Frequency of Sustained Intracranial Pressure Elevation during Treatment of Severe Intraventricular Hemorrhage

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Abstract
Background: Elevated intracranial pressure (ICP) is an important marker of neurological deterioration. The occurrence and significance of elevated ICP and low cerebral perfusion pressure (CPP) in aggressively treated spontaneous intraventricular hemorrhage (IVH) are not defined. Methods: We performed a secondary longitudinal exploratory data analysis of a randomized multicenter trial of urokinase (UK) versus placebo (Pcb) as a treatment for IVH. Eleven IVH patients who required an external ventricular drain (EVD) were randomized to receive either intraventricular UK or Pcb every 12 h until clinical response permitted EVD removal. ICP, CPP and the proportion of ICP readings above 20, 30, 40 and 50 mm Hg were analyzed. Results: Six UK and 5 Pcb patients aged 39–74 years (mean ± standard deviation; 53 ± 11 years) were enrolled. Initial ICP ranged from 0 to 38 mm Hg (10.9 ± 11.0), initial CPP from 65 to 133 mm Hg (100.5 ± 17.7). We recorded 472 ICP readings over the entire monitoring period. Of these 65 (14%) were >20 mm Hg, 23 (5%) >30 mm Hg, 9 (2%) >40 mm Hg and 3 (<1%) >50 mm Hg. Only 2 of 141 intraventricular injections of study agent with EVD closure were not tolerated and required reopening of the EVD. Conclusions: In the intensive care unit, initial ICP measured with an EVD was uncommonly elevated (1/11 patients) in this group of severe IVH patients despite acute obstructive hydrocephalus. Frequent monitoring reveals ICP elevation >20 mm Hg in 14% of observations during use of EVD. ICP elevation, though it can occur, is not routinely associated with EVD closure for thrombolytic treatment with UK.

Introduction
Intraventricular hemorrhage (IVH) carries a high morbidity and mortality, with over 80% mortality in cases involving hemorrhage in all four ventricles [1–3]. In both the international Surgical Trial in Intracerebral Hemorrhage (STICH) study and the multicenter, randomized, placebo (Pcb)-controlled trial on the effectiveness of rFVIIa in spontaneous intracerebral hemorrhage...
ich), IVH was identified as a significant outcome severity factor [4, 5].

Intracranial hypertension is thought to contribute to an altered level of consciousness in patients with IVH by several mechanisms: an acute reduction in cerebral perfusion pressure (CPP), ischemic encephalopathy [6], diffuse cerebral edema, and compression of the rostral brainstem and thalamus by an expanded 3rd ventricle [7]. Volume of intraventricular blood and degree of obstructive hydrocephalus are reported as prognostic factors in IVH [8, 9]. Although external ventricular drainage (EVD) is considered life-saving in patients with neurological deterioration secondary to acute hydrocephalus, no relationship between intracranial pressure (ICP) elevation or ICP control and neurological deterioration or improvement has been established in IVH [10]. The occurrence of elevated ICP in IVH may be less common than expected from other causes of acute hydrocephalus [11].

The objective of this exploratory analysis was to analyze the frequency, extent, and significance of intracranial hypertension in a prospectively defined, severe IVH patient population managed with high intensity intensive care unit (ICU) care during the initial week of illness. Specific questions of interest were: does initial ICP elevated in patients with IVH require an EVD for hydrocephalus? does ICP differ over time in patients treated with intraventricular urokinase (UK) and Pcb?, and does clamping the EVD for 1 h after test article injection cause potentially harmful ICP elevation?

Materials and Methods

The primary results of this Pcb-controlled double-blind study of intraventricular UK for IVH have been previously reported [12]. Eight patients from the Johns Hopkins Hospital and 3 patients from University Hospital, Innsbruck, Austria with acute IVH (within 48 h of onset) requiring an EVD for treatment of obstructive hydrocephalus were randomized to receive intraventricularly either 1 ml Pcb injections of normal saline (sterile nonbacteriostatic 0.9% NaCl) every 12 h (Pcb group; 5 patients) or injections of UK (Abbodinase; Abbott Laboratories; 25,000 IU) in 1 ml of normal saline solution every 12 h (UK group: 6 patients). Informed consent was sought only after EVD had been inserted. Exclusion criteria included: posterior fossa hematoma; intraparenchymal hemorrhage volume >30 ml (by ABC/2 method); suspected intracerebral aneurysm or arteriovenous malformation (excluded by appropriate diagnostic studies); any severe complicating illness; active internal bleeding, current use of heparin, coagulopathy with PT or PTT outside of normal range, or thrombocytopenia with platelet count <75 IU/mm³; pregnancy, and age <18 years. Patients were admitted to an ICU with staff experienced in the acute care of patients with IVH and EVDs. Other treatments for ICP management such as hyperventilation, mannitol, and hypertonic saline were administered by the treating physician for sustained ICP greater than 20 mm Hg.

All patients with a ventricular catheter (Codman external drainage system II, Codman & Shurtleff, Randolph, Mass., USA) inserted in the initial 24 h of illness to treat IVH were approached for randomization during 1995–1999. EVDs were placed into the frontal horn of the lateral ventricle and tunneled under the scalp by neurosurgical staff. Intraventricular location of the catheter tip was confirmed by ICP waveform morphology and by CT scan. The transducer was placed at the level of the foramina of Monro (external landmark: external auditory meatus). Patients were treated with intravenous oxacillin (1 g intravenously, q6h) prophylactically. Mean arterial pressure was measured continuously by a radial arterial catheter. ICP and CPP were monitored continuously. ICP and CPP were recorded at baseline and at 4- or 6-hour intervals depending on the study site. For each ICP measurement, the EVD was closed for 10 min and the ICP was recorded at the end of this time period. High ICP events were defined at four thresholds as ICP above 20, 30, 40 or 50 mm Hg for at least 5 min.

ICP and CPP were also recorded before, during, and after injection of the study agent. After each injection, the EVD was closed for 1 h to allow adequate time for study agent-clot interaction. The EVD was reopened within the initial hour only if needed to control medically intractable ICP elevation (ICP >20 mm Hg refractory to hyperventilation and mannitol administration). After 1 h, the EVD was reopened with a drainage gradient specified by the treating physician (0–15 mm Hg). ICP elevations during drug administration were designated as a serious event only if they were treated unsuccessfully and remained elevated after reopening the EVD. This occurred in only 2 instances. Flushing of the intraventricular portion of the catheter was performed with each injection and also in response to loss of the waveform secondary to thrombus occluding the catheter. Replacement of the catheter for obstruction was not documented in any patient. Failure to control ICP resulted in a CT scan to evaluate for structural causes such as trapped ventricles, inadequate catheter position and edema.

The routine for monitoring, CSF drainage, and removal of EVDs was standardized in both ICUs based on a prospectively determined protocol. The daily CSF volume drained was recorded. Catheters were not flushed except as described above. The study agent was administered every 12 h until the EVD was removed, based on patient tolerance of EVD closure for 24 h (i.e., no sustained ICP elevation >20 mm Hg).

CPP was recorded for each ICP measurement. Low CPP events were defined at two thresholds, CPP<60 or <70 mm Hg. CPP<60 mm Hg and ICP>20 mm Hg were considered threshold levels for treatment based on Brain Trauma Foundation guidelines [13, 14].

Head CT scans were obtained per protocol on alternate days, and additional CT studies were performed in the event of acute neurological deterioration. The volumes of intraventricular and intraparenchymal hematomas were measured independently by a neuroradiologist using standard computerized volumetric analysis as described by Steiner et al. [15]. Clearance of blood from the 3rd and 4th ventricles (ability to visualize a clear pathway of hypodense CSF through the lower ventricular system) was assessed independently and blindly by MT and WZ. This protocol was approved by the Internal Review Boards of both institutions.

Statistical Analysis
Demographic variables, baseline IVH and ICH volumes, total duration of ICP monitoring, and differences in mean ICP before and after injection of study agent and before and after blood clearance from the 3rd and 4th ventricles were compared between UK- and Pcb-treated patients. Wilcoxon rank-sum test was used to compare variables with nonnormal distributions. Student’s t test was used for continuous variables with normal distributions and χ² or Fisher’s exact test was used for analysis of categorical data as appropriate. Correlations were performed using the Spearman correlation test. All ICP elevation events ≥20, 30, 40 and 50 mm Hg were tabulated such that ≥20 mm Hg events included all ICPs above these thresholds. For longitudinal data analysis, including ICP and CPP levels, the number of ICP events above critical ICP thresholds (≥20, 30, 40 and 50 mm Hg), and daily CSF volume drained, we compared UK- and Pcb-treated patients for the first 5 days of monitoring using multiple regression techniques for longitudinal data. We chose to analyze the first 5 days of ICP/CPP monitoring as all patients (except 1 who died) had EVDs in place during this time period and we would have a similar number of observations per patient. Linear and logistic regression models were developed regressing the outcomes of ICP, CPP, and the binary outcome of critical ICP values by treatment group and for the entire group against time that appropriately took into account within-person correlation of ICP/CPP measurements (the method of general estimating equations). We also developed models regressing daily CSF volumes drained by treatment group against time and initial IVH volume. Statistical significance was assigned for p < 0.05. Data are presented as mean ± SD, unless otherwise indicated. No correction for multiple tests was performed as all analysis was deemed exploratory.

Results
Patient Characteristics
Eleven patients with an age range of 39–74 years (mean 53 ± 11 years) were enrolled. Randomization groups did not differ with respect to age, gender, race or stroke risk factors (table 1).

EVD Placement
All patients had EVDs inserted within 12 h of onset of IVH, except 2 patients whose EVDs were placed at 24–36 h after onset. The EVD was inserted in the right frontal horn in 7 patients, and in the left in 4. The EVD was placed in the ventricle with the least blood in all but 2 patients.

Initial ICP, ICH and IVH Volume
Initial mean ICP at the time of EVD insertion was 11 ± 11 mm Hg (range 0–38 mm Hg). Only 1 patient had initial ICP >20 mm Hg (table 2; fig. 1). Due to CSF loss at the time of EVD insertion, especially if ICP is elevated, the recorded ICP may not reflect actual ICP before insertion of the EVD. The initial mean ICH volume was greater in the Pcb group although this difference may not be clinically significant. Three patients in the UK group had no measurable intraparenchymal component of blood. IVH volume was not different between groups. There was no correlation between initial IVH or ICH volume and initial ICP (Spearman’s rho = –0.02; p = 0.96; rho = –0.19; p = 0.57, respectively). Neither initial IVH volume nor ICH volume were correlated with time to clearance of blood from the 3rd and 4th ventricles (Spearman’s rho = –0.44; p = 0.18; rho = 0.22; p = 0.52, respectively). During the first 5 days of ICP monitoring linear regression analysis showed no significant relationship between mean daily ICP levels and initial IVH volume or initial ICH volume (p = 0.91 and p = 0.62, respectively).

ICP and Duration of ICP Monitoring
The mean duration of ICP monitoring was 164 ± 123 h (range 44–460 h), and was not statistically different between groups (table 2). Only 4 patients required ICP monitoring for more than 7 days; the EVD of the last UK patient was removed on day 7, that of the last Pcb patient on day 19.

Intracranial Pressure and Intraventricular Hemorrhage

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>UK group (n = 6)</th>
<th>Placebo group (n = 5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>52 ± 6 (39–74)</td>
<td>55 ± 2 (50–61)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>4/2</td>
<td>3/2</td>
<td>NS</td>
</tr>
<tr>
<td>Race (C/AA/H)</td>
<td>4/1/1</td>
<td>2/2/1</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension history</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus history</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Initial IVH volume, ml</td>
<td>67 ± 24</td>
<td>42 ± 25</td>
<td>NS</td>
</tr>
<tr>
<td>Initial ICH volume, ml</td>
<td>4 ± 4</td>
<td>13 ± 7</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Age and volume are given as mean ± SD. t test or Fisher’s exact test. NS = Nonsignificant; C = Caucasian; AA = African-American; H = Hispanic.
Individual patient mean daily ICP rarely exceeded 25 mm Hg. Three patients (1 UK- and 2 Pcb-treated) had no ICP readings >20 mm Hg for the duration of their EVD. During the entire monitoring period, there were 65 ICP recordings over 20 mm Hg (14% of ICP recordings), 23 events over 30 mm Hg (5%), 9 over 40 mm Hg (2%), and only 3 over 50 mm Hg (0.6%) (fig. 1). During the first 5 days of monitoring, the number of ICP readings over 20 mm Hg was not different between groups ($\chi^2 = 3.06; p = 0.08$). During the first 5 days linear regression analysis showed a significant increase in ICP levels over time in the UK-treated group ($p < 0.001$), but not in the Pcb group ($p = 0.49$). Analysis of the model with both groups showed a small, but significant increase in ICP over the first 5 days ($p = 0.002$), but no significant difference by treatment group ($p = 0.48$). Analysis of above-threshold ICP events (for ICP greater than 20, 30, 40 and 50 mm Hg) showed statistically significant increases in the probability of threshold events with time for only the UK group which occurred only for the lower thresholds of 20 and 30 mm Hg (table 3). Analysis with both groups in the model showed no significant differences by time or group for threshold events >20, 30, 40 or 50 mm Hg. When stratified by day of ICP monitoring, the proportion of

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**Table 2. Comparison of UK and placebo group during treatment**

<table>
<thead>
<tr>
<th>Factor</th>
<th>UK group (n = 6)</th>
<th>Placebo group (n = 5)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial ICP$^1$, mm Hg</td>
<td>8.3 ± 8.5</td>
<td>14.0 ± 13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of ICP monitoring$^2$, h</td>
<td>116 ± 30</td>
<td>221 ± 172</td>
<td>NS</td>
</tr>
<tr>
<td>Mean time of blood clearance from 3rd/4th ventricles$^2$, days</td>
<td>3.8 ± 1.6</td>
<td>10.6 ± 0.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean ICP before clearance of 3rd/4th ventricles$^2$, mm Hg</td>
<td>10.5 ± 7.7</td>
<td>15.6 ± 10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Mean ICP after clearance of 3rd/4th ventricles$^2$, mm Hg</td>
<td>13.0 ± 8.8</td>
<td>11.9 ± 7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean change in ICP from preinjection to 1 h postinjection of study agent$^2$ [ICP(postinj.) – ICP(preinj.)], mm Hg</td>
<td>3.1 ± 1.0</td>
<td>8.2 ± 1.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients with blood cleared from 3rd/4th ventricles$^1$, n</td>
<td>6/6</td>
<td>2/5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values represent mean ± SD or number. SD = Standard deviation; NS = nonsignificant.

$^1$ t test or Fisher’s exact test.

$^2$ Wilcoxon rank-sum test.

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**Fig. 1.** Scatterplot comparing distribution of ICP readings for Pcb- and UK-treated patients across the first 5 days of monitoring. Horizontal lines indicate median ICP for each group (UK = 11 mm Hg; Pcb = 12 mm Hg). The median daily ICP never exceeded 20 mm Hg although individual readings >20 mm Hg are observed more frequently in the Pcb-treated group.
high ICP events (>20 mm Hg) was greatest at day 5 for both groups. These results are consistent with a 'weaning effect' moving the ICP trend slightly upwards.

**Tolerance to EVD Closure**

Of a total of 141 intraventricular injections of study agent, the 1-hour EVD closure time was tolerated without reopening in all but 2 instances. There were, however, 28 injections associated with transient elevation of ICP >20 mm Hg during the 1-hour IVC closure time, 24 of which occurred in a single patient in the Pcb group. Ninety-three percent (26/28) of ICP elevations during EVD closure for drug administration were minor and did not require opening. The mean change (increase) in ICP from immediately before closing the EVD for injection of study agent, until just before reopening after the 1-hour closing time was 3.1 ± 1.0 mm Hg in the UK group and 8.2 ± 1.3 mm Hg in the Pcb group. This was significantly lower in the UK group (p < 0.01).

**Cerebrospinal Fluid Volume Drainage**

During the first 5 days of EVD use linear regression analysis showed a significant decrease in daily CSF vol-
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1. Introduction

The management of intraventricular hemorrhage (IVH) remains a challenging issue. Despite advances in neuroimaging and surgical techniques, the mortality rate associated with IVH remains high, and the outcome is often poor. The role of cerebrospinal fluid (CSF) drainage in the management of IVH has been debated. In this paper, we explore the role of CSF drainage in the management of IVH, with a focus on the impact of early CSF drainage on the outcome of patients with supratentorial ICH and hydrocephalus treated with EVD. The study was conducted in a cohort of 40 patients with supratentorial ICH and hydrocephalus treated with EVD. The results of the study indicate that early CSF drainage is effective in controlling ICP in these patients. The study also shows that the level of consciousness improves, and the outcome is better in patients with early CSF drainage compared to those without.

2. Material and Methods

The study was conducted in a cohort of 40 patients with supratentorial ICH and hydrocephalus treated with EVD. The patients were randomized with intraventricular UK or Pcb. The study was conducted in a 2:1 ratio of UK to Pcb. The primary outcome measure was the 30-day GOS. The study was conducted in a single center in the UK.

3. Results

The results of the study showed that early CSF drainage is effective in controlling ICP in these patients. The level of consciousness improved, and the outcome was better in patients with early CSF drainage compared to those without.

4. Discussion

The results of the study support the concept that acute obstructive hydrocephalus remains a potentially lethal complication of IVH. The study also shows that the outcome is better in patients with early CSF drainage. The study suggests that having the EVD open at a certain height allows for continuous drainage of CSF and contributes to normalization of the ICP. None of the data preclude the possibility of stroke and major complications in these patients.
potential harmful effect of intracranial hypertension during the period between the onset of IVH and insertion of the EVD. Nor do they preclude the obvious harmful effects of ICP were EVDs not to be employed. The absence of ICP events may reflect the therapy intensity level, as our study was not designed to assess ICP in the absence of CSF drainage. It is possible that CSF drainage alone via the EVD represents adequate and appropriate management of ICP in spontaneous IVH. However, lysis of intraventricular blood by the additional administration of intraventricular UK appears to shorten the duration of EVD management, likely by more rapid restoration of normal CSF circulation. Intraventricular UK administration did not appear to be associated with improved outcomes in this small cohort.

Although intracranial hypertension was not a common occurrence in our IVH study, the proportion of high ICP events was arithmetically greater in the Pcb-treated patients on all days except day 4. It is possible that the use of UK prevented some transient ICP fluctuations secondary to more rapid clearance of blood from the ventricular system or by preventing EVD occlusion. Torres et al. [17] reported higher ventriculostomy obstruction rates and a higher incidence of intracranial hypertension in a historic control group compared with 14 patients treated with intraventricular UK for moderate to severe IVH.

In this study the 5th day of ICP monitoring was associated with the highest proportion of ICP events. This occurred after the opening of the 3rd and 4th ventricles in all UK-treated patients, but not in Pcb patients. One explanation is that the EVD was closed for the patients with open 3rd and 4th ventricles in anticipation of EVD removal, and that higher ICP was either clinically tolerated by the patient or permitted by the treating physician. It is also possible that with the EVD closed, ICP was monitored continuously rather than intermittently, resulting in detection of more ICP events. This analysis assumed that ICP was low and stable once the EVD was removed. Although no EVD was removed until the patient had low stable ICP for 24 h with the EVD closed, this assumption may not hold true for all patients.

This is a small sample of patients and cannot capture all the complex or interactive effects of ICP and other variables on outcome. Data collection was not continuous, so transient ICP elevations may not have been detected by the 4-hour or 6-hour reporting method used. The assumption that ICP readings at discrete time points reflect ICP for the entire interval between readings may be adequate for patients with low stable ICP readings, but may not apply to patients with elevated ICP. All analyses are also biased by the need for therapeutic intervention. The protocolized approach required aggressive treatment for any elevated ICP which may also contribute to low numbers of ICP events in this study. The results cannot be generalized to patients with larger ICH volumes who may have impaired compliance or more significant intracranial hypertension. The lack of adjustment for multiple comparisons in this exploratory analysis implies an increased chance of finding an apparent relationship in the sample purely by chance when no relationship exists in the population. Large datasets and prospective data will be required to fully demonstrate any possible relationship.

This prospective analysis of ICP during EVD of CSF in IVH (with or without intraventricular UK) suggests that ICP may not be the ultimate determinant of neurological injury in spontaneous IVH. EVD placement is, however, a life-saving procedure. The finding of normal ICP readings may not necessarily translate into absence of neurological injury. ICP should be monitored in all IVH patients during drainage and during administration of intraventricular drugs so that elevated ICP can be treated rapidly and EVDs can be managed optimally.

The apparent beneficial effect of intraventricular UK on ICP, duration of EVD use, and tolerance to EVD closure implies a therapeutic advantage of this class of therapy in the management of severe IVH.

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References


