Barbiturates Use and Its Effects in Patients with Severe Traumatic Brain Injury in Five European Countries

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Abstract

The guidelines for management of traumatic brain injury (TBI) recommend that high-dose barbiturate therapy may be considered to lower intracranial pressure (ICP) that is refractory to other therapeutic options. Lower doses of barbiturates may be used for sedation of patients with TBI, although there is no mention of this in the published guidelines. The goal of this study was to analyze the use of barbiturates in patients with severe TBI in the European centers where the International Neurotrauma Research Organization introduced guideline-based TBI management and to analyze the effects of barbiturates on ICP, use of vasopressors, and short- and long-term outcome of these patients. Data on 1172 patients with severe TBI were collected in 13 centers located in five European countries. Patients were categorized into three groups based on doses of barbiturates administered during treatment. Univariate and multivariate statistical methods were used to analyze the effects of barbiturates on the outcome of patients.

Fewer than 20% of all patients with severe TBI were given barbiturates overall, and only 6% was given high doses. High-dose barbiturate treatment caused a decrease in ICP in 69% of patients but also caused hemodynamic instability leading to longer periods of mean arterial pressure <70 mm Hg despite increased use of high doses of vasopressors. The adjusted analysis showed no significant effect on outcome on any stage after injury. Thiopental and methohexital were equally effective. Low doses of thiopental and methohexital were used for sedation of patients without side effects. Phenobarbital was probably used for prophylaxis of post-traumatic seizures.

Key words: barbiturates; guidelines; intracranial pressure; medication; traumatic brain injury

Introduction

SEVERE TRAUMATIC BRAIN INJURY (TBI) has serious health and socioeconomic consequences and is considered a major clinical and public health challenge.^{1–3} For Europe, an aggregate hospitalized and fatal TBI incidence rate of 235/100,000/year and an average mortality rate of about 15/100,000/year have been reported.³ TBI is the primary cause of death in the United States and other developed nations in persons younger than 45 years.¹ The International Neurotrauma Research Organization (INRO) serves as a leading research platform for TBI in the region of Central, Eastern, and Southern Europe. Since 1999, INRO has been collecting and analyzing data on patients with TBI and has introduced guideline-based management of patients with TBI in many neurotrauma centers in this region.^{4–6}

Intracranial hypertension is a common neurologic complication in critically ill patients,⁷ including patients with severe TBI⁸; it is associated with poor prognosis and with high rates of mortality,

especially when cerebral perfusion pressure (CPP) cannot be maintained.⁹ Intracranial hypertension has been reported to occur in 25–40% of patients with severe TBI.¹⁰ In 10–15% of patients with severe TBI, refractory intracranial hypertension may persist despite the use of management strategies such as head-of-bed elevation, sedation, osmotherapy, neuromuscular blockade, and surgical interventions.¹¹

Decompressive craniectomy and barbiturate coma are the only treatment strategies for patients with refractory intracranial hypertension; these can be used alone or in combination. Thus, barbiturate coma remains the only non-surgical option. Although high doses of barbiturates effectively lower intracranial pressure (ICP) by suppressing cerebral metabolism and thus by reducing cerebral blood volume, they may also be associated with hypotension and consecutive decrease of CPP.¹²

The guidelines for management of TBI published in 1996¹³ and revised in 2000¹⁴ and 2007¹⁵ recommend that high-dose barbiturate therapy may be considered in hemodynamically stable patients

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with severe head injury who have intracranial hypertension refractory to maximal medical and surgical ICP lowering therapy. Lower doses of barbiturates may also be used for sedation of patients with TBI, although there is no mention of this in the published guidelines.

The goal of this study was to analyze the use of barbiturates in patients with severe TBI in the European centers where INRO introduced guideline-based TBI management and to analyze barbiturate effects on ICP, use of vasopressors, and short- and long-term outcome of these patients.

Patients and Methods

Data collection

Data for this study were collected in 13 centers located in five European countries (Austria, Bosnia, Croatia, Macedonia, and Slovakia). All centers were of tertiary care level; they included six university departments of neurosurgery, five large city hospitals, one center for neurosurgery and neurology, and one free-standing trauma center.

Data were collected prospectively for three different, purely observational studies. The goal of these studies was to document pre-hospital and in-hospital treatment as well as outcomes and to study the effects of guideline implementation. The International Traumatic Coma Project database¹⁶ was used for data collection in all three studies.

The data collection took place between January 2001 and June 2005. Patients were included if they had "severe TBI" according to the criteria defined by the U.S. National Traumatic Coma Database,¹⁷ such as a Glasgow Coma Scale (GCS) score of 8 or less after resuscitation or a GCS score deteriorating to 8 or less within 48 h of injury. Only patients who survived at least until admission to the intensive care unit (ICU) were enrolled in this study.

Basic demographic data of the patient, cause and location of trauma, severity of trauma, pre-hospital treatment, results of CT scans and laboratory testing, data on surgical procedures, and outcome data were recorded. Patient status and treatment information was collected for the first 10 days. Information on status and location was recorded at 3, 6, and 12 months after injury. In most centers, data were collected by a local researcher. In the Austrian centers, data were extracted from the prospectively collected records by a single researcher (IW) who visited the centers at regular intervals. Personal data protection was observed, and the identifiers were kept separately from the data.

The whole treatment process in each center was supposed to be based on the guidelines for the management of patients with severe TBI published by the Brain Trauma Foundation in 1996.¹³ These guidelines were implemented at the start of the projects in each center. Country economy level was determined according to the World Bank's Classification of Countries.¹⁸ Austria was classified as a high income (HI) country, Slovakia and Croatia are classified as upper middle income (UMI) countries, and Bosnia and Macedonia as lower middle income (LMI) countries.

Analysis approach

Patients were divided into three groups: high barbiturate (HB), low barbiturate (LB), and no barbiturate (NB). This was based on the doses of barbiturates received and number of days of barbiturate administration. We considered doses of >2 g/24h to be high and doses lower than that as low. Patients receiving high doses of barbiturates for at least 3 consecutive days or until death were

included in the HB group. Patients receiving lower doses of barbiturates or for fewer than 3 days were included in the LB group. Patients with no barbiturates administered were included in the NB group.

We compared demographic characteristics (age, sex, country economy level), injury characteristics (type of trauma, mechanism of injury), injury severity measures (Injury Severity Score [ISS],¹¹ first GCS, pupils reactivity, main diagnosis, number of additionally injured body regions), treatment factors (transfer from other hospital, number of days at ICU and in hospital, intubation, ICP monitoring, cranial and other surgery), and outcome (ICU mortality, long-term outcome) between the three groups of patients. The long-term outcome is based on the last available Glasgow Outcome Scale (GOS) score (6 months or 12 months after injury) and was coded as "favorable" if the GOS was "good recovery" or "moderate disability," and was coded as "poor" if the GOS was "severe disability," "persistent vegetative state," or "dead."

To evaluate the effect of the administration of high doses of barbiturates on the ICP, the number of hours of ICP >25 mm Hg per day were used, and to evaluate the effect on blood pressure, the number of hours of mean arterial pressure (MAP) <70 mm Hg per day were used as indicators. Means and medians of hours of ICP >25 mm Hg and MAP <70 mm Hg for the day before and the first day of administration of high doses of barbiturates were calculated and compared to quantify the effects. For the purposes of this analysis we excluded: (1) patients with other than high doses of barbiturates; (2) with barbiturates administered from day 1; (3) patients with number of hours of ICP >25 mm Hg = 0 on the day before the barbiturates administration started. The latter two conditions were needed to allow for an analysis of the change of hours of ICP >25 mm Hg between the 2 days. We also analyzed the doses of vasopressors given on the day before and on the first day of barbiturate administration, respectively. Vasopressor doses were classified as high (dose of norepinephrine >25 mg/day and/or dopamine >500 mg/day), low (defined as doses lower than 25 mg/day or 500 mg/day, respectively), or no (neither norepinephrine nor dopamine given).

The expected outcome of the patients was calculated using three different prognostic scores: the Trauma and Injury Severity Score (TRISS) was used for prediction of ICU and hospital survival¹⁹ and the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) extended score was used for prediction of 6-month mortality and 6-month poor outcome.²⁰ Actual outcomes of the patient groups at the respective time points after injury were compared with the expected outcomes predicted by the scores, and observed versus expected (O/E) outcome ratios were calculated.

Statistical methods used

The chi-square test or the Fisher exact test was used as appropriate to test for differences in case of categorical variables. Medians along with corresponding interquartile ranges and means with standard deviations were used as central measures in case of continuous variables, and subsequently the Kruskal-Wallis test (when comparing three groups) or the Wilcoxon test (when comparing two groups) were used to test for differences in medians. Logistic regression was used in the multivariate analysis. The R project and its packages were used as the statistical tool.

Results

Table 1 presents the basic demographic characteristics of our patients and the economy level of the country of hospitalization.

TABLE 1. DEMOGRAPHIC CHARACTERISTIC AND COUNTRY ECONOMY LEVEL

Category	High barbiturates	Low barbiturates	No barbiturates	Total	p value
Patients (N; %)	71 (6%)	140 (13%)	961 (81%)	1172	
Age (median; IQR)	36 (29–49)	41 (23–54)	45 (27–63)	44 (26–62)	0.006
Sex male (N; %)	51 (72%)	113 (81%)	737 (77%)	901 (77%)	0.333
Economy level:					
HI (Austria) (N; %)	69 (97%)	49 (35%)	288 (30%)	406 (35%)	<0.001
UMI (Slovakia, Croatia) (N; %)	2 (3%)	50 (36%)	285 (30%)	337 (29%)	
LMI (Bosnia, Macedonia) (N; %)	0	41 (29%)	388 (40%)	429 (37%)	

IQR, interquartile range; HI, high income economy; UMI, upper middle income economy; LMI, lower middle income economy.

Only 6% of the patients fell into the HB group; almost all of these were from the centers located in the HI country (Austria). Patients from the HB group were significantly younger than LB and NB patients. In all groups, more than 70% of the patients were male.

Table 2 shows mechanism and severity of the injuries. Traffic-related TBI were most common (more than 40% in all groups). In the HB group, we found the highest proportion of high level falls (from 3 m or above) and the lowest proportion of low level falls (from below 3 m). The differences in injury mechanisms were statistically significant. Most injuries (more than 90% in all groups) were blunt with the lowest proportion of penetrating injuries in the HB group. The HB group had the lowest proportion of isolated TBI and the

highest proportion of severe injuries to more than two additional body regions. The mean ISS in the HB group (29 ± 12) was significantly higher than that of the LB group (24 ± 13), although the medians were similar. The distributions of first GCS and pupillary reactivity were not significant between the three groups, although bilaterally fixed and dilated pupils were seen more frequently in the LB and NB groups. Contusion and epidural hematoma (EDH) were most commonly found in the HB groups; intraventricular hemorrhage and subdural hematoma (SDH) were less prevalent in the HB group. These differences were statistically significant.

Treatment factors and outcomes of patients are presented in Table 3. Patients from the HB group needed field intubation

TABLE 2. INJURY CHARACTERISTICS AND TRAUMA SEVERITY

Category	High barbiturates	Low barbiturates	No barbiturates	Total	p value
Patients (N, %)	71 (6%)	140 (13%)	961 (81%)	1172	
Injury mechanism					0.011
Low level fall (N, %)	12 (19%)	37 (28%)	270 (31%)	319 (30%)	
High level fall (N, %)	13 (20%)	12 (9%)	69 (8%)	94 (9%)	
Traffic accident (N, %)	28 (43%)	67 (51%)	423 (49%)	518 (49%)	
Other (N, %)	12 (19%)	16 (12%)	97 (11%)	125 (12%)	
Type of trauma					0.043
Blunt (N, %)	70 (99%)	134 (96%)	874 (92%)	1078 (93%)	
Penetrating (N, %)	1 (1%)	6 (4%)	76 (8%)	83 (7%)	
Additional injuries					0.27
None (N, %)	35 (49%)	84 (60%)	505 (53%)	624 (53%)	
One region (N, %)	17 (24%)	29 (21%)	219 (23%)	265 (23%)	
Two regions (N, %)	8 (11%)	19 (14%)	146 (16%)	173 (15%)	
More than two (N, %)	11 (16%)	8 (6%)	87 (9%)	106 (9%)	
ISS (median; IQR)	25 (19–36)	25 (16–33)	26 (17–34)	26 (17–34)	0.004
1st GCS score (median; IQR)	6 (3–7)	6 (4–8)	5 (3–8)	5 (3–8)	0.359
Pupils on admission					0.063
Asymmetric (N, %)	19 (27%)	33 (24%)	250 (28%)	302 (27%)	
One fixed and dilated (N, %)	2 (3%)	8 (6%)	79 (9%)	89 (8%)	
Two fixed and dilated (N, %)	4 (6%)	15 (11%)	125 (14%)	144 (13%)	
Normal (N, %)	45 (64%)	79 (59%)	448 (50%)	572 (52%)	
Main CT diagnosis					0.002
aSDH (N, %)	23 (32%)	58 (41%)	409 (43%)	490 (42%)	
EDH (N, %)	19 (27%)	20 (14%)	121 (13%)	160 (14%)	
Contusion (N, %)	16 (23%)	32 (23%)	145 (15%)	193 (16%)	
Edema (N, %)	2 (3%)	6 (4%)	18 (2%)	26 (2%)	
IVH (N, %)	5 (7%)	15 (11%)	155 (16%)	175 (15%)	
SAH (N, %)	5 (7%)	5 (4%)	50 (5%)	60 (5%)	
Normal (N, %)	0	2 (1%)	30 (3%)	32 (3%)	
Not determined (N, %)	1 (1%)	2 (1%)	33 (3%)	36 (3%)	

ISS, Injury Severity Score; IQR, interquartile range; GCS, Glasgow Coma Scale; CT=computed tomography; aSDH, acute subdural hematoma; EDH, epidural hematoma; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

TABLE 3. TREATMENT AND OUTCOMES

Category	High barbiturates	Low barbiturates	No barbiturates	Total	p value
Patients (N; %)	71 (6%)	140 (13%)	961 (81%)	1172	
Treatment factors					
Field intubation (N; %)	61 (86%)	85 (63%)	527 (57%)	673 (59%)	<0.001
Secondary transfer (N; %)	17 (24%)	40 (29%)	336 (35%)	393 (34%)	0.065
Neurosurgery (N; %)	59 (91%)	95 (87%)	541 (80%)	695 (82%)	0.068
Other surgery (N; %)	13 (20%)	23 (21%)	117 (17%)	153 (18%)	0.59
ICP monitoring (N; %)	66 (93%)	68 (49%)	352 (37%)	486 (42%)	<0.001
ICP days (median; IQR)	12 (9–15)	8 (4–12)	5 (3–8)	6 (4–10)	<0.001
Days of barbiturates (median; IQR)	8 (6–9)	2 (1–3)	0	3 (1–7)	<0.001
Methohexital dose/day (mg; median; IQR)	4000 (2880–5000)	1400 (720–1920)	0		<0.001
Thiopental dose/day (mg; median; IQR)	5000 (3600–6000)	500 (300–1000)	0		<0.001
Phenobarbital dose/day (mg; median; IQR)	0	110 (110–220)	0		–
Intubation days (median; IQR)	13 (8–21)	6 (3–11)	4 (2–9)	5 (2–10)	<0.001
Days on ICU (median; IQR)	24 (14–40)	10 (4–19)	6 (3–11)	7 (3–14)	<0.001
Days in hospital (median; IQR)	34 (18–52)	12 (5–35)	11 (4–23)	12 (4–28)	<0.001
Outcomes					
ICU death (N; %)	21 (30%)	55 (37%)	415 (39%)	491 (38%)	0.244
Hospital death (N; %)	24 (37%)	51 (44%)	388 (50%)	463 (48%)	0.643
6-month death (N; %)	24 (37%)	51 (44%)	401 (51%)	476 (50%)	0.035
6-month poor outcome (N; %)	37 (53%)	69 (52%)	482 (54%)	588 (53%)	0.859
Observed vs. expected outcomes					
Predicted hospital survival (mean, SD)	68.1 (27.1)	72.8 (28.1)	62.2 (33.1)	63.9 (32.3)	<0.01
O/E ratio (hospital survival)	0.92	0.9	0.8	0.81	
Predicted poor outcome (mean, SD)	55.4 (16.4)	52.2 (23.1)	56.8 (25.1)	56.1 (24.3)	0.106
O/E ratio (6-month poor outcome)	0.96	1	0.95	0.94	
Predicted ICU survival (mean, SD)	68.1 (27.1)	72.8 (28.1)	62.2 (33.1)	63.9 (32.3)	<0.01
O/E ratio (ICU survival)	1.03	0.87	0.98	0.97	
Predicted 6-month death (mean, SD)	34.1 (14.9)	33.4 (20.9)	38.5 (23.4)	37.5 (22.7)	0.035
O/E ratio (6-month death)	1.1	1.3	1.3	1.3	

ICP, intracranial pressure; IQR, interquartile range; ICU, intensive care unit; SD, standard deviation; O/E ratio, observed vs. expected ratio.

significantly more frequently, and nearly all of them needed neurosurgical interventions. They had ICP monitoring significantly more frequently, and needed it for significantly more days. They received barbiturates for more than a week while the LB patients had these for just a few days. In the HB group, the 54 (76%) patients received methohexital, while thiopental was given in only 17 (24%) patients. The doses used were comparable (median 4 vs. 5 g/day). The type of barbiturate used (methohexital vs. thiopental) was not associated with any significant differences in patient's outcomes. In the LB group, most patients received thiopental ($n=85$; 61%) followed by phenobarbital ($n=37$; 26%) and methohexital ($n=18$; 13%). Again, the type of barbiturate used was not associated with any significant differences in patient outcomes.

Seizure activity was observed in 3/71 (4%) HB group patients, 17/140 (12%) LB group patients, and 89/961 (9%) NB patients, respectively. In the HB group, these seizures were observed while patients received either low doses of methohexital ($n=2$) or no barbiturate ($n=1$), and were recorded on a single day only in all cases. In the LB group, nine patients had seizure activity on 2 or more days, despite administration of either thiopental ($n=6$) or phenobarbital ($n=3$). Another eight patients from the LB group had seizures on a single day; three of these before barbiturate administration, two during thiopental or phenobarbital use, respectively, and one during methohexital use. Patients from the HB group needed intubation for almost 2 weeks while those from the other groups needed less than 1 week. The HB patients spent more than 3 weeks in the ICU, while those from the other groups were discharged much earlier, and HB patients also had a significantly longer hospital stay.

Patients from the HB group had the lowest rates of death in the ICU, in the hospital, and at 6 months after trauma. After adjustment for the factors age, ISS, and first GCS score (Table 4), however, this difference was not significant. This was probably because predicted mortality was significantly lower in the HB group (Table 3). With

TABLE 4. CRUDE AND ADJUSTED ODDS RATIOS OF OUTCOME OF PATIENTS ON DIFFERENT STAGES AFTER THE INJURY

Factor	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Survival after ICU		
No barbiturates	1	1
Low barbiturates	1.02 (0.94–1.12)	0.95 (0.88–1.02)
High barbiturates	1.1 (0.97–1.23)	1.08 (0.98–1.2)
Hospital survival		
No barbiturates	1	1
Low barbiturates	1.26 (0.85–1.86)	0.77 (0.49–1.23)
High barbiturates	1.69 (0.99–2.85)	1.48 (0.82–2.65)
6-Month survival		
No barbiturates	1	1
Low barbiturates	1.34 (0.91–1.99)	0.84 (0.52–1.33)
High barbiturates	1.8 (1.07–3.04)	1.6 (0.89–2.88)
Long-term favorable outcome		
No barbiturates	1	1
Low barbiturates	1.09 (0.76–1.57)	0.68 (0.44–1.05)
High barbiturates	1.03 (0.63–1.68)	0.94 (0.53–1.64)

OR, odds ratio; CI, confidence interval; adjusted OR, adjusted for age, Injury Severity Score, and first Glasgow Coma Scale score; ICU, intensive care unit.

TABLE 5. HOURS OF INTRACRANIAL PRESSURE >25 mm Hg AND MEAN ARTERIAL PRESSURE <70 mm Hg IN RELATION TO ADMINISTRATION OF HIGH DOSES OF BARBITURATES (N=32 PATIENTS)

	Day before mean (SD)	First day mean (SD)	Mean of differences (CI 95%)	p value (paired t test)
ICP (h > 25 mm Hg)	6.4 (7.05)	4.2 (5.9)	2.25 (0.4–4.4)	<0.05
MAP (h < 70 mm Hg)	6.2 (6.1)	9.4 (8.2)	3.2 (0.3–6.2)	<0.05
	Median (IQR)	Median (IQR)	-	p value (paired Wilcoxon test)
ICP (h > 25 mm Hg)	3 (1.75–10)	2 (0–5)	-	<0.05
MAP (h < 70 mm Hg)	5 (2–10)	7.5 (2.75–17.5)	-	<0.05

SD=standard deviation; CI=confidence interval; ICP=intracranial pressure; MAP=mean arterial pressure; IQR=interquartile range.

regard to hospital mortality, patients from all groups had worse than predicted outcomes while rate of ICU survival, rate of poor outcome at 6 months, and mortality rate at 6 months were at or below the predicted values.

We were able to investigate the effects of high doses of barbiturates on ICP and MAP in a subsample of 32 patients from the HB group (Table 5). Barbiturate administration was associated with a significant reduction in the daily hours of ICP > 25 mm Hg, but was also associated with a significant increase in daily hours of MAP < 70 mm Hg. The number of patients who needed high doses of vasopressors increased, and the number of patients without vasopressors decreased significantly (Fig. 1) after start of barbiturate coma ($p=0.029$). The effect of barbiturate administration on ICP was not associated with improved outcomes: the rates of ICU death, hospital death, 6-month death, and poor outcome, respectively, were not significantly different between the 22 responding and the 10 non-responding patients. With regard to the ICP response, 6 (19%) patients had full control of ICP (i.e., hours of ICP > 25 mm Hg = 0 on day 1 of barbiturate coma), and 16 (50%) had partial control of ICP (i.e., a reduction in hours of ICP > 25 mm Hg compared with the day before barbiturate coma).

Discussion

The goal of our analysis was to investigate the use of barbiturates in patients after severe TBI. We found that fewer than 20% of all patients with severe TBI were given barbiturates, and the majority of these were given only low doses of barbiturates.

High-dose barbiturate treatment

High-dose barbiturate treatment was administered in 6% of all patients with severe TBI (32% of patients who received any barbiturates). The treatment was based on the recommendations given in the guidelines¹³: nearly all patients had ICP monitoring, and ICP had been elevated for considerable periods during the day before the start of treatment. We were only able to analyze this in about half of the HB patients; in many cases, treatment was started as soon as ICP started to rise > 25 mm Hg, and therefore, we were not able to calculate reliable ICP values before and after the start of barbiturate treatment, because only daily values of hours of ICP > 25 mm Hg had been recorded. The patients who received high-dose barbiturate treatment were significantly younger, had higher rates of EDH and contusions, had lower rates of acute SDH, had the lowest rates of fixed and dilated pupils, and nearly all of them had had neurosurgery before admission to the ICU. This suggests that patients were selected for high-dose barbiturate treatment if their prognosis was not considered hopeless.

High-dose barbiturate treatment caused a decrease in ICP in 22/32 (69%) patients, but also caused hemodynamic instability leading

to longer periods of MAP < 70 mm Hg despite increased use of high doses of vasopressors. All these effects have been described before.¹² Our univariate analysis showed a statistically significant survival benefit at 6 months after trauma for the HB patients. After adjustment for age, GCS score, and ISS, however, this effect was lost. No other significant differences were apparent in the observed outcomes. None of the studies published so far, however, have demonstrated a significant effect on survival.^{10,21,22}

How do these results compare with those from previous studies? In most other studies, pentobarbital has been the drug of choice, whereas in our analysis, methohexital and thiopental were used to achieve barbiturate coma, because pentobarbital for intravenous use is no longer available in Europe. Methohexital is known to have proconvulsive effects, similar to clonidine²³; this may be the reason why it has rarely been used in patients with severe TBI. In the present analysis, however, we found no increased rate of seizure activity in the patients who received methohexital. Pérez-Bárcena and associates²⁴ compared the effects of thiopental and pentobarbital in 44 patients; they found that thiopental was more effective in controlling intracranial hypertension. In the thiopental group, more patients (8/22; 36%) had favorable outcomes than in the pentobarbital group (4/22; 18%); severity of TBI, however, was higher in the pentobarbital group.

Earlier studies on barbiturate coma reported mortality rates of 60%,²² 57%,¹⁰ and 62%,²¹ in addition to significant rates of

FIG. 1. Changes in administration of vasopressors before and after use of high doses of barbiturates (N=65 patients).

survivors with poor functional status. Only 15%²² and 18%¹⁰ of the patients had favorable outcomes 1 year after trauma. In our study, 37% of the HB patients died within the first 6 months, and 47% had favorable outcomes. These differences are difficult to explain. It seems possible that in our study, high doses of barbiturates were given preferably to patients whose prognosis was not considered hopeless, whereas within a prospective study protocol, even patients with very poor prognoses might be included. The patients who received high-dose barbiturates had the lowest predicted mortality of all three groups in our study.

With the exception of the study by Ward and colleagues,²⁵ all studies found that ICP could be fully or at least partially controlled in many patients: the response rates were 38%,²² 45%,¹⁰ and 32%.²¹ In our study, full control of ICP was rare (19%), but at least partial control of ICP was achieved in 50% of the patients. All earlier studies found that non-responders had worse outcomes than responders; in our study, however, we were unable to find an association between the degree of ICP control and patient outcomes.

Low-dose barbiturate treatment

Low doses of barbiturates were given to 13% of all patients. About one quarter of these patients received phenobarbital in low doses; this was probably done to prevent early post-traumatic seizures. Only a few patients received phenobarbital for treatment of seizures; most patients in whom seizures developed were treated with thiopental. It is most likely that patients with seizures were given other drugs such as phenytoin or valproate, too; this, however, was not documented in the database. It is also possible that phenobarbital was administered to prevent late post-traumatic seizures, although this “prophylactic use” is “not recommended” by the guidelines.¹³ In most patients who were given low doses of methohexital and thiopental, these were probably intended to increase depth of sedation, or to avoid use of high doses of propofol. We were unable to find any studies on the use of low doses of barbiturates as sedatives for patients with TBI. According to the result of our study, the use of low doses of barbiturates for sedation of TBI patients seems to be safe. It is unclear whether it is associated with any beneficial effects. This topic warrants further investigations.

It is unclear why high-dose barbiturates were used almost exclusively in the centers from the HI country (Austria). As shown in a previous article,⁵ the centers from the UMI and LMI countries sometimes had difficulties in providing ICP monitoring, probably because of economic reasons. Without ICP monitoring, the use of high-dose barbiturates is not recommended. The lack of ICP monitoring is probably the main reason why high-dose barbiturates were not used in UMI and LMI countries. We did not find any significant differences in the use of low-dose barbiturates between countries or between centers.

Limitations of the study. One significant limitation is the retrospective nature of this analysis. This analysis is based on data collected in observational studies designed to document treatment of patients with severe TBI. Therefore, use of barbiturates was not randomized, and the three groups we created (HB, LB, NB) were significantly different. We used the IMPACT extended prognostic models and the TRISS survival prognosis model to overcome this problem. These models, however, have not been validated for our study population. The IMPACT model²⁰ that we used to predict 6-month outcome has been created from the dataset collected for the IMPACT study.²⁶ It is quite likely that our patients are comparable

to patients in this database. There could, however, be subtle differences, and the O/E ratios estimated for our groups of patients may be incorrect. The use of these scores seemed justified, however, because interpretation of the results would be difficult without comparison to the predictions.

Conclusions

Patients with severe TBI were more likely to be treated with barbiturates if they were younger, had lower severity of TBI, and had “epidural hematoma” or “contusion” as their main diagnosis. Use of high doses of barbiturates was associated with hemodynamic instability and effectively lowered ICP in most patients but had no significant effect on the outcomes of patients with severe TBI. Thiopental and methohexital were equally effective. Low doses of thiopental and methohexital were used for sedation of these patients without side effects. Phenobarbital was probably used for prophylaxis of post-traumatic seizures.

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