Ischemic brain damage is extremely common after severe head injury. Eighty to 90% of patients who die of TBI show ischemia on histopathological examination of the brain. The cerebral metabolic rate probably increases transiently and therefore substrate demand may vary over time, being the highest early after trauma, which makes an increase in substrate delivery via CBF necessary. Nonetheless, in approximately one third of patients, CBF is low in the early phase after TBI. Early flow-metabolism mismatch may cause secondary damage to neurons. The optimal method for measuring CBF has yet to be discovered. Both CBF and CPP are variables that represent the best means of monitoring severely head injured patients. In this study, we aimed to report the outcome of three groups of severely head injured patients based on both CPP and CBF (Group A); ICP alone (Group B) and no monitoring of CPP, CBF, or ICP (Group C). This was done to determine if our CPP and CBF protocols would benefit patients in the long term.

**Clinical Material and Methods**

**Study Protocol**

In Malaysia, all individuals 12 years of age and older receive their national identity cards and are legally considered adults. All examinations were performed continuously except for TCD ultrasonography, which was performed hourly. All signals for the multimodality study (Group A), ICP values (Group B), and arterial blood gas parameters were recorded for 4 days and then were gradually tapered off. During the time between these periods...
(4 years), there was no change in the treatment of head injuries at our hospital and these cases were all managed by the same team from the Department of Anesthesiology and Critical Care Medicine as well as the Neurosciences Unit. This was a prospective randomized study conducted during two time periods. Patients were treated on initial arrival according to a standard protocol for severe TBI.26 All patients were treated in the intensive care unit of the Hospital Universiti Sains Malaysia. The study was approved by the local ethics committee.

Description of the Three Study Groups

Patients in Group A underwent treatment between March 2001 and March 2002 with CBF-based monitoring; those in Groups B and C were treated based on ICP monitoring alone and no monitoring, respectively, between July 1, 1996, and June 30, 1997. All severely head-injured patients who met the following criteria were eligible to participate in the study: 1) age of 12 years or older; 2) consent by next of kin to be involved in the study; 3) GCS score of 8 or lower; and 4) CT scan of the brain revealing no significant infratentorial pathology. All CT scans of the brain were interpreted according to the Marshall classification.27 Exclusion criteria included gunshot wound, coma due to alcohol, drug overdose, or epilepsy, and other major organ injuries. Patients who on arrival had unilateral or bilateral fixed and dilated pupils believed to be due to ongoing herniation, were brain dead, had a known history of hemiparesis, or had any other condition that lowered the patient’s functional status score were also excluded. Follow up was conducted at 3, 6, and 12 months. A patient’s condition at follow up was graded according to a DRS and the final score at the end of 1 year was recorded.

Multimodality Monitoring: Group A

Intracranial pressure was monitored until an acceptable upper limit of 20 mm Hg in adults and 14 mm Hg in patients between the ages of 12 and 18 years was attained by using a compliance monitor (Spiegelberg GmbH & Co., Hamburg, Germany) (CI >1 and PVI > 0.5). A CPP of more than 70 mm Hg was maintained using one or more inotropic supports with a central venous pressure between 5 and 10 mg. The Saber 2100 CBF sensor (Flowtronics, Phoenix, AZ) works by the thermal diffusion technique, which measures regional cortical blood flow (ml/100 g/min) in the cortex where the measured area is approximately 1 cm deep in the cerebral hemisphere and 3 cm by implication. The sensor measures an area approximately 8 mm hemispheric due to the size of the gyrus. Its sensor plates are 24-k gold, whereas its wires are solid silver and Teflon-coated. Regional cortical blood flow was maintained by expanding the plasma volume, by using inotropic support, or by implementing other medical methods to maintain a value higher than 50 ml/100 g/min at all times. Brain tissue PO2 (Licox, Kiel-Miekendorf, Germany) was kept at a minimal level of 15 mm Hg, with a fractional inspired O2 level of 1 for a duration of 24 hours.32 SiCO2 (Invos, Somanetics, USA) was used to monitor each frontal lobe and was maintained at a level higher than 75%. A cerebral oximeter (Invos, model 4100; Somanetics Corporation, Troy, MI) was used with a disposable regional cerebral O2 saturation sensor on both frontal lobes in adults and was maintained at levels higher than 75%. Laser Doppler flowmetry was maintained using a commercially available machine (model DRT4; Moors Instrument, Devon, UK). The LDF measurements were maintained at values of greater than 5 AU with pulsatility. Regional cortical blood flow, brain tissue PO2, and LDF were measured in the most damaged brain according to CT scanning results. Microdialysis was performed at the cortical–subcortical junction in the most damaged brain tissue by using a microdialysis analyzer (CMA 600; Solna, Sweden). Jugular venous saturation was maintained from a baseline of 65 to 75% by using an optical catheter in the dominant jugular bulb (Oximetrix3 system; Abbott Laboratories, Chicago, IL). All patients with impaired cerebral vasomotor reactivity underwent a cerebral vasomotor reactivity test during which the flow velocity in the middle cerebral artery was monitored intermittently by using a 2-MHz pulsed TCD ultrasonography probe (model MultiDop 2; DWL Electronics System GmbH, Sipplingen, Germany) inserted at depths of between 4 and 6 cm.15,28,33,42,44,45 All patients were positioned with their heads elevated 30°.

Monitoring of ICP Alone: Group B

Monitoring of ICP alone was performed in patients in Group B by using a ventriculat catheter in the right frontal horn, which was attached to an external transducer for a duration of 4 days. Cerebrospinal fluid was drained if ICP was ≥ 20 mm Hg. In this group, only ICP was monitored plus the basic intensive care parameters of invasive blood pressure, CPP, pulse oximetry, and respiratory rate. Tracking proceeded for at least 4 days if uneventful. Each patient’s condition at a 6-month posttreatment follow up was noted.

Conservative Management: Group C

Group C included those patients whose family refused ICP monitoring but agreed to conservative treatment. These patients underwent hyperventilation to the standard PaCO2 range of 30 to 35 mm Hg via an endotracheal tube for a period of 24 to 48 hours. Repeated CT scans were obtained to decide whether a patient should be weaned from ventilation.

Statistical Analysis

Data analysis was completed using commercially available software (SPSS, version 10; SPSS, Inc., Chicago, IL). Chi-square and Fisher exact tests were also applied for statistical analysis. Significance was set at a probability level of 0.05.

RESULTS

Multimodality Measures: Group A

Seventeen patients underwent multimodality monitoring, the majority (58.8%) of whom were between the ages of 15 and 20 years. Fourteen (82.4%) were male. A total of 52.9% of these patients reached the hospital between 4 and 8 hours postinjury. Computerized tomography studies obtained 6 weeks posttreatment revealed normal findings.
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in eight patients (47.1%). A total of 12 patients (70.6%) had abnormal pupil reactions, whereas the rest had normal pupillary reactions. Diffuse axonal injuries with Marshall grades of 4 and 3 (17.6%) were associated with extracerebral mass lesions, all of which were subdural hematomas. They received craniotomies and ICP monitoring was done in 14 (82.4%). Autoregulation was absent in eight patients (47.1%). Jugular venous O₂ saturation was abnormal in nine (52.9%). Cutaneous infrared spectroscopic measurement of regional CBF (StO₂) was abnormal in 12 patients (70.6%). Brain tissue PO₂ was abnormal in 15 patients (88.2%). Values for ICP, brain tissue PCO₂, CBF, TCD ultrasonography, and microdialysis were abnormal in 13 patients (76.5%). Results of electroencephalography and evoked potential studies were abnormal in 12 patients (70.6%). Laser Doppler flowmetry was abnormal in 10 patients (58.8%). Brain temperature was higher than 36.6°C in 14 patients (83.4%). Brain pH was less than 7.45 in 10 patients (58.8%). All patients were treated aggressively to increase their CPP, CBF, and Brain tissue PO₂, as well as to decrease their ICP. None of these patients died. Eight patients (47.1%) had a DRS score between 7 and 29 points, whereas nine (52.9%) had a DRS score less than 7 points.

The characteristics of patients and their injuries were compared between those who underwent the single modality and those who underwent multimodality treatment. These characteristics included age, sex, time between injury and admission, GCS score, pupillary reaction to light, cranietomy/craniotomy, and CT scanning results. Among these, time between injury and admission (p = 0.001) was statistically significant (Table 1). The relationship between modality type and patient outcome based on Glasgow Outcome Scale scores was also studied. There was a statistically significant difference in outcome among patients in the three different treatment groups (p = 0.003; Table 2).

Groups Subject to Single-Modality Monitoring (Group B) and no Monitoring (Group C)

Sixty-five patients were in both Groups B and C, of whom the majority were male (55 male patients [84.6%] and 10 female [15.4%]; Table 1). The majority of these victims were within the age group of 13 to 39 years with a mean age of 27.4 years.

Most (72.3%) of these cases were seen within 8 hours postinjury, and 76.9% had been referred from within a 50-km radius.

A total of 69.2% of patients were motorcyclists and drivers, with motorcyclists being the dominant group. Forty-four (67.7%) of these patients had an initial GCS score of less than 8 at the time of their accident. Patients who had a GCS score of more than 9 were referred to HUSM when their scores had decreased to less than 8 within a period of 8 hours of trauma. A total of 44.6% of the patients who were referred to our Emergency Department were intubated on arrival.

Most of the referred cases were those in which CT scanning had demonstrated signs of diffuse axonal injury (41.5%) had a diffuse head injury with a Marshall Grade 4, 26.2% had diffuse head injury with Marshall Grade 3, and 32.3% had extracerebral mass lesions). These patients required cerebral protection and hyperventilation.

A total of 32.3% of patients had extradural (10 patients) and subdural hematomas (11 patients) and underwent emergency evacuation of the clots. Statistically, there was no significant difference in the number of patients who underwent ICP monitoring compared with those who did not. As mentioned earlier, Group B included patients who had undergone ICP monitoring and those in Group C were treated without ICP monitoring. All patients in Group B were on solely intraventricular pressure monitoring, allowing for CSF drainage.

The mean duration of hyperventilation was 43.5 hours. During that period, the condition of 10 patients (15.4%) had deteriorated and their pupils had become fixed and dilated. Fourteen patients (21.5%) had a period of hypothermia had demonstrated signs of diffuse axonal injury.

In terms of outcome at 1 year, of 65 patients, 42 (64.6%) had a favorable outcome according to the DRS and 17 (26.2%) died. Only six patients (9.2%) had a poor outcome.

<table>
<thead>
<tr>
<th>Frequency distribution of patient characteristics and injuries</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
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<tr>
<td>---------------</td>
</tr>
<tr>
<td><strong>age (yrs)</strong></td>
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<tr>
<td>12–20</td>
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<tr>
<td>21–30</td>
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<td>&gt;30</td>
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<td><strong>sex</strong></td>
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<tr>
<td><strong>time between injury and admission</strong></td>
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<td>≤4 hours</td>
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<td>&gt;4 hours</td>
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<td><strong>GCS score</strong></td>
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<tr>
<td><strong>pupillary reaction to light</strong></td>
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<td>normal</td>
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<td><strong>CT scan results</strong></td>
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<td>normal</td>
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* The level of significance was set at a probability value of 0.05.

<table>
<thead>
<tr>
<th>Relationship between type of monitoring modality and patient outcome</th>
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<tr>
<td><strong>Monitoring Modality</strong></td>
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<tr>
<td>multimodality</td>
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* The DRS scores were as follows: good outcome, less than 7 points; poor outcome, 7 to 29 points; death, 30 points.
† The level of significance was set at a probability value of 0.05.
Twenty patients were older than 30 years of age and the rest were between 10 and 21 years. We found that there was a dramatic increase in the mortality rate in patients older than 30 years. Mortality rates were 14% in the 10- to 30-year-old age group and 55% in those older than 30 years.

With respect to the distribution of age and catheter insertion, the mean age for those in Group B was 26 years and the mean age for those in Group C was 28.7 years. In Group B, the youngest patient was 3.2 years and the oldest was 66.1 years. In Group C, the youngest patient was 4 years and the oldest patient was 71.2 years. There was no significant difference in the age distribution in both groups.

Of the group of 31 patients who had undergone monitoring (Group B), 27 were male and four were female. In the group of 34 patients who did not receive monitoring (Group C), 28 were male and six were female. There was no significant difference in sex distribution in both groups (p = 0.42, Fisher exact test).

A total of 47 patients (72%) arrived within 4 hours postinjury, whereas 18 patients (28%) arrived between 4 and 12 hours. The mean time delay between injury and evaluation/treatment for patients with and those without ICP monitoring was 7 hours 30 minutes and 5 hours 40 minutes, respectively. This difference was not significant (p = 0.24).

We found a significant difference between Groups B and C with respect to GCS scores (p = 0.03). A greater number of patients with a GCS score of less than 8 did not undergo ICP monitoring (27 of 44 patients), whereas those with a GCS score of more than 9 deteriorated within 8 hours even with ICP monitoring (14 of 21 patients). This was due to the fact that these patients’ families refused ICP monitoring and thus were put in the conservative treatment group.

There was no significant difference between the number of patients with a normal and an abnormal pupillary response to light; that is, patients were distributed equally between Groups B and C. Of the total number of patients, 31 demonstrated significant pupillary changes—fixed and dilated—indicating deterioration. Eight of these patients had not undergone ICP monitoring, but two had.

Various types of head injuries encountered and the number of cases in Groups B and C were classified according to the Marshall system on CT studies. Most patients had diffuse axonal head injury and mass lesion with cerebral edema. Both Groups B and C had an equal distribution of cases. There was not statistically significant difference (p = 0.61) between these two groups.

Also, there was no statistically significant difference in the number of cases treated with surgery for the evacuation of clots in Groups B and C. The mean duration of ventilation for patients in Groups B and C was 43.7 and 42.3 hours, respectively (p > 0.05). Of these 65 patients, 23 patients required a tracheostomy for protection of the airway during the first 2 weeks of post–intensive care for bronchial toileting. Equal numbers of patients were distributed in both groups.

During the course of cerebral protection, 14 patients experienced a period of hypotension, which required inotropic support. Equal numbers of cases were represented in the two groups. Among patients in Group B, the highest ICP recorded during the period of cerebral protection was 34 mm Hg, the lowest was 4 mm Hg, and the mean was 15.7 mm Hg.

All patients in Group B had their ICP monitored for 4 days. There was a strong relationship between patient outcome and the course of ICP during the period of cerebral protection. Patients with an ICP less than 10 mm Hg had a good recovery or were moderately disabled, whereas those with ICP greater than 20 mm Hg had a mortality rate of 55% among those with an ICP greater than 20 mm Hg. Of the nine patients who had ICP levels greater than 20 mm Hg, only four responded to intervention therapy that used CSF drainage.

**DISCUSSION**

Targets for basic intensive care practice in the area of CPP and CBF have been widely debated and the subject of recent discussion. In our group of patients we found a significantly better outcome with the use of multimodality monitoring compared with the use of ICP monitoring alone or conservative management. This was reflected by no deaths in the multimodality group compared with the other two groups, which had an approximately 25% fatality rate (p = 0.003). Other studies on CBF have demonstrated that an inadequate level of CBF is an important cause of secondary ischemic damage.

Correlation studies indicate that cerebral oximetry—whether measured invasively or noninvasively—can be related to CPP, thus improving brain tissue PO2, lactate, and glucose levels. Cerebral blood flow, CPP, and ICP will supplement brain tissue PO2 as demonstrated in our patients. This may help us in the treatment of hypertension in patients with head injuries or those with hyperemia, thus assisting with the lowering of CPP without disastrous changes in CBF and intracellular oxygen, lactate, and O2 values.

Multimodality monitoring has been proven to be helpful in the long term.

The severity and type of impact incurred during head injury will substantially influence the structural lesions that ensue. The acceleration/deceleration forces produced by falls and motor vehicle accidents can produce axonal dysfunction and injury, brain contusions, and axial extraaxial hematomas. Such a macroscopic injury is associated with microscopic and ultramicroscopic changes, including ischemia, astrocyte swelling with microvascular compromise, BBB disruption, and inflammatory cell recruitment.

Intracranial hematomas may not only raise ICP and worsen cerebral hypoxia, but also be responsible for EAA release, inflammation, and microvascular dysfunction. The microvascular dysfunction may in turn limit the ability of the injured brain to cope with minor variations in physiology, with elevation of the lower limit of autoregulation to a CPP level of 60 to 70 mm Hg (compared with that in normal individuals who tend to maintain CBF at CPP values of 50 mm Hg). At later stages, the presence of extravascular blood may predispose to large vessel spasm, with the potential for distal hypoperfusion and ischemia.

Historically, CBF is thought to show a triphasic behavior. Soon after head injury (>12 hours), global CBF is reduced, sometimes to ischemic levels. Between 12 and 24
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hours postinjury, CBF increases and the brain may exhibit supranormal CBF. Although many investigators refer to this phenomenon as hyperemia, the absence of consistent reductions in cerebral oxygen extraction indicates the retention of flow-metabolism coupling and a more appropriate label of hyperperfusion. Cerebral blood flow values begin to decrease again several days following head injury, and in some patients these reductions in CBF may be associated with marked increases in large vessel flow velocity, which can be revealed on TCD ultrasonography and suggest vasospasm.

Increases in CBF and cerebral blood volume from the 2nd day postinjury onward make vascular engorgement an important contributor to intracranial hypertension. The BBB appears to become leaky between the 2nd and 5th days posttrauma, and vasogenic edema then contributes to brain swelling.

Basic physiology supports the benefit of maintaining CBF and oxygenation, and these assumptions are confirmed by data from the Traumatic Coma Data Bank\(^1\) and other sources demonstrating the detrimental effects of hypotension (systolic blood pressure < 90 mm Hg) and hypoxia (PaO\(_2\) levels < 60 mm Hg [8 kPa]) in the early and later phases of head injury on patient outcome. Data from several studies focused on break points for cerebral autoregulation in patients with head injury have demonstrated preserved cerebrovascular autoregulation with the maintenance of CBF at CPP levels greater than 60 to 70 mm Hg.\(^9,10,40\) Furthermore, ischemia is a consistent finding in fatal head injury,\(^3\) and retrospective studies from several groups have revealed that outcome is improved in patients with fewer episodes of CPP or MABP reduction,\(^38\) aggressive CPP management,\(^44\) or retained autoregulation.\(^45\)

The need to maintain cerebral oxygenation and CPP predicates the use of the monitoring required to achieve the therapeutic targets. Commonly used bedside monitoring techniques include TCD ultrasonography for noninvasive estimation of CBF, jugular venous saturation monitoring, and monitoring of electrical activity in the brain. With these techniques, investigators seek to estimate CBF in the presence of an adequate CPP, to estimate the adequacy of oxygen delivery to the brain, and to document the consequences of a possible oxygen deficit or a particular drug therapy on brain function.

Reductions in the flow velocity of the middle cerebral artery provide a useful marker of reduced CPP in the setting of intracranial hypertension, although episodic rises in ICP may also be caused by hyperemia, which may be diagnosed by increases in flow velocity demonstrated on TCD ultrasonography.

Despite the neuropathological evidence of ischemia in patients with fatal head injury, antemortem evidence of ischemia from reductions in CBF were generally modest in the first few days following injury. Furthermore, most patients exhibited arteriojugular venous difference of O\(_2\) within the normal range, implying that the CBF reductions were appropriately coupled to decreases in cerebral metabolic rates for oxygen.\(^37\) Two different approaches have provided explanations for these observations. Ultra-early (< 12 hours) CBF measurements following head injury have provided clear evidence that more than 30% of patients exhibit global CBF reductions lower than commonly accepted ischemic thresholds (< 18 ml/100 g/ min). Later measurements showed elevation of CBF to nonischemic levels by 24 to 48 hours postinjury.\(^29\) These findings have been generally confirmed by other study data; however, even at early time points, arteriojugular venous difference of O\(_2\) remained relatively low despite a markedly low CBF, with few patients demonstrating increases above 9 ml/100 g/min.\(^29,57\)

One explanation for the conflict between these clinical findings and the neuropathological evidence of ischemia may be found in the physiological heterogeneity of the injured brain.\(^22\) Both conventional monitoring methods and newer techniques are limited by the fact that they detect either globally averaged or highly localized abnormalities in cerebral physiology and may be unable to detect regional abnormalities in the metabolically heterogeneous injured brain.

Although individual monitoring techniques provide information regarding specific aspects of cerebral function, the correlation of data from several modalities has several advantages in the management of head injury. Integration of monitored variables allows cross-validation and artifact rejection, better understanding of pathophysiology, and the potential to target therapy.

Most center personnel agree on the need to maintain CPP higher than 60 to 70 mm Hg by either decreasing ICP or increasing MABP. Although MABP is usually maintained with volume expansion, inotropes, and vasopressors, the relative efficiency of each of these interventions in maintaining CPP has not been investigated. Indeed, we have no data on the safety of high doses of vasoactive agents in the presence of BBB disruption. Drainage of CSF (when possible), mannitol administration, induction of hyperventilation, and the use of central nervous system depressants (typically barbiturate agents) have all been used to reduce ICP. The debate in this area has focused on the means of optimizing CPP at a level higher than 70 mm Hg and maintaining CPP values between 50 and 60 ml/100 g/min.\(^9,10,14,15,40\) Rosner, et al.,\(^40\) have been the most enthusiastic proponents of the use of hypertensored and hyper- tension to increase MABP and induce secondary reductions in CPP. Cruz,\(^44\) on the other hand, has proposed the use of "optimized hyperventilation" (guided by jugular venous oxygen saturation monitoring) to reduce intracranial pressure and hence increase CPP. It is likely that several different pathophysiological mechanisms coexist in individual patients, and both approaches are likely to have a role if applied appropriately. It must be remembered that both hyperventilation and induced hypertension have clearly recognized systemic and cerebral side effects, and the extent of their use will be limited by a risk/benefit ratio.\(^11\)

In both Groups A and B, the time between injury and admission was much better in the CPP management group when compared with the ICP management group. Note that the establishment of the Masters of Medicine (Emergency Medicine) course in June 1998 and the national upgrading of the emergency services occurred during the 4 years between these studies. These improvements would have enhanced the pre-hospital management of patients with head injuries, and thus prevent hypotension and hypoxia.
In Table 2, the relationship between modality type and patient outcome is shown. Even though there were no deaths in the patients in the multimodality group, eight patients (47%) had poor outcomes with a DRS score between 7 and 29. Of these eight patients, seven had DRS scores between 7 and 11 (moderate disability) and one had a score of 12 (severe disability). None of them was in a vegetative state.

In practice, our established head injury protocols represent a hybrid approach. Initial baseline monitoring and therapy are applied to all patients, and refractory problems are dealt with by escalating therapy, with the choice of intervention being determined by clinical presentation and physiological monitoring. Rarely, interventions or present significant risks (for example, barbiturate coma) are used as a last resort. In our group of patients, no one required induction of thiopentone coma.

Age and time of admission together with the mode of monitoring has been found to be significant in improving patient outcome after a 12-month follow-up period. Death has been the focus of outcome in this study, in which multimodality monitoring was associated with superior results compared with the others. Aggressive CBF: CPP, brain tissue PO₂, CO₂, pH with laser flowmetry guided with TCD velocity values, and intracellular microdialysis monitoring and active management will improve patient outcome. A prospective study is currently underway to subanalyze the multimodalities and their importance as well as their cost effectiveness in treating children with head injuries.

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References

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Address reprint requests to: Jafri Malin Abdullah, M.D., Ph.D., Neurosciences Unit, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia. email: unitneurosainsppspusm@yahoo.com.