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Refractory intracranial hypertension and "second-tier" therapies in traumatic brain injury

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Abstract *Objective:* To quantify the occurrence of high intracranial pressure (HICP) refractory to conventional medical therapy after traumatic brain injury (TBI) and to describe the use of more aggressive therapies (profound hyperventilation, barbiturates, decompressive craniectomy). *Design:* Prospective study of 407 consecutive TBI patients *Setting:* Three neurosurgical intensive care units (ICU). *Measurements and results:* Intracranial pressure (ICP) was studied during the first week after TBI; 153 patients had at least 1 day of ICP > 20 mmHg. Early surgery was necessary for 221 cases, and standard medical therapy [sedation, mannitol, cerebrospinal fluid (CSF) withdrawal, $PaCO_2$ 30–35 mmHg] was used in 135 patients. Reinforced treatment ($PaCO_2$ 25–29 mmHg, induced arterial hypertension, muscle relaxants) was used in 179 cases (44%), and second-tier therapies in 80 (20%). Surgical decompression and/or barbiturates were used in 28 of 407 cases (7%). Six-month outcome was recorded in 367 cases using the Glasgow outcome scale (GOS). The outcome was favorable (good recovery or moderate disability) in 195 cases (53%) and unfavorable (all the other categories) in 172 (47%). HICP was associated with worse outcome. Outcome for cases who had received second-tier therapies was significantly worse (43% favorable at 6 months, $p = 0.03$). *Conclusions:* HICP is frequent and is associated with worse outcome. ICP was controlled by early surgery and first-tier therapies in the majority of cases. Profound hyperventilation, surgical decompression and barbiturates were used in various combinations in a minority of cases. The indications for surgical decompression and/or barbiturates seem restricted to less than 10% of severe TBI.

Keywords Intracranial pressure · Surgical decompression · Barbiturates · Hyperventilation · Outcome · Traumatic brain injury

Introduction

The degree and duration of high intracranial pressure (HICP) are associated with outcome [1], and therefore HICP prevention or control is a fundamental therapeutic goal.

Intracranial pressure (ICP) rises when the sum of normal intracranial volumes and pathological masses exceeds the capacity of the cranial cavity, which is inextensible. Many therapeutic interventions are therefore aimed at reducing these volumes, either by removing abnormal volumes (e.g., surgical hematoma removal) or reducing normal components (e.g., decreasing the blood content by vasoconstriction). An alternative is to increase the space available, by opening the container and allowing the brain to expand outside the cranial vault (decompressive craniectomy). While the efficacy of surgical decompression in reducing HICP has been proven [2], the final effect

on outcome has still to be tested, and trials are under way. Decompression is a surgical intervention and, like other treatments for HICP, such as barbiturates and hypothermia, may be associated with various complications [3–6].

According to the guidelines for the management of traumatic brain injury (TBI) [7], current ICP treatment is split into "first tier" (CSF removal, mannitol, sedation, paralysis, mild hyperventilation) and "second tier", including hyperventilation with a $PaCO_2$ level less than 30 mmHg, barbiturates and surgical decompression.

Information on how often ICP after TBI is not adequately controlled by first-tier treatments, and how frequently second-tier therapies become necessary, is scant in the literature although it would be useful in order to quantify the need for additional, sometimes controversial, interventions.

The aims of this study were to quantify the severity of HICP in a group of severe TBI cases, focusing on the subgroup with HICP refractory to conventional first-tier therapies, and to describe the use of second-tier therapies.

Materials and methods

Data describing pre-hospital and intensive care unit (ICU) course together with 6-month outcome of TBI were prospectively collected in a computerized database described elsewhere [8]. The Ethics committee of the institution where the database was developed (Ospedale Policlinico, Milan, Italy) granted permission to use the data for research and publication. Because the patients were unconscious when admitted, relatives or next of kin were informed that clinical data were being rendered anonymous and stored for research. The inclusion criteria for this study were:

- TBI with or without extracranial injuries, requiring ICU admission
- Glasgow Coma Scale (GCS) motor component less than 6
- ICU admission within 24 h of the trauma
- age $\geq$ 14 years
- ICP monitoring
- ICP data recorded for at least one full day.

The arithmetic mean of the ICP data recorded during every 24-h period, after filtering to exclude inaccurate readings (i.e., during CSF withdrawal), was calculated and expressed as "mean ICP". This value was used for analysis. When multiple days of monitoring were recorded for a single patient, the highest mean ICP was indicated. For instance, if the mean ICP values for 4 days were 19, 21, 23 and 18 mmHg, the highest mean ICP was 23 mmHg. Three ICP blocks were considered for further analysis: less than 20 mmHg, 20–30 mmHg and more than 30 mmHg. ICP measurements were discontinued when ICP stayed below 20 mmHg for 24 h without active treatment.

The protocols for respiratory and hemodynamic stabilization, CT scan controls, sedation, nutrition, ICP monitoring and treatment were very similar among the three centers contributing to the data base. Therapy to control HICP was applied as published elsewhere [9] and graded as follows:

- Standard (sedation, mannitol, CSF withdrawal, $PaCO_2$ 30–35 mmHg)
- Reinforced ($PaCO_2$ 25–29 mmHg, induced arterial hypertension, muscle relaxants)
- Second tier ($PaCO_2 < 25$ mmHg, barbiturates, surgical decompression).

Barbiturates were used with the end-point of ICP control, rather than burst suppression, even if burst suppression was documented in most cases. Because various levels of therapy could have been used in a single patient (for instance standard therapy on day 2 and reinforced on day 3), for each patient the highest level used was noted. In order to verify the consistency of this attribution, we added another score because of the theoretical risk of assigning a patient who had been hyperventilated for only 1 day to second-tier therapy, while a patient who had received mannitol and moderate hyperventilation for 7 days could be scored as standard. We called this score DDT (day-by-day therapy). For each patient, the level of therapy on every single day was counted using a simple arbitrary scale (no therapy = 0, standard = 1, reinforced = 2, hyperventilation = 3, barbiturate = 4, decompressive craniectomy = 5) and the count per day was summarized. For instance, a patient who received standard therapy for 2 days, reinforced therapy for 2 days and finally needed surgical decompression had a total score of 11 (standard for two days = 1 + 1; reinforced for two days = 2 + 2; decompression = 5).

As follow-up, the nonextended Glasgow Outcome Score [10] was assessed by a structured interview, either personally or by phone [11], 6 months after the injury.

Statistical analysis

The statistical methods used were predominantly descriptive. Mean and standard deviation were calculated for continuous data with normal distribution; median and range were reported when the distribution was not normal or in the case of categorical data. We evaluated the incidence of intracranial hypertension and the use of different levels of therapy using ANOVA or chi-square test when appropriate, taking $p < 0.05$ as significant. The data were analyzed using the statistical software Data Desk v.6 (Data Description, Ithaca NY).

Results

Out of 1086 patients with TBI admitted to three neuro-ICUs in the Milan area from January 1999 to December 2002, 407 patients (respectively 163, 151 and 93 from the three centers) fulfilled the inclusion criteria. There were 316 males (78%). Mean age was 41 years (range 14–91, median 35). After stabilization, the median GCS score was 7 (range 3–15); the median motor component of the GCS was 5 (range 1–6). All had a GCS motor component less than 6 before ICP placement.

Anisocoria was present in 101 patients (25%) and bilateral mydriasis in 36 (9%).

Epidural hematoma was diagnosed on admission in 71 cases and subdural in 105; all of these patients underwent early surgical removal. Basal cisterns were compressed or absent in 216 patients (56%). Subarachnoid hemorrhage was detectable in 228 (57%).

In the data base only two IJ venous saturation data are recorded daily: the saturation value, measured at 8 a.m., and the occurrence of desaturations. This was measured in 288 cases, with a total of 909 determinations; 28 had jugular vein desaturation ($SjvO_2 < 50\%$).

The distribution of these parameters was not different among centers.

Six-month outcome was recorded in 367 cases: 127 patients made a good recovery, 68 suffered moderate disability, 60 severe disability, 16 remained in a vegetative state and 96 died. The outcome was therefore favorable (good recovery or moderate disability) for 195 patients (53%) and unfavorable (all the other categories) for 172 (47%).

Severity of HICP and outcome

One hundred twenty-eight patients had ICP monitored up to 3 days, 195 up to 6 days, while 84 were still being monitored at the end of the study week. Altogether, 153 patients had at least 1 day of ICP > 20 mmHg. The distribution of ICP during the first week after trauma is summarized in Table 1. A total of 129 patients had a highest mean ICP between 20 and 30 mmHg, and 54 exceeded 30 mmHg. The proportion of cases achieving favorable outcome was higher in patients with ICP < 20 mmHg than in patients with HICP ($p < 0.0001$) as shown in Figure 1.

Table 1 Mean ICP recorded per day during the first week after trauma, as a percentage of the total number of cases monitored every day

Day	Mean ICP						Patients with ICP monitoring
	< 20 mmHg		20–30 mmHg		> 30 mmHg		
	n patients	%	*n* patients	%	*n* patients	%	
1	151	74	30	15	24	12	205
2	302	80	52	14	24	6	377
3	280	79	61	17	15	4	356
4	236	77	60	20	10	3	306
5	186	72	65	25	9	3	260
6	144	67	61	29	9	4	214
7	120	67	55	31	4	2	179

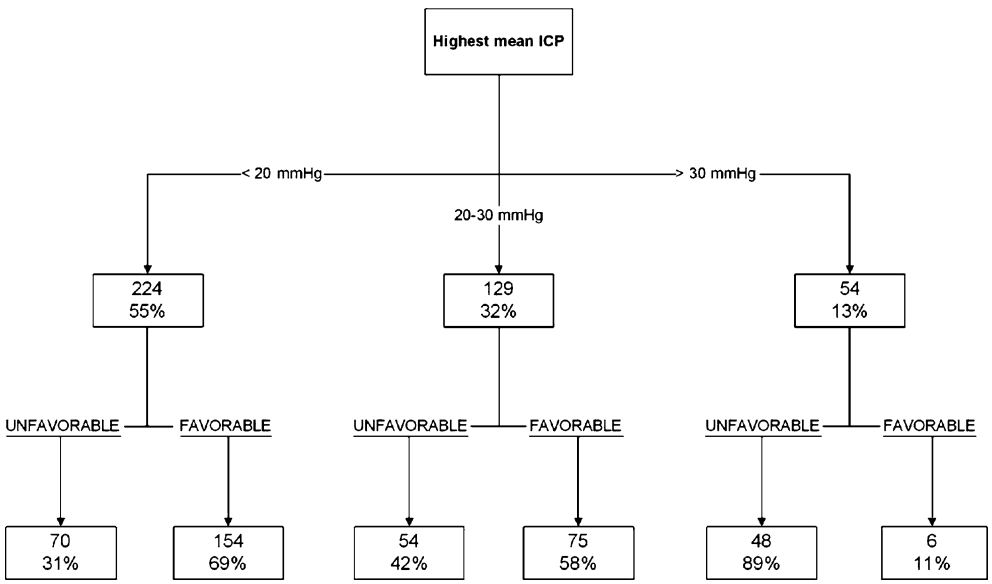

Fig. 1 Six-month outcome according to highest mean ICP

Treatment of HICP

Figure 2 shows the flow chart of the combined surgical and medical treatments. Some patients received both hyperventilation and barbiturates or surgical decompression; therefore, the total number of cases with second-tier therapy is less than the sum of the single treatments.

In all, 221 patients had emergency removal of intracranial masses, and 22 of them were left without the bone flap at the end of surgery, usually with a small-diameter decompression. Four of them subsequently suffered very severe HICP.

The average DDT was 8.3 (median 8, standard deviation 5.1, range 1–22). Patients who were classified as having had second-tier therapy had a median DDT of 14.5 (range 3–22) while patients with reinforced therapy had a score of 9 (range 2–14), and patients with standard treatment, 5 (range 1–7). Both the DDT score and the same score corrected for the days of ICP monitoring were significantly different among the three categories of therapy ($p < 0.0001$).

A very small proportion of cases were judged unsalvageable. These were 24 patients, mostly old, who after reinforced treatment developed nonreactive bilateral pupil dilation, and no motor response or extension to pain. No second-tier therapy was attempted in these patients.

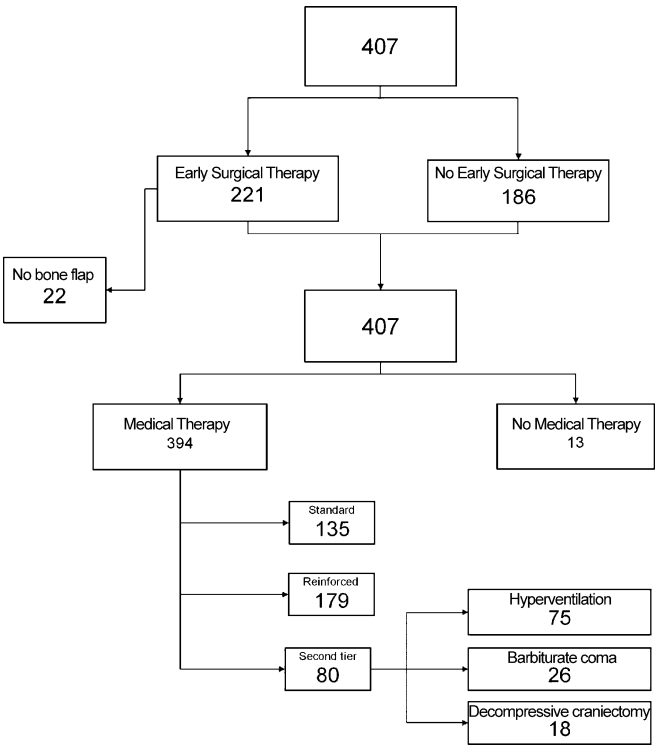

Fig. 2 Flow chart describing the combination of surgical and medical treatment. Among the surgical cases, 22 were left without the bone flap at the end of surgery. Only 13 patients did not require any medical treatment of ICP because values below 20 mmHg were recorded during monitoring

Second-tier therapies

The 80 patients who received second-tier therapies had a highest mean ICP of 34 (median 26) mmHg. Profound hyperventilation, with $PaCO_2$ lower than 25 mmHg, was used in 75 cases. Among these 80 patients, jugular vein saturation was intermittently measured in 76 cases, with an average of three samples per patient. $SjvO_2$ was lower than 50% on one occasion in five patients; three of them were hyperventilated.

Barbiturates (thiopental) were used in 26 patients. The loading dose averaged 15 mg/kg followed by infusion of 100 mg/kg/day. The average duration of infusion was 4 days (range 2–12 days).

Surgical decompression was performed in 18 patients, using a large temporal bone removal with opening of the dura, or a bi-frontal approach; 14 were operated upon after barbiturates failed to control HICP. In these cases the policy was to test barbiturates, carefully watching ICP: if satisfactory control was not achieved in 1–2 h, surgical decompression was performed. In four cases surgeons and intensivists opted for immediate decompression.

Pupils were dilated, on admission, in 31 cases: there were 27 monolateral and 4 bilateral dilations.

Six-month outcome in patients who required second-tier therapies (assessed in 78 patients) was: good recovery in 14 patients, moderate disability in 19, severe disability in 12, and vegetative state in 3; the remaining 30 patients had died. This outcome was significantly worse than in those not submitted to second-tier therapies ($p = 0.03$).

Discussion

Main findings

HICP during the first week after trauma is frequent and is associated with worse outcome. The combination of early surgery, careful monitoring, and medical therapy was effective in controlling HICP in most of the present cases, leaving 54 out of 407 (13%) with a highest mean ICP above 30 mmHg. To achieve this, different degrees of therapy were used, with 80 patients receiving deep hyperventilation, barbiturates or surgical decompression. Specifically, barbiturates were used in 26 cases and surgical decompression in 18. Since 16 patients received both, a total of 28 (7%) received barbiturates or surgical decompression. Six months after injury, results were favorable in 195 cases (53% of all assessed).

We posit, then, that barbiturates or surgical decompression are necessary only for a small proportion of patients. Despite the recent renewed enthusiasm for decompression

in the literature, further evidence is needed and decompression could possibly be restricted to a minority of cases of TBI.

To substantiate this, however, we must demonstrate that we have successfully treated a TBI population severe enough to be comparable with other published series. Using the status of the basal cisterns at CT scan, GCS score and pupil dilation as accepted indicators of severity, our patients were at least as severely affected as in other recent series, as shown in Table 2. Moreover, the incidence of HICP in our series was comparable with other published data [12, 13]. Our rate of favorable outcome at 6 months was similar to, or slightly better than, those in other series (53%, compared with 45%, 54%, and 53% in the series reported in Table 2). However, the mean age of our patients was 41 years, approximately 7–10 years more than in the series shown in Table 2. Because age is an independent predictor of outcome [14], older patients should do worse than younger cases with the same degree of severity. We therefore conclude that the therapeutic strategy followed led to results comparable with those in international studies.

Hyperventilation

We applied hyperventilation in 75 patients, and for 52 this was the only "second-tier" treatment. Profound, prophylactic and prolonged hyperventilation was believed to be deleterious for a subgroup of TBI with GCS score 4–5 [15], but the data are scant [16, 17]. Hyperventilation constricts the cerebral vessels, with a potential risk of ischemia. In our cases jugular vein saturation, indicative of inadequate oxygen transport to the cerebral tissue, was low in 4% of patients (3/75) receiving deep hyperventilation. Because we used intermittent sampling, and jugular vein saturation can miss focal areas of cerebral ischemia [18], we cannot exclude an undesirable reduction of cerebral blood flow due to hyperventilation, undetected by our surveillance. However, since metabolism was profoundly depressed in our cases because of the injury and concomitant sedation, an imbalance between flow and metabolic need is not very likely.

Barbiturates, surgical decompression and complications

Barbiturates have been used against HICP for the past 20 years and are effective in reducing it [19], but their effect on outcome is unproven [20], mainly because of severe medical complications. Hypotension, respiratory complications, immune depression, infections, hepatic and renal dysfunction are associated with high-dose barbiturates [21].

Surgical decompression is a very old strategy for reducing HICP and is effective both for pressure control [4, 22, 23] and for improving cerebral oxygenation [24]. Its effects on outcome are still controversial. A recent reappraisal of the literature on the effects of secondary decompressive craniectomy on outcome and quality of life in patients with severe TBI, however, found only one study, in pediatric patients, suitable for analysis [25]. To complicate matters further, the term "surgical decompression" is used to describe both bony decompression for diffuse brain swelling and combined decompressive craniotomy with removal of mass lesions. In a recent survey on surgical management of TBI, decompressive craniectomy, usually of a diameter inadequate to control ICP, was done in 134 cases during 404 emergency procedures and formed a part of 47 of 154 delayed procedures for mass removal. Surgical decompression was performed in the absence of a mass lesion in only 9 patients [26]. It appears that in the 67 centers participating in that study, surgical decompression as second-tier therapy for HICP was used very rarely. In a recent report [27] surgical decompression was performed in 104 of a total of

Table 2 The findings in our series (*N-Link*), a series from the Baylor College of Medicine [12] and the results of a pharmacological trial with tirilazad mesylate [13]

	Patients	Age, years (mean)	GCSm		Pupillary response	CT scan	Outcome
N-Link	407	≥ 14 (41)	1–3	138 (34%)	Anisocoria 101 (25%)	Basal cisterns	Favorable
			4–5	230 (57%)		compressed 216 (53%)	195 (53%)
			6	37 (9%)	Bilateral mydriasis 36 (9%)		
Baylor	189	22–43 (31)	1–3	59 (31%)	Abnormal pupillary	Basal cisterns	Favorable
			4–5	113 (59%)	reactivity 103 (56%)	compressed 81 (43%)	68 (45%)
			6	14 (8%)			
Tirilazad	1149	15–65 (32.8)	1–3	352 (39%)	Only one reactive	Basal cisterns	Favorable
USA			4–5	488 (53%)	111 (12%)	compressed 495 (44%)	769 (54%)
			6	73 (8%)	Bilateral mydriasis 186 (20%)		
Tirilazad	1028	15–65 (33.7)	1–3	346 (37%)	Only one reactive	Basal cisterns	Favorable
Europe			4–5	515 (56%)	156 (16%)	compressed 485 (48%)	727 (53%)
			6	67 (7%)	Bilateral mydriasis 113 (12%)		

In the third column the motor component of GCS (*GCSm*) is divided in three groups in order to facilitate comparison

967 cases. In 45 patients surgical decompression followed the removal of surgical masses, and only 59 (6%) had decompression as treatment of intracranial hypertension.

Some authors, however, advocate wider use of surgical decompression [4, 22, 28, 29].

Considering the severity of systemic complications related to barbiturates, it might also be argued that surgical decompression could be safer than barbiturates, but unfortunately both approaches have complications. After surgical decompression the swollen brain can herniate through the decompression breach, with tissue deformation, vein compression, and further engorgement and edema. Increased brain swelling and hemorrhagic contusions are reported in a minority of cases [27]. Wound infections may occur after reimplantation of the bone flap. Delayed subdural hygromas at the site of decompression may require drainage and/or ventricular or lumbar shunting [27]. There are also reports of the "syndrome of the trephined": complaints of severe headache, dizziness, fatigue, poor memory, depression, and intolerance of vibration in patients with a craniectomy defect [30]. The benefits and side effects of either barbiturates or surgical decompression require further investigation.

Limitations

Our study has several limitations. Our data depend on somewhat arbitrary clinical decisions: who was monitored with ICP, how long ICP was monitored, who was treated (including second-tier therapies) and who was judged unsalvageable. In order to minimize the influence of local policies or personal judgment we pooled data from three centers, but our sample may represent specific situations rather than a "general" picture.

We have included 25 patients (6%) in the range 14–18 years, who in some other countries would have been considered pediatric. There is no strong evidence, however, indicating different thresholds, therapies and mechanisms for ICP in this age range.

Our analysis was restricted to the first week after injury. Late increase of ICP, sometimes after 7–10 days, has been described for a minority of TBI [31], and this would not be captured by our data. However, this late ICP rise in all reports started between day 3 and day 6, well inside the time-frame covered here.

Surgical decompression was done to control HICP in 18 patients, but 22 operated upon for early removal of subdural hematomas did not have the bone replaced after surgery. The dura was not left open, nor was dural repair performed; moreover, usually the bone "opening" was small. It is debatable whether these patients should be considered "decompressed".

Conclusions

Notwithstanding these limitations, the main findings of our study are well supported by data: HICP is frequent, is associated with worse outcome, but is controlled by surgery and first-tier therapies in most cases. In 80 cases with HICP refractory to conventional treatments, a combination of hyperventilation, surgical decompression and barbiturates has been the last resort. There is no clear proof which strategy out of the three, in particular between barbiturates and surgical decompression, offers most benefit and least harm [32]. Trials currently in progress [33, 34] are therefore expected to provide extremely important information. Second-tier therapies should in the meantime be restricted, however, to selected TBI patients.

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