Intracranial pressure–based barbiturate coma treatment in children with refractory intracranial hypertension due to traumatic brain injury

Fartein Velle, MD, Anders Lewén, MD, PhD, Timothy Howells, PhD, Per Enblad, MD, PhD, and Pelle Nilsson, MD, PhD

Section of Neurosurgery, Department of Neuroscience, Uppsala University, Uppsala, Sweden

OBJECTIVE Refractory intracranial pressure (ICP) hypertension following traumatic brain injury (TBI) is a severe condition that requires potentially harmful treatment strategies such as barbiturate coma. However, the use of barbiturates may be restricted due to concerns about inducing multiorgan system complications related to the therapy. The purpose of this study was to evaluate the outcome and occurrence of treatment-related complications to barbiturate coma treatment in children with refractory intracranial hypertension (RICH) due to TBI in a modern multimodality neurointensive care unit (NICU).

METHODS The authors conducted a retrospective cohort study of 21 children ≤ 16 years old who were treated in their NICU between 2005 and 2015 with barbiturate coma for RICH following TBI. Demographic and clinical data were acquired from patient records and physiological data from digital monitoring system files.

RESULTS The median age of these 21 children was 14 years (range 2–16 years) and at admission the median Glasgow Coma Scale score was 7 (range 4–8). Barbiturate coma treatment was added due to RICH at a median of 46 hours from trauma and had a median duration of 107 hours. The onset of barbiturate coma resulted in lower ICP values, lower pulse amplitudes on the ICP curve, and decreased amount of A-waves. No major disturbances in blood gases, liver and kidney function, or secondary insults were observed during this period. Outcome 1 year later revealed a median Glasgow Outcome Scale score of 5 (good recovery), however on the King's Outcome Scale for Childhood Head Injury, the median was 4a (moderate disability).

CONCLUSIONS The results of this study indicate that barbiturate coma, when used in a modern NICU, is an effective means of lowering ICP without causing concomitant severe side effects in children with RICH and was compatible with good long-term outcome.

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KEYWORDS traumatic brain injury; barbiturate coma; refractory intracranial hypertension; outcome; trauma

TRAUMATIC brain injury (TBI) in childhood is a common cause of death and acquired disability in the developed world and even more so in less-developed parts of the world. According to recent publications, the estimated annual median incidence of childhood TBI in North America, Europe, Australia, and New Zealand is 691 per 100,000 people treated in emergency departments; 74 per 100,000 are hospitalized, and 9 per 100,000 result in death.³⁸ According to the Swedish National Board of Health and Welfare,³⁶ the total death rate in Sweden in

the age group of 1–14 years is 8/100,000 per year. Trauma deaths account for 1/100,000 per year in the same patient group, but was twice as high a decade earlier (<http://nowbase.org/>).^{35,36} Of Sweden's 1.9 million children (0–17 years old) in 2014, approximately 18,300 children were hospitalized due to trauma and 3600 of these admissions were due to TBI.³⁶ During 2014, 160/100,000 children in Sweden 0–14 years of age were diagnosed with intracranial injury and 5.4/100,000 required cranial surgery that was related to the trauma.³⁶

ABBREVIATIONS CPP = cerebral perfusion pressure; CVP = central venous pressure; EVD = external ventricular drain; GCS = Glasgow Coma Scale; GMT = good monitoring time; GOS = Glasgow Outcome Scale; ICP = intracranial pressure; KOSCHI = King's Outcome Scale for Childhood Head Injury; MAP = mean arterial pressure; MVO = motor vehicle occupant; NICU = neurointensive care unit; pCO₂ = partial pressure of carbon dioxide; RICH = refractory intracranial hypertension; TBI = traumatic brain injury.

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Children with moderate to severe TBI require advanced neurointensive care to minimize secondary brain injury. Despite first-tier therapy focused on prevention of secondary insults and surgical evacuation of mass lesions, some patients still develop refractory intracranial hypertension (RICH). In many neurointensive care units (NICUs), RICH is treated with barbiturate coma. Barbiturate coma treatment in adults is well established,^{9,17,20,21,28} but many neurosurgical centers have a more restrictive attitude toward this treatment in children.^{24,37} The reasons for this include unclear outcome results and risk of adverse events related to the toxic effects of barbiturates.^{15,20,31,32} Only one article has so far been published covering this topic,²² which is the only new reference directly addressing this topic added to the chapter content on barbiturate coma treatment of the third edition of Brain Trauma Foundation Guidelines for the Management of Pediatric Severe Traumatic Brain Injury.¹⁶ There also exists uncertainty concerning the most appropriate barbiturate to use.^{8,26} Experimental research has demonstrated that the level of neuroprotection attained by the various barbiturates is not equal.^{2,4,26,35} In a prospective randomized Spanish cohort of 44 patients in 2008, thiopental appeared to be more effective than pentobarbital in controlling RICH.²⁶ More knowledge concerning different aspects of barbiturate coma treatment in children is needed.

The aim of this study was to determine the outcome and occurrence of side effects/complications when barbiturate treatment (thiopental) was used in children with RICH in a modern intensive care unit setting with structured care and advanced multimodality monitoring with digitized acquisition systems.

Methods

Study Population

Uppsala University Hospital is a level 1 trauma center serving the middle part of Sweden with a population of 2 million people. In addition to all neurosurgical cases admitted to the department, all severe neurotrauma cases in both adults and children are admitted to the NICU from 24 local hospitals located within a distance of approximately 300 km.

During a 10-year period (2005–2015), 60 children ≤ 16 years of age, with severe TBI and a Glasgow Coma Scale (GCS) score ≤ 8 (GCS motor score ≤ 5), who were intubated and had received an intracranial pressure (ICP) monitor, were treated at the NICU. Twenty-one of these patients developed RICH despite surgical evacuation of mass lesions or hemicraniectomy and had barbiturates added to their treatment. These patients were included in this retrospective study. Demographic data and clinical information were retrieved from patient records. Physiological minute-by-minute data were retrieved from our database of digital monitoring system recordings.

This study was approved by Uppsala University's ethical committee. Informed consent was not required.

Study Variables

The following variables were studied: cause of injury; time from trauma to NICU; neurological status according

to GCS score at admittance to the NICU and at departure; Rotterdam CT score of initial brain CT scan;^{18,19} start and length of barbiturate coma treatment; serum thiopental concentrations; dose of thiopental; side effects observed during barbiturate coma (infections, hepatocellular toxicity, and renal dysfunction); and deviations from goals. A Glasgow Outcome Scale (GOS)¹⁴ score and a more specific estimated King's Outcome Scale for Childhood Head Injury (KOSCHI) score was determined at 1 year based on information from patient rehabilitation records.^{3,6,25}

NICU Procedures and Patient Management

Uppsala has a dedicated NICU with standardized treatment protocol-based organization and a specific focus on identifying and treating secondary insults.¹⁰ All levels of staff have specified roles for achieving the goals in the unit's protocols (Table 1). The Odin monitoring system¹³ is used for collection and visualization of all monitoring data bedside (minute and high resolution). All documentation is recorded in an electronic patient management system. Specific interfaces have been created for daily rounds and the end of nurses' shifts, where results of treatment goals over the shift are evaluated and recorded.²³

Neurological state (GCS motor score) is assessed regularly by wakeup tests if the patient has stable ICP. All admitted patients not responding to commands (GCS motor score ≤ 5) are routinely intubated, and in the acute phase mild hyperventilation partial pressure of carbon dioxide ($p\text{CO}_2$) at 30–34 mm Hg (4–4.5 kPa) is applied until ICP monitoring is in place. All patients with GCS motor scores ≤ 5 receive an ICP monitor, preferably an external ventricular drain (EVD).

Sedation is maintained with infusions of propofol at first, but in children it is replaced by midazolam and morphine as soon as they are stable. The primary aim is that the patients are normovolemic with adequate colloid osmotic pressure. Sodium concentrations are kept around 140 mmol/L and a zero or slightly negative water balance. Central venous pressure (CVP) is maintained at 0–5 mm Hg. Albumin (20%) infusions are used to maintain intravascular colloid osmotic pressure. Noradrenaline or dobutamine infusions are administered if hypotension occurs.

The neurointensive care management in Uppsala is ICP oriented and not primarily cerebral perfusion pressure (CPP) oriented. The goal is to keep ICP < 20 mm Hg and CPP around 60 mm Hg in adults and as low as 45–50 mm Hg is accepted in children depending on age. During barbiturate coma, CPP levels down to 50 mm Hg are accepted in adults and 40–45 mm Hg in children. In cases of high ICP, no attempt is made in general to actively increase CPP above 60 mm Hg by increasing blood pressure above normal levels, but spontaneous CPP levels over 60 mm Hg are not actively lowered unless the raised CPP has a detrimental effect on ICP levels. The aim of this strategy is to prevent the development of secondary brain edema in tissue with a disturbed blood-brain barrier and/or cerebral vascular autoregulation.^{11,12}

If ICP increases despite this basal therapy, a reevaluation of the occurrence of secondary insults is conducted and a new CT scan is performed to rule out surgical mass lesions before escalation of ICP therapy to step 1. This es-

TABLE 1. Uppsala NICU treatment goals in children

Variable	Goal (depending on age)
ICP	<20 mm Hg
CPP	45–60 mm Hg (40–50 in BC)
BP _{syst}	>80–100 mm Hg
CVP	0–5 mm Hg
pCO ₂	30–34 mm Hg (4.0–4.5 kPa; normoventilation ASAP)
pO ₂	>90 mm Hg (>12 kPa)
SaO ₂	>96%
B-glucose	5–10 mmol/L
Temperature	Normothermia <38°C
Hb	>100 g/L
Electrolytes	Normal references (K > 2.3 mmol/L in BC)
Water balance	Normovolemic to slightly negative

ASAP = as soon as possible; BC = barbiturate coma; BP_{syst} = systolic blood pressure; Hb = hemoglobin; K = potassium; pO₂ = partial pressure of oxygen; SaO₂ = oxygen saturation.

calated therapy includes: deeper sedation with midazolam and morphine; stress reduction with beta-blockers in the form of metoprolol and centrally acting alpha-adrenoceptor stimulators (clonidine); and intermittent drainage of CSF from an EVD if possible. If there is no radiological sign of development of expanding mass lesions, the intermittent drainage of CSF can, after some time (1–2 days), be changed to continuous drainage against a pressure level of 15–20 mm Hg.

If these measures do not alleviate ICP problems, step 2 therapy is initiated. A new reevaluation of all parameters is performed and if cerebral CT shows no significant mass lesion or midline shift, a barbiturate coma is initiated. Osmotherapy is not included in the protocol. Midazolam infusion is changed to thiopental infusion as a monosedative (pentocur, Abcur AB) in the lowest dose needed to decrease ICP. Burst suppression on EEG is not a primary goal. Barbiturate coma is initiated with thiopental bolus doses (total 8–10 mg/kg in adults and 3–5 mg/kg in children) given as small repeated doses (50-mg doses in adults and between 10 and 50 mg doses in children depending on weight) until ICP normalizes. Intermittent doses are given to ensure that there is minimal effect on mean arterial blood pressure. A continuous infusion of thiopental is started at the same time as the boluses are given (initial dose 5–10 mg/kg/hr), which is adjusted over time depending on ICP levels, suppression periods on EEG, and serum concentrations of thiopental. The EEG monitoring is primarily used to observe and prevent excessive thiopental doses causing excessively long periods of suppression and to monitor for seizures. Serum thiopental levels less than 300 µmol/L are the preferred primary serum concentration levels. This strategy using the lowest possible dose of thiopental to decrease ICP is intended to minimize the risk of medication-related complications.¹¹ Patients receive only parenteral nutrition during barbiturate coma treatment. Patients are kept on thiopental as short a time as possible depending on clinical status, interpretation of intracranial dynamics (mean ICP, amplitude, and plateau

waves), CT brain findings, and severity of complications. If ICP cannot be controlled in this way, a decompressive craniectomy is performed.

Results

Patient Characteristics

The median age of the 21 children was 14 years (range 2–16 years); there were 12 boys and 9 girls, with a median weight of 58 kg (range 12–82 kg). The causes of injury were motor vehicle occupant (MVO; n = 5), pedestrian hit by car (n = 6), bicycle accidents (n = 4), and sport/play related (n = 6). At NICU admission the median GCS score was 7 (range 4–8) and GCS motor score was 5 (range 2–5). Nine of the children had fixed dilated pupils at admission, 3 bilateral and 6 unilateral, of whom 3 had orbital facial fractures. Seven children showed focal motor deficits at admission. On the first CT scan of the brain the median Rotterdam CT score was 4 (range 4–5). The average time from accident to arrival at the initial local ICU was approximately 2.9 hours (range 0.5–9 hours). All children were intubated on site or at the primary hospital. After arriving at our NICU they received ICP monitoring, either by intraparenchymal (Codman; n = 17) or by intraventricular catheter (Smiths Medical; n = 11). As shown in Table 2, 3 children were operated on using unilateral hemispherectomy, 2 before thiopental onset (patients 15 and 17) due to unilateral diffuse contusions causing midline shift, and 1 during thiopental treatment (patient 14). Patient 19 developed a small frontal postoperative intracerebral hematoma after an intraparenchymal pressure-monitoring device was inserted at day 1, but at 11 days after trauma this patient had bifrontal craniectomies due to a sudden late expansion of this hematoma and diffuse edema causing a prolonged barbiturate coma. Patient 21 underwent bifrontal craniectomy 2 days after barbiturate coma discontinuation. Five other children (patients 4, 9–11, and 13) had mass lesions evacuated prior to thiopental administration. Patient 8 developed a frontal intracerebral hematoma 7 days after trauma, below a conservatively treated impression fracture. This was surgically evacuated before onset of barbiturate coma.

The median time period from trauma to onset of thiopental treatment was 46 hours (range 4.7–197.5 hours). Nineteen children were treated with intravenous thiopental and received a median bolus at initiation of 5.5 mg/kg (range 2.3–15.2 mg/kg) followed by a median infusion rate of 5.5 mg/kg/hr (range 4–8 mg/kg/hr). Median duration of barbiturate coma infusion was 107 hours (range 25–329 hours). Two children received thiopental as suppositories and had a mean bolus dose of 7.73 mg/kg followed by 1.43 mg/kg/hr with suppositories at regular intervals. Median maximum serum thiopental for all children was 220 µmol/L (range 30–460 µmol/L). Twelve children had continuous EEG recordings, 7 of whom (patients 3, 6, 10–12, 18, and 20; Tables 2 and 3) showed burst suppression during thiopental treatment, and 5 children (patients 4, 9, 15, 16, and 19; Tables 2 and 3) showed generalized slowing.

Complications

Blood gases were continuously followed (Table 4). Dif-

TABLE 2. Patient characteristics

Case No.	Sex/Age (yrs)/Weight (kg)	Accident Mechanism	GCS Motor Score at Admission	Rotterdam CT Classification	Evacuated Mass Lesion		DC	Duration (hrs)		GCS Motor Score at Departure*	GOS Score	KOSCHI Category
								TBI to ICU	TBI to BC			
1	F/2/12	Ped	5	4	No	No	No	2.0	25.5	6	5 GR	4b
2	F/6/22	SP	5	4	No	No	No	0.5	46.0	5	5 GR	4b
3	M/6/23	Ped	4	4	No	No	No	2.0	12.0	4	5 GR	4a
4	M/7/27	SP	2	4	Yes, EDH	No	No	0.5	53.5	5	5 GR	4a
5	M/11/44	Bike	3	4	No	No	No	1.0	94.5	6	4 MD	4a
6	F/12/40	Ped	5	4	No	No	No	1.0	91.7	6	5 GR	4b
7	F/12/53	Ped	5	4	No	No	No	5.0	4.7	6	5 GR	5a
8	F/13/53	SP	5	4	Yes, ICH	No	No	2.0	197.5	6	5 GR	5a
9	M/13/47	Ped	5	4	Yes, EDH	No	No	1.0	24.0	6	5 GR	4b
10	M/14/61	SP	3	4	Yes, EDH	No	No	8.0	44.5	3	3 SD	3a
11	F/14/60	Bike	3	5	Yes, SDH	No	No	4.0	40.5	6	5 GR	5a
12	M/14/58	Bike	2	4	No	No	No	4.0	156.5	4	4 MD	4a
13	M/14/59	SP	5	4	Yes, EDH	No	No	5.0	68.2	6	5 GR	4b
14	M/15/62	MVO	4	4	No	No	Yes, after BC	3.5	41.3	6	5 GR	4a
15	M/15/82	Bike	5	4	No	No	Yes, before BC	1.0	11.0	6	4 MD	4a
16	F/15/55	SP	5	4	No	No	No	1.0	78.0	Dead	1 D	1
17	M/16/65	MVO	2	5	No	No	Yes, before BC	9.0	30.8	2	2 VS	2
18	M/16/80	MVO	5	5	No	No	No	6.0	94.0	5	4 MD	4a
19	F/16/60	Ped	4	4	Yes, ICH	No	Yes, bifrontal day 11	1.0	124.0	6	5 GR	5a
20	F/16/58	MVO	5	5	No	No	No	1.0	68.0	6	4 MD	4b
21	M/16/65	MVO	4	5	No	No	Yes, bifrontal after BC	2.0	37.0	4	4 MD	3b
Median	14/58		5	4				2.0	46.0	6	5 GR	4a

BC = barbiturate coma; D = death; DC = decompressive craniectomy; EDH = epidural hematoma; GR = good recovery; ICH = intracerebral hematoma; MD = moderate disability; Ped = pedestrian; SD = severe disability; SDH = subdural hematoma; SP = sport/play; VS = vegetative state.

* Departure from the NICU, but remaining in the hospital.

TABLE 3. Patient characteristics

Case No.	BC Duration (hrs)	Max Serum Thiopental ($\mu\text{mol/L}$)	ICP >20 (% GMT)	ICP >25 (% GMT)	Mean (mm Hg)			MAP <60 (% GMT)	MAP <50 (% GMT)
					ICP	CPP	MAP		
1*	107.0	30	10.0	1.4	15	54	68	13.4	0.0
2*	187.5	130	17.2	7.5	15	55	70	6.3	0.0
3*	74.0	350	5.7	0.0	14	48	62	35.2	0.0
4	158.5	160	22.7	3.3	19	59	77	0.7	0.0
5	70.7	190	7.7	3.2	15	64	79	0.0	0.0
6	70.7	150	42.7	4.2	17	51	67	3.4	0.0
7	109.6	240	23.6	6.7	17	58	75	0.1	0.0
8	121.0	230	0.4	0.1	10	75	84	0.0	0.0
9	118.5	370	7.1	0.8	15	63	78	0.0	0.0
10	114.0	400	13.0	0.3	18	59	77	0.8	0.0
11	166.5	460	15.3	1.7	17	64	81	0.9	0.0
12	75.0	240	14.6	3.7	15	64	78	0.9	0.0
13	96.3	220	4.8	0.3	15	61	75	2.1	0.0
14	129.0	400	9.1	1.0	15	65	80	0.0	0.0
15	99.0	200	0.5	0.0	13	78	91	0.0	0.0
16	25.0	90	31.1	4.3	18	57	73	15.4	8.4
17	50.8	140	30.7	4.6	16	60	75	0.9	0.0
18	170.5	300	6.1	2.2	16	62	78	0.0	0.0
19	329.0	220	27.1	9.2	17	68	85	0.3	0.0
20	66.0	140	10.6	2.5	15	64	78	0.2	0.0
21	41.0	290	28.1	3.7	18	56	74	0.4	0.0
Median	107.0	220	13.0	2.5	15	61	77	0.7	0.0

* Hourly values recorded.

difficulties were observed in patient 17 (Table 4), who had a maximum sodium level of 170 mmol/L and a minimum potassium level of 1.6 mmol/L. At initiation of barbiturate coma the median sodium concentration was 141 mmol/L (range 132–148 mmol/L) and was above 140 mmol/L in all patients, except patients 5 and 13 who had 132 mmol/L due to salt-wasting syndrome and showed daily sodium losses in urine of > 400 mmol/day. In patients 8 and 9, serum sodium was only temporarily lower at initiation of barbiturate coma. Blood samples did not show any clinically significant renal dysfunction or hepatocellular toxicity, except transiently in one patient (patient 10, Table 4). All of the parameters in Table 4 normalized by the end of the NICU period. All children required inotropic infusions during barbiturate coma using noradrenaline or dobutamine at continuously adjusted levels to maintain sufficient mean arterial pressure (MAP) and prevent hypotension, and thereby also maintaining sufficient CPP. No hypotensive episodes with MAP < 50 mm Hg were recorded during the barbiturate coma treatment (Table 3), except in patient 16 (described below).

Another complication observed during thiopental treatment was respiratory infections. Seventeen children were diagnosed with ventilator-associated pneumonia (verified by pulmonary infiltrations on chest radiography) and treated with antibiotics. None of these children developed severe respiratory problems. One child with multitrauma

developed peritonitis due to a perforated ulcer despite prophylaxis. Meningitis was not verified by CSF culture or analysis in any of the cases. Patient 16 (Tables 2 and 3) received high-dose cefuroxime prophylaxis due to extensive skull base fractures, but developed sepsis after 3 days from suspected meningeal focus, causing circulatory instability and requiring high-dose noradrenaline. This was followed by progressive multiorgan failure. Due to ICP problems, barbiturate coma was initiated later on the same day. Thiopental infusion continued for 25 hours with a maximum serum concentration of 90 $\mu\text{mol/L}$, but was discontinued due to circulatory instability and cardiac arrest. The patient was resuscitated, but died 10 hours afterward, 5 days after trauma.

Length of Stay

The average length of stay at our NICU was 21 days (range 11–44 days). At discharge, 11 children had been extubated with a mean intubation period of 16 days (range 10–28 days) and 9 children had a tracheostomy due to insufficient neurological recovery, of whom 4 were still in need of mechanical ventilation.

Neurological Outcome

At the end of the NICU period most children showed neurological improvement (Table 2). When leaving the

TABLE 4. Electrolytes, renal, and hepatocellular function

Case No.	Sodium Range (mmol/L)	Potassium Range (mmol/L)	Max Creatinine (μ mol/L)	Max Urea (mmol/L)	Max ALAT (μ kat/L)	Max ASAT (μ kat/L)
1	132–145	3.1–4.2	27	5.3	0.29	1.25
2	134–140	2.9–4.7	36	6.0	3.21	3.82
3	134–142	3.1–3.5	61	7.2	1.44	4.30
4	132–144	2.4–4.1	77	4.0	1.33	3.93
5	128–143	3.1–4.0	35	4.7	0.72	1.02
6	136–144	2.4–4.5	86	14.8	1.13	2.94
7	137–149	3.1–5.1	50	3.3	0.60	1.79
8	136–145	3.4–4.2	53	6.5	0.41	0.81
9	134–146	3.2–4.4	81	4.1	1.01	0.61
10	132–151	2.7–5.5	278	29.0	2.49	2.14
11	135–147	2.7–5.3	75	7.0	0.76	2.43
12	133–152	2.8–4.6	95	9.4	0.79	0.96
13	132–145	3.4–4.2	56	7.8	0.38	0.93
14	135–142	3.2–4.5	89	9.0	0.68	1.07
15	132–142	3.1–3.9	50	3.9	0.50	0.97
16	136–146	2.8–4.9	65	2.0	0.27	1.24
17	137–170	1.6–5.3	164	6.1	1.45	7.70
18	141–149	3.3–5.0	96	11.0	2.01	1.43
19	135–144	2.4–4.0	70	8.7	1.66	1.87
20	144–152	2.5–4.0	50	5.2	0.97	0.89
21	148–168	1.9–3.4	85	6.1	0.86	2.12

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase.

Reference values: creatinine 39–83 μ mol/L, urea 2.7–7.1 mmol/L, ALAT < 0.7 μ kat/L, ASAT < 0.7 μ kat/L.

NICU, the median GCS motor score was 6 compared to 5 at admission. Assessing recovery and outcome 1 year later, the median GOS score was 5, indicating good recovery (range 1–5). But the more specific KOSCHI scale (Fig. 1) gave a more modest score, with a median of 4a, indicating moderate disability (range 1–5a); 4 children with good outcome (KOSCHI 5a), 13 children with moderate disability (KOSCHI 4a and 4b), 2 children with severe disability (KOSCHI 3a and 3b, including patient 10 [Tables 2 and 3] due to tetraplegia caused by a cervical fracture and high medullary injury), and 1 child remained in a vegetative state (KOSCHI 2) and died 2 years after trauma. As described above, patient 16 died during the NICU period.

In the children who developed RICH, continuous ICP curve data showed escalation of disturbances in intracranial dynamics in the form of elevated ICP values, high amplitudes, and increasing number of A-waves prior to the addition of barbiturates. However, mean ICP was below 20 mm Hg. After initiation of thiopental treatment these ICP problems gradually improved. Examples of this are shown in Fig. 2. In Table 3 the percentage of ICP good monitoring time (GMT) above 20 mm Hg and 25 mm Hg is shown.

Discussion

In the NICU in Uppsala, 21 of 60 children (≤ 16 years of age) with severe TBI developed RICH and were subsequently treated with barbiturate coma. These 21 children had a median GCS score of 7 on admission to the NICU

and a median Rotterdam CT score of 4 at first CT scan. At 1-year follow-up, the median GOS score was 5 and median KOSCHI score was 4a. Thus, in this subgroup of children with severe TBI and RICH, it is possible to achieve good outcomes. The monosedative, high-dose barbiturate coma treatment appeared to be an effective approach in children with RICH when used in the modern and structured NICU setting and was associated with minor complications that could be managed.

From a historical perspective, uncertainty about effects on outcome and drug-related complications have led to a restrictive attitude about the use of this treatment in many centers.^{15,27,29} However, the low complication rates and relatively favorable outcome results found in this study indicate that barbiturates have a place in the management of RICH in children. This is also supported by the study of Mellion et al. in 2013,²² who presented a series of children also treated in a modern NICU setting using pentobarbital with comparable results to ours. In both studies, complications related to the barbiturate treatment (i.e., infection, hepatocellular, and cardiovascular) were not the cause of any serious medical events. In the past these types of complications contributed to increased mortality, which negatively influenced outcome.¹⁰ Thus, a modern NICU with multimodality monitoring, maximal focus on avoiding secondary insults, and improved cardiopulmonary care probably provides better conditions for successful barbiturate treatment.

The 21 children included in this study developed RICH

FIG. 1. Graph of outcome 12 months after TBI according to the KOSCHI classification (n = 21): D = death; VS = vegetative state; 3 = severe disability; 4 = moderate disability; 5 = good recovery.

and therefore received barbiturate coma treatment, but 5 underwent decompressive craniectomy. However, 16 of these patients did not need decompressive craniectomy to control ICP. Compared to the other 39 children with severe TBI who did not develop RICH and did not receive barbiturates, 4 underwent decompressive craniectomy, all due to midline shift. The study does not compare barbiturate coma to decompressive craniectomy, but shows that in many cases RICH can be handled and controlled using

barbiturate coma, thereby avoiding the surgical procedure of decompressive craniectomy and its potential complications.

The percentage of responders in this study is higher than that reported by most other groups.^{9,17,20–22,28,37} A possible explanation for this could be different approaches in management. The patients in this study were treated according to protocols based on Swedish ICU traditions that were more ICP-oriented than traditional CPP-oriented protocols.³⁰ We have reported earlier that this type of strategy can be advantageous when patients have disturbed pressure autoregulation of cerebral blood flow and RICH.^{17,13} Because there is no need to increase blood pressure to excessive levels, this decreases the risk of raising ICP as a result of increased cerebral blood volume due to a blood-pressure elevation in pressure-passive patients. Lower blood pressure also probably lowers the risk of cerebral vasogenic edema associated with blood-brain barrier breakage.

Another probable effect of the ICP-oriented therapy was that no patient developed severe pulmonary edema. In CPP-based treatment this is a common problem,⁵ which is even worse if the patient is receiving barbiturate treatment. These complications are believed to be related to the fluid and inotropic treatment that is given to achieve sufficient CPP levels. This type of physiological challenge is not required in ICP-oriented therapy. Seventeen (81%) of the 21 patients in this study developed ventilator-associated pneumonia compared to 11 (28%) of the 39 remaining children with severe TBI who were not treated with barbiturate coma at our NICU during the same period (data not illustrated). The high incidence of pneumonia in the

FIG. 2. Case 18. ICP before and after onset of barbiturates (BC) at 11:00 (arrow). Marked time periods from the graph in the upper part of the figure (red bars) are highlighted below and show “classic” Lundberg presentation of ICP waveform data, with A-waves before onset of barbiturates (lower left) and a smoother ICP curve with lower amplitudes and no A-waves after onset of barbiturates (lower right). Figure is available in color online only.

barbiturate coma–treated group was probably a side effect of the barbiturate coma because such treatment causes a general depression of the immune response³⁴ as well as affecting the lungs' capacity to handle fluid secretion. However, these pulmonary complications did not lead to severe respiratory distress. Reducing the risk of pulmonary edema probably also reduces the severity of a pulmonary infection.

The child with RICH and sepsis (patient 16, Tables 2 and 3) had unstable circulation. Because of the circulatory instability, surgery using decompressive hemicraniectomy was deemed impossible and barbiturates were added as a last chance option.

There are inherent limitations in the present study. It is based on a retrospective cohort, a small number of patients, and there is no comparative patient group. However, the results are interesting because of the limited number of published results on the use of barbiturates in children with RICH in a modern NICU treatment environment.^{16,22} In the newly updated third edition of the Guidelines for the Management of Pediatric Severe Traumatic Brain Injury,¹⁶ the chapter content on barbiturate coma treatment is unchanged. The present evidence for barbiturate treatment in children is still very weak. To our knowledge, only one study has directly addressed the topic and reported results of barbiturate coma in children.²² Considering the almost complete absence of reported results of thiopental coma treatment in children, our study provides important additional knowledge. Our study supports the idea that RICH can be managed using barbiturate coma without severe side effects and with an overall good outcome in a modern ICU setting. The study also gives an indication of the increased safety that the modern ICU provides even if it is difficult to identify any specific factor of importance. Instead, protocol-based treatment strategies, imaging, computer-based multimodality monitoring, and a focus on avoiding all kinds of secondary insults have all together probably contributed to this level of safety. Another important factor in achieving this level of safety, in an advanced treatment such as barbiturate coma, is to have a high competence level among all types of staff specialized in neurointensive care so that implementation of secondary insult prevention and standardized care can be maintained.^{10,11}

Conclusions

The results of this study indicate that monosedative high-dose barbiturate coma, when used in a modern NICU, can be an effective means of lowering ICP without causing concomitant severe side effects in children with RICH. This treatment strategy in children with RICH was compatible with good long-term outcome.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Velle, Enblad, Nilsson. Acquisition of data: Velle, Howells. Analysis and interpretation of data: Velle, Lewén, Enblad, Nilsson. Drafting the article: Velle, Nilsson. Critically revising the article: Velle, Lewén, Enblad, Nilsson. Reviewed submitted version of manuscript: all authors. Statistical analysis: Howells. Administrative/technical/material support: Howells. Study supervision: Enblad.

Correspondence

Fartein Velle: Uppsala University Hospital, Uppsala, Sweden. fartein.velle@neuro.uu.se; fartein.velle@akademiska.se.