than unity, similar to the ratio determined for prerandomization cardiovascular complications (Table 7).

TABLE 9

Postrandomization use of dopamine among patients classified as hypotensive prior to randomization by treatment group

Prerandomization Status	Postrandomization Dopamine Use		Total Cases
	Yes	No	
conventional treatment			
hypotensive	7 (70.0%)	3	10
not hypotensive	11 (42.3%)	15	26
barbiturate treatment			
hypotensive	10 (83.3%)	2	12
not hypotensive	13 (52.0%)	12	25

After declaration of treatment failure, 26 of the patients randomly assigned to the conventional therapy arm were crossed over to receive barbiturates. Only four failures were continued on conventional therapy. The response rate (seven of the 26 cases crossed over) was similar to the rate seen in those initially assigned to the barbiturate arm (32% vs. 27%). Survival at 30 days is shown for the three groups (the barbiturate therapy arm, the conventional therapy arm, and the conventional therapy arm crossovers) in Table 10. The likelihood of survival at 1 month was 92% for those patients who responded as defined (Fig. 2) while 83% of the nonresponders died. Eighty percent of all deaths in each of the treatment arms were due to uncontrolled ICP. Last follow-up examination (a median of 6 months postinjury) showed that 36% of the responders and 90% of the nonresponders were vegetative or had died.

Discussion

The results are consistent with the hypothesis that high-dose pentobarbital, when added to our routine of conventional management, is useful for aborting elevations of ICP. Approximately one-third of our patients randomly assigned to the barbiturate arm had their ICP controlled compared with one-sixth who were continued on conventional management. This result is impressive considering the limitations of sample size and the apparent efficacy of our conventional management plan. Subgroup analysis adjusting treatment effect (ICP control) for the prerandomization cardiovascular complications and time from injury to randomization suggested that these variables were prognostic of ICP control with high-dose pentobarbital. The likelihood of pentobarbital ICP control in the presence of prerandomization cardiovascular complications was reduced to that obtainable with conventional management. The results suggest that barbiturates can abort ICP elevations in the uncomplicated case even after brain compliance is maximized using conventional means. Therefore, high-dose barbiturates can be considered as an appropriate adjunctive therapy for ICP control.

The rationale for a study design using control of ICP rather than survival as the primary outcome criterion

TABLE 10
One-month survival and control of ICP by treatment group

Status of ICP*	Vital Status		Total Cases
	Alive	Dead	
barbiturate treatment (37 cases)			
controlled	11 (91.7%)	1	12
uncontrolled	3	22	25
total	14	23	37
conventional treatment only (10 cases)			
controlled	6 (100.0%)	0	6
uncontrolled	2	2	4
total	8	2	10
conventional treatment crossovers (26 cases)			
controlled	6 (85.7%)	1	7
uncontrolled	3	16	19
total	9	17	26

* Status of intracranial pressure (ICP) was assessed according to the study criteria (see text).

is discussed in the introduction, and, as stated, relates to the ethical issue of prohibiting the use of barbiturates (when there was some evidence indicating its efficacy) even when an investigator considered that a patient's ICP was approaching lethal levels. While this is an unavoidable weakness of the study, as is discussed in the introduction, the association between uncontrolled ICP and mortality is sufficiently robust. The ICP levels chosen for randomization and outcome criterion are, however, admittedly arbitrary and some may consider our lowest values to be too low. For example, a patient could enter and exit the study never having reached an ICP of 30 mm Hg and that was in fact the case for the two patients who were conventional treatment failures, were never given barbiturates, and survived (Table 10). However, it can be argued that, in the context of our conventional management plan, even an ICP of 25 mm Hg should be considered potentially dangerous considering that these patients had undergone removal of early- and late-appearing intracerebral as well as extracerebral mass lesions, were given maximal doses of mannitol, were hyperventilated, and in many cases had drainage of ventricular fluid before randomization. Furthermore, as presented in the introduction, there is now evidence that in the setting of traumatic brain injury pressures even lower than formerly presumed to be safe may be harmful.[10,20]

How do the data from this study compare with other clinical studies designed to examine the effect on ICP in patients with severe head injuries? Nonrandomized studies from San Diego[19] and Minnesota[18] both indicated a somewhat greater drug efficacy than did our study. The ICP was controlled in more than one-half of those patients compared to only one-third in our study. More important is the comparison between our study and the two reported randomized trials. Those studies indicated that no benefit was derived from high-dose barbiturates with regard either to control of ICP or to survival. One explanation is the difference in how the drug was given when the three studies are compared. The Richmond group[26] defined a patient population they believed at risk for development of elevated ICP. The predictors were low admission GCS scores and CT scan findings. The Toronto study[21] was designed to compare the efficacy of high-dose barbiturates with mannitol administration. In both studies high-dose barbiturates were then given as an initial therapy. On the other hand, in this study the drug was given only after elevated ICP was observed and it was impressive how few (12%) of our patients who were screened actually reached randomization criteria. That is not to say that more of our potentially eligible patients would have qualified for the at-risk group in the Richmond study, but it is probable that many more would have qualified for that group than we included. Since we have demonstrated (although outside the study design) that our conventional management is effective, at least according to the ICP criteria that were proposed, some of the Richmond study patients may not have required barbiturates in the context of our study, and the effect of barbiturates may, therefore, have been diluted in that study.

The three studies are similar in that all showed that hypotension is a frequent complication in severely head-injured patients. In our study, slightly more patients in the barbiturate arm became hypotensive than in the conventional therapy arm. The difference (10% vs. 13%) was not as impressive as might be expected from the other studies. It is conceivable that our observed negative interaction between prerandomization cardiovascular complications (mainly hypotension) and barbiturates is due, at least in part, to a reduction in the amount of the drug given to those patients who developed postrandomization hypotension.

Assuming high-dose barbiturates are effective, at least in controlling ICP, how far can one generalize from these data? The study was carried out in five specialized intensive care units. The patients were managed by neurosurgeons with a professed interest in this kind of intensive care and in head injury. These neurosurgeons were assisted by full-time intensive-care providers and around-the-clock care from a specially trained team of residents, fellows, and nurses. There is little doubt that the use of barbiturates involves risks beyond pure hypotension. This study demonstrates that in head-injured patients control of ICP can generally be accomplished by the rigorous application of therapy that does not include barbiturates. The question of whether and when to use high-dose barbiturates arises for the small subset of patients who have failed an aggressive medical management plan. The question as to whether barbiturates should be introduced somewhat earlier in the treatment regimen cannot be answered from this study. What can be concluded is that, when ICP control using other regimens fails, high-dose barbiturates can be effective, provided that the patient is cared for by experienced staff. Our study confirms the findings of others in demonstrating a robust association between uncontrolled ICP and mortality from head injury.

APPENDIX

The centers and individuals involved in this study were as follows:

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Acknowledgment

We thank Liz Zindler for typing and editing the manuscript.

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Manuscript received November 9, 1987.

This research was supported by National Institutes of Health Grant NS 9-2314, NS 9-2123, and NS 3-2340.

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