The University of Toronto Head Injury Treatment Study: A Prospective, Randomized Comparison of Pentobarbital and Mannitol

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ABSTRACT: Fifty-nine patients were treated in a prospective, randomized comparison of pentobarbital and mannitol for the control of intracranial hypertension resulting from head injury. Patients with elevated intracranial pressure (ICP) after evacuation of intracranial hematomas were randomized to one of two treatment groups; mannitol initially or pentobarbital initially, followed by the second drug as required by further elevation of ICP. Similarly, patients with raised ICP but without hematomas requiring evacuation were randomly assigned to two treatment groups in an identical paradigm.

Those with ICP elevation and no hematoma treated with pentobarbital as initial therapy had a 77% mortality compared to a 41% mortality for those with mannitol as initial treatment. Patients with evacuated hematomas had mortalities of 40% and 43% (no significant difference) for pentobarbital and mannitol respectively. In both no-hematoma and hematoma streams pentobarbital was less effective than mannitol for control of raised ICP.

Multivariable statistical analysis indicates that pentobarbital coma is not better than mannitol for the treatment of intracranial hypertension and may be harmful in no-hematoma patients with intracranial hypertension after head injury.

RÉSUMÉ: Au cours d'une étude prospective randomisée, 59 patients ont été traités par Pentobarbital et Mannitol pour contrôle de l'hypertension intracrânienne secondaire à un traumatisme crânien. Les patients dont la pression intra-crânienne (PIC) était élevée après évacuation d'un hématome intra-crânien ont été rangés au hasard dans deux groupes respectifs de traitement: administration, initialement, soit de Mannitol, soit de Pentobarbital; addition, subséquemment, de l'un ou l'autre agent, advenant une nouvelle élévation de la PIC. De même, des patients avec PIC élevée, mais sans hématome à évacuer, ont été disbribués au hasard dans deux groupes de traitement selon le même protocole.

Le groupe avec pression intra-crânienne élevée et sans hématome, qui fut traité initialement par Pentobarbital a eu un taux de mortalité de 77%, contre 41% pour le groupe débutant le traitement par du Mannitol. Les patients porteurs d'hématomes opérés ont eu des morbidités de 40% et 43% (sans différence significative), selon qu'ils étaient traités respectivement par Pentobarbital ou Mannitol. Dans les deux groupes — avec et sans hématome — le Pentobarbital fut moins efficace que le Mannitol pour le contrôle de la PIC élevée.

L'analyse statistique multifactorielle indique que le coma par Pentobarbital n'est pas préférable au Mannitol dans le traitement de l'hypertension intra-crânienne et qu'il peut être néfaste chez les patients sans hématome porteurs d'une hypertension intra-crânienne secondaire à un traumatisme crânien.

Multiple injuries, particularly from automobile accidents, continue to be a major cause of death and disability in North America. In a report of five years' experience at the Trauma Unit of Sunnybrook Medical Centre (Wright et al., 1983) the cause of death in fatally injured patients coming to autopsy was considered to be a head injury in 61 percent. Barbiturate coma therapy for patients with severe head injuries appeared promising and motivated this study.

Although many patients die or are disabled because of the primary mechanical damage done to the brain on impact, a significant number of patients develop increased intracranial pressure (ICP) as a result of cerebral swelling that is severe

enough by itself to cause death (Becker et al., 1977; Miller et al., 1977). In North American neurosurgical units, high intracranial pressure is generally treated by artificial ventilation, the administration of intravenous mannitol, and drainage of cerebrospinal fluid. The use of barbiturate coma for patients with severe head injuries is experimental treatment predicated upon information derived from animal studies (Bricolo and Glick, 1981; Clasen et al., 1974; Clubb et al., 1980; Ishii, 1966; Michenfelder, 1974; Michenfelder and Theye, 1973; Simeone et al., 1979).

In 1973 Shapiro et al. reported a reduction in intracranial hypertension in patients when anesthesia was induced with pentothal (Shapiro et al., 1973). Marshall et al. (1979) then reported that pentobarbital was effective in controlling raised intracranial pressure resulting from cerebral edema secondary to brain injury, and, in a subsequent paper, Rockoff et al. (1979), reviewed their experience in the treatment of 45 patients with severe head injuries. They reported good recovery in eight of 16 patients whose intracranial pressure initially responded to barbiturates even though all these patients had had an ICP of greater than 40 torr despite aggressive measures to reduce intracranial pressure prior to the administration of pentobarbital.

In a pilot study at Sunnybrook Medical Centre we were unable to duplicate these excellent results but we did find that pentobarbital was indeed effective in lowering raised ICP following severe head injuries in some patients, and that although systemic arterial hypotension was frequently induced by the administration of pentobarbital, adequate cerebral perfusion pressure (CPP) could be maintained by the use of dopamine or dobutamine (Gilman et al., 1980). This pilot study furnished evidence that the effect of pentobarbital on intracranial pressure was short-lived in certain patients (Rowed and Souri, 1980) and that other patients went on to die despite ICP control.

In an editorial that accompanied the report by Rockoff and his colleagues in the Annals of Neurology, Miller (1979) discusses the effect of barbiturate therapy and renders a Scottish legal verdict of "not proven", which, as he puts it, "implies that the case may be held open pending the arrival of fresh evidence".

METHODS

A prospective, randomized study design was chosen to evaluate the relative efficacy of pentobarbital and mannitol. We chose to treat patients as soon as possible after the development of intracranial hypertension with pentobarbital rather than using it exclusively for the most severely injured patients as a last resort, as there is some evidence that pentobarbital given late may be harmful (Spetzler and Selman, 1980). Mannitol, an osmotically active solution, given intermittently in response to measured ICP elevation, is the standard drug therapy for intracranial hypertension. With full knowledge that mannitol has a different mechanism of action (Schenkin et al., 1962; Wise and Chater, 1961; Wise and Chater, 1962) from pentobarbital in the reduction of raised intracranial pressure, we nevertheless chose mannitol as a basis for comparison with pentobarbital in a prospective, randomized trial. Two aspects of these drugs were compared; the effectiveness of each drug in reducing raised intracranial pressure and the outcome in terms of survival at three months.

Although it is often difficult to obtain reliable data in clinical studies carried out at more than one hospital (Sylvester et al.,

1981) it was elected to utilize the resources of four of the major teaching hospitals at the University of Toronto to shorten the patient entry period. It was estimated that enough acceptable patients would be entered into the study within two years.

It is well-known that barbiturates induce hypotension when given in doses sufficient to alter cerebral metabolism (Michenfelder, 1974). Pentobarbital coma abolishes spontaneous respiration and erases the clinical signs of brain function, making one entirely dependent upon ICP measurements to assess treatment. In effect, the patient undergoes a ten-day general anesthetic with attendant costs and risks. Accordingly, consideration was given to how much better than mannitol the drug must be demonstrated to be in order to justify its clinical use in preference to mannitol, which is much simpler and possibly safer to administer. Considering the availability of patients and the difference in the potential risks of mannitol and pentobarbital, it was elected to devise a trial to test (single-tailed) with 90 percent certainty, the hypothesis that pentobarbital was 25 percent better than mannitol with respect to the control of intracranial hypertension and with respect to survival.

$$\left(\frac{\text{Pentobarb Good Outcome}}{\text{Pentobarb Total}} \geq \frac{\text{Mannitol Good Outcome}}{\text{Mannitol Total}} \times 1.25 \right)$$

A sequential analysis surveillance program (Armitage, 1975) was devised so that the results of the trial could be followed closely and continuously as data accrued. Any important difference between the two drugs could then be detected quickly and the trial brought to a close as soon as possible. In this way, we sought to avoid administering an inferior mode of therapy to some patients or withholding a better therapy from others, as might occur in an unmonitored, randomized, prospective comparison of two treatments with a fixed sample size.

On admission to hospital, all patients were resuscitated in the same way. Concomitant injuries were treated according to their recognized priorities (American College of Surgeons, 1981). Clinical neurological function was assessed and the Glasgow Coma Score (Teasdale and Jennett, 1974) was recorded. The Glasgow Coma Score is a good predictor of outcome in head injury (Jennett et al., 1981). Only severely injured patients with a Glasgow Coma Score equal to or less than 7/14 were considered eligible for the study. A rapid intravenous infusion of 20 percent mannitol solution was frequently given to patients thought to have, but not as yet proven to have (no intracranial pressure measuring device yet placed) raised intracranial pressure. The patient's condition permitting, a CT scan was obtained.

On the basis of the scan results, an intracranial hematoma was then evacuated. If no clot was seen but raised ICP was suspected on the basis of the CT scan appearance, a Richmond screw or intraventricular catheter was placed. Those patients requiring evacuation of an intracranial clot on clinical grounds alone were taken directly to the operating room, a CT scan being obtained later. In this way, subjects were stratified at the outset into two groups, those with intracranial hematomas and those without, as it is known that the type of intracranial lesion has a significant predictive effect on outcome after severe head injury (Gennarelli et al., 1982). Figure 1 shows the study plan.

The patients were then monitored for raised intracranial pressure. Approximately two-thirds of monitored patients never developed raised ICP and never entered the Head Injury Treatment Study. Those with severe intracranial hypertension

(25 torr or greater for more than 15 minutes) were randomly assigned to either of the two treatment groups; mannitol or pentobarbital. The mechanism of randomization was the opening of a serially-numbered, sealed envelope taken from one of two packages of envelopes, one for patients who had had intracranial hematomas removed and one for those who developed raised intracranial pressure from brain injury alone. The sealed envelopes contained an instruction to begin treatment with either mannitol or pentobarbital and a card to forward to the Study office so that the initial drug given could be checked against a master list. The starting drug was determined by a random number generator. The physician caring for the patient could not predict which drug was to be prescribed as initial treatment prior to opening the envelope.

Informed consent was obtained. If consent for randomization was denied, the patient was not entered into the study. The method of administration of the drugs and concomitant care, described below, were rigidly governed by the study protocol.

In the mannitol treatment group, mannitol was administered as a 20 percent solution in an initial dose of 1 gm/kg. Prior to the administration of mannitol, an arterial blood sample for blood gas measurements was obtained to be sure that $PaCO_2$ was in the range of 25 - 30 torr. Additional increments of mannitol, usually less than 350 cc, were given as required for continued intracranial hypertension to maintain the intracranial pressure at less than 20 torr, provided that serum osmolality did not exceed 320 mOs/L.

In the pentobarbital treatment group, pentobarbital was given as an initial intravenous bolus of up to 10 mg/kg, followed by a continuous infusion of pentobarbital at 0.5 - 3 mg/kg/hr, provided that cerebral perfusion pressure (CPP = mean systemic BP—mean ICP) remained above 50 torr. Prior to administration

of pentobarbital, an arterial blood sample for blood gas measurements was obtained to be sure that the $PaCO_2$ was within therapeutic range. Additional increments of pentobarbital were given to maintain the intracranial pressure at less than 20 torr. The maximum suggested barbiturate level was 45 mg/L. When necessary, dopamine plus volume infusions were administered to raise the systemic arterial blood pressure and hence the cerebral perfusion to at least 50 torr. Pentobarbital levels from all hospitals were determined by the Addiction Research Foundation of Toronto, using a gas chromatography technique.

With the exception of randomization to one or other of the treatment groups, all patients were treated alike. Although the evidence for the efficacy of glucocorticoids in severe head injury is inconclusive (Gudeman et al., 1979; Cooper et al., 1979) all patients were given dexamethasone in an initial dose of 10 mg IV followed by 4 mg q6h, as this regimen was most characteristic of standard neurosurgical practice in Toronto at the outset of the Head Injury Treatment Study. Patients were positioned with the head of the bed elevated to 30 degrees above the horizontal to enhance cerebral venous drainage. All patients in the study were ventilated mechanically. Mechanical ventilation was adjusted so that the arterial PCO_2 was greater than 25 torr and less than 30 torr (Rowed et al., 1975).

All patients were given an initial dose of pancuronium, 0.1 mg/kg, when mechanical ventilation was begun and maintenance doses of 1 - 2 mg IV prn. The patient's body temperature was maintained between 35° and 37°C.

Although most patients had intracranial pressure measured by means of a Richmond screw, ventricular catheters were placed when ventricular size permitted. When considered advisable in both the mannitol and pentobarbital groups, cerebrospinal fluid drainage was arranged so as to provide continuous
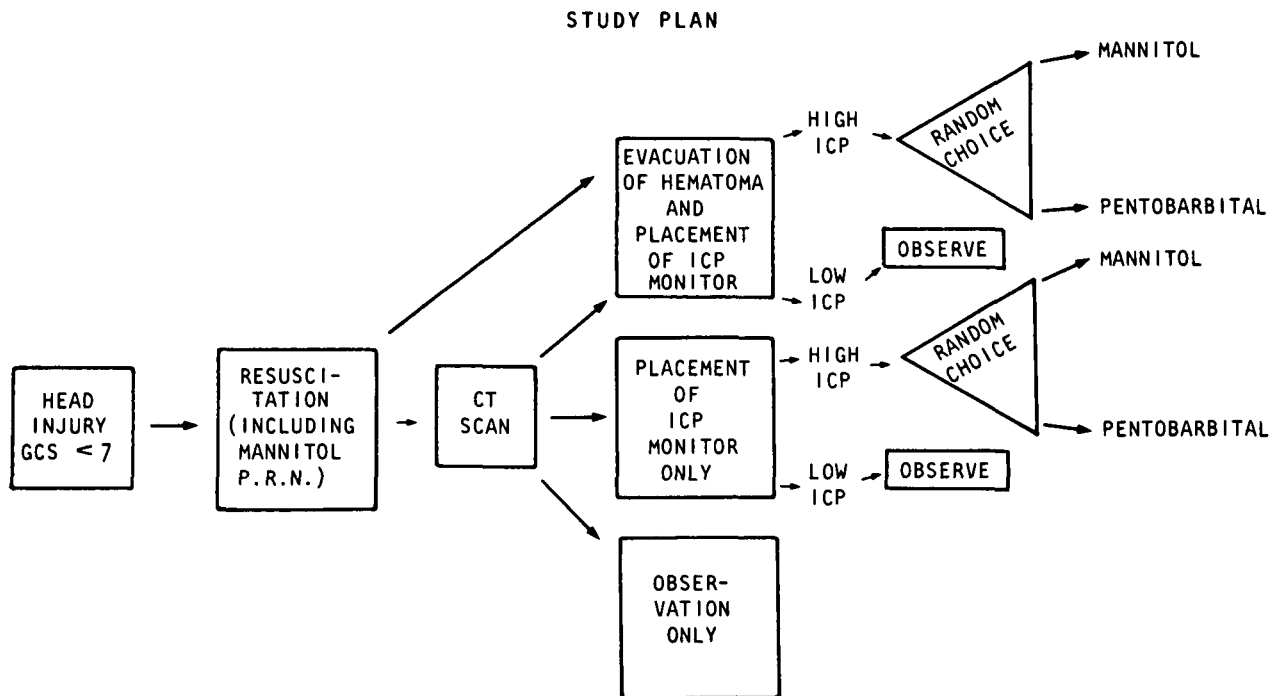
STUDY PLAN

Figure 1 — Study Plan. All subjects were resuscitated in a standard way and stratified into two clinical streams prior to randomization to pentobarbital or mannitol treatment groups.

drainage when intraventricular pressure exceeded 15 torr (approximately 200 mm of water) by positioning the closed system reservoir at 20 cm above the foramen of Monro.

Patients in the mannitol treatment group whose ICP proved intractable to maximal doses of that drug were started on pentobarbital as described for the pentobarbital group patients and the mannitol was continued as required. Patients who were given pentobarbital initially and failed to respond to maximal doses had mannitol administered in addition to the pentobarbital. The pressure criteria for introducing the second drug were the same as for entry into the study. Both drugs were withdrawn as the patient's improving condition permitted. The requirement for the second drug, that is, pentobarbital in addition to mannitol or mannitol in addition to pentobarbital, was considered to be a treatment failure of the initial drug with respect to intracranial pressure control. The requirement for the second drug, in this way, served as a criterion for evaluating the efficacy of the first drug chosen at random. No patient who required both pentobarbital and mannitol for the control of intracranial hypertension was denied both treatments.

In those cases where intracranial pressure was successfully controlled, mechanical ventilation was continued for at least 48 hours after mannitol and pentobarbital were no longer required. As necessary, in both groups, the mechanical ventilation was prolonged until spontaneous respiration was adequate.

Seventy patients were admitted to the Head Injury Study. Eleven patients were rejected from the study after review of their charts indicated unacceptable departure from the study protocol. During a 30-month period ending in October 1982, 59 patients were entered into the study and the protocol successfully followed. There were minor protocol violations. These included short periods of $PaCO_2$ outside the prescribed range, pentobarbital blood levels exceeding 45 mg/L and brief reductions in the cerebral perfusion pressure when volume loading or dopamine administration was insufficient to maintain adequate systemic arterial pressure.

RESULTS

The study patients represent the most severely injured of the patients admitted to the University of Toronto neurosurgical services that participated in the study. Most patients with head injuries do not require intracranial pressure monitoring, and of those who do, only approximately one-third develop sufficiently severe intracranial hypertension to be eligible for entry into the study. In this highly selected, severely injured group of 59 patients, 43 were victims of motor vehicle accidents, 33 as occupants of automobiles, 6 as motorcyclists and 4 as pedestrians. Fourteen head injuries were caused by falls and two occurred at work. There were 47 men and 12 women.

Table I shows the mean age, mean Glasgow Coma Score and mean Injury Severity Score (Baker et al., 1974) for the study population. Thirty-four patients suffered isolated head injuries. Twenty-five had associated injuries of varying severity. The Injury Severity Score (American Association for Automotive Medicine, 1980; Baker, 1976; Baker et al., 1974) (ISS) was calculated in all cases. All study patients had a minimum score of 25 by virtue of their head injury. A patient with a score of 30 might have a head injury plus a fractured humerus or a fractured rib. The ISS had little effect on outcome until an ISS of 50 was reached. There was a single survivor of four patients with

Table 1: Mean values for age, Glasgow Coma Score (GCS) and injury severity score (ISS) in 59 head injury patients treated with pentobarbital or mannitol.

PENTOBARBITAL

| P / M |

MANNITOL

	SAMPLE SIZE	MEAN AGE	MEAN GCS	MEAN ISS
Evacuated Hematoma (29 patients)	15	32.8	5.1	29.6
	14	35.7	4.9	27.8
No Hematoma (30 patients)	13	24.9	4.2	33.5
	17	24.4	4.4	31.5

an ISS of 50. Two patients with scores of greater than 50 died. Below 50, the major determinant of survival or death was the head injury. A patient was considered to have survived if he was alive three months after his injury, as many vegetative survivors will succumb from secondary complications of their injuries in the first three months (Jennett et al., 1981).

In contrast to the Injury Severity Score, which for values of less than 50 was not a strong predictor of survival in our patients, the Glasgow Coma Score, as shown in Figure 2, correlated well with survival.

Table 2 shows survival and death at three months and gives, in addition, a crude report of quality of survival of three-month survivors at approximately one year after injury. Two vegetative patients, alive at three months, succumbed within the year and at least one vegetative survivor was following simple commands. Some of the apparently vegetative survivors showed some low level, intermittent sentient behavior. Because of these uncertainties, institutionalized patients are reported as a group. At the upper end of the intellectual scale, formal neuropsychological testing which was carried out in some, but
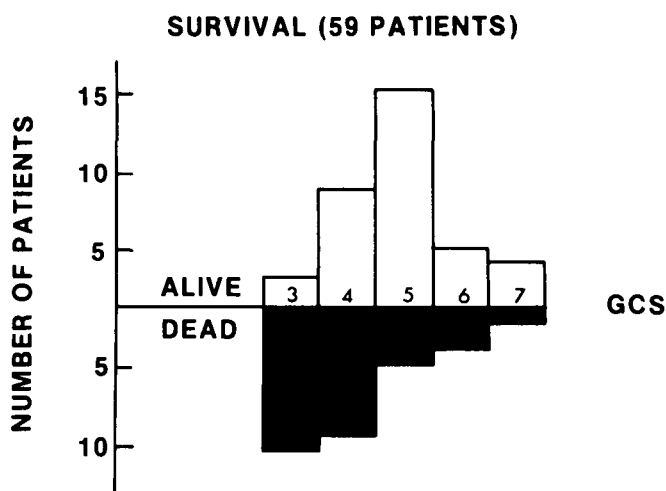
Figure 2 — Glasgow Coma Scores on admission to hospital, comparing scores for patients who survived with those for patients who died. The GCS has a maximum value of 14 and was a reasonably good predictor of survival in this group of patients.

Table 2: Response to treatment of intracranial hypertension and eventual outcome in head injury patients receiving pentobarbital or mannitol.

NUMBER [N/%] PERCENTAGE

		ICP Control (Second drug not required)	Dead at 3 months	3-Month Survivors Reassessed at about one year		
				Dead	Hospitalized	Home
Hematoma	Pentobarbital (15)	6 / 40	6 / 40	0	5	4
	Mannitol (14)	9 / 64	6 / 43	1	2	5
No-Hematoma	Pentobarbital (13)	3 / 23	10 / 77	0	1	2
	Mannitol (17)	10 / 59	7 / 41	1	6	3

not all, of the good quality survivors, often revealed cognitive deficits that constituted a significant handicap. For this reason, all patients living at home are included in a single group. Even with this simplification, there are too many categories and too few patients to draw conclusions regarding quality of survival.

A sequential review according to the method described by Armitage (1975) was carried out as patients accrued to the study. During the course of the study no significance boundaries were crossed and accordingly, the trial was never stopped prior to the end of the planned entry of patients.

The statistical analysis was a computerized multivariable analysis using a general linear logistic model (Cox, 1970). Age, Glasgow Coma Score, Injury Severity Score, pupillary reaction, injury-to-operation interval, injury-to-study-entry interval and ICP at entry were studied as potential covariates. The sex of the patient and hospital of treatment had been included in a preliminary analysis and were excluded from the final one as there was not strong evidence that they affected outcome.

Of the patients with intracranial hypertension following the evacuation of an intracranial hematoma, 14 received mannitol initially by random assignment and 15 received pentobarbital. The mean age in these two treatment groups was nearly identical with that of the pentobarbital patients slightly younger. The mean Glasgow Coma Scores were comparable, with pentobarbital slightly better. The mean Injury Severity Score was slightly greater in the barbiturate group. There was no significant difference in the mortality of the two groups, with 6 of 14 mannitol patients dying as compared with 6 of 15 pentobarbital patients. Nearly twice as many patients starting with pentobarbital required the other regimen (mannitol) in addition for control of raised intracranial pressure than did patients starting with mannitol. Considering the dependence of pressure control on treatment, these results indicate that pentobarbital is not 25 percent better than mannitol for the control of intracranial pressure (P = 0.04).

The results of treatment in patients who developed intracranial hypertension as a result of brain damage alone without an intracranial hematoma, were quite different from the patients who required evacuation of a hematoma. The mean age of the entire no-hematoma group was nearly 10 years younger (34.3 years for hematoma patients compared to 24.6 years for no-hematoma patients) and was quite similar in the mannitol and pentobarbital treatment limbs. Glasgow Coma Scores and Injury Severity Scores were comparable between the two groups, although this time the pentobarbital group was slightly more severely injured by these two criteria. There was a higher rate of failure to control intracranial pressure in the pentobarbital group than in the mannitol group, indicating that pentobarbital is not 25 percent better than mannitol for this purpose (P<0.001). In the no-hematoma group there was a striking difference in mortality between the two treatment groups. Ten of 13 pentobarbital patients died as compared with only 7 of 17 mannitol patients. The two treatment groups, that is, pentobarbital and mannitol, were different, in that there were three patients with Injury Severity Scores 50 or greater in the pentobarbital group, all of whom died and none with equally high scores in the mannitol group. Even when these three patients with severe multiple injuries are excluded from the analysis, there is still a 70 percent mortality in the group of patients begun on pentobarbital as initial treatment compared with mortality of only 41 percent in the patients without intracranial hematomas treated initially with mannitol. Assuming that pentobarbital really is 25 percent better than mannitol, the likelihood of an outcome this poor is very small (P = 0.03).

DISCUSSION

An analysis of the factors that may have contributed to this striking difference in outcome was made. The cerebral perfusion pressures in the no-hematoma patients were analyzed. In general, in both the pentobarbital and mannitol treatment groups, the cerebral perfusion pressure was maintained at greater than 50 torr. Since even short periods of inadequate cerebral perfusion are sufficient to cause brain damage or even death, a worst case analysis of cerebral perfusion pressures was made. The continuous ICP record of each patient was examined. For each of the 59 patients, the worst cerebral perfusion pressure for each day was identified. Very low perfusion pressures that occurred as terminal events were excluded. Readings that occurred after the introduction of the second drug, that is, after the failure of the initial treatment drug to control intracranial pressure, were also excluded. A total of 202 observations in the 30 no-hematoma patients were included and histograms of the frequencies of cerebral perfusion pressure values by decade were plotted and are illustrated in Figure 3. The mean value for the worst pentobarbital cerebral perfusion pressures was 49.1 torr with a standard deviation of 16.5 as compared with the mean of 62.6 torr for the worst mannitol cerebral perfusion pressures with a standard deviation of 12.7. The populations of pressures are quite distinct.

The difference in perfusion pressures, while a significant factor, is not by itself a sufficient explanation of the striking difference in mortality in the no-hematoma patients as there was a similar difference in worst perfusion pressures among the patients with evacuated hematomas. The worst cerebral perfusion pressure mean for the pentobarbital patients in this latter group was 55.4 torr (S.D. = 17.3) and that for mannitol patients was 67.3 torr (S.D. = 13.1).

Among the survivors of the no-hematoma pentobarbital group were two patients treated with pentobarbital who had partial
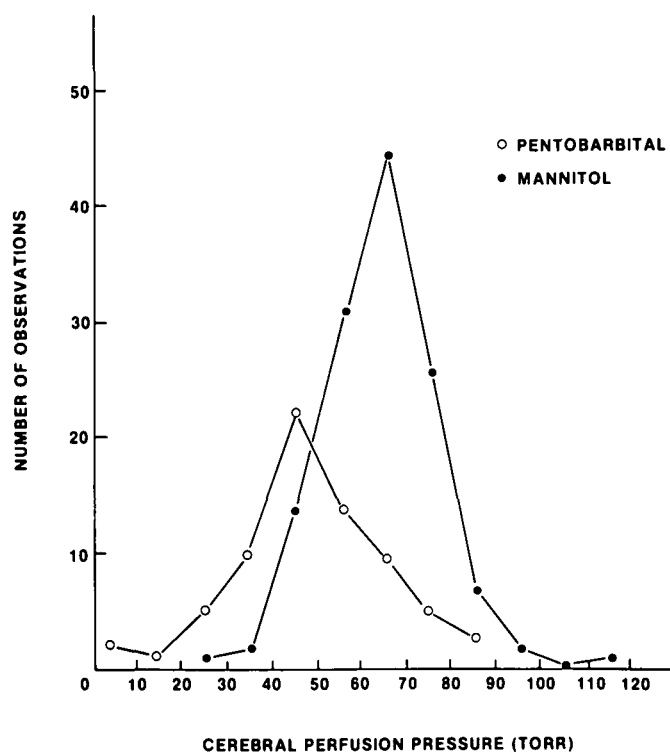
Figure 3 — Cerebral perfusion pressures in head injury patients without intracerebral hematomas treated with pentobarbital or mannitol. The lowest values for each day, obtained from continuous pressure recordings, were totalled and arranged into bins of 10 torr width.

frontal lobectomies for internal decompression. The first patient developed intracranial hypertension intractable to treatment with both pentobarbital and mannitol. A repeat CT scan then showed a region of low density with considerable mass effect in the right frontal lobe with compression of the anterior horn of the right lateral ventricle. A right frontal lobectomy at four days after her injury permanently relieved intracranial hypertension. A second patient, also randomized to pentobarbital, was shown to have a right frontal contusion with edema and a small midline shift. A Richmond screw was placed but within three hours his intracranial pressure rose and a right frontal lobectomy was done. Following this second operative procedure his intracranial pressure responded to maximal doses of pentobarbital. In both these cases cerebral perfusion pressures were only slightly lower than specified by the protocol with values as low as 42 torr in the former and 48 torr in the latter. They would likely have been much lower had the internal decompressions not been done.

There were also two patients who began on mannitol and required pentobarbital in addition and also had decompressive procedures. Both showed regions of decreased attenuation on the CT scan interspersed with small ill-defined regions of slightly increased density suggesting a mixture of infarcted cerebral tissue and petechiae. Both responded to maximal doses of mannitol and pentobarbital following debridement of devitalized brain. Both of these patients had periods of suboptimal perfusion pressure, the former with a low of 41 and the latter with a low of 47. Again, had there been no decompression, the cerebral perfusion pressures would likely have been lower. One might argue that the two pentobarbital patients who had

intracranial decompressive procedures, even though they lacked intracranial hematomas, resembled patients in the hematoma group by virtue of having had a decompressive operation, and for that reason survived. Debridement of traumatized brain may reduce intracranial pressure sufficiently that subsequent administration of pentobarbital does not cause infarction in marginally perfused tissue. Perhaps initial treatment with mannitol serves a similar purpose by mitigating intracranial hypertension.

CONCLUSIONS

There is no evidence that pentobarbital is 25 percent better than mannitol, either for the control of raised intracranial pressure or for improving survival in patients with intracranial hypertension due to head injury. It is clear that even in intensive care units experienced in the management of patients with severe brain and multiple injuries and considerable expertise in the management of pentobarbital, average cerebral perfusion pressures are reduced in patients in pentobarbital coma compared with those receiving mannitol only. In patients who developed raised intracranial pressure as a result of diffuse cerebral injury without intracranial hematoma this reduction in cerebral perfusion pressure may have been the cause of the increased mortality (77% as compared with 41%). Among the no-hematoma survivors were four patients who had partial cerebral lobectomies for internal decompression. These procedures likely served as an adjunct in the reduction of intracranial hypertension and the maintenance of adequate cerebral perfusion pressure.

RECOMMENDATIONS

On the basis of these conclusions we can make four practical recommendations to physicians who care for patients with severe head injuries. First, intermittent doses of mannitol should continue to be the mainstay of management of intracranial hypertension following severe head injury. Particular attention should be paid to the cerebral perfusion pressure in these patients. When it is possible to define regions of particularly severe brain damage on CT scanning, there should be a readiness to consider partial cerebral lobectomies for internal decompression, especially if the use of pentobarbital is contemplated. Finally, pentobarbital should be used only as a last resort when mannitol and surgical decompression have failed and then only in an intensive care setting which can provide close supervision "around the clock" by a team of experienced physicians. As soon as a more effective drug is available for the treatment of raised intracranial pressure, pentobarbital should be abandoned.

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