Comparison of mannitol regimens in patients with severe head injury undergoing intracranial monitoring

Harold P. Smith, M.D., David L. Kelly, Jr., M.D., Joe M. McWhorter, M.D., Darlene Armstrong, R.N., Rayetta Johnson, R.N., Carole Transou, R.N., and George Howard, M.S.P.H.

Section on Neurosurgery, Department of Surgery, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina

Eighty patients sustaining head injuries and presenting with Glasgow Coma Scale scores of 8 or less were entered into a prospective randomized study to assess the benefit of intracranial pressure (ICP) monitoring with two regimens of mannitol administration. Group I was treated with mannitol for ICP elevations greater than 25 mm Hg, while Group II received empirical mannitol therapy irrespective of ICP readings. No statistically significant differences in mortality rate or neurological outcome were demonstrated between the two groups. These results are comparable to those of several published series of head-injured patients receiving similar treatment from 1977 to 1982. However, those series must be reassessed in light of recently published studies with treatment initiated at lower levels of ICP.

Key Words • intracranial pressure monitoring • head injury • mannitol

In 1977, Miller, et al., demonstrated the significance of intracranial hypertension in 160 patients with severe head injury: those patients manifesting an intracranial pressure (ICP) of greater than 40 mm Hg on admission had a 69% mortality rate. In their expanded series of 225 patients published in 1981, they documented a mortality rate of 92% in patients whose ICP was elevated above 20 mm Hg and was not reducible, an 18% mortality rate in those with normal ICP (< 20 mm Hg), and a 26% mortality rate in those with raised but reducible pressures of above 20 mm Hg. In that study, intracranial pressure greater than 20 mm Hg developed in 70% of all patients with surgical lesions and in 33% of patients with diffuse injuries, with the intracranial hypertension being uncontrollable in 31% and 4%, respectively.

Other authors have demonstrated similar results, and ICP monitoring has become common in the management and study of the head-injured patient. Although ICP monitoring has been proven to have prognostic value and to be of benefit as an early-warning system of neurological deterioration or catastrophe, no prospective randomized study has been reported to date to demonstrate the efficacy of ICP monitoring per se in reducing mortality and morbidity from closed-head injury. Other than the report by Bowers and Marshall in 1980 on the benefit of ICP monitoring in patients presenting with Glasgow Coma Scale (GCS) scores between 3 and 5, there is a paucity of statistically significant information.

We report a prospective randomized study of 80 patients that was designed to detect statistically significant differences between patients treated on the basis of ICP readings and those empirically treated for ICP elevation with a fixed dosage of mannitol.

Clinical Material and Methods

From April, 1980, through April, 1982, every patient with head injury (other than gunshot wounds) having presented within 6 hours of injury to the North Carolina Baptist Hospital and having a GCS score of 8 or less for 6 hours' duration was entered into the study. Eighty patients, of whom 60 (80%) were male, qualified for the study. The mean age of all patients was 27 years (range 8 months to 78 years). The patients were randomly assigned to one of two groups by means of sealed envelopes containing cards designating the assigned protocol: Group I (mannitol therapy based on ICP monitoring) or Group II (empirical mannitol therapy). All patients were intubated and given intermittent mandatory ventilation (IMV) to achieve a ventilatory PaO₂ of greater than 70 mm Hg and a PaCO₂ of 25 to 30 mm Hg. Computerized tomography (CT) scans of the head were obtained when each patient was first
Mannitol and ICP monitoring in severe head injury

admitted. Following operative procedures for surgical lesions and placement of a Richmond ICP monitoring screw in the frontal area, the patients were admitted to the intensive care unit for monitoring and therapy. The ICP monitor was changed routinely to the other side of the head every 5 days. Computerized tomography scans were repeated routinely at 48 to 72 hours, or earlier if a patient developed uncontrolled ICP or showed neurological deterioration. No patient received steroid therapy.

In Group I therapeutic interventions were based on the level of ICP. For ICP of greater than 25 mm Hg, an initial 250-ml bolus of mannitol (20%), or 0.75 gm/kg, was administered. For uncontrollable ICP, subsequent 100-ml or 0.25-gm/kg boluses were administered incrementally to a maximum of 1.5 gm/kg/hr or until serum osmolality was greater than 310 mOsm/liter. Pentobarbital coma was initiated whenever ICP rose above 35 mm Hg while mannitol was being given. Mannitol was discontinued on the basis of the ICP level. Extubation and weaning from IMV was based on ventilatory values, the GCS score, arterial blood gas values, and the level of ICP.

In Group II, although ICP was recorded, it was not used to guide therapeutic intervention or mannitol administration. Rather, an initial mannitol bolus of 250 ml (or 0.75 gm/kg if the patient's weight was less than 70 kg) was administered to the patient in the emergency room following group assignment, and then subsequent 0.25-gm/kg doses were given every 2 hours or until serum osmolality was greater than 310 mOsm/liter. Whenever neurological deterioration was evident, a second bolus of 0.75 gm/kg was given and a CT scan was obtained. Since ICP was not being used for therapeutic intervention in this group, there was no protocol limb for barbiturate coma. Mannitol was discontinued after 96 hours, or earlier if the patient was awake and alert. It was restarted if neurological deterioration developed (as assessed by clinical findings and the GCS score). Extubation and weaning from IMV was based on ventilatory values, GCS score, and arterial blood gas levels, but not on the ICP.

In both groups, the mannitol dosage was chosen on the basis of a report by Marshall, et al., that demonstrated the efficacy of low doses in controlling ICP. Continuous polygraph recording of ICP was performed on all patients for subsequent analysis. Also, electrolytes, serum osmolalities, and arterial blood gas values were measured at least once every 12 hours in all patients. All surviving patients were assessed neurologically 1 year after injury; included in the evaluation were the Karnofsky Scale and the Activities of Daily Living Scale.

In assessing the data, we elected to look at highest ICP readings during the monitoring period, as well as average ICP readings, believing that the highest ICP readings would more accurately characterize a patient's course throughout the monitoring period. The Student t-test was used to determine statistical significance.

### Results

Follow-up data were available for 37 patients in Group I and for 40 patients in Group II. Table 1 demonstrates almost identical findings in both groups with respect to GCS score, frequency of surgical lesions, and CT findings.

#### Neurological Outcome

Death occurred in 13 (35%) of the 37 patients in Group I and in 17 (42.5%) of the 40 patients in Group II (p = 0.26) (Table 2). None of the 30 patients who died had had normal CT scans. Four (8.5%) of the 47 survivors had had normal CT scans; ICP in those four had remained lower than 25 mm Hg throughout. The overall mortality rate was 39%. Twenty-two (73%) of the 30 deaths were deemed secondary to head injury or increased ICP, and eight (27%) were deemed secondary to sepsis, pulmonary complications, or medical complications.

Neurological outcome is shown in Table 2 and is correlated (for survivors) with the admission GCS score in Table 3. In the entire series of patients, those presenting with GCS scores of 6 to 8 had a mortality rate
of 28% and those presenting with GCS scores of 3 to 5 had a mortality rate of 57%.

Table 4 correlates the highest ICP readings with treatment and survival. Twenty of the 77 patients had ICP readings lower than 25 mm Hg throughout their monitoring period and, of these, 16 (80%) survived; in contrast, only eight (35%) of 23 patients with the highest ICP’s survived. Thirty-one (54%) of 57 patients with ICP’s greater than 25 mm Hg at some point in the study period survived. However, while average ICP readings of lower than 25 mm Hg were less common in patients who died than in those who survived, the discrepancy was less obvious in Group II than in Group I (Table 5).

Figure 1 compares the mean highest ICP readings for patients who survived and for patients who died in both groups. The mean highest ICP’s for survivors in Groups I and II were 35.2 mm Hg and 29.7 mm Hg, respectively, and for nonsurvivors were 46.2 mm Hg and 40.7 mm Hg, respectively. Mean highest ICP in nonsurvivors from both groups was 11 mm Hg higher than that in survivors from both groups (p = 0.0002). In Group II the mean highest ICP was 5.5 mm Hg lower for survivors and nonsurvivors than in Group I (p = 0.048).

Pentobarbital coma was initiated in 11 patients in Group I who had uncontrollable ICP. Six of these 11 patients subsequently died, and of the five surviving,

Three presenting with GCS scores of 6 to 8 were categorized as having a good recovery or moderate disability and two presenting with GCS scores of 3 to 5 remained in a severely disabled, vegetative state.

Complications

No infections occurred in the 80 ICP-monitored patients. One epidural hematoma was present on a 48-hour follow-up CT scan in a patient who had been admitted with multiple diastatic fractures of the calvaria. Whether the hematoma was due to insertion of the monitor or to epidural oozing from the multiple fracture sites could not be determined. One patient in Group II developed progressively elevated renal function tests after the start of the mannitol regimen. When the serum creatinine value, which had been normal on admission, reached 5.8 mg/100 ml and the blood urea nitrogen value reached 67 mg/100 ml, fluid replacement was started and mannitol was discontinued. However, the GCS score then deteriorated, ICP increased to greater than 60 mm Hg, and he subsequently died. His renal function studies had returned to normal before his death.

Discussion

This study is limited in that, essentially, we were comparing two regimens of mannitol treatment, rather than purely assessing the effect of ICP monitoring. However, we did not consider that we could ethically design a study in which ICP would be ignored completely. When this study was initiated, we believed strongly that patients treated on the basis of ICP readings would experience a better outcome than those treated empirically. To our surprise, the results did not support that expectation. The finding that empirically treated patients had lower mean ICP than patients given mannitol only when ICP rose above 25 mm Hg suggests that the regular and frequent administration of mannitol provides a smoother ICP curve overall and prevents ICP from rising above 25 mm Hg or becoming “out of control.”

A statistical review of the results shows that there would be only an 8% chance that these results would occur if there were a 20% difference in mortality rates between Groups I and II. Based on our reported results, it would require 300 patients in each group to detect a

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
\text{Outcome} & \text{Group I} & \text{Group II} \\
\hline
\text{GCS score: 3-5} & 4 & 4 \\
\text{GR/MD} & 3 & 1 \\
\text{SD/V} & 16 & 15 \\
\hline
\text{GCS score: 6-8} & 16 & 15 \\
\text{GR/MD} & 1 & 3 \\
\text{SD/V} & 24 & 23 \\
\hline
\end{array}
\]

\* Group I: mannitol therapy based on intracranial pressure (37 cases); Group II: empirical mannitol therapy (40 cases). GR = good recovery; MD = moderate disability; SD = severe disability; V = vegetative state.

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{ICP (mm Hg)} & \text{Alive} & \text{Dead} & \text{Total} \\
\hline
> 50 & 5 & 3 & 8 & 7 & 13 & 10 \\
40-49 & 2 & 0 & 0 & 1 & 2 & 1 \\
30-39 & 8 & 6 & 4 & 5 & 12 & 11 \\
25-29 & 6 & 4 & 0 & 1 & 3 & 5 \\
< 25 & 6 & 10 & 1 & 7 & 7 & 13 \\
\text{total} & 24 & 23 & 13 & 17 & 37 & 40 \\
\hline
\end{array}
\]

\* Group I: mannitol therapy based on intracranial pressure; Group II: empirical mannitol therapy.

\[
\begin{array}{|c|c|c|}
\hline
\text{Survival} & \text{Group I} & \text{Group II} \\
\hline
\text{alive} & 25/27 & 93 \\
\text{dead} & 9/13 & 69 \\
\hline
\end{array}
\]

\* ICP = intracranial pressure. Group I: mannitol therapy based on ICP (37 cases); Group II: empirical mannitol therapy (40 cases).
Mannitol and ICP monitoring in severe head injury

10% difference in mortality rates and 1160 patients per group to detect a 5% difference. This emphasizes the fact that even in series of patients closely matched in terms of clinical characteristics, as our patients were, large numbers of patients are required to reveal small, albeit statistically significant, variations between two groups of patients treated in different fashions with multiple treatment variables used.

Our results with respect to mortality rates closely approximate those reported by Miller, et al.,6 in 1981. In their series, patients with an ICP of less than 20 mm Hg had an 82% survival rate, whereas patients with an ICP of greater than 20 mm Hg, either reversible or nonreversible, had a survival rate of only 55%. Furthermore, our results with respect to mortality and morbidity do not differ significantly from those of several series summarized by Langfitt and Gennarelli.4 In those series, which in 1982 represented the current “state of the art” for treatment (ICP monitoring, hyperventilation, administration of mannitol and steroids, and intensive care monitoring), the mortality rate ranged from 36% to 49%; a good result/moderate disability outcome was achieved in 46% to 52% of the cases. In those series, treatment was started when the ICP elevation was 20 mm Hg or more. The study by Saul and Ducker,10 also published in 1982, led to one major change in the “state of the art,” and it is probable that comparing present-day series with those reviewed by Langfitt and Gennarelli is no longer valid.

Saul and Ducker10 found that the mortality rate decreased from 46% to 28% when ICP elevations were treated at 15 mm Hg instead of at 20 to 25 mm Hg. Initiation of treatment at 15 mm Hg also decreased from 34% to 25% the incidence of patients having elevations greater than 25 mm Hg. In 1979, Marshall, et al.,6 reported a series of patients in whom treatment was also initiated at 15 mm Hg and mortality was 28%. These improved results with treatment initiated at lower levels of ICP may well explain the reason for the absence of statistically significant differences between our two groups of patients when we began treatment in the Group I patients only when ICP had reached the 25-mm Hg level. It may be that ICP of 25 mm Hg or greater already reflects a patient whose intracranial compliance is out of control so that treatment (and subsequent ability to control ICP at that point) becomes far less effective. This speculation may explain in part our observation of a 5.5-mm Hg difference in mean highest ICP values between Groups I and II. It is possible that in Group II patients, who were all receiving regular doses of mannitol, ICP of 15 mm Hg was being treated at that point, so that it was not always allowed to rise to higher levels.

In 1983, Stuart, et al.,11 reported a 34% mortality rate in 100 patients with GCS scores of 8 or less for 6 hours who were not monitored and in whom IMV was used in only 43%. That mortality level equaled the level reported by Miller, et al.,4 which was the lowest figure in the review by Langfitt and Gennarelli.4 Comparing the series of monitored patients with its mortality of 28% reported by Marshall, et al.,6 and the series of unmonitored patients with its mortality of 34% reported by Stuart, et al., the question then becomes, “Does a 6% decrease in mortality justify the risk inherent in ICP monitoring?”

We believe that the results demonstrated following ICP monitoring might well be significantly better if patients are treated at the lower level of 15 mm Hg. We also believe that there are probably subsets of patients within large groups who will significantly benefit from monitoring. The problem is to recognize those subsets, and to consider assigning only patients in those subsets to ICP monitoring protocols.

The use of the CT scan to elucidate which patients should be monitored was addressed in 1982 by Narayan, et al.8 They showed that patients with a normal CT scan had only a 13% incidence of ICP elevation greater than 20 mm Hg. Use of further variables allowed them to predict accurately the ICP course in 96% of these patients: abnormal multi-evoked potentials, presence of motor posturing, age greater than 40 years, and systolic blood pressure less than 90 mm Hg on admission were all indicative of higher ICP during the patient’s course. We agree with the conclusions of Narayan, et al., and would, on the basis of the work done at this institution by Holliday, et al.,3 add a fifth parameter as a criterion for monitoring: the presence of significant pulmonary contusion as revealed radiographically and/or abnormal blood gas levels on admission when there is a normal CT scan.

References


Fig. 1. Correlation of intracranial pressure (ICP) with survival in head-injured patients treated with mannitol on the basis of ICP (Group I) or empirically (Group II).

J. Neurosurg., Volume 65 / December, 1986

Manuscript received September 10, 1985. Accepted in final form June 2, 1986.
This paper was presented at the Annual Meeting of the American Association of Neurological Surgeons, Washington, D.C., on April 25, 1983.
Address reprint requests to: David L. Kelly, Jr., M.D., Section on Neurosurgery, Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.