Dose response to cerebrospinal fluid drainage on cerebral perfusion in traumatic brain–injured adults

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Object. Intracranial hypertension remains a common complication of traumatic brain injury (TBI). Ventriculostomy drainage is a recommended therapy to decrease intracranial pressure (ICP), but little empirical evidence exists to guide treatment.

The authors conducted a study to examine systematically the effect of cerebral spinal fluid (CSF) drainage on ICP and indices of cerebral perfusion.

Methods. Intracranial pressure, cerebral perfusion pressure (CPP), cerebral blood flow velocity (CBFV), and near-infrared spectroscopy–determined regional cerebral oxygenation (rSO_2) were measured in 58 patients (with Glasgow Coma Scale scores ≤ 8) before, during, and after ventriculostomy drainage. Three randomly ordered CSF drainage protocols varied in the volume of CSF removed (1 ml, 2 ml, and 3 ml). Physiological variables were time averaged in 1-minute blocks from baseline to 10 minutes after cessation of ventricular drainage.

There was a significant dose–time interaction for ICP with the three-extraction volume protocol, with incremental decreases in ICP ($F [20, 1055] = 6.10$; $p = 0.0001$). There was a significant difference in the CPP depending on the amount of CSF removed ($F [2, 1787] = 3.22$; $p = 0.040$) and across time ($F [10, 9.58] = 11.9$; $p = 0.0003$) without a significant dose–time interaction. A 3-ml withdrawal of CSF resulted in a 10.1% decrease in ICP and a 2.2% increase in CPP, which were sustained for 10 minutes. There was no significant dose, time or dose–time interaction with CBFV or rSO_2.

Conclusions. Cerebrospinal fluid drainage (3 ml) significantly reduced ICP and increased CPP for at least 10 minutes. Analysis of these findings supports the use of ventriculostomy drainage as a means of at least temporarily reducing elevated ICP in patients with TBI.

KEY WORDS • traumatic brain injury • intracranial hypertension • cerebral perfusion • ventriculostomy

Intracranial hypertension occurs in the majority of patients within the first few days after sustaining a severe TBI.[20,35] These elevations in ICP, if persistant, can have a significant negative impact on the outcomes of these patients.[35] Although the majority of patients with elevations in ICP are successfully treated, those in whom uncontrollable intracranial hypertension is present are at greater risk for cerebral ischemia and poor functional outcome.[38]

The complex relationship among factors that contribute to elevations in ICP following a TBI is still not completely understood. Elevations in ICP are thought to result primarily from increases in CSF formation, outflow resistance, or dural sinus pressure.[21] There is accumulating evidence to support the hypothesis that the vascular mechanism of increased dural sinus pressure is responsible for elevations in ICP.[18,21] The vascular mechanistic theory provides support for the treatment of elevated ICP by using ventriculostomy. After CSF is drained using ventriculostomy, there should be arterial vasoconstriction and a decrease in CBFV that result in a decrease in ICP.[36,37]

Cerebrospinal fluid drainage is one of several therapies used to treat intracranial hypertension. According to the *Guidelines for the Management of Severe Head Injury*,[7] if a ventricular drain is inserted and the patient has intracranial hypertension (ICP $>$ 20–25 mm Hg), ventriculostomy drainage should be the first step in the management of elevated ICP. There are, however, individual differences in the response of ICP to ventriculostomy drainage.[15] Marmarou[21] has suggested that this differential response is dependent on the autoregulatory state of the patient or his/her position on the pressure-volume curve.

There are few studies in which the authors have critically examined the effect of ventriculostomy drainage on elevated ICP and fewer in which authors have assessed whether ventriculostomy drainage improves cerebral perfusion.[9,12,14,15,17,28] Fortune, et al.,[12] found that ventriculostomy drainage was as effective as mannitol administration for decreasing ICP; however, mannitol was more effective for simultaneously improving jugular venous O_2 saturation. In an earlier study we found that ventriculostomy drainage decreased ICP by approximately 4 mm Hg in patients with severe TBI.[15] The treatment effect was transient, however, and by 10 minutes after cessation of ventriculos-

Abbreviations used in this paper: CBFV = cerebral blood flow volume; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; CT = computerized tomography; $ETCO_2$ = end-tidal carbon dioxide; GCS = Glasgow Coma Scale; HR = heart rate; ICP = intracranial pressure; MABP = mean arterial blood pressure; PI = pulsatility index; rSO_2 = regional cerebral oxygenation; SAH = subarachnoid hemorrhage; SD = standard deviation; SE = standard error; TBI = traumatic brain injury; TCD = transcranial Doppler.

tomy drainage, the ICP was only 1.8 mm Hg lower than that determined at baseline. In a subset of patients (16%) ventriculostomy drainage did result in a sustained reduction in ICP for longer than 10 minutes. The purpose of the present study was to determine whether there is a dose-response effect of intracranial hypertension to ventriculostomy drainage treatment.

CLINICAL MATERIAL AND METHODS

Patient Population

Patients were recruited into the study if they were admitted to the emergency department or neurotrauma intensive care unit within 12 hours of injury; had a severe TBI and a GCS score of 8 or lower without influence of paralytic agents or sedatives; were intubated and on a ventilator; had an intraventricular catheter and arterial catheter in place, with evidence of stability on waveforms; and were 16 to 65 years of age. Patients were excluded if there was clinical evidence of brain death, cardiac arrest, CSF leakage, or gunshot injuries. The study protocol and consent were reviewed and approved by the appropriate institutional review boards. All patients were medically treated based on the *Guidelines for the Management of Severe Head Injury.*[7] This included monitoring the ICP by using a ventriculostomy placed within the frontal horn of the right lateral ventricle. In the event that the ICP increased above 20 mm Hg, ventriculostomy drainage was initiated, followed by mannitol administration (25–50 g bolus). Refractory intracranial hypertension unresponsive to ventriculostomy drainage and mannitol administration was treated with pentobarbital therapy, short-duration hyperventilation, or surgical intervention. Every attempt was made to maintain the CPP above 70 mm Hg.

Ventriculostomy Drainage Protocol

All patients in whom intracranial hypertension (ICP $>$ 20 mm Hg) developed underwent CSF drainage in which three different volumes were removed in random order (1 ml [16 drops], 2 ml [32 drops], and 3 ml [48 drops]) and in which a Latin square design was used for the ordering of amounts drained. A drop counter was placed around the drip chamber of the closed CSF drainage system and connected to the computerized data acquisition system. If the time period between the drops passing through the drip chamber and across the light sensor was greater than 11 seconds, CSF drainage was terminated. A CSF extraction rate of 0.341 ml/minute (1 drop/11 seconds) was estimated as the period when CSF extraction rate equaled the reformation rate in patients with TBI.[22] Stimulation of the patient was avoided during ventriculostomy drainage to eliminate stimuli-induced changes in CPP and to minimize signal artifact.

Signal Processing

The analog signals of the physiological parameters (ICP, arterial pressure, CBFV, rSO_2, $ETCO_2$, and HR) and the CSF drop counter were digitalized at 100 Hz in real time. In the first 20 patients, the data were continuously acquired and analyzed using the Gould software. The system was later upgraded with the BioPac data acquisition system and AcKnowledge software on a portable bedside computer. A hard copy of the signal tracing was acquired during the protocol by using a recording system.

Time-averaged values of monitored physiological variables (ICP, arterial pressure, CPP, CBFV, rSO_2, $ETCO_2$, and HR) were calculated into 11 phases: 1) 1-minute baseline (B), and 2) minute-by-minute blocks for 10 minutes following CSF drainage (P1–P10). In patients in whom the prescribed CSF volume was not removed, the actual extended volume (in drops) was recorded and handled in analysis.

Physiological Monitoring

The predetermined physiological variables were continuously recorded during the ventricular drainage protocol by using a computerized bedside monitoring system. Secondary transducers were connected to the arterial, intraventricular, and jugular venous catheters. All transducers were calibrated against a mercury manometer. Cerebral perfusion pressure was calculated as the difference between MABP and ICP.

Blood Flow Velocity. The systolic, diastolic, and mean CBFV were measured using a TCD device that was precalibrated. The CBFV was insonated using a 2-mHz probe and applied over the transtemporal window by a member of the research team trained in transcranial ultrasonography. The CBFV was monitored continuously during the protocol by securing the probe to the temporal area via a specially designed Velcro head holder. The envelope of the CBFV spectral array was converted to an analog signal, and the output of the signal was connected to the computerized data acquisition system for digitalization and future determination of the systolic, diastolic, and mean CBFV rates. The PI was calculated according to the following: (systolic CBFV $-$ diastolic CBFV)/mean CBFV.[3]

Cerebral Oximetry. Near-infrared spectroscopy was used to monitor and record rSO_2. The oximeter sensors were placed on the forehead ipsilateral to the site of injury. The analog output of the monitor was connected to the computerized data acquisition system.

Jugular bulb venous O_2 tension was determined in a subsample of 20 patients by assessing serial serum samples taken from a catheter placed within the jugular bulb and verified by radiography. Samples were obtained immediately prior to ventriculostomy drainage and at 1, 5, and 10 minutes postdrainage.

Control Parameters. Control physiological parameters monitored included the $ETCO_2$ and HR. The analog output of the monitors was connected to the computerized data acquisition system.

Statistical Analysis

Descriptive statistics were computed for selected demographic and acuity variables to characterize all patients with TBI. Independent sample t-test and chi-square test analyses were used to compare baseline characteristics between: 1) patients whose families did and did not consent to be in the study; and 2) those who participated and those where consent was obtained but for whom data were not collected for clinical or technical reasons.

Repeated measures analysis[6,10] was used to investigate the within-subject effects of the amount of CSF drained; both prescribed (1 ml, 2 ml, and 3 ml) and actual (6–23 drops, 24–41 drops, and 42–56 drops) and time (baseline and P1–P10); and the relationship between the amount

drained and time. A mixed model analysis of variance statistical technique was applied based on the following: 1) patient effects are treated as random; and 2) the amount of CSF removed, number of observation points, and their interaction were viewed as fixed effects.[6] Correlations among repeated measures over time and among drainages were evaluated.[1,33] Descriptive statistics based on least-squares means and F statistics for hypothesis testing were computed based on the repeated-measures analyses. Statistical significance was set at $p = 0.05$ (two tailed) when testing main and interaction effects. Bonferoni corrections were applied when evaluating point-by-point differences over time and over drainage amounts at specific assessments.

To differentiate and model subsets of patients in whom ICP, flow velocity, or oxygenation improved by a minimum of 20% over baseline, a categorical longitudinal regression analysis was conducted.[6] Additional post-hoc analyses were performed to classify patients based on completion of the drainage protocol. Logistic regression analysis identified factors that differentiated between patients in whom the prescribed volume of CSF was drained and those in whom it was not; statistical significance was established at $p = 0.05$ (two tailed). Predictor variables for these regression analyses included the amount of CSF drained, demographic details (sex and race), severity of injury (GCS and Acute Physiology and Chronic Health Evaluation scores on admission to the emergency department), baseline physiological parameters (ICP and CPP), findings on head CT scanning (compressed cisterns and presence of SAH), and the time from injury to ventriculostomy drainage.

Sources of Supplies and Equipment

The Acq4600 and View II software used to analyze the physiological parameter data were manufactured by Gould Instrument Systems Inc. (Valley View, OH), as was the TA11 recorder device that was used to obtain a hard copy of the data tracings. We later upgraded our system, using the BioPac data acquisition system, which was purchased from BioPAC Systems, Inc. (Santa Barbara, CA). Secondary transducers (Baxter Summit disposable transducers) used to record physiological variables were obtained from Baxter Healthcare Corporation (Irvine, CA). To monitor CBFVs, two devices were acquired from Nicoloet Biomedical, Inc. (Madison, WI): the EME Transcranial Doppler TC2-64C device and the Velco head holder used while measurements were made. The rSO_2 was monitored using a cerebral oximeter (model 3100A) manufactured by Somanetics Corporation (Troy, MI), and control phyiological parameters were monitored using a device (Normocap 200) acquired from Datex Medical Instrumentation Inc. (Tewskbury, MA).

RESULTS

Patient Characteristics

From August 1994 through December 1998, 257 patients with TBI were admitted to the neurotrauma unit at two university-affiliated hospitals. Of the 105 patients who met the inclusion criteria, 99 (94.3%) agreed to participate in this study. Of these 99 patients whose families consented to the study, the CSF drainage protocol was conducted in 58 (58.6%). Reasons for not undertaking the CSF drainage protocol in the remaining 41 cases included: absence of intracranial hypertension requiring ventriculostomy drainage (13 patients); medical complications (one patient); technical difficulties (for example, catheter placement six patients); no CSF available for drainage (three patients); CSF leak developed after inclusion in study (five patients); brain death (four patients); GCS score progressed to greater than 8 (four patients); ventriculostomy was opened to continuous drain (two patients); or a combination of these reasons (three patients).

There were 45 men (77.6%) and 13 women (22.4%) who ranged in age from 16 to 65 years (mean 31.6 years, SD 14.1 years, median 26.5 years). The mechanisms of injury were primarily motor vehicle accidents (34 patients [58.6%]) and falls (11 patients [19%]). The admission GCS score in patients without evidence of sedation or paralytics ranged from 3 to 8 (mean score 5.7, SD 1.6, median 6), and the admission trauma score ranged from 3 to 13 (mean score 6.4, SD 2.6). Table 1 provides a summary of findings revealed on the admission CT scans. Multimodal monitoring of the CSF drainage protocol was conducted an average of 49.3 hours from the time of injury (SD 18.6 hours, median 46.5 hours). No significant differences were found between those in whom the CSF drainage protocol was performed and those in whom it was not in terms of age, admission trauma, GCS, or Acute Physiology and Chronic Health Evaluation III scores.

A mean of 100.9 ml of CSF (SD 94.5 ml) was drained within 24 hours prior to initiation of the CSF drainage protocol. The mean volume of CSF extracted during the CSF drainage protocol was 27.2 drops or 1.7 ml (SD 13.6 drops) and required a mean of 61.1 seconds (SD 65 seconds).

One hundred forty-two (81.6%) of the prescribed 174 drainage procedures were achieved in the 58 patients. The overall rates for successful drainage of CSF, by prescribed dose, were as follows: 1 ml, 100%; 2 ml, 79.3%; and 3 ml, 65.5%. Table 2 provides a summary of the success rates of the randomly assigned drainage protocols. Based on these results, the data were analyzed by both the prescribed volume drained and by the actual volume removed (treatment received). No significant ordering effect was demonstrated based on the volume removed. The following analysis is focused on the effect on physiological parameters of volume of CSF drained via the ventriculostomy.

Effects of CSF Drainage on CPP

ICP Response to CSF Drainage. There was a significant

TABLE 1

*Findings on admission CT studies in 58 patients with TBI**

Findings on Admission CT Report	No. of Patients (%)			
	Absent	Rt Side	Lt Side	Other
SDH	32 (55.2)	11 (19)	10 (17.2)	5 (8.6)
EDH	52 (89.7)	5 (8.6)	1 (1.7)	0 (0)
IVH	35 (60.3)	5 (8.6)	3 (5.2)	15 (25.9)
ICH	24 (41.4)	5 (8.6)	11 (19.0)	18 (31.0)
SAH	22 (37.9)	4 (6.9)	6 (10.4)	26 (44.8)
skull fracture	37 (63.8)	10 (17.2)	8 (13.8)	3 (5.2)
brain shift	39 (67.2)	14 (24.2)	5 (8.6)	0 (0)

* EDH = epidural hematoma; ICH=intracranial hemorrhage; IVH = intraventricular hemorrhage; SDH = subdural hematoma.

dose-by-time interaction for ICP with the three prescribed volumes (1 ml, 2 ml, and 3 ml) demonstrating incremental decreases in ICP (Fig. 1 *upper*). When 1 ml of CSF was drained, ICP decreased from baseline by 2.4 mm Hg (9.6%) within 1 minute after drainage, and by 10 minutes, it had decreased 1 mm Hg (4%) relative to the baseline value. When 2 ml of CSF was drained, ICP decreased from baseline by 3.4 mm Hg (13.5%) within 1 minute after drainage, and by 10 minutes, it had decreased 1.7 mm Hg (6.6%) relative to the baseline value. When 3 ml of CSF was drained, ICP decreased from baseline by 4.5 mm Hg (17.8%) within 1 minute after drainage, and by 10 minutes, it decreased 2.6 mm Hg (10.1%) relative to the baseline value. Similar results were found when analyzed by the actual amount of drainage (Fig. 1 *lower*), although no statistically significant interaction was observed. Table 3 provides a summary of mean changes in the physiological variables. Post-hoc regression analysis showed that the amount of CSF drained was the only statistically significant positive predictor of a 20% improvement in ICP following CSF drainage ($p < 0.0001$).

Response of CPP to CSF Drainage. A significant difference in the CPP was demonstrated according to the prescribed amount of CSF removed and across time. There was, however, no significant dose–time interaction with CPP when any of the three prescribed volumes was analyzed (Fig. 2 *upper*). For all three drainage protocols, there was a transient improvement in CPP. When 1 ml was drained, CPP increased by 2.4 mm Hg (3.2%) within 1 minute after drainage, and by 10 minutes it had increased by 0.6 mm Hg (1%) relative to the baseline value. When 2 ml was drained, CPP increased by 1.9 mm Hg (2.5%) within 1 minute after drainage, and by 10 minutes, it had increased by 0.9 mm Hg (1.2%) relative to the baseline measurement. When 3 ml was drained, CPP increased by 3.5 mm Hg (4.6%) within 10 seconds after drainage, and by 10 minutes, it had increased by 1.6 mm Hg (2.2%) relative to baseline CPP. Similar results were found when analyzed by the actual treatment received (Fig. 2 *lower*). The mean values are presented in Table 3.

Response of CBFV and rSO_2 to CSF Drainage. The mean baseline values for CBFV, PI, and rSO_2 were 68.8 cm/second (SE 3.3), 1.1 cm/second (SE 0.1), and 70.7 cm/second (SD 1.4). There was no change from the baseline values as a result of CSF drainage (Table 3). There was no significant dose, time, or dose–time interaction with CBFV, PI, or rSO_2 (49 cases) with the three prescribed drainage volumes (Fig. 3). Similar results were found when analyzed according to the actual treatment received. An improvement in flow velocity or oxygenation was observed in only two patients, making statistical modeling untenable.

TABLE 2

Summary of successful CSF drainage protocols stratified by order

Order of CSF Drainage Protocol	No. of Drainages (%)			
	CSF Volume Drained			Total No. of Completed Drainages by Order (%)*
	1 ml (5–23 drops)	2 ml (24–41 drops)	3 ml (42–57 drops)	
1/2/3 ml	22 (100)	22 (100)	18 (81.8)	62 (93.9)
2/3/1 ml	18 (100)	12 (66.7)	7 (38.9)	37 (68.5)
3/1/2 ml	18 (100)	12 (66.7)	13 (72.2)	43 (79.6)
total no. of completed drainages by actual volume drained (%)	58 (100)	46 (79.3)	38 (65.5)	142 (81.6)

* Total number of CSF drainages was 174.

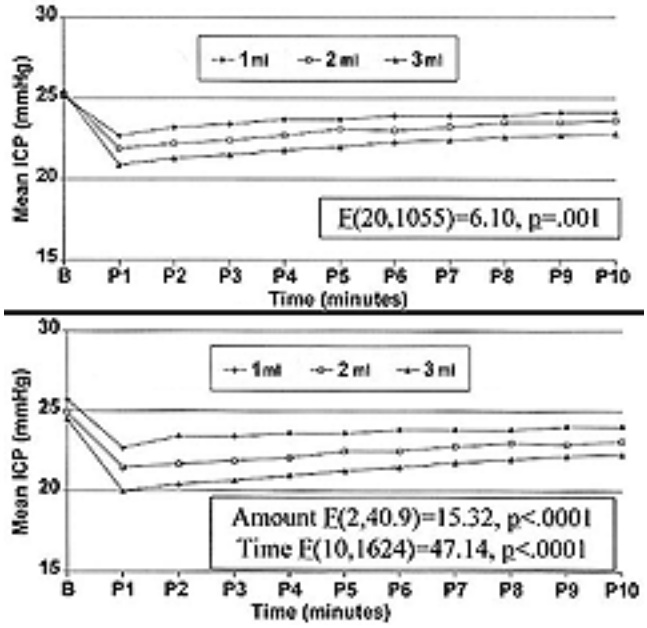

Fig. 1. *Upper:* Graph showing ICP responses by prescribed protocol of CSF drainage. *Lower:* Graph showing responses by prescribed protocol of drainage treatment received.

Other Physiological Variables. There were no statistically or clinically significant changes in the jugular bulb venous O_2 tension values or any other physiological parameters (MABP, $ETCO_2$, and HR) as a result of CSF drainage (Table 3).

Prediction of Failure to Drain Prescribed Amount of CSF

Using logistic regression analysis, two factors significantly differentiated between individuals in whom CSF could and could not be drained: the presence of SAH ($p = 0.023$) and baseline ICP ($p = 0.01$). In patients with SAH, the rate of CSF drainage failure was 4.7-fold higher (95% confidence interval 1.29–17.19) than in those without SAH. Additionally for every 1–mm Hg increase in baseline ICP, there was a 1.2-fold increase in the odds for CSF drainage failure (95% confidence interval 1.05–1.4). There was no statistically significant interaction effect indicating that the impact of one predictor (for example, baseline ICP) on the probability of CSF drainage failure was independent of the other predictor (such as presence or absence of SAH).

DISCUSSION

Since the middle 1700s, when CSF was first described within cerebral ventricles and the subarachnoid space,

TABLE 3

*Changes in physiological parameters over time following drainage of actual CSF amounts**

Physiological Parameters	Actual Amount Drained (ml)	Baseline Value		Minutes Following CSF Drainage						Statistics for Amount, Time, & Interaction Effects	
				1		5		10			
		Mean	SE	Mean	SE	Mean	SE	Mean	SE		
ICP (mm Hg)	1	25.7	0.6	22.7	0.6	23.6	0.6	24	0.6	F_{Amount} (2, 40.9) = 15.3	$p < 0.0001$
	2	24.9	0.6	21.5	0.6	22.5	0.6	23.1	0.6	F_{Time} (10, 1624) = 47.1	$p < 0.0001$
	3	24.5	0.7	20	0.7	21.3	0.7	22.3	0.7	$F_{A\times T}$ (20, 1624) = 1.4	p = 0.10
MABP (mm Hg)	1	100.7	1.5	100.3	1.5	99.7	1.5	99.8	1.5	F_{Amount} (2, 83) = 0.68	p = 0.51
	2	101.9	1.6	100.1	1.6	99.7	1.6	100.9	1.6	F_{Time} (10, 1626) = 0.71	p = 0.72
	3	99.6	1.6	99	1.6	99.9	1.6	100	1.6	$F_{A\times T}$ (20, 1627) = 0.63	p = 0.89
CPP (mm Hg)	1	75	1.5	77.6	1.5	76.1	1.5	75.8	1.5	F_{Amount} (2, 83.3) = 7.21	p = 0.0013
	2	76.9	1.6	78.6	1.6	77.2	1.6	77.8	1.6	F_{Time} (10, 1625) = 2.9	p = 0.0013
	3	74.9	1.7	79	1.7	78.6	1.7	77.6	1.7	$F_{A\times T}$ (20, 1626) = 0.74	p = 0.78
CBFV (cm/second) (56 cases)	1	70.1	3.3	70	3.3	69.5	3.3	68.7	3.3	F_{Amount} (2, 40.6) = 1.67	p = 0.20
	2	68.7	3.5	69.5	3.5	68.7	3.5	67.9	3.5	F_{Time} (10, 1570) = 1.61	p = 0.10
	3	67.7	3.4	68.2	3.4	68.2	3.4	68.3	3.4	$F_{A\times T}$ (20, 1570) = 0.67	p = 0.86
rSO_2 (51 cases)	1	70.7	1.4	70.8	1.4	70.7	1.4	70.7	1.4	F_{Amount} (2, 39.6) = 0.55	p = 0.58
	2	70.5	1.4	70.9	1.4	70.6	1.4	70.8	1.4	F_{Time} (10, 1442) = 0.64	p = 0.78
	3	71	1.4	71	1.4	71.1	1.4	70.6	1.4	$F_{A\times T}$ (20, 1442) = 0.72	p = 0.81
$ETCO_2$ (torr) (55 cases)	1	31	0.7	30.9	0.7	30.9	0.7	30.9	0.7	F_{Amount} (2, 76.4) = 2.3	p = 0.11
	2	30.8	0.7	30.8	0.7	30.8	0.7	30.4	0.7	F_{Time} (10, 1512) = 1.8	p = 0.19
	3	30.7	0.7	30.6	0.7	30.5	0.7	30.4	0.7	$F_{A\times T}$ (20, 1512) = 0.54	p = 0.95

* Measurements obtained in all 58 patients except where noted. Abbreviation: A×T = amount and time interaction.

direct observation and recording of the CSF has been used to assess ICP.[8,23,25] Research on the treatment of elevated ICP through CSF drainage has focused primarily on individuals with hydrocephalus.[2,4,29]

The negative impact of elevated ICP on cerebral function has been known for nearly 50 years.[32] In patients who have sustained a severe head injury, elevations in ICP have been associated with increases in morbidity and mortality rates.[26]

Treatment for Intracranial Hypertension

Lundberg[19] first demonstrated that removal of CSF via ventriculostomy provided temporary relief of ICP. Ryder, et al.,[32] suggested that in patients who have sustained a TBI, drainage of CSF via ventriculostomy decreased the extent of cranial space used by the ventricle, allowing dilation of the cerebral vessels. This work provided the foundation of belief by which the removal of CSF was potentially thought to have a positive effect on cerebral perfusion. Removal of CSF in the presence of cerebral edema will reduce ICP; however, the change in total brain volume will be compensated for by an increase in brain volume (such as blood volume or edema volume), potentially worsening cerebral edema.[11] To date, these questions, as they apply to the treatment of the traumatic brain–injured patient, remain unanswered.

In this study, we hypothesized that decreasing the ICP by draining CSF from the ventricles would decrease total intracranial volume and improve cerebral perfusion. We anticipated that this decrease in ICP would be accompanied by an increase in the blood flow velocity and cerebral oxygenation. We also anticipated that these changes would occur in a dose–response fashion. Analysis of our findings supports the hypothesis that the ICP was lowered in a dose–response fashion relative to the amount of CBF removed; however, a lowering of ICP was not associated with an improvement in CBFV or oxygenation.

Decrease in ICP and Outcome

We took two approaches to the analysis of the data, both an "intent-to-treat" (analyzed as randomized) and a treatment-received method, and found similar results. We

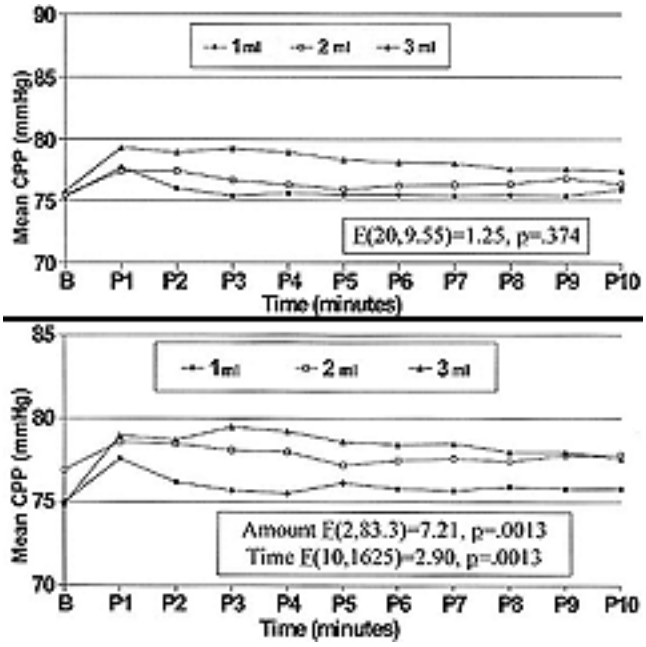

Fig. 2. *Upper:* Graph showing CPP response by CSF drainage prescribed. *Lower:* Graph showing CPP response by CSF drainage treatment received.

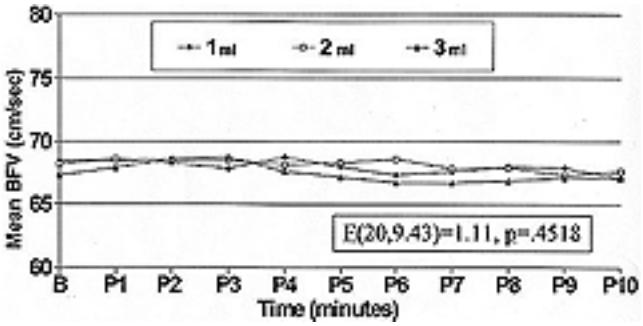

Fig. 3. Graph showing CBFV response by CSF drainage prescribed.

found a significant decrease in ICP even after 10 minutes of drainage. Some may argue that the magnitude of response is sufficiently small to render the intervention of ventriculostomy drainage insignificant, but there is evidence to suggest that small increases in ICP can negatively impact outcome. Miller, et al.,[26] reported that any increase in the ICP (> 20 mm Hg) was associated with a higher rate of morbidity in patients harboring mass lesions and those with diffuse brain injury. Unterberg, et al.,[35] reported that ICP frequently rises within the first 96 hours and that treatment with CSF drainage can yield satisfactory results, although its effect on outcomes was not clear. In this study, therapy was administered, on average, within the first 96 hours after injury. Thus, the results of this study are more reflective of the primary increase in ICP reported by Unterberg, et al., than in the secondary rise they described. They noted that patients with a secondary rise in ICP were less likely to respond to treatment and more likely to experience poorer outcomes.[35]

The post-hoc analyses revealed that TBI patients with elevated ICP and in whom SAH was present were less likely to have sufficient CSF available for treatment. Drainage of CSF has been shown to be effective in reducing ICP in patients with SAH without trauma and improving clinical neurological symptoms, particularly in those with a low-grade hemorrhage (Hunt and Hess Grade I or II).[24,34] Using a piglet model, Glass, et al.,[13] have shown that a hemorrhage insult following a head injury substantially increased ICP and decreased CPP over a head injury alone. The presence of an SAH alters CSF absorption[27] and increases CSF outflow resistance.[16] Intracranial hypertension that occurs as a result of trauma-induced SAH may be caused by an increase in CSF outflow resistance combined with intracranial volume loading and may be responsible for intracranial hypertension in patients, making CSF drainage more problematic in this patient population.[5]

The results of this study also demonstrated a dose-response increase in CPP by the volume of CSF removed. Rosner and colleagues,[30,31] for the past 10 years, have advocated a multimethod intervention that included removal of CSF via venticulostomy in combination with vascular volume expansion as well as use of systemic vasopressors and mannitol, directed at maintaining a level of CPP of at least 70 mm Hg, for the improvement of outcomes. By design, medical management of the patients in this study included maintaining the CPP at a level above 70 mm Hg. Further, whereas this study demonstrated that ventriculostomy drainage also improved CPP, one's enthusiasm f or this response is tempered because no other indices of cerebral perfusion were improved. One major reason for the lack of change in the other indices of perfusion may be that with the maintenance of the CPP above 70 mm Hg, the downward changes in ICP that occurred with drainage required minimal compensation in cerebral delivery or oxygenation.

Limitations of the Study

One limitation of this study may be the types of injuries sustained by the patients (as noted on CT scans [Table 1]), which could be a factor affecting CSF drainage. Although we controlled for severity of injury by limiting the patient sample to those with a maximum GCS score of 8, we did not control for the type of injury. The presence of SAH and compressed cisterns did not significantly explain the response to CSF. It is plausible that alternative effects may be noted when draining CSF in patients with different injuries or combinations of injuries. A larger sample size would allow subgroup analysis.

Blood flow velocity measured using TCD ultrasonography and cerebral near-infrared spectroscopy–determined rSO_2 are more reflective of regional O_2 delivery and availability. These paramaters may not have been sufficiently sensitive to demonstrate changes in cerebral perfusion that may occur within regions of injury as the ICP decreases or CPP improves. The use of TCD ultrasonography was limited to the middle cerebral artery. Change in cerebral perfusion may have occurred either within the microcirculation or in vessels that were not monitored in this study; thus changes may have occurred but were not detected within this larger vessel. The near-infrared technology, although extremely convenient for maintaining changes in regional oxygenation continuously, it is not the most valid or sensitive measure. Whereas it provided access to minute-by-minute changes in these indices, it did not provide the resolution in cerebral perfusion that can be obtained by other measures such as positron emission testing or xenon CT cerebral blood flow technology.

An additional limitation of this study was that several patients did not undergo the entire CSF drainage protocol due to an insufficient volume of CSF within the ventricles. Explanations for a lack of sufficient CSF drainage include increased absorption or decreased production of CSF or cerebral edema. Patients in whom CSF leakage caused the volume of CSF to be insufficient were removed from this study. This suggests that the subset of patients most at risk for elevations in ICP may be inadequately represented. In an attempt to examine patients with inadequate volumes of CSF, an intent-to-treat analysis was conducted, and there were no differences in the results found between those individuals who completed the CSF protocol and those who did not. There were no effects in terms of the order of volume drainage, and the slope of response showed similar patterns; thus the order of drainage yielded minimal effect on ICP and CPP response to therapy. There were significant ICP changes that correlated with the amount of CSF drained, with drainage of 3 ml of CSF decreasing the ICP the most. This provides evidence that maximal drainage up to 3 ml has no untoward effects and is the optimum dose for decreasing ICP and increasing

CPP. Further investigation in which the amount of cerebral edema controlled would be of additional value.

CONCLUSIONS

The results of this study provide empirical evidence that there is a dose-response effect in the use of ventriculostomy drainage to improve ICP and CPP in the severe traumatic brain–injured patient without causing changes in CBFV or rSO_2. What it does not show, however, is whether ventriculostomy drainage has an impact on cerebral perfusion and ultimately improves patients'outcomes. Further work with more sensitive indicators for cerebral perfusion is needed.

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