Resolution of brain edema in severe brain injury at controlled high and low intracranial pressures

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A series of 87 patients with severe brain injury were studied. Intracranial pressure (ICP) monitoring and external ventricular drainage were used to control ICP at high and low levels. Clearance of ytterbium-169-labeled diethylenetriaminepentaacetic acid (169Yb-DTPA), Evans blue dye, and ventricular cerebrospinal fluid protein was measured at the two ICP levels over consecutive periods of 4 hours to confirm clearance of brain edema. The results support the hypothesis that brain edema is in part absorbed in the cerebrospinal fluid via transventricular flow.

KEY WORDS: head injury • intracranial pressure monitoring • cerebral edema • cerebrospinal fluid • ventricular drainage

Severe cerebral trauma is accompanied by vasogenic brain edema as a result of blood-brain barrier injury. Reulen, et al.,27-30 have studied the resolution mechanism of brain edema in animals with standardized cryosurgically produced local brain injury. They reported that the pressure of the edematous brain tissue is higher than the relatively normal brain tissue adjacent to it, and that this pressure gradient causes bulk flow of the edema fluid from the high-pressure to the low-pressure regions, and eventually into the ventricles. Hochwald, et al., were unable to confirm this or to detect clearance of edema fluid into the cerebrospinal fluid (CSF) in a cold-injury lesion.28

We report a series of 87 patients with severe brain injury who were admitted to the First Affiliated Hospital of the Hunan Medical College between January, 1982, and February, 1983. The intracranial pressure (ICP) of each patient was controlled at high and low levels by external ventricular drainage (EVD) to observe if there was clearance of edema fluid into the ventricles, and if the amount of edema fluid passing into the ventricles was different at each pressure level. The purpose of this study was to establish a basis for EVD as treatment for posttraumatic brain edema.

Clinical Material and Methods

Selection of Patients

Patients selected for the study were comatose following severe cerebral trauma, and did not open their eyes, respond verbally, or follow commands for at least 6 hours after the injury (Glasgow Coma Scale scores of 7 or less). Some of these patients had undergone removal of a traumatic hematoma.15,31 All patients had elevated ICP, ranging from 18 to 65 mm Hg.

Protocol

Ytterbium-169-labeled diethylenetriaminepentaacetic acid (169Yb-DTPA) and Evans blue dye, injected intravenously, were measured in the ventricular fluid, and the total protein content of the ventricular CSF was monitored to determine the amount of edema fluid passing into the ventricles from the extracellular space of the brain. Since 169Yb-DTPA passes through the kidneys and is excreted quickly, rapid changes in blood concentration were minimized by not using hypertonic agents or diuretics for 4 hours before the experiment was performed. An intravenous injection of 169Yb-DTPA (1 mCi) was given at the beginning of each study period. Evans blue dye (1 mg/kg) was also given intravenously at the beginning of the experiment. This agent is not excreted by the kidneys, and remains at a relatively constant concentration in the blood stream.

Most patients were subjected to studies when the acute traumatic episode was over. In each patient, ICP was maintained at a high level for 4 hours and at a low level for 4 hours, consecutively. The experimental design was randomized as to whether the high- or low-pressure study was performed first. The high pressures were no greater than 30 mm Hg and the low pressures...
were no lower than 5 mm Hg. All patients were maintained so that the minimum difference between the high and low pressures was at least 15 mm Hg. Patients with bloody CSF or those in whom the experiment could not be carried to completion (such as if the patient died during the experiment or the drainage tube became clogged) were excluded from the study. The total volume of CSF drained during the test periods was measured, and levels obtained at high and low ICP were compared. Samples of CSF were sent to the laboratory to determine the content of \(^{169}\)Yb-DTPA, Evans blue dye, and total protein.

Each patient served as his own control. A repeat study similar to the experimental study was conducted during convalescence. All of these control studies were performed at least 10 days after the injury when the clinical symptoms were significantly improved and ICP was normal. Evans blue dye concentration was determined by spectrophotometry, and \(^{169}\)Yb-DTPA activity was counted with a well-counter scintillation gamma spectrometer. The phenol method was used for determination of the total CSF protein.

### Results

**Intracranial Pressure Monitoring**

A total of 87 patients were included in the study, ranging in age from 6 to 70 years. One patient (1.15%) contracted an infection after intraventricular drainage. A total of 133 ventricular punctures were performed with three failures, for a failure rate of 2.26%. Either high- or low-pressure tests were completed in 76 cases. The average ICP was 23.7 ± 0.6 mm Hg (± standard error) in the high-pressure studies and 9.0 ± 0.5 mm Hg in the low-pressure studies. The average pressure differences between groups was 14.7 mm Hg.

**Total CSF Outflow**

Total CSF outflow was measured in 68 patients in whom both the high and low ICP studies were completed. The average volume of fluid drained in the high-pressure tests was 16.0 ± 1.8 and 51.2 ± 3.3 ml/4 hrs, respectively. The difference between results at the two pressure levels was statistically very significant (p < 0.001).

**Clearance of \(^{169}\)Yb-DTPA**

Clearance of \(^{169}\)Yb-DTPA was measured in 26 patients in whom both the high and low ICP studies were completed. The experiments were performed, on the average, 3.6 days after the injury. The average rate of \(^{169}\)Yb-DTPA clearance in the high- and low-pressure studies was 318 ± 68 and 390 ± 62 ct/ml/min, respectively. The difference between results at the two pressure levels was not significant (0.20 < p < 0.50). The total clearance rate of the isotope in the 26 trials was, on the average, 5721 ct/4 hrs in the high ICP studies and 21,358 ct/4 hrs in the low ICP studies. The difference between results at the two pressure levels was very significant (0.005 < p < 0.001).

In the control studies during patient convalescence, 15 experimental trials were performed between 10 days and 2 months after the injury. The ventricular CSF content of \(^{169}\)Yb-DTPA was negative in six trials and positive in nine trials. The average content in the nine positive trials was 401 ct/ml/min.

**Clearance of Evans Blue Dye**

Clearance of Evans blue dye was measured in 30 cases each among the high and low ICP studies. The experiments were performed, on the average, 3.3 days after the injury. The clearance of the average concentration of Evans blue in the high-pressure studies was 1.39 ± 0.19 and 2.08 ± 0.29 mg%, respectively. The difference between results at the two pressure levels was very significant (0.001 < p < 0.002). The total clearance of Evans blue dye was measured in 26 studies. Average rate of clearance in the high ICP tests was 0.23 mg/4 hrs and in the low ICP tests 1.02 mg/4 hrs (p < 0.001).

Ten control studies were conducted during patient convalescence. The time of study ranged from 10 days to 1 year after injury; nine patients were studied between 10 days and 2 months, and one patient 1 year posttrauma. The CSF was negative for Evans blue dye in three cases and positive in seven. The average clearance of dye in the seven positive trials was 0.46 mg%.

**Clearance of Total Protein**

Clearance of total CSF protein was measured in 57 studies in each of the high and low ICP tests. The experiments were performed, on the average, 4.0 days after the injury. The average total protein clearance in the high and low ICP studies was 57.3 ± 3.8 and 65.9 ± 5.8 mg%, respectively. The difference between results at the two pressure levels was significant (0.02 < p < 0.05).

In 51 trials, the average rate of clearance of total protein in the CSF outflow at the high and low ICP levels was 8.69 and 37.8 mg/4 hrs, respectively. The difference between results at the two pressure levels was very significant (p < 0.001).

In 40 convalescent patients, clearance of total CSF protein was measured between 10 days and 2 months after the injury. The average total protein concentration was 47.4 mg%. In another 16 convalescent patients, trials were conducted from 3 months to 1 year after the injury, with an average concentration of total protein of 44.0 mg%. Brain scans was performed in three of these latter patients at 3, 5, and 12 months after the injury, and were negative. The total protein concentrations of ventricular CSF were still 40.6, 49.7, and 28.8 mg%, respectively, and the average concentration in these three cases was 40.0 mg%.

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Discussion

In the normal human condition, when the blood-brain barrier is intact, $^{169}$Yb-DTPA, Evans blue dye, and plasma protein do not pass through brain capillaries. Protein content of ventricular CSF remains within normal limits. In cases of severe brain injury, the blood-brain barrier is disrupted, the permeability of the capillaries in the damaged area is increased, and plasma substances extravasate; thus, vasogenic edema results and the total protein level of ventricular CSF is increased. In this study, the presence of $^{169}$Yb-DTPA and Evans blue dye, and the increase of protein content in the ventricular CSF were used to indicate the passage of edema fluid through the intercellular space into the ventricles after disruption of the blood-brain barrier.

This study shows that: 1) The average concentration of Evans blue dye during low ICP was much higher than at high ICP levels in each of 30 trials (0.001 < p < 0.002). 2) The average total clearance of Evans blue during the 4-hour period of low ICP maintenance was also much higher than that at high ICP's. The above differences were statistically very significant (p < 0.001). 3) The rate of clearance of the average total CSF protein at low ICP's was higher than that of the high-pressure group in 57 trials. The difference was statistically significant (0.02 < p < 0.05). 4) The total amount of protein cleared in the CSF outflow during the 4-hour maintenance period of low pressure was also much higher than that during high pressure maintenance in 51 trials. The difference was statistically very significant (p < 0.001). These results suggest that, because of the greater pressure gradient in the low ICP group as compared with the smaller pressure gradient in the high ICP group, the concentration of Evans blue dye and total CSF protein as well as the total clearance of these substances were much more in the low ICP group. Therefore, when ICP is kept at a lower level, it may facilitate the clearance of edema fluid from the brain.

It is commonly considered that the reduction of ICP by external ventricular drainage (EVD), as with hyperventilation, hyperbaric oxygen, and decompressive craniotomy, is not the result of reducing brain edema. It is well known that EVD reduces ICP rapidly and significantly; however, this effect was thought to be caused by withdrawal of the original intraventricular CSF, not by reduction of edema. This study demonstrates that edema fluid flowed into the ventricle in both high- and low-pressure periods, but obviously more edema fluid flowed into the ventricle in the low-ICP tests. Therefore, EVD has a double effect in reducing ICP, because it not only reduces the amount of CSF in the ventricle, but also decreases brain edema, especially at lower pressures.

Controversy still exists as to whether, in the early stage of brain injury, intracranial hypertension is due to brain edema and/or to vessel dilatation. Tornheim and McLaurin showed in animal experiments that the contused hemispheres contained signifi-

cant brain edema 30 minutes after brain injury. On the other hand, Corales, et al., showed experimentally that there was no brain edema 5 minutes or 30 minutes after brain injury. Kobrine, et al., reported a case of brain injury in which computerized tomography showed cerebrovascular dilatation within 20 minutes after the injury. Another case of brain injury reported by Waga, et al., suggested that the early intracranial hypertension was caused mainly by vasodilatation in the brain, and only partly by brain edema. However, persistent severe vasodilatation will inevitably be followed by vasogenic brain edema. The peak level of brain edema usually occurs 2 to 3 days after brain injury, sometimes even as late as the 7th day. The results of this study show that 3 to 4 days after injury, brain edema was present in all cases.

There have been only a few reports concerned with the resolution of vasogenic brain edema, and controversy still exists about its mechanism. Based on their studies, Klatzo, et al., presented the hypothesis that the resolution of vasogenic edema was primarily caused by uptake and digestion of extravasated protein by glial cells, particularly astrocytes, and that the removal of osmotically active proteins from the extracellular space released water and reestablished normal transcapillary fluid exchange. However, as stated above, the studies of Reulen, et al., have shown that the difference in pressure gradient between the edematous region and the relatively normal brain surrounding it promotes the bulk flow of edema fluid toward the ventricles, where it is absorbed along with CSF; they demonstrated that a pressure gradient exists as long as the damaged vessels leak and the transcapillary exudation of fluid is sustained. Resolution by bulk flow prevails as long as a pressure gradient exists. With reestablishment of the blood-brain barrier, the remaining edema would have to be removed by reabsorption into the blood stream by diffusion as a second mechanism for edema removal. Reabsorption by diffusion into the capillaries is certainly much slower than removal of edema fluid into the CSF by bulk flow. Reulen, et al., also calculated the clearance rate of the edema fluid in the cat to be 1.15 to 1.5 ml/day. When this value is recalculated for the human brain on a weight basis, the corresponding edema clearance would be 80 to 90 ml/day. Our clinical study showed that lowering the ventricular CSF pressure significantly facilitated the entrance of brain edema fluid into the ventricle.

The effectiveness of EVD in treating brain injury associated with intracranial hypertension remains a controversial issue. Papo, et al., considered that EVD was only suitable for cases of intracranial hypertension caused by disturbances in CSF dynamics after brain injury, and that it was not effective during the acute stage (within 3 days) of diffuse brain injury. In these cases, the ventricles are usually small or collapsed, successful drainage is difficult or impossible and, even if ICP could be temporarily lowered, EVD could hardly influence the final clinical course. On the other
hand, Johnston, et al.,16 Becker, et al.,3 and Auer1 believed that EVD had a therapeutic effect. No matter whether these investigators supported the clinical application of EVD or not, they all considered that the EVD only drained CSF from the ventricle but not edema fluid from the brain.

In our study, of 133 attempts at ventricular puncture for EVD, only three failed, for a low failure rate of 2.26%. Of the three patients in whom EVD failed, two died and one survives in a vegetative condition. Papo and Caruselli25 reported nine patients in whom attempts at EVD failed due to collapsed ventricles; all of these patients died. It seems that patients with collapsed ventricles have a higher risk of mortality and morbidity. In the 68 patients whose CSF outflow was measured at low ICP levels, average outflow was 51.2 ml/4 hrs. This means that the drainage was successful in most cases, and quite a large amount of fluid could be drained. Therefore, if ICP can be controlled at a constant and appropriate level by even and continuous CSF drainage, ICP can be reduced to a rather low level for a long duration. Controlled continuous EVD can play an obvious part in reducing ICP unless the ventricles are collapsed.

In patients with severe brain injury, intracranial hypertension is very common. This may be caused by brain edema, cerebrovascular dilatation, an intracranial mass lesion, subarachnoid hemorrhage, or changes in CSF dynamics. Since EVD not only drains the CSF originally in the ventricle but also drains the edema fluid from the brain, as has been shown in this study, EVD effectively lowers the ICP in all the above-mentioned conditions.

In the 26 measurements of the clearance rate of 169Yb-DTPA at high and low ICP’s, results showed an average of 318 ± 68 and 390 ± 62 ct/ml/min, respectively. The difference between the two groups was not significant (0.20 < p < 0.50). This relates to the fact that 169Yb-DTPA is excreted quickly by the kidneys. The rate of excretion is approximately 50%, 60% to 70%, and 80% at 1, 2, and 3 hours, respectively, after intravenous injection.11,21,35 Therefore, the concentration of 169Yb-DTPA could not be maintained at a constant level in the blood and, in turn, in the ventricular CSF. Although the rate of clearance was greater at low ICP’s than at high ICP’s, the difference is not statistically significant; however, as the amount of CSF outflow in the 4-hour experimental low ICP period was significantly greater than that in the high ICP period, the total amount of 169Yb-DTPA cleared in the low ICP period was significantly greater than in the high ICP period (0.005 < p < 0.01).

Evans blue combines with serum albumin after intravenous injection. The clearance of this dye is mainly by phagocytosis of the reticuloendothelial system, and the rate of clearance is very slow. According to the reports by Gibson, et al.,8 there is a total excretion of Evans blue of 53.3% in 24 hours, so its concentration in the blood stream is maintained at a rather constant level. Based on this phenomenon, in the latter part of our study we chose Evans blue as an index of brain edema instead of 169Yb-DTPA. The results of the 30 trials with Evans blue supported the hypothesis of edema fluid flowing into the ventricle.

It is generally acknowledged that the normal protein content of ventricular CSF is 5 to 15 mg%.4,36 The total CSF protein concentration found in our convalescent patients gradually declined over time in 40 tests ranging from 10 days to 2 months posttrauma and in 16 tests ranging from 2 months to 1 year after the injury. This suggests that the blood-brain barrier recovered gradually. Among 16 cases, three patients were symptom-free and the brain isotope scans were negative in the 3rd, 5th, and 12th month, respectively, after the injury, but the total protein concentration in the ventricular CSF was still 40.6, 49.8, and 29.8 mg%, respectively. The average concentration of these three cases was 40.0 mg%, which was lower than the average total protein concentration (47.4 mg%) of the convalescent patients tested between 10 days and 2 months after the injury, but it was still higher than normal. These results need further investigation.

It is usually believed that traumatic brain edema is resolved within 7 to 14 days.12 In our convalescent patients tested between 10 days and 2 months after injury, whose ICP had already returned to normal, 169Yb-DTPA and Evans blue in the ventricular CSF had disappeared in only a small number. This suggests that the blood-brain barrier had returned to normal in this period in only a few cases. In the majority of cases, 169Yb-DTPA and Evans blue crossed the blood-brain barrier and total protein in the ventricular CSF did not return to normal levels, although these substances were significantly lower than in the experimental ICP-manipulation groups. This result might be explained by the fact that our patients were severely injured and that in severe brain injury the repair of the blood-brain barrier may take several months, since tissue repair is a slow process.2

With ventricular CSF pressure monitoring, and controlled continuous closed ventricular drainage, CSF outflow and ICP could be easily adjusted by controlling the height of the drainage bag. Adjustment is difficult by the three-way stopcock or other techniques. When the average amount of CSF outflow in the low-pressure group of experiments was 0.2 ml/min, we could control the ICP within an average level of approximately 9 mm Hg. Because the ICP could be controlled and stabilized at an ideal level, collapse of the ventricle, upward herniation of the cerebellum, brain congestion, edema, intracranial hemorrhage, and other disturbances of the intracranial dynamics due to sudden drop of pressure could be kept to a minimum. This technique is also of benefit in maintaining free drainage of CSF.2 The whole apparatus can be kept as a closed system; thus the chance of infection is minimized. The rate of infection associated with continuous ventricular drainage was reported by Lundberg, et al.,22 to be 1% in their 100
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cases and was 1.15% in our 87 cases. The controlled continuous closed EVD apparatus designed for this study is quite simple and practical.

Conclusions

Eighty-seven cases of severe brain injury were studied, with ICP monitoring and EVD. The ICP was controlled at a high and a low level consecutively to observe possible clearance of edema fluid. The results showed that, during a 4-hour period of low ICP, the total amount of CSF outflow, the concentration of Evans blue dye, and the total ventricular CSF protein, as well as the clearance rates of $^{169}$Yb-DTPA, Evans blue, and CSF protein were significantly greater than those of the high ICP period. The clearance rates of $^{169}$Yb-DTPA, Evans blue, and total protein in control studies in the convalescent period were reduced gradually as the blood-brain barrier was completely repaired. Thus, it was shown that, with the use of EVD, not only could ICP be lowered by the outflow of ventricular CSF, but there was also removal of edema fluid. When the ICP was controlled at a lower level, more edema fluid could be removed. In conclusion, controlled continuous EVD may be a treatment with at least two mechanisms that lower ICP in cases of severe brain injury.

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