Severe Traumatic Brain Injury in Austria IV: Intensive care management

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Schweres Schädelhirntrauma in Österreich IV: Intensivmedizin


Ergebnisse: Die Mortalität an der Intensivstation betrug 30.8%, die 90-Tage-Mortalität war 35.7%. Nach einem Jahr war das Ergebnis „gut“ bei 33.4%, „schlecht“ bei 51.6%, und bei 16% war das Ergebnis unbekannt. Hirndruckmessung wurde in 64% durchgeführt; am häufigsten (77%) wurden Parenchymsonden verwendet. Für folgende Ereignisse wurde eine Mortalität von > 50% erbracht: Hirndruck > 25 mm Hg für > 12 Std/Tag, zerebraler Perfusionssdruck < 50 mm Hg für > 12 Std/Tag, und arterieller Mitteldruck < 70 mm Hg für > 18 Std/Tag. Hirndruckmessung hatte eine signifikante Reduktion der Intensivstations-Mortalität zur Folge. Folgende Maßnahmen konnten zu einer Verbesserung des Behandlungsergebnisses geführt haben: Gaben von Barbituraten (für < 7 Tage) und hypertoner NaCl, mäßige Hyperventilation (33 < PCO2 < 37 mm Hg), und Normothermie. Bei Patienten mit Hyperglykämie fand sich ein signifikant schlechteres Langzeitergebnisse.

Schlussfolgerungen: Die Studie zeigte, dass die Intensivbehandlung den internationalen Richtlinien weitgehend folgte, und dass die Ergebnisse mit denen anderer Autoren vergleichbar waren. Ein zerebraler Perfusionssdruck < 50 mm Hg war mit schlechtem Ergebnis assoziiert, und war häufiger durch niedrigen Blutdruck als durch hohen Hirndruck verursacht. Ein Perfusionssdruck > 50 mm Hg sollte aufrecht erhalten werden, die Verwendung von Katecholaminen, Flüssigkeitsgabe, Gaben von Barbituraten (kurzfristig), mäßige Hyperventilation, Gaben von hypertonomem Kochsalz, und Gaben von Insulin können das Behandlungsergebnis möglicherweise verbessern.

Summary. Objectives: The goal of this paper is to describe the ICU management of severe traumatic brain injury (TBI) in Austria.

Patients and methods: Data sets from 415 patients included by 5 Austrian hospitals were available. The analysis focused on complications and outcomes of intensive care, monitoring of intracranial pressure (ICP), efficacy of interventions to control ICP, management of hemodynamics and cerebral perfusion pressure (CPP), ventilation, and effects of hyperglycaemia.

Results: Overall ICU mortality was 30.8%; 90-day mortality was 35.7%. Final outcome was favorable in 33%, unfavorable in 51%, and in 16% the final outcome was unknown. An ICP monitoring device was used in 64%; most patients received intraparenchymal sensors (77%). Events associated with mortality >50% were CPP < 50 mm Hg for > 12 hours/day, ICP > 25 mm Hg for > 12 hours/day, and MAP < 70 mm Hg for > 18 hours/day. The use of ICP monitoring was associated with significantly reduced ICU mortality. Interventions that may have improved the outcome included the use of barbiturates (short-term), hypertonic saline, moderate hyperventilation (33 < PCO2 < 37; p < 0.001 vs. aggressive hyper- and normoventilation), and normothermia. Hyperglycaemia was associated with poor outcome.

Conclusions: Our study showed that ICU management of patients with severe TBI mostly follows international guidelines, and that outcome was comparable to or even better than that reported by other authors. Low CPP was associated with poor outcome, and was more often due to low MAP than to elevated ICP. The use of barbiturates and hypertonic saline was more common than expected. CPP should be maintained > 50 mm Hg, the use of catecholamines, fluid loading, barbiturates (short-
term), moderate hyperventilation, hypertonic saline, and insulin may improve outcome after severe TBI.

Key words: Brain injury, traumatic, monitoring, intracranial pressure, cerebral perfusion pressure, hyperventilation, hypertonic saline, glucose levels, outcome.

Introduction

The Austrian Severe Traumatic Brain Injury (TBI) Study was done in five participating Austrian hospitals and enrolled a total of 492 patients with severe TBI. Detailed information regarding the background, goals, and methods of the study has been published in a previous paper [1]. The goal of this paper is to describe the intensive care management of these patients. It will focus on the outcomes and complications of intensive care, monitoring of intracranial pressure (ICP) and management of intracranial hypertension, management of hemodynamics and cerebral perfusion pressure (CPP), ventilation, and the effects of hyperglycemia.

Patients and methods

The methods of the Austrian Severe TBI Study have previously been described in detail [1]. Briefly, data on accident, prehospital treatment, hospital treatment, and patient status were collected using internet-based databases [2]. All patients admitted to the participating hospitals were included if they fulfilled the criteria for severe brain trauma [3]. Patients who died at the scene, during transport to the hospital, or immediately after admission to the emergency room were excluded. For this paper, only data sets that included the relevant ICU data as well as CT scan evaluations were used. Data from 415 patients was extracted into Microsoft Excel files for analysis. The analysis focused on:

- complications and outcomes of intensive care;
- monitoring of ICP: which patients had, and which did not have ICP monitoring; type of ICP devices used, periods of use, effects of ICP monitoring upon outcome;
- the course of ICP and CPP in survivors and non-survivors;
- efficacy of interventions (analgesia, sedation, barbiturates, steroids, mannitol, hypertonic saline, hyperventilation, hypothermia);
- management of hemodynamics and CPP: use of catecholamines, fluid balance;
- ventilation strategies: peak inspiratory pressure (PIP), PEEP, and P02/FiO2 ratio;
- effects of hyperglycemia.

Data on clinical effects was gained from day-by-day analysis of treatment options vs. patient status. For analysis of effects upon outcome, daily treatment data was re-organized according to each patient, so that repeated treatments in a single patient could be assessed. Daily values for data on treatment (e.g. body temperature, pCO2) and patient status (e.g. hours of ICP > 25 mmHg) was averaged over the first 10 treatment days (or less, if the patient did not survive 10 days, or was discharged before day 10). For all treatment options correlations between these averaged data and ICU outcome (survival or death), 90-day outcome (survival or death) and final outcome (last available Glasgow Outcome Score, see [1]) were performed. Final outcome is reported as “favorable” (good recovery, moderate disability) or “unfavorable” (severe disability, vegetative state, death). The mortality prediction made possible by the Trauma and Injury Severity Score (TRISS; [4]) was used to calculate the Observed vs. Expected mortality ratio (O/E mortality ratio) at day 90; a detailed regression discussion is provided in the first paper of this series [1].

The XLSTAT add-in for Microsoft Excel [5] was used for statistical processing of the data. The analyses were done using standard descriptive statistics and univariate correlation, and the significances of differences between treatment options were tested by means of Chi² for nominal variables, and t-test as well as one-way ANOVA for numeric variables. Logistic regression was used to perform analysis of multiple variables while controlling for age, first Glasgow Coma Scale score (GCS), and Injury Severity Score (ISS). A p < 0.05 was considered significant.

Results

Data sets of 415 patients were available for analysis. Many of the ICU survivors (n = 277) had a full set of data (10 ICU days), while most ICU non-survivors (n = 128) had fewer days (1–6 days from admission to death). In total, 3258 treatment days were analyzed. The majority of patients were male (299; 72%), mean age was 48.9 ± 21 years, mean ISS was 27.2 ± 12.9 points, mean first GCS was 5.7 ± 2.9 points, and expected hospital survival was 63 ± 29%. Overall ICU mortality was 30.8% (128/415), and 90-day mortality was 35.7% (148/415). The most common complications of intensive care were pneumonia (36; 9%), sepsis (15; 4%), acute renal failure requiring renal replacement therapy (11; 3%), and adult respiratory distress syndrome (5; 1%). The final outcome was favorable in 33% (good recovery 23%, moderate disability 10%), unfavorable in 51% (severe disability 8%, persistent vegetative state 6%, death 38%), and in 16% of the cases the final outcome was unknown.

Monitoring of ICP

An ICP monitoring device was used in 264 (63.6%) patients, and was not used in 151 (35.6%) patients. Patients were significantly less likely to receive ICP monitoring if their age was > 60 years and/or basal cisterns were closed on the first CT scan [OR = 2.43 (± 95% CI 2.4; 2.46), p < 0.01]. Other factors like TRISS < 40, ISS < 18, abnormal pupils and GCS > 6 were associated with differences of at least 10% in monitoring rates, but these differences were not significant. Patients who were not monitored were significantly older (53 vs. 46 years; p < 0.05) and had a significantly lower TRISS (60 vs. 64%, p < 0.05).

Most patients received intraparenchymal sensors (77%), followed by ventricular drains (10%), epidural sensors (3%), and unknown (2%) devices. In 19 patients (8%) a combination of ventricular drains plus intraparenchymal sensors was used. Patients who received ventricular drains had intraventricular hemorrhage more frequently (22% vs. 9% for intraparenchymal), and all (100%) had 2 or more parenchymal lesions, vs. 52% for patients with intraparenchymal sensors (p < 0.05). In most patients monitoring was started on day 1 (80%) or day 2 (12%); in only 8% monitoring was started on day 3 or later. The start of ICP monitoring after day 2 was associated with higher ICU mortality [OR = 1.07 (± 95% CI 1.02; 1.12)
p < 0.05]. The longest duration of use in survivors was 10.1 ± 5.7 days for intraparenchymal sensors, followed by ventricular drains (8.8 ± 4.9 days) and epidural sensors (6.0 ± 4.0 days). The type of ICP monitoring device (intraparenchymal vs. ventricular) was not associated with any differences in the amount of mannitol or hypertonic saline used for control of ICP.

The use of any type of ICP monitoring was associated with lower ICU mortality [OR = 1.17 (± 95% CI 1.15; 1.2), p < 0.05]. At all levels of ISS, and most levels of GCS, ICU mortality within each risk group was lower for patients with ICP monitoring (Fig. 1). The notable exceptions were patients with high GCS; in this group, mortality was higher for patients with ICP monitoring. The use of ICP monitoring was associated with improved outcome at day 90 (33 vs. 42%) and a higher rate of favorable outcome. However, after correction for age, ISS and first GCS by means of logistic regression none of these differences were significant.

**Course of ICP and CPP**

To evaluate the course of ICP and CPP in survivors and non-survivors, the number of hours with ICP > 25 mm Hg and/or CPP < 70 mm Hg and/or CPP < 50 mm Hg were analyzed for a total of 1825 treatment days where ICP and CPP had been recorded. On 301 (16.5%) days, neither ICP nor CPP were abnormal. Having elevated ICP without associated CPP problems was a rare event (48 days, 2.6%), low CPP without associated ICP problems was a quite frequent event (752 days, 41.2%). On 724 days (39.7%), elevated ICP was associated with low CPP, and the numbers of hours of abnormal CPP and ICP were fairly similar.

To investigate the clinical relevance of abnormal ICP or CPP, we calculated ICU mortality for various durations of abnormal CPP and ICP for each treatment day. The results are given in Table 1. The most critical events were CPP < 50 mm Hg for more than 12 hours (all days), ICP > 25 mm Hg for more than 12 hours (all days), and ICP > 25 mm Hg for 1–12 hours (day 1); all these events were associated with >50% mortality (OR = 0.59 [± 95% CI 0.58; 0.61]; p < 0.005). Mortality exceeding mean ICU mortality (31%) was also observed for >12 hours of CPP < 70 mm Hg (days 1–4), and 1–12 hours of CPP < 50 mmHg (days 1 and 2).

The total hours/day of abnormal CPP and ICP were correlated to ICU outcome as well as final outcome. ICU survivors had shorter periods of ICP > 25 mm Hg (2.3 vs. 6.4 h/d), of CPP < 70 mm Hg (7.1 vs. 10.6 h/d), and of CPP < 50 mm Hg (0.8 vs. 3.9 h/d); all these differences were statistically significant (p < 0.001). With regard to final outcome, there were no differences between survivors with favorable or unfavorable outcome. There were, however, significant differences similar to those mentioned above between all groups of survivors and patients who died [OR = 1.54 (± 95% CI 1.52; 1.56); p < 0.05].

**Interventions to control ICP**

Analgiesia and/or sedation were used in all patients (see below); in patients with ICP monitoring the mean duration was 11.8 ± 9.0 days. All patients that had ICP monitoring were ventilated; the mean duration was 14.5 ± 10.7 days. In addition to these, other specific interventions were done quite frequently. Table 2 gives an overview of the effects of these interventions.

Barbiturates were used in 39% of the patients (total 694 days); in 2/3 of these patients treatment was limited to <7 days. Barbiturate use was not associated with shorter durations of abnormal ICP and CPP. The use of barbiturates was associated with lower ICU and 90-day mortality [OR = 1.15 (± 95% CI 1.12; 1.18), p < 0.05]; and this difference was still significant after correction for age, first GCS and ISS. The rates of favorable outcome and O/E ratios were equal. Patients who received barbiturates for >75% of their treatment days had higher rates of pneumonia (13% vs. 6%, n.s.) and sepsis (9% vs. 2%, p < 0.05), and had significantly higher ICU and 90-day mortality than patients who received barbiturates for <75% of treatment days. After correction for age, first GCS and ISS with logistic regression this difference was not significant.

![Fig. 1. ICP monitoring vs. ICU mortality: mortality (%) for patients with (striped bars) and without (black bars) ICP monitoring at various levels of Glasgow Coma Scale (GCS) and Injury Severity Score (ISS)](image-url)
Corticosteroids were used in 12% of the patients for a mean of 3 days (total 155 days). Steroid use was associated with higher levels of blood glucose (165 ± 50 vs. 135 ± 36 mg%; p < 0.001), higher insulin doses (3.0 ± 2.2 vs. 2.3 ± 1.8 U/h; p < 0.001), and higher rates of sepsis (9 vs. 3%; p = 0.06). Durations of abnormal CPP and ICP as well as ICU and 90-day mortality, rates of favorable outcome, and O/E ratios were not different.

Mannitol was used in 43% of patients; it was given on 621 (20%) days. Mannitol use was not limited to patients with ICP monitoring, but was also used in 40 patients (22% of those that received mannitol) without ICP monitoring. There was no obvious relationship between daily hours of ICP > 25 mm Hg and mannitol dose; patients without intracranial hypertension received a mean dose of 30 ± 15 g/d, patients with > 12 hours of ICP > 25 mm Hg received 36 ± 21 g/d. Even after correction for age, first GCS, and ISS mortality was significantly higher in patients who did receive mannitol than in those who did not receive mannitol [OR = 0.6 (± 95% CI 0.57; 0.62); p < 0.005]. There also were differences in ICU and 90-day mortality [28 vs. 44%; OR = 0.73 (± 95% CI 0.73; 0.74); p < 0.001] between patients who received low doses of mannitol (< 30 g/day) and those who received higher doses (> 30 g/day).

Hypertonic saline was used in 40% of the patients; it was given on 553 (17%) days. Of these patients, 52% also received mannitol (mean dose 25 ± 15 g/day). Hypertonic saline was used in 27 (16%) patients who did not have ICP monitoring. The daily dose of hypertonic saline was higher in patients who had longer periods of abnormal ICP and CPP, ICU, and 90-day mortality [OR = 1.57 (± 95% CI 1.55; 1.6); p < 0.05], rates of favorable outcome, and O/E ratios were better in patients who received hypertonic saline; however, higher daily doses were associated with a poor outcome.

Hyperventilation, defined as mean pCO₂ < 37 mm Hg, was done in 64% of the patients; there was a clear relationship between longer periods of abnormal ICP and CPP and level of pCO₂. Aggressive hyperventilation (pCO₂ < 33 mm Hg) as well as normoventilation (pCO₂ > 37 mm Hg) were associated with poor ICU and 90-day outcomes, and O/E ratios > 1.0, while moderate hyperventilation (33 < pCO₂ < 37) was associated with better outcomes and lower O/E ratios [OR = 1.2 (± 95% CI 1.2; 1.2); p < 0.01 vs. normoventilation and aggressive hyperventilation].

Hypothermia, defined as a mean body temperature maximum < 36.5 °C, was observed in 24% of the patients, and was associated with poor ICU and 90-day outcomes and high O/E ratios. Normothermia and moderate hyperthermia (36.6 < body temperature < 38 °C) were associated with better outcomes, and O/E ratios < 1.0. There was a significant association between ICU survival and normothermia over the first 5 days [OR = 1.75 (± 95% CI 1.73; 1.76); p < 0.0001]. There was no clear relationship between hours of abnormal ICP and CPP and body temperature.

Management of hemodynamics and CPP

Low systolic arterial pressure (SAP) was associated with longer periods of abnormal ICP and CPP (Fig. 2). Normal SAP was associated with significantly shorter periods of CPP < 50 mm Hg and ICP > 25 mm Hg (p < 0.05), while SAP > 130 mm Hg was associated with longer periods of abnormal ICP. Longer periods of mean arterial pressure (MAP) < 70 mm Hg were associated with significantly longer periods of abnormal CPP (p < 0.05), while hours of abnormal ICP remained unchanged (Fig. 2).

To investigate the effects of low blood pressure on mortality the values of lowest SAP and hours/d of MAP < 70 mm Hg were averaged over the first treatment days (max. 10). All patients who had a mean lowest SAP < 90 mm Hg died (ICU mortality 84%, 90-day mortality 100%). The best final outcome was observed in patients who had a mean lowest SAP between 110 and 129 mm Hg (44% good recovery; p < 0.05). The association between
Table 2. Interventions to control ICP. For each intervention, the percentage of patients treated, ICU mortality (%), 90-day mortality (%), the rate of patients with favorable outcome, and the ratio of observed vs expected death (O/E) are given.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>% of patients</th>
<th>ICU mortality (%)</th>
<th>90-day mortality (%)</th>
<th>Favorable outcome (%)</th>
<th>O/E ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates ( &gt;500 mg/treatment day/first 10 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used &lt;75% of days</td>
<td>25.0</td>
<td>22.2</td>
<td>26.2</td>
<td>43.5</td>
<td>0.87</td>
</tr>
<tr>
<td>Used &gt;75% of days</td>
<td>14.0</td>
<td>41.8</td>
<td>43.4</td>
<td>42.0</td>
<td>1.23</td>
</tr>
<tr>
<td>Used (total)</td>
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<td>29.2</td>
<td>32.1</td>
<td>42.9</td>
<td>1.00</td>
</tr>
<tr>
<td>Never used</td>
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<td>32.1</td>
<td>38.6</td>
<td>37.2</td>
<td>1.00</td>
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<td>Corticosteroids</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>Used</td>
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<td>27.7</td>
<td>27.7</td>
<td>41.7</td>
<td>0.93</td>
</tr>
<tr>
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<td>31.5</td>
<td>37.6</td>
<td>38.6</td>
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</tr>
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<td></td>
<td></td>
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</tr>
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<td>25.0</td>
<td>45.0</td>
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<td>29.4</td>
<td>31.6</td>
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</tr>
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<td>37.5</td>
<td>41.7</td>
<td>30.0</td>
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<td>45–60</td>
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<td>Used (total)</td>
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<td>33.1</td>
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<tr>
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<td>30.4</td>
<td>38.4</td>
<td>42.6</td>
<td>0.93</td>
</tr>
<tr>
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<td>1–99</td>
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<td>20.0</td>
<td>53.8</td>
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<td>100–149</td>
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<td>20.5</td>
<td>54.1</td>
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<td>150–199</td>
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<td>1.05</td>
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<td>57.1</td>
<td>61.9</td>
<td>25.0</td>
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<td>52.1</td>
<td>54.2</td>
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<td>1.32</td>
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<td>33.0–34.9</td>
<td>22.4</td>
<td>25.0</td>
<td>29.5</td>
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<td>22.3</td>
<td>50.0</td>
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<td>31.8</td>
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<tr>
<td>&gt;40.0</td>
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<td>35.1</td>
<td>43.9</td>
<td>38.0</td>
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<td>Hypothermia (mean body temperature [°C]/first 5 days)</td>
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<td>&lt;36</td>
<td>13.1</td>
<td>69.2</td>
<td>73.1</td>
<td>17.6</td>
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<td>40.5</td>
<td>50.0</td>
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<td>36.6–37</td>
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<td>36.8</td>
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<td>37.1–37.5</td>
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<td>22.8</td>
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<td>37.6–38</td>
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<tr>
<td>&gt;38</td>
<td>16.4</td>
<td>27.7</td>
<td>33.8</td>
<td>30.2</td>
<td>1.01</td>
</tr>
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</table>

ICU outcome and the median of the lowest SAP was still significant after controlling for age, first GCS, and ISS [OR = 1.08 (± 95% CI 1.08; 1.08); p < 0.0001]; there also was a negative relation to total hours of SAP < 90 mm Hg [OR = 0.84 (± 95% CI 0.83; 0.84); p < 0.0001]. Longer periods of low MAP were associated with significantly higher mortality; if MAP was < 70 mm Hg for > 18 hours/day for the first days ICU mortality reached 63% (p < 0.05). This association was not confirmed by logistic regression.

Catecholamines: The definition of “catecholamine use” was administration of any dose of epinephrine and/or norepinephrine by continuous infusion. Catecholamines were used for > 75% of the first treatment days in 44% of the patients, were used for shorter periods in 32%, and were not used in 24%. The mean hours/day of abnormal ICP or CPP were not influenced by the duration of catecholamines use. The use of catecholamines was associated with improved ICU survival [OR = 1.2 (± 95% CI 1.2; 1.2); p < 0.0001]; no association with outcome after 90-days was found. However, strong correlations were found between days of catecholamine use and final survival [OR = 3.35 (± 95% CI 3.31; 3.4); p < 0.005], severe disability [OR = 1.35 (± 95% CI 1.32; 1.33); p < 0.005] and good outcome [OR = 1.12 (± 95% CI 1.11; 1.12); p < 0.05].
Fluid balance: There was a significant correlation (ANOVA, p < 0.001) between lowest SAP and daily fluid balance: at SAP < 60 mm Hg, patients had a fluid balance of +1547 ± 965 ml/day which decreased to +479 ± 1410 ml/day at 110 < SAP 129 mm Hg, and decreased further to +6 ± 1469 ml/day at SAP > 149 mm Hg. There was, however, no correlation between the number of hours of MAP < 70 mm Hg and fluid balance. There was no effect of fluid balance on ICP; the duration of elevated ICP was between 2.7 and 3.7 h/day at all levels of fluid balance (less than -2000 ml/day to more than +2000 ml/day). A mean daily fluid balance of more than +2000 ml/day during the first (max 10) treatment days was significantly associated with poor ICU outcome (OR = 0.39 (± 95% CI 0.34; 0.43); p < 0.05). The best final outcome (43% good recovery, 27% death; p < 0.05) was observed in patients with a mean daily fluid balance between -500 and 0 ml/day.

Ventilation

Only 7 patients (1.7%) were neither intubated nor ventilated; none of these patients had ICP monitoring, and all 7 survived. All other patients were intubated and/or ventilated. Compared to patients who died on the ICU, survivors had significantly more days of ventilation, intubation, and tracheostomy.

Analgesia & sedation: 3258 treatment days were analyzed. The most frequently used analgesics were sufentanil (1455 days; 45%), fentanyl (475; 15%), piritramide (445; 14%), and ketamine (242; 7%); other drugs (e.g. remifentanil, morphine) were rarely used (total: 146; 4%). The most frequently used sedatives were propofol (1740; 53%), midazolam (1380; 42%); methohexital (501; 15%) and thiopentone (193; 6%). Relaxants, mostly rocuronium, pancuronium, atracurium, and vecuronium, were given on 1338 (41%) of days.

Effects of airway pressures: Peak inspiratory pressure (PIP), mean airway pressure (AP), and positive end-expiratory pressure (PEEP) were correlated to the mean hours of abnormal ICP and CPP for each day of ventilation. Daily hours of elevated ICP increased from 2.4 ± 5.5 at PIP < 15 mm Hg to 4.4 ± 7.4 at PIP > 20 mm Hg (p < 0.05) while duration of abnormal CPP remained unchanged. Higher levels of AP or PEEP had no such effects.

Hyperglycaemia

Mean daily values for serum glucose and insulin dose were available for 414 patients; these values were averaged over the first (max, 10) treatment days and correlated to ICU, 90-day, and final outcome. Higher glucose levels were associated with higher mortality and lower rates of good recovery (Fig. 3). Only 22 (5%) patients had normal mean glucose levels (< 110 mg%; in 60% of these patients insulin was administered to control blood glucose. These patients had lower ICU (5%) and 90-day mortality (9%; O/E ratio 0.35), and also had better final outcomes (27% good recovery, 9% death) compared to patients with higher glucose levels. Mean glucose levels between 110 and 130 mg% were observed in 150 (36%) of the patients; 61% of these patients received insulin. These patients had higher ICU (27%) and 90-day-mortality (32%; O/E ratio 0.85), and final outcome was worse (25% good recovery, 40% death). In 148 (36%) patients,
mean glucose levels between 130 and 150 mg\%/ were found; 73\% of these patients received insulin. ICU (34\%) and 90-day mortality (39\%; O/E 1.06) were higher, the rate of good recovery was only 20\%, and final death rate was 41\%, 94 (22\%) patients had mean glucose levels over 150 mg\%; 83\% of these patients received insulin. These patients had the highest ICU (41\%) and 90-day mortality (45\%; O/E ratio 1.14) and the worst final outcome (22\% good recovery, 46\% death). When controlled for age, first GCS, and ISS, none of these correlations was signifi-

cant.

Discussion

The goal of this paper was to describe the medical management of patients with severe TBI in Austria. The results have to be interpreted with caution because the interventions reported here were done without randomiza-
tion. It has to be considered that for most interventions there were differences between those patients who were and those who were not treated. To correct for that O/E ratios have been reported together with mortality, and all mortality data have been controlled for age, ISS, and first GCS by logistic regression. Some key aspects will be discussed below.

The results of our study are comparable to those found in other studies. ICU mortality was 31\%, very similar to that reported in a French study [6] on severe TBI (30\%), quite low compared to a German study which gave an average mortality of 50\% [7], and to another French study where mortality was 52\% [8]. Bulger et al. [9] reported a hospital mortality of 27\% for patients man-
aged at “aggressive” centers (i.e., centers that routinely use ICP monitoring); patients from “nonaggressive” centers had a mortality of 45\%. Long term outcome (at 6 months post injury) has been reported by Stocchetti et al. [10]: Favorable outcome was found in 41\% of patients with ICP monitoring, and 36\% of those without ICP monitoring.

Monitoring of ICP is an important management op-
tion for patients with severe TBI. Despite the lack of Class I evidence, ICP monitoring is recommended by all avail-
able guidelines for management of severe TBI [11–13].

There is one study where the effect of guideline imple-
mentation has been tested [14], and the results were better in the “guideline” group: hospital mortality was lower (30
	

44\%), and “favorable outcome” was observed more frequently (49 vs. 25\%). A large retrospective study [15] concluded that ICP monitoring is associated with a signifi-
cantly decreased death rate among patients with severe TBI. These results are confirmed by those from our study as well as by other authors [9, 10]. Different results have recently been reported by Cremer et al. [16] who com-
pared the 1-year outcome of patients after severe TBI treated at two different centers. At Center A, ICP was not monitored, MAP was maintained at 90 mm Hg, and all treatment decisions were based on clinical observations and CT findings, while at Center B, ICP monitoring was used in most (67\%) patients. Despite a higher level of treatment intensity at Center B, there was no difference in hospital outcome (34\% vs 33\% mortality) and long-term outcome. To date, this is the only study that questions the value of ICP monitoring, and differences in case mix might have contributed to the results. A prospective, ran-
domized study on the use of ICP monitoring is urgently required, but is unlikely to be done as all guidelines re-
commend ICP monitoring.

This raises the question why about 1/3 of the patients in our study did not receive ICP monitoring. In some patients this might be explained by an obviously hopeless situation (nonsurvivable injuries seen on first CT scan), and some patients might have been classified as “too good” (low ISS, high GCS). More than 70\% of the pa-
tients without ICP monitoring, however, had GCS and ISS scores as well as CT findings comparable to those who were monitored. They were, however, significantly older. It seems that in our study older patients were treated less aggressively, possibly because of the increased likelihood of poor outcome. A large Dutch study on 5.612 patients demonstrated that age is an independent risk factor after severe TBI [17]: the odds for poor outcome increased by 40 to 50\% per 10 years of age.

All available guidelines [11–13] recommend inserting ventricular drains for ICP monitoring. In our study, ven-

tricular drains were used in only 10\% of the cases. The use of ventricular drains was limited to patients with intraventricular hemorrhage and/or more severe lesions. Patients treated by neurosurgeons had the same low rate as those treated by trauma surgeons. There is no convinc-
ing explanation for this. It might be that Austrian surgeons prefer intraparenchymal devices because they are less in-
vasive, or because of the higher rate of infections and intracranial hemorrhage associated with ventricular drains [18].

Despite numerous trials, the “optimal” level of CPP is unknown. While some authors [19, 20] as well as most guidelines [11, 12] suggest that CPP should be >70 mm Hg, other authors have shown that a CPP as low as 50 mm Hg (the “Lund concept”) may even be beneficial [21]. In our study, CPP values of both CPP <50 mm Hg and CPP >70 mm Hg were associated with increased mortality. Low CPP was more frequently associated with low MAP than with increased ICP; maintenance of normal MAP, therefore, is as important as control of elevated ICP. All patients who had prolonged hypotension (mean lowest SAP <90 mm Hg) were dead by day 90. This con-

firms results from Chesnut et al. [22] who found that hypotension carries a >10-fold risk of unfavorable out-
come. The use of catecholamines and fluids to maintain MAP is safe. There was no correlation between daily fluid balance and hours of abnormal ICP. Large daily fluid balances were observed in patients with low SAP, and were associated with poor outcome. This, however, is most probably attributable to the underlying cause of hae-
modynamic instability, and not to the effects of volume loading. A recent paper suggests that long periods of ICP >40 mm Hg may be survived with good outcome as long as CPP >60 mm Hg is maintained [23]; the authors used large volumes of fluids as well as catecholamines to achieve that.

There is a general consensus that ICP should be treat-
ed if it increases above 20 or 25 mm Hg [11, 12]. Our study confirms the validity of that recommendation: a longer duration of elevated ICP was associated with higher mortality. Interventions to control ICP include analge-
sia and sedation, barbiturates, corticosteroids, osmotic
agents, (hyper)ventilation, and hypothermia [24]; all these options have been used in some of our patients. Mortality was higher in patients who required more aggressive treatment; this only reflects the fact that these patients were more seriously injured.

With regard to analgesia and sedation, the most unusual finding was the frequent use of sufentanil; most authors prefer fentanyl or remifentanil [25]. Barbiturates are recommended as “third tier” treatment [12]. The short-term use of barbiturates was associated with a better outcome in our patients. A recent meta-analysis [26] stated that it is unlikely to expect barbiturates to improve outcomes, and that associated problems include hypotension. While that was not an obvious problem in our patients, a significant increase in sepsis rate was observed with prolonged use of barbiturates. This confirms an earlier study where increased rates for pneumonia and sepsis were seen [27].

Corticosteroids were used in few of our patients, with significant side effects (glucose levels, infections) but without significant effects on ICP, CPP, or mortality. The CRASH trial [28] included 3944 patients with severe TBI (out of a total of 10 008 patients); 1972 (50%) of these patients received steroids (21.2 g methylprednisolone / 48 hours). Mortality within the first 2 weeks was significantly higher in the steroid group (39.8% vs. 34.8%). The conclusion from this trial was that corticosteroids should no longer be used to treat brain edema in TBI patients.

Mannitol and hypertonic saline were both used quite frequently. The most surprising finding was that osmotic agents were used in patients who did not have ICP monitoring. It is unclear how the decision to use osmotic agents was made in these patients. Patients who received low to moderate doses of hypertonic saline had improved outcomes, while no such effect was observed with the use of mannitol. It is well known that hypertonic saline (with or without additional hydroxyethyl starch) can be used to treat intracranial hypertension [29], and more recent studies suggest that it may be more effective than mannitol [30, 31]. The results from our study seem to confirm these findings.

As suggested by an inverse relation between duration of intracranial hypertension and level of pCO₂ hyperventilation was used to treat elevated ICP. Aggressive (pCO₂ < 30 mm Hg) hyperventilation, however, was used in only a few patients. The guidelines for TBI management [12] state that hyperventilation is an option that should be used cautiously, and should never be done as prophylaxis. The rationale behind these recommendations has recently been discussed in detail by Stocchetti et al. [32]: hyperventilation may compromise cerebral blood flow. In our study, hyperventilation to pCO₂ < 33 mm Hg was associated with higher than expected mortality, while moderate hyperventilation (33 < pCO₂ < 37 mm Hg) was associated with a significantly better outcome. With regard to airway pressures, some studies have shown an increase in ICP and a decrease in CPP with higher levels of PEEP, while other studies found no changes. An explanation for this was recently proposed by Caricato et al. [33] who found that the effects of PEEP depend on the compliance of the respiratory system. In patients with normal compliance, high levels of PEEP caused a reduction of CPP, while no changes were observed in patients with low compliance. This could explain why airway pressures seemed to have no relevant effects in our study.

It is well known that hypothermia can protect the brain against secondary ischemic insults, and there have been several clinical trials to study the effects of hypothermia after severe TBI. There are some studies where hypothermia improved outcome [34, 35], but a large multicentric trial [36], and a recent meta-analysis [37], failed to demonstrate any benefits. Interpretation of the data from our study is difficult because only daily minimum and maximum body temperatures were recorded, and we do not know whether cooling devices were used. However, considering the fact that patients with normal temperature had the best outcomes, any beneficial effect of hypothermia is quite unlikely.

We found that higher glucose levels were associated with higher mortality and lower rates of good recovery. It is well known that TBI may cause elevated glucose levels, and that hyperglycaemia is more frequently observed in patients with severe TBI [38]. Recently, it has been reported that hyperglycaemia is an independent risk factor for poor outcome [39]. Anaerobic glycolysis in a partially hypoxic brain with consecutive acidosis has been suggested as a possible mechanism. In our study, hyperglycaemia was not an independent risk factor, but was associated with higher age and ISS, and lower GCS. Zygun et al. [40] investigated the relationship between blood glucose levels and brain tissue pH. They found an inverse correlation between these, and also reported that the use of insulin improved brain tissue pH by lowering blood glucose levels. It seems possible that control of blood glucose levels may improve outcomes after severe TBI; this, however, should be studied prospectively.

In conclusion, our study showed that ICU management of patients with severe TBI mostly follows international guidelines, and that outcome was comparable to or even better than that reported by other authors. Two thirds of the patients had ICP monitoring, and the most common devices were intraparenchymal sensors. ICP monitoring was associated with significantly lower ICU mortality but had no effects on 90-day mortality or final outcome. Low CPP was associated with poor outcome, and was more often due to low MAP than to elevated ICP. The use of barbiturates and hypertonic saline was more common than expected. Based on our results the following treatment options might improve outcome after severe TBI: the use of ICP monitoring, maintenance of CPP > 50 mm Hg, use of catecholamines and fluid loading to maintain MAP, short-term use of barbiturates, moderate hyperventilation, use of hypertonic saline instead of mannitol, and control of blood glucose levels. Further prospective studies need to be done to investigate some of the aspects reported here, e.g. moderate hyperventilation, use of hypertonic saline, less restrictive use of barbiturates, and glucose control.

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References

5. Downloaded from www.xlstat.com/


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