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REVIEW ARTICLE

Advances in Neurocritical Care

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Abstract The neurologically injured child, whether from trauma or other causes, is a common admission into any Pediatric critical care unit. Whatever the cause, the risk for death and life long disability remains very high. Unlike the adult population, neurological diseases in children are diverse and arise from a variety of factors that vary greatly in age and presentation. Nervous system dysfunction is often a complication of critical illness and interventions. While neurointensive care units may be ideal for the at-risk child, in mixed units, 40 % of admissions may be neurological or have neurological complications. Improved quality of care and the application of protocols and bundles, appear to have contributed significantly to improved outcomes. Since we are constantly facing an uphill task of dealing with deterioration while trying to preserve function, detection of early shifts of any nature would be deemed helpful. The intensivist must focus not only on saving life but also on preventing disability with full awareness that responsibility does not end with discharge from the pediatric intensive care unit (PICU). Outcome audits should include not only deaths and discharge from PICU but also one year mortality and even degree of disability at the end of one year from discharge.

Keywords Neurocritical care · Monitoring · Intracranial pressure · Cerebral perfusion pressure

Introduction

This article focuses on some recent advances in research in the field of neuroprotection that have thrown up several treatment and monitoring modalities that are applicable in clinical practice. Most of these are directed towards the preservation of cerebral perfusion pressure and reducing intracranial pressure. The emphasis is not only on survival but also on the quality of that survival [1]. Other areas of clinical research have given new treatments for conditions like status epilepticus and immune mediated encephalopathies. The pediatric literature and relevant adult literature was scanned for review articles, meta-analyses and trials and guidelines [2] of any nature appropriate to the topic have been used.

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Management

Management issues revolve around keeping the Intracranial pressure (ICP) under control (less than 20 mmHg) and the cerebral perfusion pressure (CPP) in the recommended range for age, which the guidelines state, should be at a minimum of 40 mmHg or in a range of 40–50 mmHg for children [2].

The equation: CPP=MAP-ICP implies that merely raising the mean arterial pressure (MAP) to overcome the effect of the ICP will preserve CPP. This is oversimplifying the issue of CPP. A Chandigarh study in a pediatric population, found that while it was possible to maintain CPP by MAP control in the early hours of brain injury, after 24 h it was essential to be aggressive with ICP control as well [3].

Blood Pressure is a Key Factor Hypotension and low cerebral perfusion pressure (CPP) are known to be associated with unfavorable outcome in children and adults with traumatic brain injury.

Almost all sedative and analgesic agents have the potential to cause hypotension. The sympathetic response is blunted and there is vasodilatation, leading to venous pooling and often an increased need for fluids and vasopressors. Hutchison's group reported a higher incidence of hypotension

and / or low cerebral perfusion in their hypothermia group. This is associated with poor outcome whenever it occurs and should be vigorously prevented whenever hypothermia is used [4]. The IMPACT analysis demonstrated that both low and high blood pressures are associated with poor outcome [5].

Osmotherapy

Both mannitol and hypertonic saline reduce ICP. In one randomized controlled trial (RCT) [6] in adults, 20 % mannitol was titrated against 7.5 % saline and 6 % dextran-70 solution; both given as a bolus over 5 min. The latter caused a significantly greater decrease in intracranial pressure than mannitol (p=0.044) and had a longer duration of effect than mannitol (p=0.044). Other trials have revealed similar findings and 23.4 % saline was not found to be more efficacious than 14.6 % but resulted in significantly higher serum sodium levels [7]. Hyperchloremic metabolic acidosis, hypernatremia, renal insufficiency and water retention add to the innate problems of sodium balance of the brain injured child. Contrary to the thinking earlier, that sodium levels should be allowed to rise, preferred values are now accepted as being between 155–160 mmol/L. In a recent study published by Levy's group in 2013, children with sustained (>72 h) serum sodium levels above 170 mEq/L had a significantly higher occurrence of thrombocytopenia, renal failure, neutropenia, and acute respiratory distress syndrome [8].

While accepting that mannitol is useful, practice has now shifted to the use of hypertonic saline (HTS). The non availability of stronger than 3 % solutions in some parts of the world is an issue.

Hypothermia

Outside of neonatal hypoxic ischemic encephalopathy (HIE), hypothermia has been used both, for early institution of neuroprotection in traumatic brain injury and post cardiopulmonary resuscitation (CRP), as well as for the treatment of *refractory* raised intracranial pressure (ICP). Most trials have reported its use in neuroprotection. The usual method quoted by Hutchison as being widely practiced is to institute it for 48–72 h at 32−33^{o} C within 8 h after injury and for a further 24 h if the ICP is>20 mmHg. Rewarming is done very slowly, preferably over several days. In most randomized trials, patients in the normothermia (Control) group were maintained at 36.5 - 37.5 °C [9].

In the study led by the Adelson group, there were 21 % deaths in the hypothermia group and 12 % in the normothermia group [10]. The need for vasoactive agents was seen to be higher too, especially during the rewarming period. The original planned sample size of 340 could not be achieved in this study, as it was terminated early due to the results of previous studies and a futility analysis. The mortality rate was not statistically higher in the hypothermia group, (15 % *vs.* 2 % p=0.15) and this could be attributed to the less than ideal sample size. All patients need intracranial pressure, arterial BP, CVP and frequent if not continuous EEG monitoring. Cardiac arrythmmias are often seen in seriously head injured patients and it may be difficult to separate those occurring from interventions and those from the brain injury. In one study, 5/7 patients in the hypothermia group and 2/9 in the normothermia group developed arrhythmias [11]. The clinical impact of these was unclear. Other complications of hypothermia include dyselectrolytemia, disseminated intravascular coagulation (DIC), sepsis, gut ischemia and skin breakdown. Only tertiary care fully equipped and well staffed PICUs should undertake this. In a metaanalysis of 5/34 studies done by Hutchison, it was remarked that "The risk ratio of death in the hypothermia group compared with the normothermia group was not statistically significant but the suggestion of an increased risk of death with hypothermia therapy is concerning" [12].

The authors make this statement in their document and this is the current practice in PICUs:

> *"In the final analysis, hypothermia is not recommended as a primary modality for neuroprotection due to the possibility of increased mortality. However, when faced with refractory ICP, the inherent risks could be acceptable when offset against the high risks of threat to life and severe disability that high ICP causes"*

Monitoring

The importance of monitoring vital signs, blood pressure, especially mean arterial pressure (MAP) electrolytes with special attention to Na and glucose, can never be underemphasised. Any "advanced" systems would be doomed to failure if simple neuroprotective strategies of sedation, analgesia, fever and seizure control, head end elevation and using Lidocaine prior to interventions, were ignored.

Most monitoring that is done for the brain injured child is of vital signs, hemodynamics and pressures in the brain. The numbers seen by these parameters are used as surrogate markers of presumed changes in the brain. Often the figures obtained are after an adverse event has occurred and may be late in predicting problems, rendering such readings completely insufficient to detect subtle and early secondary insults to the brain, such as ischemia, cerebral edema and metabolic

derangements. While there is research ongoing in several areas of neuro-intensive monitoring, very little is of such robust proven clinical value to be strongly recommended as standard of care, especially in resource poor settings.

ICP- and CPP-driven management protocols do not guarantee the prevention of ischemia or hypoxia. Available best practice guidelines may help in decision making and best resource utilization [2].

Intracranial Pressure (ICP)

While clinical methods are very important in assessing ICP, they have great limitations in the acute setting. Many signs like unequal pupils or decerebrate posturing are seen after the ICP is already very high and the window of opportunity for intervention is lost. In the 1960s, Lundberg et al. described the intraventricular catheter for the direct measurement of ICP [13, 14]. They also described the various wave patterns associated with intracranial pathology. Other devices like screws and bolts, too were developed but it was recognized that as the brain swelled, baseline measurements drifted with time. The intraventricular catheter remains the standard for ICP measurement today. In the early 1990s, microsensor devices, which read ICP when placed within the brain parenchyma, were developed based on either fibre-optics (Camino) or electrical impedance (Codman Microsensor). They give readings comparable to intraventricular catheters, are minimally invasive, and have minimal baseline drift even if placed for 1 wk or more. They have become the standard method of accurately measuring ICP by neurosurgical teams worldwide [15].

While several meta-analyses do not show improved mortality with the use of the device, the measurements obtained help to guide therapy and offer the opportunity for timely interventions.

It is said that in the normal brain, when Cerebral blood flow (CBF) falls below 18 ml/100 g/min, ischemia results and infarction occurs at 10 ml/100 g/min [16]. The relationship between supply and demand of oxygen is unclear. Tissues that are injured may have a lower metabolic rate and therefore require a lower CBF but may also be hypermetabolic and normal blood flow may prove inadequate. Just as in shock, the ability to measure the adequacy of extraction and delivery may help tailor therapy. Brain tissue oxygen tension ($PbtO_2$) and jugular venous bulb oxygen saturation- $SjvO_2$ (akin to the $ScvO_2$ in shock) are the most commonly used methods to assess extraction. $SjvO_2$ monitoring may be done continuously, by a commercial set or by intermittent blood sampling. Placement should be correct at just above the C1 vertebral level. The range is 50–75 % in the adult literature and extrapolated to children. Values of <50 % and >75 % are associated with poor outcome [17] (similar to the $ScvO_2$ used in the management of shock).

The $PbtO_2$ catheter is inserted in a chosen parenchymal spot and the O_2 tension measured. This may not reflect the milieu of the entire brain. The figure obtained is directly influenced by the delivery, utilization and diffusion in that area. The uninjured brain has a value of 20–30 mmHg and levels of 10 mmHg have been associated with ischemia and poor outcome. Packed red blood cell transfusions and hyperoxia challenges both show a transient rise in $PbtO_2$ but a higher rise in value was associated with a worse outcome probably from free radical production and secondary neuronal injury [18]. The 2012 TBI guidelines give a level III recommendation for keeping the $PbtO_2$ above 10 mmHg if the catheter is used [2].

Another indirect measurement of cerebral oxygenation is with Near-infrared spectroscopy (NIRS). This noninvasive method estimates regional saturation which, under certain assumed tissue conditions, closely approximates regional venous saturations and therefore, reflects mixed venous saturations of the brain, akin to the $SjvO_2$.

Cerebral microdialysis, although still a research tool, can measure markers of brain metabolism like lactate, pyruvate, glucose, neurotransmitters like glutamate or markers of tissue damage like glycerol.

Transcranial Doppler measures the CBF velocity in the middle cerebral artery. The CPP and ICP are derived from a pulsatility index (PI). However studies have shown a poor correlation between the PI and ICP in children [19]. It may be more useful in studying the intactness of autoregulation in the injured brain as it may be impaired in 40 % of brain injured children and is associated with a poor outcome [20].

Cerebral Function Monitoring (CFM)

CFM is a specific monitor for bedside, limited channel, continuous electrocortical monitoring, called amplitude integrated EEG (aEEG). It has gained popularity being an easy to use, noninvasive, be it expensive, bedside tool.

The use of this is almost exclusively confined to the neonatal unit. A single channel EEG record is obtained from two electrodes and one additional electrode acts as a ground. The signal is filtered and rectified and the range of amplitude is displayed on the monitor. The underlying EEG is displayed as “raw EEG” and helps in identifying seizures. Newborns with any form of encephalopathy are candidates for monitoring. Deeply sedated babies where subtle seizures or non convulsive seizures are likely, are also monitored. Indications include neonatal HIE, seizures, any encephalopathic process with or without seizures and during rewarming from therapeutic hypothermia; as hypothermia may gives a low amplitude trace and

seizures are commonly seen to reemerge during rewarming [21, 22]. In preterm infants, interpretation under 35 wk gestation may be difficult as voltage patterns are less well defined.

Monitoring should be started as early as possible after admission and continued till the baby has clinically stabilized and the background pattern has become stable for 24 h/ no seizures for 12–24 h. An abnormal reading in the first six hours may improve over 12–24 h and the initial trace should not be used to prognosticate a bad outcome to parents [23]. From the different studies done over the years in HIE/ seizure patients, in comparison of aEEG over conventional EEG, sensitivity differs from 39 % to 90 % [24, 25]. Sensitivity improves with prolonged duration of monitoring and evaluation by an expert.

The drawbacks of this modality are the capital expense of the equipment which costs upwards of Rs 10–15 lacs in India. In addition, some experience is needed in accurate interpretation of the wave-forms for good clinical and EEG correlation. The CFM only displays the amplitude of the EEG and not the frequency. EEG activity of <2Hz and>12 Hz cannot be recorded. Focal abnormalities cannot be identified because the signal is obtained from a single channel. Artifacts are commonly seen due to head bobbing from respiratory distress. The lower border may vary and give an error in reading. Conventional 16 lead EEGs must be done at regular intervals to corroborate both, abnormal readings as well as apparent normal readings.

Because of poor inter-observer agreement, some degree of expertise is required for accuracy

Continuous EEG Monitoring (cEEG) [26]

Seizures, whether overt or only electrical, are associated with a rise in ICP and need to be aggressively treated. In the sedated and possibly paralysed patient, clinical seizures will often not be apparent. In a retrospective analysis from Classen's group [27] clinical seizures prior to cEEG and coma were more common among patients who developed Non convulsive seizures (NCSz) or Non convulsive status epilepticus (NCSE) compared to patients without NCSz or NCSE. Nonconvulsive seizures occurred in 16 % of patients with altered mental status and were associated with poor outcome at discharge. The authors found that NCSzs (including NCSE) were independently associated with poor outcome (20 *vs.* 3 %, OR 10.4, 95 % CI 1.0–53.7; $p=0.039$). The Neurocritical Care Society Status Epilepticus Guidelines [28], strongly recommend that the duration of continuous EEG monitoring "should be at least 48 h following acute brain insult in comatose patients". cEEG is a useful method of monitoring in severe trauma as well as coma. Early recognition and treatment of NCSE may contribute to improved outcome.

Imaging

It is easily available, useful and readily interpretable. While the CT scan is of limited value in non-traumatic coma, the MRI is useful in several situations barring the very acute one of trauma where a decision for evacuation of a hematoma needs to be made. MRI diffusion weighted imaging (DWI) and its more complex form, diffuse tensor imaging (DTI) are sensitive to differences in the diffusion rate of water into the tissues and can detect vasogenic and cytotoxic edema. Increased diffusion is thought to occur with vasogenic edema due to increased water in the extracellular space where there is increased mobility, while restricted diffusion due to decreased water movement in the intracellular space is thought to be due to injured tissue unable to take up water and can be interpreted as being cytotoxic edema. Vasogenic edema is more amenable to treatment than cytotoxic edema. Injured brain usually has restricted diffusion [29].

The radiologist can also derive other information using the data and more confidently diagnose diffuse axonal injury (DAI) and shearing injury of non-accidental trauma. The Apparent diffusion coefficient (ADC) helps in further detailing the degree of DAI, which may not carry as poor a prognosis as was previously presumed.

MR spectroscopy is of help in measuring brain metabolites and often in help to corroborate the clinical diagnosis of inborn errors of metabolism before the laboratory results come back.

Key Messages

1. Basic monitoring and meticulous care is of prime importance.
2. CPP targeted therapies hold promise for better outcomes.
3. ICP monitoring is useful in appropriately targeting therapy.
4. Hypertonic saline is the osmolar agent of choice.
5. Hypothermia should be used only in advanced centres and only in refractory life threatening ICP.
6. Frequent or continuous EEG monitoring recognizes non convulsive seizures and should be employed.
7. Attention not only to mortality but also to good outcome without disability is vital.

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