Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury*

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Object. Recently, a renewed emphasis has been placed on managing severe head injury by elevating cerebral perfusion pressure (CPP), which is defined as the mean arterial pressure minus the intracranial pressure (ICP). Some authors have suggested that CPP is more important in influencing outcome than is intracranial hypertension, a hypothesis that this study was designed to investigate.

Methods. The authors examined the relative contribution of these two parameters to outcome in a series of 427 patients prospectively studied in an international, multicenter, randomized, double-blind trial of the N-methyl-D-aspartate antagonist Selfotel. Mortality rates rose from 9.6% in 292 patients who had no clinically defined episodes of neurological deterioration to 56.4% in 117 patients who suffered one or more of these episodes; 18 patients were lost to follow up. Correspondingly, favorable outcome, defined as good or moderate on the Glasgow Outcome Scale at 6 months, fell from 67.8% in patients without neurological deterioration to 29.1% in those with neurological deterioration. In patients who had clinical evidence of neurological deterioration, the relative influence of ICP and CPP on outcome was assessed. The most powerful predictor of neurological worsening was the presence of intracranial hypertension (ICP \( \geq \) 20 mm Hg) either initially or during neurological deterioration. There was no correlation with the CPP as long as the CPP was greater than 60 mm Hg.

Conclusions. Treatment protocols for the management of severe head injury should emphasize the immediate reduction of raised ICP to less than 20 mm Hg if possible. A CPP greater than 60 mm Hg appears to have little influence on the outcome of patients with severe head injury.

Key Words • head injury • intracranial pressure • cerebral perfusion pressure • intracranial hypertension • critical care • outcome measurement

Head injury is one of the leading causes of death in the industrialized world and is responsible for more than 50% of the 100,000 deaths from trauma in the United States each year. Furthermore, hundreds of thousands of people live with long-term disabilities from head injury. The impact of secondary insults, particularly hypertension and hypoxia, on outcome after head injury has been described previously, but there has been little attention focused on deterioration following hospitalization. Stein, et al., have shown that the patients who deteriorate neurologically have a far worse outcome compared with those who do not. In our study this subgroup of patients was selected for detailed analysis of the influence of different levels of ICP and CPP. In an attempt to improve outcome in patients with traumatic head injury, a renewed emphasis has been placed on CPP. Some authors have even suggested that therapy directed at improving CPP is more important than that aimed at elevated ICP.

In the present manuscript we examine the relationship and relative importance of ICP and CPP in severely head injured patients by examining the higher risk group who manifest neurological deterioration following initial resuscitation after admission to the hospital.

Clinical Material and Methods

Database for the Analysis

This analysis was performed using prospectively collected data from the international trial of the competitive N-methyl-D-aspartate receptor antagonist Selfotel (CGS 19755). The study was a randomized, double-blind, controlled trial involving more than 50 treatment centers in Europe, Australia, Canada, and Argentina. Patients were enrolled in the study between November 1, 1994 and December 31, 1995. In all centers participating in this study the investigators had a history of dedication to head injury care and research. Case report forms for all patients were carefully reviewed for compliance with the protocol. Adherence to the general principles now known as the Amer-
Patients randomized within the trial had GCS scores of 4 to 8 and at least one reactive pupil following nonsurgical resuscitation. Patients who suffered high-velocity missile injuries, such as gun shot wounds, were excluded.

Information collection began as close to the time of injury as possible, with particular emphasis on the acute care period, and throughout rehabilitation. The primary outcome measure was the 6-month GOS score. Prospectively, clinical data were collected hourly during the first 5 days of hospitalization or until the time of discharge from the intensive care unit, and included ICP, MAP, and CPP.

Neurological deterioration was defined as occurring in patients who manifested clinically identified episodes of one or more of the following: 1) a spontaneous decrease in GCS motor scores of 2 points or more from the previous examination; 2) a further loss of pupillary reactivity; 3) development of pupillary asymmetry greater than 1 mm; or 4) deterioration in neurological status sufficient to warrant immediate medical or surgical intervention. In the event of such an occurrence, a standardized form was completed by the investigators elucidating the circumstances, pertinent clinical and CT scan data, and the cause of the deterioration. Hypoxia was defined as PaO2 less than 60 mm Hg and/or arterial saturation less than 85%. Shock was defined as systolic blood pressure less than 90 mm Hg. Cerebral perfusion pressure was calculated as the MAP minus the ICP. Patients in each of the study centers were treated using a defined protocol for head injury management with emphasis on prevention of secondary injury, including criteria for the initiation of treatment for elevated ICP and for maintenance of CPP at levels higher than 60 mm Hg when possible.

Data Analysis
Outcome analysis was performed using the GOS score modified with special reference to favorable outcome (defined as good or moderate on the GOS) and death. Chi-square, univariate, and multivariate studies were used for statistical analysis. Significance was determined at the 5% level. Commercially available software (version 7.0; SPSS, Inc., Chicago, IL) was used for data processing and analysis.

Results
A total of 427 patients were enrolled in the study, 117 of whom had documented episodes of neurological deterioration. Twenty patients were lost to follow up, leaving 407 for data analysis. The basic demographic data are listed in Table 1 and are as follows. In the study population the median age was 28 years (range 15–79 years) with 71% younger than 40 years of age; 78% of the patients were male. Seventy-seven patients (20%) suffered either shock or hypoxia before hospital admission and 5% suffered both of these secondary insults.

There were 117 patients who had experienced one or more episodes of neurological deterioration. Thirteen of these patients were excluded from further analysis because of a delay in initiating ICP monitoring or because their records did not contain complete data. The excluded group of patients with neurological deterioration and the studied group had similar demographic and severity data. In the majority of cases, the identification of episodes of
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neurological deterioration was based on accepted objective criteria as seen in the first four items in Table 2. As previously stated, the analysis was intentionally focused on this group of patients who had a significantly higher mortality rate.15

Comparing the two groups (with or without neurological deterioration), no differences were seen with regard to gender or the incidence of preadmission shock and hypoxia. Slight differences were seen in the age of patients with neurological deterioration; the median age was 32 compared with 27 years (p > 0.05). Patients with surgically treated lesions had a higher incidence of neurological deterioration, 40% compared with 27% (p < 0.05).

There was a mortality rate of 9.6% for patients in whom no episode of neurological deterioration occurred and 67.8% had a favorable outcome. If neurological deterioration did occur, the mortality rate was 56.4% (p < 0.0001) and favorable outcomes were 29.1% (p < 0.0001). The identifiable reasons for neurological deterioration were increased intracranial volume in 66 (63.4%) of the 104 patients, cerebral ischemia in five (4.8%), systemic complications in 13 (12.5%), seizures in seven (6.7%), and no definable cause in 13 (12.5%).

The median time from injury to neurological deterioration was 29 hours (range 3.3–447 hours). In 61 of 80 patients who suffered neurological deterioration in the first 72 hours, increased intracranial volume was the reason for deterioration, whereas in the patients in whom neurological deterioration occurred more than 72 hours postinjury, increased intracranial volume was the cause in only 20 of 37 (p < 0.05).

Risk of Neurological Deterioration

A univariate analysis of the clinical variables related to neurological deterioration was performed. The potential risk factors and their importance are delineated in Table 3. The risk of experiencing neurological deterioration was greater for patients older than 40 years of age, compared with a younger population (p < 0.01). The presence of compressed or absent cisterns or midline shift on the CT scans was associated with increased risk. In contrast, GCS score, hypoxia, and presentation with shock on admission were not linked to an increased risk of neurological deterioration. No effect on risk was seen with either gender or study medication. Of all the factors analyzed, the initial ICP reading was the most powerful predictor, with the risk of neurological deterioration almost threefold greater than average if the initial ICP was higher than 20 mm Hg (p < 0.01). Somewhat surprisingly, the initial CPP reading was not a significant predictor for neurological deterioration.

Using a logistical regression analysis, an algorithm was built in which the earliest available data were used for determining the patients in greatest danger for neurological deterioration. The following variables were tested in the initial model: age 40 years or older, gender, GCS motor score lower than 4, admission GCS score lower than 6, shock or hypoxia before or at admission, nonreactive pupil(s) at admission, drug treatment (Selfotel or placebo), abnormal basilar cisterns, midline shift, traumatic SAH, traumatic intraparenchymal hemorrhage, multiple sites of traumatic SAH, Traumatic Coma Data Bank CT classification 5 or 6, initial ICP 20 mm Hg or higher, and initial CPP less than 70 mm Hg. The CT scan data were obtained from the initial postinjury scan. The number of variables was reduced to the following by using stepwise regression: initial ICP 20 mm Hg or higher, compressed or absent cisterns, multiple sites of traumatic SAH, and admission GCS score lower than 6. The initial CPP had no influence on the prediction. With this model, elevated ICP and its related variables, such as appearance of the mesencephalic cisterns on CT scan, were clearly the most important predictors. However, in this model only approximately 45% of the episodes of neurological deterioration were predicted because the data were modeled using initial physiological variables and the first CT scan. In approximately 30% of patients, repeated CT scanning revealed worsening of the appearance of the brain, such as swelling or the development of mass lesions.

Neurological Deterioration, CPP, and ICP

Intracranial hypertension is generally considered to be present and requires therapy when the ICP level is at or below 20 to 25 mm Hg. When the threshold of 20 mm Hg is examined, ICP becomes a strong predictor of relative risk for the occurrence of neurological deterioration and eventually a worse outcome. An inadequate CPP has been shown to affect outcome adversely and, thus, most neurointensivists attempt to keep the CPP level higher than 60 to 65 mm Hg at all times. In recent studies it has additionally been proposed that higher levels of CPP would be beneficial in head-injured patients. The effects of ICP and CPP were therefore examined at three separate time periods in our study: at initial presentation, before the episode of neurological deterioration, and at the time of its occurrence. Both parameters were examined individually and as paired variables.

In this trial, patients with an initial ICP of less than 20 mm Hg have a relative risk of 0.341 (95% CI 0.252–0.461, p < 0.00001). In contrast, an ICP of greater than 20 mm Hg was predictive of an increase in the occurrence of neurological deterioration: ICP at 20 mm Hg or higher

### TABLE 3
Univariate analysis: risk of neurological deterioration*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>age ≥40 yrs</td>
<td>1.626</td>
<td>1.177–2.247</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GCS motor score &lt;4 on admission</td>
<td>1.245</td>
<td>0.894–1.733</td>
<td>NS</td>
</tr>
<tr>
<td>GCS score &lt;6 on admission</td>
<td>1.388</td>
<td>0.996–1.929</td>
<td>NS</td>
</tr>
<tr>
<td>shock preadmission</td>
<td>0.867</td>
<td>0.426–1.765</td>
<td>NS</td>
</tr>
<tr>
<td>hypoxia preadmission</td>
<td>1.273</td>
<td>0.861–1.884</td>
<td>NS</td>
</tr>
<tr>
<td>shock &amp; hypoxia preadmission</td>
<td>1.405</td>
<td>0.475–4.157</td>
<td>NS</td>
</tr>
<tr>
<td>pupil unreactive on admission</td>
<td>1.664</td>
<td>1.202–2.359</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>abnormal cisterns on initial CT scan†</td>
<td>2.224</td>
<td>1.539–3.213</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>midline shift on initial CT scan</td>
<td>1.647</td>
<td>1.194–2.273</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>presence of traumatic SAH</td>
<td>1.766</td>
<td>1.064–2.929</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>multiple sites of traumatic SAH</td>
<td>1.702</td>
<td>1.232–2.350</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>temporal lesions</td>
<td>1.362</td>
<td>0.954–1.941</td>
<td>NS</td>
</tr>
<tr>
<td>CT classification 5 or 6</td>
<td>1.530</td>
<td>1.108–2.114</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

* For definitions of shock, hypoxia, and CT classification, see Table 1. Abbreviation: NS = not significant.
† Abnormal cisterns = compressed or absent cisterns on the first CT scan.

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**Note:** The table and text above represent the natural reading of the provided document. The table includes univariate analysis data related to neurological deterioration, including parameters such as age, GCS score, and various clinical conditions. The text details the risk factors and their significance, emphasizing the importance of initial ICP and CPP in neurological deterioration.
entailed a relative risk of 2.934 (95% CI 2.169–3.968, p < 0.00001), and ICP at 25 mm Hg or higher resulted in a relative risk of 2.934 (95% CI 2.169–3.968, p < 0.00001) (Table 4).

In general, we could not predict from CPP levels which patients would suffer from neurological deterioration and, thus, ultimately manifest a worse outcome. With an initial CPP of less than 60 mm Hg, the relative risk was 1.181 (95% CI 0.970–1.437, p > 0.05). If the initial CPP was 60 mm Hg or higher, the relative risk was 0.590 (95% CI 0.338–1.030, p > 0.05). At the higher initial CPP value of 70 mm Hg or higher, the relative risk was 0.634 (95% CI 0.398–1.009, p > 0.05), and at an initial CPP of 80 mm Hg or higher, the relative risk was 0.753 (95% CI 0.471–1.203, p > 0.05) (Table 4).

In this subgroup we also examined ICP and CPP 1 hour before and at the time of clinically observed worsening. At both time points, ICP but not CPP was predictive of neurological deterioration: assessment of ICP and CPP

### TABLE 4

<table>
<thead>
<tr>
<th>Parameter (mm Hg)</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial ICP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0.341</td>
<td>0.252–0.461</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>≥20</td>
<td>2.934</td>
<td>2.169–3.968</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>≥25</td>
<td>3.042</td>
<td>2.288–4.045</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>initial CPP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.181</td>
<td>0.970–1.437</td>
<td>NS</td>
</tr>
<tr>
<td>≥60</td>
<td>0.590</td>
<td>0.338–1.030</td>
<td>NS</td>
</tr>
<tr>
<td>≥70</td>
<td>0.634</td>
<td>0.398–1.009</td>
<td>NS</td>
</tr>
<tr>
<td>≥80</td>
<td>0.753</td>
<td>0.471–1.203</td>
<td>NS</td>
</tr>
</tbody>
</table>

comes were observed in 35% of the patients. In those with an ICP of 20 mm Hg or higher, but with an adequate CPP of 70 mm Hg or higher, the mortality rate was 90% (p < 0.05) and there were no favorable outcomes (p < 0.05). In patients in whom CPP became subtherapeutic (CPP < 70 mm Hg) before and at the time of neurological deterioration and in the absence of intracranial hypertension, the mortality rate was 36% (p > 0.7) and favorable outcome was 45% (p > 0.4). In all comparisons, patients with an ICP of 20 mm Hg or higher had a significantly higher mortality rate and a poorer outcome than patients with an ICP of less than 20 mm Hg, regardless of CPP.

### Discussion

Until the pathophysiological mechanisms that occur during and after head injury are better elucidated and more specific medical treatment has been developed, we must find better ways to protect head-injured patients from secondary insults. A management regimen of immediate diagnosis by CT scan, surgical decompression of significant mass lesions, artificial ventilation, and ICP monitoring is being used worldwide in neurosurgical trauma centers. Even with current aggressive treatment modalities, the outcome of severe head injury is often suboptimal as evaluated according to the 6-month GOS. By examining a subgroup of patients in whom an early identifiable marker of worse outcome was observed, a comparison could be made between the traditionally accepted management of ICP and the more recent emphasis on CPP.14

Currently there is controversy regarding ICP as opposed to CPP management. The trend has been toward a greater emphasis on CPP, according to the concept that relative cerebral perfusion is more important than any potential increase in ICP.17 However, our data strongly indicate that elevated ICP is the major risk factor for neurological deterioration in severely head injured patients.
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implying a potentially worse neurological outcome. If the initial CPP exceeded 60 mm Hg or that level was maintained before or during neurological deterioration, then CPP was not a significant factor in predicting outcome according to our data. Because most patients (82%) with CPP less than 60 mm Hg in the present analysis exhibited increased ICP, it was impossible for us to distinguish between inadequate CPP or raised ICP as the reason for their poor outcome. It seems prudent, however, to conclude that in such patients the emphasis should not only be on raising CPP, but also on lowering ICP. Furthermore, higher levels of CPP were not protective regardless of the concurrent ICP. In striking contrast, the presence of intracranial hypertension at these defined time points was the most powerful single predictor of neurological deterioration. The effects of ICP remain dramatic throughout the subgroup analysis and clearly translate into worse patient outcomes, manifesting as increases in both the morbidity and mortality rates.

These data provide some evidence to suggest that the recent emphasis on management of CPP, without vigorously treating raised ICP, is likely to be in error. Our data indicate that an ICP greater than 20 mm Hg is associated with increased mortality rates compared with ICPs of less than 20 mm Hg, as Miller and Narayan, et al., have shown. In our analysis, the outcome appears to be relatively independent of CPP. Thus, algorithms aimed at increasing CPP to levels greater than 70 to 80 mm Hg in patients with severe head injury, while not attempting to reduce the ICP if it is greater than 20 mm Hg, appear to be unacceptable.

In severely head injured patients, our data indicate that the lower level of acceptable CPP is in the 60 to 70 mm Hg range. Although there may be some theoretical benefit in raising CPP to 80 mm Hg from 70 mm Hg, according to our data we were unable to show any improved outcome in patients with higher CPP. It must also be recognized that high-dose pressor or high-volume therapies used in CPP management entail known substantial risks of systemic complications. Because blood-brain barrier breakdown occurs after 72 to 96 hours, it may be possible to push solute and then fluid into the brain and, by so doing, exacerbate rather than alleviate brain swelling. Furthermore, in a small series of patients treated at the University of California in San Diego, in whom CPP was raised to levels of greater than 90 mm Hg beyond the first 3 to 4 days, diffuse brain swelling persisted for much longer than had been previously observed.

Our findings are consistent with a number of earlier investigations with regard to maintaining CPP above 60 mm Hg. Unterberg, et al., found that a CPP greater than 60 mm Hg appears to be a crucial factor in improving patient outcome. In an analysis of the relationship between CPP and either pulsatility index or jugular venous oxygen saturation during ICP treatment, Chan, et al., demonstrated that there was a linear correlation when pretreatment CPP was less than 70 mm Hg. At values higher than 70 mm Hg, the pulsatility index and jugular venous oxygen saturation were unaltered when CPP rose. However, these results do not support the concept of pushing CPP to very high levels, as has been advocated by Rosner.

Today, early diagnosis is performed with the aid of CT scanning, which enables the clinician to identify patients with elevated ICP. Our experience confirms observations made by Toutant, et al., Teasdale, et al., and van Dongen, et al., that the status of the mesencephalic cisterns on CT scans is an extremely powerful predictor, not only of patient outcome, but also of intracranial hypertension. Other risk factors associated with intracranial hypertension were also more frequently present in the group with neurological deterioration, including a greater frequency of midline shift, intracranial hematomas, and unreactive pupils. However, in many instances these factors developed after admission, and in at least some cases might have been avoidable with earlier intervention for intracranial hypertension. Thus, even before ICP monitoring is instituted, therapy can be targeted to elevated ICP. Clearly, better information regarding disturbances of the cerebral circulation, metabolism, and brain edema occurring in the first hours and days of severe brain injury is essential for improving treatment in these patients.

There is also room for improvement in the outcome of patients without neurological deterioration. A 9% mortality rate and 31% poor outcome in the “no neurological deterioration” group is no trivial matter. In approximately one third of these patients severe extracranial complications developed. In the group as a whole, the presence of extensive SAH was also associated with a poor outcome. Better treatment for traumatic SAH, particularly the availability of pharmacological therapy, is likely to have a beneficial effect on both populations described in this study.

We have demonstrated that nearly one third of severely head injured patients cared for in medical centers specializing in treatment of neurotrauma manifest clinically determined neurological deterioration during their hospital course. The almost sixfold higher mortality rate in this subgroup clearly indicates the need for earlier effective treatment. Obviously, adequate perfusion of the brain is essential and should not be overlooked. However, treatment of CPP without therapy aimed at decreasing intracranial hypertension appears to be inappropriate and is likely to fail. Thus, it appears safe to conclude that when efforts to keep the CPP between 60 and 70 mm Hg are successful, intracranial hypertension remains a major predictor of neurological deterioration and, ultimately, of outcome.

Conclusions

We were unable to demonstrate any significant benefit of a CPP greater than 60 mm Hg in the outcome of patients with severe head injury. This does not mean that CPP should be ignored; rather, that use of extraordinary means to push it well above 60 mm Hg may not be warranted and that a balanced approach to maintaining CPP and reducing ICP appears appropriate.

Acknowledgments

Special thanks to all of the investigators through whose efforts this study was made possible. Executive Committee of the International Selfotel Trial, Ciba-Geigy Pharmaceuticals: Drs. Albino Bri-colo, Michael Fearnside, Hans von Holst, J. Largarrigue, Ramiro D. Lobato, Andrew Maas, Jurgen Piek, C. Plets, Michael Schwartz, Franco Servadei, Andrew Unterberg, and Goeril Karlsson, Ph.D. (ex officio).
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The data collection was funded by Ciba-Geigy Pharmaceuticals, Basel, Switzerland. Partial support was provided by grants from the Leardal Foundation for Acute Medicine, Oslo, Norway, and The Head Trauma Foundation, Aalborg Hospital, Aalborg, Denmark.

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