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Abstract *Purposes:* The aims of this study are to describe a cohort of head-injured pediatric patients, focusing on current practice for intracranial pressure (ICP) monitoring and treatment and to verify the relationship between clinical and radiological parameters and the six-month outcome in a multivariable statistical model. *Methods:* A retrospective review was done of a prospectively collected database considering patients younger than 19 years admitted to three neurointensive care units (ICU). Patients were divided into four age groups: 0–5 (infant), 6–12 (children), 13–16 (pre-adolescent) and 17–18 years (adolescent). The ICP and cerebral perfusion pressure (CPP) were analyzed calculating average data and values exceeding thresholds for more than 5 min. Outcome was assessed 6 months after trauma using the Glasgow Outcome Score. *Results:* There were 199 patients, 155 male, included. Sixty percent had extracranial injuries. Pupils were abnormal in 38 %. Emergency evacuation of intracranial hematomas was necessary in 81 cases. The ICP was monitored in 117 patients; in 87 cases ICP was higher than 20 mmHg, with no differences among age groups. All but six patients received therapy to prevent raised ICP; barbiturates, deep hyperventilation or surgical decompression were used in 31 cases. At 6 months, mortality was 21 % and favorable outcome was achieved by 72 %. Significant predictors of outcome in the multivariable model were the Glasgow Coma Scale (GCS) motor score, pupils and ICP. *Conclusions:* Pediatric head injury is associated with a high incidence of intracranial hypertension. Early surgical treatment and intensive care may achieve favorable outcome in the majority of cases.

Keywords Neurotrauma · Pediatrics · Intracranial pressure · Cerebral perfusion pressure · Outcome

Introduction

Traumatic brain injury (TBI) is among the main causes of death in children, and may have life-long consequences in survivors [1]. Published evidence on pediatric TBI (pTBI) is scarce, reflecting the shortage of evidence for TBI in general, with the aggravating factor that most of the pharmacological TBI trials, instrumental in acquiring detailed clinical information in many centers worldwide, have focused solely on adults. All the eight trials on neuroprotective drugs analyzed in the IMPACT data-base excluded patients younger

than 14 years, and four were limited to cases older than 16 [2].

There are several areas of uncertainty in pTBI, particularly regarding intracranial pressure (ICP) monitoring and treatment, and the recommended cerebral perfusion pressures (CPP) at different ages [3].

The aims of this study are:

- To describe a cohort of head-injured pediatric patients admitted to three neuro-intensive care units;
- To analyze current practice for ICP monitoring and treatment;
- To verify the relationship between clinical and radiological parameters and 6-month outcome in a multivariable statistical model.

Materials and methods

This is a retrospective review of a prospectively collected database, Neurolink, whose main characteristics have been published elsewhere [4]. The Ethical Committee of the institution where the database was developed granted permission to use the data for research and publication. Since the paediatric patients were unconscious when admitted and nearly all minors, relatives were informed that clinical data were being rendered anonymous and stored for research. We focused on patients younger than 19 years, admitted at Ospedale Maggiore Policlinico, Ospedale San Raffaele and Monza San Gerardo between 1997 and 2007. All TBI patients, with or without extracranial injuries, requiring Intensive Care Unit (ICU) admission within 24 h from trauma were included in the database. Patients whose severity was probably over-estimated on admission due to sedation were identified by four criteria, previously published [5]: (1) no surgical intracranial masses; (2) could not follow commands at neurological assessment; (3) were dismissed from the ICU in $\leq$3 days to a regular ward; and (4) had regained the ability to obey commands. Those cases, considered mistakenly severe, were excluded from further analysis.

Patients were divided into four groups: 0–5 (infant), 6–12 (children), 13–16 (pre-adolescent) and 17–18 years (adolescent). Each patient's oxygenation and hemodynamic status before arrival at the neurotrauma center was recorded using the following definitions:

- Definite hypoxia: arterial saturation <90 % and/or blood gas analysis with $PaO_2 < 60$ mmHg.
- Suspected hypoxia: saturation or blood gas analysis not available but the patient appeared cyanotic, and/or with airways obstruction.
- Definite hypotension: systolic pressure <95 mmHg.
- Suspected hypotension: blood pressure not measured but the patient had a weak or undetectable arterial pulse.

After admission to the neurotrauma center, when hemodynamic and respiratory stability had been attained, a neurological examination was performed and the following data were recorded:

- Glasgow coma score (GCS), divided into its three components;
- Status of pupils, coded as bilateral reactive (normal), anisocoria or bilateral dilatation (pathological).

Out of each patient's CT scans, the one indicating the worst brain damage was entered in the database. The CT characteristics recorded were:

- Presence of mass lesion, defined as a lesion with a volume >25 ml or a lesion that has been surgically evacuated;
- The status of basal cisterns;
- The amount of midline shift;
- The presence of traumatic subarachnoid hemorrhage (tSAH).

To identify the most severe cases, defined as "severe pTBI", we selected those with:

- GCS motor component (mGCS) <6 and,
- GCS eye component 1, both assessed after stabilization,
- CT scan not classified as negative.

ICP and CPP monitoring and therapy

The ICP and CPP monitoring started as soon as the patient was stabilized and/or after neurosurgery, and continued until ICP was below 20 mmHg without therapy to lower intracranial hypertension (HICP) for at least one day. The ICP was recorded during the first week in the ICU, after filtering to exclude any inaccurate readings (e.g., during cerebrospinal fluid (CSF) sampling), collecting daily the highest value lasting at least 5 min and the 24 h average. For CPP the lowest value lasting at least 5 min and the 24 h average were recorded. When a patient required several days of monitoring, we calculated the highest 24 h average ICP during the recording period and the lowest 24 h average CPP [6].

Patients were managed according to published protocols [7]. Lower CPP values (50 mmHg) were considered acceptable for babies up to 2 years old. Therapy to control HICP was 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).

Coupled with ICP, jugular venous saturation (SjO_2) was measured, recording episodes of desaturation [8]; data on this item are reported in ESM1.

Outcome

Six months after the trauma the Glasgow Outcome Score (GOS) was assessed by a structured interview, either personally or by phone [9].

Statistical analysis

Mean and standard deviation were used for statistical analysis of continuous data with normal distribution. Median and range were reported when the distribution was not normal or for categorical data. Differences in the study population were assessed with the Chi-square test, taking $p < 0.05$ as significant.

The ICP data were not normally distributed, with a marked positive skew, so non-parametric tests were used to analyze differences in ICP between various parameters (age, level of therapy, etc.).

Each categorical variable was initially fitted in a univariate model to establish the relation with outcome. As a dependent variable, outcome was split into favorable (good recovery and moderate disability) and all other categories. Then a logistic regression model was built, including all the variables that were significant in the univariate analysis, and keeping only the predictors that gave a p level <0.1. The odds ratios (OR) were calculated so that a value greater than one indicated a higher risk of a poor outcome than the reference category. We calculated the ratio of the difference to the reduced negative log-likelihood values (indicated as R-square). Finally, a lack-of-fit test was run to assess whether there was enough information using the variables entered in the model.

The data were analyzed using the Data Desk v.6 statistical software (Data Description, Ithaca, NY, USA), GraphPad Prism software (San Diego, CA) and R v 2.15.0 (The R Foundation for Statistical Computing).

Results

Between 1997 and 2007, 235 patients younger than 19 years who suffered a TBI were admitted to the three neurosurgical ICUs. Thirty-six were classified as mistakenly severe, leaving 199 cases suitable for subsequent analysis. Just over half (114, 57 %) were transported directly from the accident scene to the emergency department and 85 (43 %) were secondarily transferred from other hospitals without a neurosurgical department.

All clinical and radiological characteristics are summarized in Table 1.

The proportion of mass lesions was different in the various age groups (Chi-square $p = 0.026$), but there was no significant difference in the other radiological variables.

The presence of midline shift >5 mm, traumatic subarachnoid hemorrhage and basal cisterns compressed or absent were associated with a worst clinical presentation, with a lower median mCGS (Table 2).

Out of the 199 patients, 129 were classified as severe pTBI, whom clinical characteristics are summarized in Table 1. Sex, age, occurrence of hypoxia or hypotension and extracranial injuries did not differ in severe TBI patient in comparison with the entire population, while there were a significantly higher incidence of pathological pupils in severe TBI patient ($p = 0.006$).

Eighty-one (40 %) patients underwent early evacuation of intracranial hematomas.

ICP and CPP monitoring

The ICP was monitored in 117 patients (59 %) for at least one day in the ICU; it was monitored in 90 (70 %) of the severe pTBI patients (Table 1). Patients with ICP monitoring were 1 year older than patients without ICP monitoring ($p = 0.017$). Pathological pupils were more frequent in patients with ICP monitoring, although the statistic is at the limit of significance ($p = 0.06$). On the contrary, the distribution of GCS motor score was different between the two groups of patients ($p < 0.001$), with lower scores for ICP cases.

The ICP was monitored less frequently in younger children also after restricting the analysis to the severe TBI patients (Chi-square $p = 0.03$).

Adequate data points for ICP and CPP analysis were available for 104 patients. In 87 cases (84 %) ICP exceeded 20 mmHg for more than 5 min; a similar proportion of raised ICP has occurred among patients with severe TBI (70 of 81 patients, 86 %). The highest 24 h average ICP was calculated and the median was 15 (2–39) mmHg in children up to 6 years old, 16 (7–74) from 6 to 12 years, 21 (5–90) mmHg from 13 to 16 years and 20.5 (4–119) mmHg in the 17–18 years group. The distribution was not significantly different among age groups.

The highest 24 h average ICP was significantly worse in patients with tSAH (Mann–Whitney test $p = 0.006$), basal cisterns compressed or absent (Mann–Whitney test $p < 0.0001$) (Table 2) and severe pTBI (Mann–Whitney U test $p = 0.0006$).

Table 1 Clinical and radiological characteristics are shown for the entire population in different age groups

	All patients	0–5 years	6–12 years	13–26 years	17–18 years	Severe TBI	ICP	No ICP
Males	78	67	82	77	80	74	79	77
Age	16 (0–18)	1 (0–5)	8 (6–12)	15 (13–16)	18 (17–18)	16(0–18)	16(0–18)	15(0–18)
Hypoxia	25	30	18	15	32	30	25	24
Hypotension	20	26	21	10	23	24	21	17
Pathological pupils	38	26	35	24	51	54	44	29
Extracranial injuries	60	52	64	55	67	64	58	63
mGCS 1	16	16	7	12	21	24	15	17
mGCS 2	8	8	11	2	10	11	11	3
mGCS 3	11	4	14	9	14	15	16	5
mGCS 4	18	24	14	23	14	22	22	12
mGCS 5	27	28	25	38	21	28	28	25
mGCS 6	20	20	29	16	21	0	8	38
Mass lesion	42	63	54	38	34	43	49	32
Shift >5 mm	30	48	25	26	28	35	35	22
tSAH	44	30	50	40	49	52	51	34
Cisterns C/A	46	52	39	38	51	60	55	33
Severe TBI	66	76	54	66	67	100	79	48
ICP monitoring	59	33	57	64	64	70	100	0
Total	**199**	**27**	**28**	**58**	**86**	**129**	**117**	**82**

Additionally, data are reported for three sub-sets of patients: severe TBI, and patients with or without ICP monitoring

Percent data are reported for all categories while age is expressed as median and range in years

Hypoxia definite or suspected hypoxia, *Hypotension* definite or suspected hypotension, *mGCS* motor score of Glasgow Coma Scale, *Mass lesion* evacuated mass lesion or not evacuated mass lesion >25 ml, *tSAH* traumatic subarachnoid hemorrhage, *Cisterns C/A* basal cisterns compressed or absent

Table 2 Motor CGS and ICP values in relationship with different CT findings

	mGCS			Highest 24 h average ICP		
	Median	Range	*n*	Median	Range	*n*
Mass lesion						
Yes	5	1–6	81	20	2–119	50
No	4	1–6	114	18.5	7–89	54
Shift >5 mm						
Yes	4	1–6	58	21	2–119	34
No	5	1–6	136	18	4–89	69
tSAH						
Yes	3–4	1–6	86	21	7–119	53
No	5	1–6	107	17	2–55	50
Cisterns C/A						
Yes	3	1–6	90	23	2–119	55
No	5	1–6	104	15	4–89	48

mGCS motor score of Glasgow Coma Scale, *Mass lesion* evacuated mass lesion or not evacuated mass lesion >25 ml, *tSAH* traumatic subarachnoid hemorrhage, *Cisterns C/A* basal cisterns compressed or absent

A total of 84, 66 and 38 children suffered episodes of CPP (lasting more than 5 min) lower than 60, 50 and 40 mmHg, respectively. The median of the lowest 24 h average CPP was 51 (29–98) mmHg up to 5 years old, 57 (0–70) mmHg from 6 to12, 64 (12–100) mmHg from 13 to16 and 60 (0–88) mmHg in patients 17–18 years old. The CPP did not differ significantly among the various age groups. Twenty-four h average ICP and CPP didn't show any evident trend over time during the first week (ESM 2).

ICP therapy

Accurate data concerning ICP therapy were available for 114 patients with ICP monitoring and are summarized in Fig. 1. As shown in Fig. 2, stronger therapies were used in cases with higher ICP. The intensity of therapy did not differ between age groups and was applied uniformly in the three centers (data not shown).

Length of stay (LOS) and outcome

The median LOS for patients discharged from the ICU was 7 (1–44) days; it was longer in severe cases (11 days, 1–44) and in patients with ICP monitoring (12 days, 2–44).

Outcome at 6 months were available for 196 cases: 41 (21 %) patients died, 39 in the ICU. Deaths were concentrated in the early days: 25 in the first two days and nine in the next two days. Only one patient remained in a vegetative state, 12 (6 %) suffered severe disability, 19 (9 %) moderate disability, and 123 (63 %) had a good recovery. Limiting the analysis to severe pTBI (125 cases available at follow-up), there were 40 (32 %) deaths, one vegetative state, ten (8 %) severe disabilities, 12 (10 %) moderate disabilities, 62 (50 %) good recovery.

Table 3 summarizes the univariate analysis.

In the multivariable logistic regression model, the only significant predictors of outcome were the admission mGCS score, pupils and highest 24 h average ICP

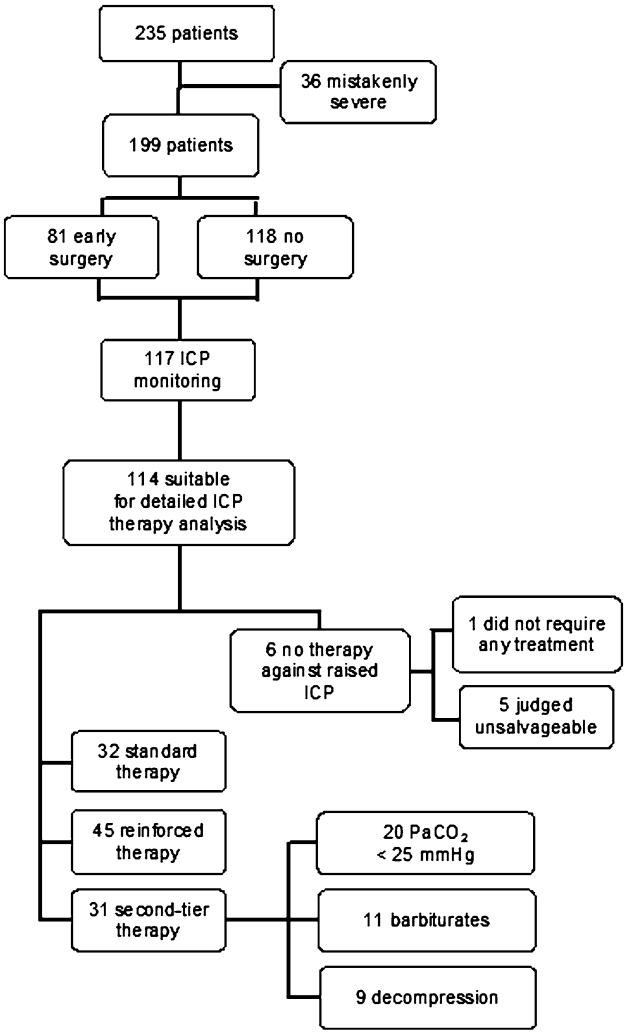

Fig. 1 Study population; ICP monitoring and therapies for intracranial hypertension

(Table 4). In our data collection the pressure target has not been changed according to age, with the potential bias of overdiagnosis in younger patients. To exclude this dilution effect of hypotension in the logistic regression model we tested two multivariable models: first, excluding cases coded as hypotensive in the class 0–5 years; then excluding all babies. In both models hypotension wasn't an independent predictor of unfavorable outcome.

No center effect could be detected in both univariate and multivariable analysis.

Discussion

In 11 years, 235 patients younger than 19 years were admitted to three neuro-ICUs in a metropolitan area. These numbers are low, with an average of one severe case admitted to each ICU every two months and approximately two emergency surgical operations per year per center. While it is encouraging that the number of TBI is low, the fragmentation of cases between several centers reduces each one's case-load, which has been clearly linked to better results for several conditions, including common medical conditions [10], SAH [11, 12], and multiple trauma [13]. Our findings underline the need to improve centralization for TBI children, an effort other countries are making as well [14].

Of these, 199 patients had serious TBI while 36, classified as severe on arrival, recovered quickly (mistakenly severe). The proportion of mistakenly severe cases in this series is higher than reported in previous findings [5], probably indicating wider use of anesthetics and myorelaxants in this pediatric population.

Mass lesions were more common in younger children. This might reflect different mechanisms of injury. Since the mechanisms of injury were not recorded in the

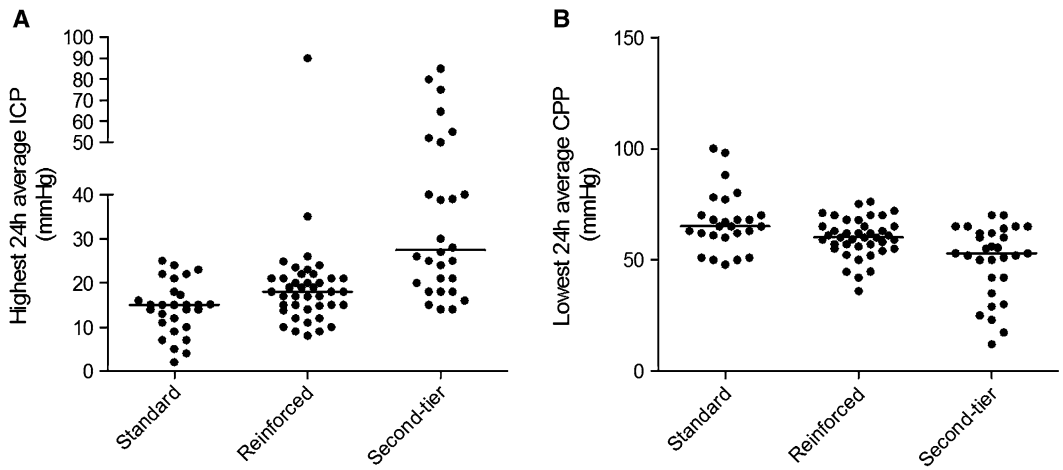

Fig. 2 ICP therapy levels. Treatment was more intense for cases with higher ICP (Kruskal–Wallis test $p < 0.0001$, *panel A*) and lower CPP (Kruskal–Wallis test $p = 0.0003$, *panel B*)

Table 3 Univariate logistic models for unfavorable outcome

	p value	Unfavorable outcome (%)	Odds ratio	95 % CI
Age	0.076		1.06	0.99–1.13
Hypoxia	<0.001	59	7.02	3.44–14.33
Hypotension	<0.001	62	6.72	3.15–14.34
mGCS	<0.001		0.32	0.24–0.44
Pathological pupils	<0.001	43	23.66	9.58–58.43
Mass lesion	0.16	22	0.62	0.32–1.21
Cisterns C/A	<0.001	45	11.02	4.95–24.52
Shift >5 mm	0.14	34	1.65	0.85–3.22
tSAH	<0.001	49	7.11	3.46–14.61
Extracranial injuries	<0.01	35	2.66	1.31–5.39
ICP	<0.001		1.10	1.05–1.16

Odds ratios >1 are associated with an increased probability of unfavorable outcome. Odds ratios for Age, mGCS and ICP are for difference of 1 unit (1 year, 1 point of mGCS and 1 mmHg respectively)
Hypoxia definite or suspected hypoxia, *Hypotension* definite or suspected hypotension, *mGCS* motor score of Glasgow Coma Scale, *Mass lesion* evacuated mass lesion or not evacuated mass lesion >25 ml, *Cisterns C/A* basal cisterns compressed or absent, *tSAH* traumatic subarachnoid hemorrhage, *ICP* highest 24 h average ICP

Table 4 Logistic regression analysis for the probability of unfavorable outcome at 6 months

	p value	Odds ratio	95 % CI
mGCS	0.01	0.49	0.29–0.84
Pathological pupils	0.02	5.36	1.30–22.15
ICP	<0.001	1.10	1.04–1.18

Odds ratios >1 are associated with an increased probability of unfavorable outcome. Odds ratios for mGCS and ICP are for difference of 1 unit (1 point of mGCS and 1 mmHg respectively). *R* square 0.65, lack-of-fit Chi-square 0.84
mGCS motor score of Glasgow Coma Scale, *ICP* highest 24 h average ICP

database, we can only offer hypotheses: a prevalence of falls from a height for young children, compared with mainly motor vehicle accidents for adolescents.

The ICP was monitored in 70 % of severe cases, with significant differences depending on age: up to 79 % in boys aged 13–16 years, much less (42 %) in children up to five. Since the predictors of raised ICP, such as hypotension or compression of the basal cisterns [15], were no different between the age groups, this data might indicate some reluctance to measure ICP in younger children.

Indications for ICP monitoring in children are based on clinical experience more than published evidence [3, 16]; there is a general consensus that ICP should be monitored in severe cases, with GCS < 9. However, it may also be indicated in less severe cases with intracranial masses, or when serial clinical assessment is precluded because of sedative drugs [16]. As a result, there is substantial variability among centers as regards ICP monitoring, in adults [17, 18] and in children [19, 20].

There is still debate about the normal ICP level and the threshold for pathological values requiring active treatment in a child's first few years [21]. For our analysis we arbitrarily applied a threshold of 20 mmHg to all patients.

The ICP rises exceeding this threshold were detected in 87/104 cases, suggesting that ICP was monitored in a subset of cases correctly identified at high risk for intracranial hypertension. In other series raised ICP was found in half the monitored cases [19].

Univariate analysis indicated that CT scan features (abnormal cisterns and tSAH) and clinical parameters (severe neurological presentation and anisocoria) were associated with HICP, which, however, was not different among the age groups.

Similar considerations hold for CPP. Adequate CPP may be lower in infants than in boys [21] but for the sake of simplicity, in CPP analysis, we accepted a threshold of 60 mmHg. This indicated that a large percentage of monitored patients had low CPP (84/104 patients), without differences among the age groups.

The ICP therapy requires a combination of surgical and medical interventions. Without early removal of intracranial masses any medical treatment is useless. There was a significant relationship between the severity of HICP and the intensity of therapy. In a previous report from our group [7] second-tier therapies were used in 19 % of cases, while in this series there were 27 %. In that series the median age was 35 years, and HICP was less frequent than in this set. A recent survey from the UK found wide differences in ICP therapies [19]: some centers never used barbiturates while others used them for one-third of children.

Decompression for HICP was used sparingly in this series, despite growing interest in that treatment [22–24]. The management of TBI in the three centers hasn't changed during the study period (1997–2007).

LOS in survivors was higher in patients with ICP monitoring. It is not clear if this increased LOS was linked to ICP monitoring "per se", as hypothesized by other authors [25], or to severity. The strong association between clinical severity and ICP monitoring does not allow this separation.

Six-month outcomes confirm the severe consequences of TBI. Mortality was 21 % for all cases considered at follow-up and 32 % for the most severe patients. Half of the cases made a good recovery. These figures are similar to other published series [26, 27]. No center effect could be observed. Univariate analysis found several parameters associated with an unfavorable outcome, but logistic regression analysis identified only the GCS motor component, the pupil status and ICP as predictors. The internal validity of the model, as assessed testing goodness of fit and *R* square, was good.

Limitations

This study suffers several limitations. The main one is the broad definition of pediatric TBI. Pooling 1-year-olds and

18-year-old is clearly questionable, even if widely described in the medical literature [28]. Mechanisms of injury, anatomical and biological features of the maturing brain, vascular responses etc., may all vary extensively in this wide age distribution.

Additionally, the distribution of age in our population is skewed, with a marked disproportion in favor of "older" children. Due to low numbers, differences in TBI characteristic and treatment in infants in the first months or years could not be captured. We have therefore arbitrarily split our cases at 5 years (pre-school), 12 years (typical interval between childhood and early adolescence) and 16 years (young adult patients), in order to analyze a reasonable number of cases, well aware that this subdivision is questionable.

The GCS and GOS, standard tools for adult TBI, may be suboptimal or not applicable in infants [29, 30]. The GOS may not capture cognitive dysfunctions that could substantially interfere with children's learning abilities. The timing of outcome assessment, which we set at 6 months, may also be questionable, and a longer follow-up might give more meaningful data [26].

The normal levels for ICP and CPP, and the thresholds for active treatment, are not well defined in infants. For the sake of simplicity, we applied the values accepted in adults.

Finally, some important data, such as the mechanisms of injury or information regarding the rehabilitation phase, were not recorded in the database.

Conclusions

Despite its limitations, this study describes a large number of pediatric TBI cases treated in the ICU, many with ICP monitoring. It illustrates the importance of combined surgical and medical treatment, since 40 % of cases had emergency evacuation of intracranial hematomas. ICP monitoring disclosed a high incidence of pathological values, and treatment was tailored to the severity. Decompression and barbiturates were used in few cases. The burden of TBI remains heavy, with early deaths and persisting disabilities; however a favorable outcome is achieved in the majority of cases.

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