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S. Naredi
E. Edén
S. Zäll
H. Stephensen
B. Rydenhag

A standardized neurosurgical/ neurointensive therapy directed toward vasogenic edema after severe traumatic brain injury: clinical results

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S. Naredi · E. Edén · S. Zäll
Department of Anesthesiology and Intensive care,
Institute of Surgical Sciences,
Sahlgrenska University Hospital,
Göteborg, Sweden

H. Stephensen · B. Rydenhag
Department of Neurosurgery,
Institute of Clinical Neuroscience,
Sahlgrenska University Hospital,
Göteborg, Sweden

S. Naredi
Department of Anesthesiology and Intensive care,
University Hospital of Northern Sweden,
Umeå, Sweden

S. Naredi (✉)
Department of Anesthesiology and Intensive Care,
University Hospital of Northern Sweden,
S-901 85 Umeå, Sweden
Tel.: + 46 (90) 785 00 00
Fax: + 46 (90) 785 38 82
email: Peter.Naredi@surgery.umu.se

Abstract *Objective:* Analysis of a standardized therapy focusing on prevention and treatment of vasogenic edema in patients suffering severe traumatic brain injury (TBI).
Design: A retrospective analysis.
Setting: Neurointensive care unit at Sahlgrenska University Hospital, Göteborg, Sweden.
Patients: 38 patients with severe TBI were included. The median Glasgow Coma Score was 5 (range 3–8) and median age 27 years (range 5–70 years).
Interventions: Measurement of intracranial pressure (ICP). Surgical evacuation of hematomas and contusions. Volume expansion aiming at normovolemia. Sedation with continuous intravenous infusion of low-dose thiopentone and reduction of stress response by clonidine. Normalization of capillary hydrostatic pressure by metoprolol and clonidine. If ICP and cerebral perfusion pressure (CPP) were not stabilized (ICP < 20 mm Hg and CPP > 60 mm Hg), a continuous infusion of dihydroergotamine was added. In 4 patients a craniectomy was performed.
Results: Of the 38 patients, 27 (71 %) survived with good recovery or moderate disability, 5 (13 %) survived with severe disability, 1 (3 %) remained in a vegetative state, and 5 (13 %) died. The mortality due to intracranial hypertension was 11 % (4 patients).
Conclusion: A therapy focusing on treatment of the assumed vasogenic edema in combination with aggressive neurosurgery resulted in an outcome as good as the best previously reported.

Key words Head injury · Cerebral edema · Cerebral perfusion pressure · Blood–brain barrier

Introduction

Head injury is a major cause of disability and death among young people [1]. Neurointensive care has reduced the mortality and improved the outcome after severe traumatic brain injury (TBI) over recent decades. In 1979, Marshall et al. [2] presented a therapeutic approach in patients with severe TBI, based upon treat-

ment with corticosteroids, mannitol, hyperventilation, and occasionally high-dose barbiturates. This standardized approach improved the outcome. In 1990, Rosner and Daughton introduced a therapy based upon maintenance of a cerebral perfusion pressure (CPP) of at least 70 mm Hg [3], and they reported a mortality due to intracranial hypertension of 8 % and a good recovery or moderate disability in 68 % of cases. In the subsequent study published in 1995, in 158 patients the mortality was 29 % and 59 % survived with good recovery or moderate disability [4]. In 1994, Asgeirsson et al. [5] introduced a therapy for post-traumatic brain edema, focusing on treatment of the vasogenic edema. Among 11 patients with severe head injury with brain edema and raised intracranial pressure (ICP), 9 survived with good recovery or moderate disability and 2 died. Their therapy aimed at inducing transcapillary fluid absorption through reduction of hydrostatic capillary pressure and preservation of normal colloid osmotic pressure [6]. The hydrostatic capillary pressure was reduced by normalizing the systemic blood pressure with metoprolol and clonidine, and by precapillary vasoconstriction with dihydroergotamine (DHE) [6–8]. DHE was also used as a venous vasoconstrictor to reduce intracranial blood volume [7, 8].

The present study is a retrospective analysis of 38 patients with severe TBI treated at Sahlgrenska University Hospital with a standardized therapy based upon the theories presented by Asgeirsson et al. [5].

Patients and methods

The inclusion criteria were age $\leq$ 70 years, history of severe blunt head trauma, Glasgow Coma Score (GCS) $\leq$ 8 before sedation and intubation, need for intensive care for $\geq$ 5 days (survivors), arrival at the Neurosurgical Intensive Care Unit (NICU) $\leq$ 24 h after the trauma, first recorded CPP > 0 mm Hg, and therapy initiated.

Between January 1993 and December 1994, 40 patients admitted to the NICU at Sahlgrenska University Hospital fulfilled the inclusion criteria. Two patients were excluded for the following reasons: fatal thoracic injury that was treated with nitrous oxide ($n = 1$) and significant cerebral pathology before the injury ($n = 1$). The remaining 38 patients were followed up from the time of injury to evaluation of outcome (median 12 months, range 5–28 months).

The patients included in the study are listed in Table 1. There were 8 females and 30 males, with a median age of 27 years (range 5–70 years). Median GCS before intubation and sedation was 5 (range 3–8) and median Reaction Level Scale (RLS85) [9, 10], was 6 (range 3–8). The comparison between the two coma scales was made on the motor response. On the GCS, our patients had no eye-opening or verbal response. The time point for coma scoring before intubation and sedation was chosen because, after sedation, the patients could not be accurately evaluated. Of the 38 patients included, 24 (63 %) were injured in traffic accidents and in 10 patients (26 %) the injury was related to a fall. Twelve of the patients (32 %) suffered multiple injuries, such as hemopneumothorax, lung contusion, fracture of the long bones, and blunt abdominal trauma. The mean Acute Physiology and Chronic Health Evaluation II score during the first 24 h was 19 ± 5.

Monitoring

An intraventricular catheter was used to monitor ICP and an arterial line to measure systemic arterial pressure. ICP, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and oxygen saturation by pulse oximetry (SaO_2) were continuously displayed on bedside monitors and recorded at least hourly by nursing staff. CPP was calculated as MAP minus ICP. Zero pressure baseline for ICP was set at forehead level and for systemic arterial pressure at heart level. During intrahospital transport, ICP, SAP, DAP, MAP, SaO_2, and electrocardiograms were displayed continuously. Computed tomography (CT) was performed regularly and in any instance when necessary according to the patients condition.

Surgery

Significant hematomas and contusions were evacuated. In 3 patients (8 %) a large craniectomy was performed unilaterally over the most expansive hemisphere. A bilateral craniectomy was performed in 1 patient. The dura was opened if there was a clot to remove, but otherwise partially incised to increase further the possibility of brain expansion. All patients who were subject to craniectomy received DHE. Two received mannitol, and in all 4 patients drainage of liquor was performed before the craniectomy. Mean MAP was 81 ± 1 mm Hg at the time of the decision for craniectomy.

Ventilation

The patients were artificially normoventilated (arterial carbon dioxide tension 4.5–5.0 kPa). Hyperventilation down to 3.5 kPa was only used for short periods of time in emergency situations [11]. Positive end-expiratory pressure (4–10 cmH_2O), was used in the majority of the patients to avoid pulmonary atelectasis [12].

Fluid balance and nutrition

Normovolemia [central venous pressure (CVP) 5–10 mm Hg] and normal colloid osmotic pressure (albumin > 40 g/l) were maintained by albumin and blood transfusions (hemoglobins > 110 g/l) [5]. A negative fluid balance was kept, if necessary with the help of diuretics [13]. The patients' weight was monitored every second day to control their fluid balance. A normal level of sodium in serum was targeted (mean sodium 139 ± 4 mmol/l). Seven patients received mannitol as a single dose in emergency situations.

Enteral nutrition was preferred and normally initiated within 3 days after admission. Blood glucose was kept within the normal range, if necessary with the help of short-acting insulin.

Pharmacological treatment

The preferred administration of drugs was by a continuous i. v. infusion. All patients received thiopentone, while 37 patients (97 %) received metoprolol and 34 patients (89 %) clonidine. Four patients did not receive clonidine. Two of these patients were de-

clared brain dead within 24 h and never achieved sufficient hemodynamic stability to receive this drug. The other 2 patients had a MAP that was considered too low to add clonidine. With continuous electroencephalographic (EEG-)monitoring, the dose of thiopentone (0.5–3 mg/kg per h) was adjusted to a delta-wave pattern on the EEG [14]. This corresponds approximately to a level of sedation where the patient reacts with coughing to different stimuli. Midazolam was added if more sedation was needed in spite of adequate EEG level. For analgesia, fentanyl was given. Muscle relaxants were not used. Metoprolol (max 0.3 mg/kg per 24 h) and clonidine (max 8.0 μg/kg per 24 h) were given to normalize arterial blood pressure and thus reduce capillary hydrostatic pressure. The hypotensive drugs were not given until the patient was normovolemic, hemodynamically stable, adequately sedated, and receiving analgesia. Six patients (16 %) received dopamine. Two of these patients were declared brain dead within 24 h and dopamine was given in an attempt to stabilize the circulation. Two patients received dopamine because of septic shock (days 6–7 and days 10–13). The clonidine infusion was reduced but not stopped because of the risk of rebound phenomena. The metoprolol infusion was stopped. In 1 patient dopamine was introduced in a low dose to improve diuresis because of a rise in creatinine. One patient received dopamine for 3 h to stabilize the circulation before therapy could start.

If ICP increased above 20 mm Hg and CPP decreased to under 60 mm Hg, in spite of the combined treatment mentioned, DHE was added. The venous constrictor effect of DHE may reduce ICP by decreasing intracranial blood volume [5, 7, 8, 15]. DHE also induces a precapillary vasoconstriction and thus lowers the capillary hydrostatic pressure [7, 8, 15]. The initial dose of DHE was maintained for 24 h and was followed by a gradual dose reduction over a 5–7-day period. At the start of this study, the initial dose was 1.5 μg/kg per h and at the end of the study the dose was reduced to 1.0 μg/kg per h. Hyperthermia (> 38 °C) was avoided [16] and treated by paracetamol, electrical fan, and in three cases by a bolus dose of methylprednisolone (15 mg/kg).

All patients were given low molecular heparin (2500 IE subcutaneously/day) as thrombus prophylaxis, and ranitidine (150 mg/day i. v.) as peptic ulcer prophylaxis.

Statistics

Data are given in median and range or mean ± standard deviation. Comparison of MAPs was done with a paired Student t-test; $p < 0.05$ was considered statistically significant.

Results

Patient condition before admission to NICU

Information about the condition at the site of the accident and during transport to hospital was available in 31 of the 38 patients (82 %). Of these 31, 14 (37 %), were hypotensive (SAP < 90 mm Hg) and/or hypoxic (SaO_2 < 90 %, and/or cyanosis, and/or insufficient ventilation) at the site of the accident or during transportation to the hospital.

All 38 patients had some kind of pathology on the initial CT, performed within 1 h of the accident in all but 1 patient. Marshall's CT classification [9] is given in Table 1. Thirty-five patients (92 %) were referred to the NICU from another hospital. Median time from injury to arrival at the NICU for the referred patients was 5 h (range 2.5–24 h).

Table 1 Clinical features of the patients

Sex	Age (years)	GCS[a]	CT (Marshall)[b]	Surgery[c]	DHE[d]	GOS
F	9	4	II	No	Yes	5
M	26	7	III/SAH	Yes	Yes	3
M	52	6	II/SDH	Yes	Yes	5
M	19	7	II	Yes	Yes	4
M	19	3	SDH	Yes	No	3
M	21	4	II	No	No	4
M	25	5	SDH	Yes	Yes	5
M	34	8	II	No	No	5
M	15	5	II	No	No	4
M	56	7	SDH	Yes	No	4
M	21	4	II/SAH	No	Yes	5
M	69	7	III	Yes	No	4
M	19	3	IV/SDH	Yes	Yes	1
M	34	5	II/SDH	No	No	4
F	41	4	II	No	No	3
M	49	6	II/SAH	No	No	5
M	29	4	III/ICH	Yes	Yes	4
F	53	8	III/SDH	Yes	Yes	5
F	10	5	III	No	No	5
M	18	3	III	No	No	4
M	17	4	EDH	Yes	Yes	4
M	38	3	III	Yes	Yes	1
M	30	5	III	No	No	4
F	20	6	II	Yes	Yes	3
M	16	6	SDH	Yes	No	3
M	9	7	II	No	No	5
M	28	3	II	Yes	No	5
M	10	7	II	No	No	5
M	70	3	III	No	Yes	1
F	45	6	II	Yes	No	4
M	6	7	II	No	Yes	5
F	5	6	III	Yes	No	5
M	57	5	IV	Yes	Yes	5
M	46	3	EDH	Yes	Yes	5
M	22	6	II	Yes	No	5
F	49	3	II	Yes	Yes	4
M	41	3	III	Yes	No	1
M	53	3	SDH	Yes	Yes	1

[a] Glasgow coma score (before sedation and intubation)
[b] CT performed within 1 h after the accident in all but 1 patient, where CT was performed when the patient deteriorated after 9 h. Marshall's classification of diffuse injury I–IV: I = diffuse injury with no visible intracranial pathology; II = diffuse injury with cisterns present and midline shift of 0–5 mm and/or lesion densities present, no high- or mixed-density lesion > 25 cc; III = diffuse injury with compressed or absent cisterns, midline shift of 0–5 mm, no high- or mixed-density lesion > 25 cc; IV = diffuse injury with midline shift > 5 mm, no high- or mixed-density lesion > 25 cc, SDH = subdural hematoma, EDH = epidural hematoma, ICH = intracerebral hematoma, SAH = subarachnoid hemorrhage
[c] Surgery: yes = mass lesions (hematomas, contusions) evacuated after the initial CT, no = no mass lesions evacuated
[d] DHE = dihydroergotamine: yes = DHE given, no = DHE not given

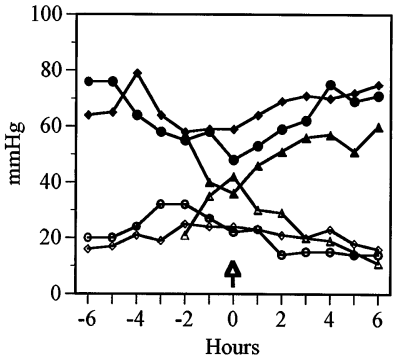

Fig. 1 The effect of dihydroergotamine (DHE) on intracranial pressure *open symbols* and cerebral perfusion pressure *filled symbols* in three patients *rhombus, circle, triangle* before and during the initial phase of DHE infusion. *Arrow* indicates the introduction of DHE

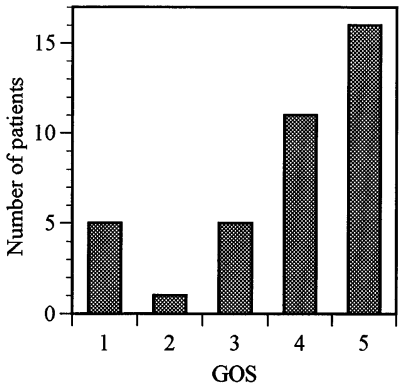

Fig. 2 Outcome 12 months (median, range 5–28 months) after the trauma according to the Glasgow outcome scale (GOS); *1* dead, *2* vegetative, *3* severely disabled, *4* moderately disabled, *5* good recovery

Patient condition in NICU

In all patients, data were collected from the time of arrival at the NICU to the time point when the intraventricular catheter was removed. The median registration period for survivors was 11 days (range 4–19 days). Mean MAP was 85 ± 8 mm Hg. Three patients (8%) had hypotensive episodes caused by hypovolemia, indicated by a low CVP. Twenty-eight patients (74%) had intracranial hypertension (ICP above 20 mm Hg for at least 2 h total time). Mean CPP was 76 ± 10 mm Hg (data from 1 patient with a mean CPP of 1.4 mm Hg excluded). CPP corrected for the difference in zero pressure baseline would be approximately 10 mm Hg lower than the measured value. If CPP persisted at a level below 60 mm Hg due to a high ICP (adequate MAP), it led to intervention such as surgery and/or introduction of DHE. There was no statistically significant difference in MAP before (90 ± 11 mm Hg) and 3 h after (87 ± 12 mm Hg) the introduction of DHE. In 15 patients (40%), ventricular drainage was also used to control ICP/CPP. Surgery (evacuation of mass lesions) was performed in 23 patients (61%), while 18 (47%) received DHE; 14 patients (44%) had a combination of surgery and DHE.

The 18 patients who received DHE had a median GCS of 4.0 (range 3–8). Surgery for contusions and/or hematomas was performed in 14 (78%) of these 18 patients. Sixteen (89%) of the 18 patients had intracranial hypertension. Two patients received DHE without a rise in ICP because of rapid clinical deterioration and signs of edema on CT. Decompressive craniectomy was performed in 4 patients (22%). In 3 patients where surgery was not performed, ICP and CPP before and after the introduction of DHE was continuously monitored (Fig. 1). After introduction of DHE, ICP decreased and CPP increased.

Outcome

Of the 38 patients, 27 survived with good recovery or moderate disability (71%), 5 survived with severe disability (13%), 1 remained in a vegetative state (3%), and 5 died (13%) (Fig. 2). Mortality due to intracranial hypertension was 11% (4 patients). The Glasgow outcome scale (GOS) evaluation was done by independent staff. Clinical features such as initial GCS and CT compared to GOS are given in Table 1.

Discussion

Severe traumatic brain injury has a high morbidity and a high mortality [1], even in cases where limited parenchymatous lesions occur. It is therefore important to treat the post-traumatic brain edema and not only evacuate hematomas and contusions. The etiology of the post-traumatic brain edema is still being debated. There are two possibilities: cytotoxic edema caused by inadequate cerebral perfusion and vasogenic edema caused by disruption of the blood–brain barrier (BBB). There are data supporting the view that the ischemic edema is the most important. But there is also support for the view that the BBB is disrupted and capillary permeability is increased after TBI. Cytokines and other inflammatory substances are released from damaged brain cells and they may trigger opening of the BBB [17, 18]. Asgeirsson et al. [5] regarded vasogenic edema as the most important in the pathophysiological process and described a treatment [5, 7, 15]. Following these principles, our results concerning outcome confirm their strategy as effective. If the BBB is damaged and capillary permeability increased, fluid exchange will be dependent on capillary hydrostatic and colloid osmotic pressure. The capillary hydrostatic pressure can be reduced by a reduction

in systemic arterial pressure (clonidine and metoprolol) and by precapillary vasoconstriction (DHE) [6]. The use of DHE has been under debate and it has been questioned whether vasoconstriction is "right or wrong" [19] in the treatment of severe TBI [7, 8]. Measurements of global cerebral blood flow in patients with severe TBI indicate increased cerebrovascular resistance as a result of precapillary vasoconstriction [8]. Therefore, DHE may aggravate cerebral ischemia. DHE must be given on strict indications only and its effect on the cerebral vessels must be further evaluated. Moreover, since DHE also constricts peripheral resistance vessels, the peripheral circulation may be compromised, especially in patients with injuries to the extremities [20, 21].

Severe TBI is associated with a massive stress response and catecholamine outflow [22–25]. In this study, clonidine was used to reduce the stress response. Clonidine might have other beneficial effects than vascular – i.e., reducing the capillary hydrostatic pressure. This would need further investigation.

The harmful effect of hypotension on outcome from severe TBI has previously been demonstrated [26, 27]. An important cause of hypotension is hypovolemia, which must therefore be aggressively treated [3, 4]. Only 3 patients in this study had hypotensive episodes caused by hypovolemia. The average MAP of 85 ± 8 mm Hg indicates that the patients were normotensive and not hypotensive.

Thiopentone was chosen for sedation. The cerebral protective and ICP lowering effect of barbiturates may relate to the coupling of cerebral blood flow to metabolic demands [14]. High doses of barbiturates have severe side effects such as hypotension, cardiac failure, hepatorenal failure, and pulmonary failure [28] and it is therefore important to use a low dose (0.5–3.0 mg/kg per h adjusted to a delta-wave pattern on EEG).

It has been argued that the CPP needs to be higher than normal to ensure adequate perfusion of the brain in cases of severe head injury [3, 4, 29]. Our mean CPP was 77 ± 10, but about 10 mm Hg lower when corrected for the difference in zero pressure baseline. Still, the outcome for our patients is as good as in series where the main purpose was to keep the CPP above 70 mm Hg.

In 34 patients with severe TBI, Rosner and Daughton [3] used a somewhat different approach in focusing on a high CPP (> 70 mm Hg). Their patient population was similar to ours, with a median inclusion GCS of 5. Their outcome figures were also similar to ours, 65 % favorable outcome and a mortality of 8 % due to intracranial hypertension compared to a favorable outcome of 71 % in our patients and a mortality due to intracranial hypertension of 11 %. They also presented the results of a subsequent study [4] in a population of 158 patients using the same type of treatment where a favorable outcome was reported in 59 % and a mortality of 29 %. It is, however, very difficult to compare treatment results between different groups in that the outcome measure (GOS) is rather crude and it is always difficult to compare the inclusion criteria.

In conclusion, a therapeutic approach based on physiologic principles for preventing and treating an assumed vasogenic edema, introduced by Asgeirsson et al. [5–7], is effective for outcome after severe traumatic brain injury.

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