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Cerebral protection – Current concepts

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INTRODUCTION

Traumatic brain injury is not a simple event entirely accomplished at the time of insult but an ongoing and gradual phenomenon. The reactions are progressive and involve brain tissue progressively via vicious circle and feed forward processes. Traumatic brain injury includes two distinct sets of disorders: first, worsening of the primary lesions which may take place from local and systemic causes, and, second, brain may suffer secondary insults.

Protection essentially means prevention and mitigation of a foreseeable insult highly likely to occur in given circumstances. The area of unstable hemodynamic conditions around traumatic lesions can be described as a "traumatic penumbra". This portion of brain tissue is at risk and cerebral protection endeavors to prevent its progression to complete destruction. Similarly a 'therapeutic window' exists during which perifocal tissues may be salvaged by reperfusion or by use of pharmacological agents that support cells at risk over a critical period. Brain protection essentially attempts to salvage tissues in this "traumatic penumbra" within this therapeutic window[1,2].

PATHOPHYSIOLOGY OF BRAIN INSULTS

A) Primary impact and related changes

Primary impact injuries include macroscopic injuries like brain contusions, axial and extra-axial hematomas and microscopic insults like axonal dysfunction, ischemic cytotoxic edema, astrocyte swelling, blood-brain barrier disruption with vasogenic edema, and phasic inflammatory cell recruitment.

B) Secondary biochemical reactions

Secondary reaction can be considered as a three-step event. The first step is a disruption of calcium hemostasis, which immediately follows trauma. A sudden rise of intracellular calcium occurs. Excessive intracellular calcium activates a number of enzymes reactions, which eventually destroy cell structures. The outburst of highly destructive free radical mediated peroxidation is the second major mechanism of damage. Acidosis is the third major mechanism of tissue disruption.

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i). Calcium Damage, Excitotoxic Mechanism and related therapies

Calcium enters the cell via two types of specific channels: those opened by membrane depolarisation (voltage operated channels VOC) and those opened by the action of a specific ligand on a receptor (receptor operated channel ROC). The VOC was initially considered to be the main route for calcium influx following energy failure. Later on emphasis was placed on the role of excitatory amino acid particularly glutamates and thus the concept of excitotoxicity – excitotoxic theory was proposed. In both, calcium overload is ultimately responsible for cell damage and that is the pivotal concept. However where as calcitoxicity may concern all cells, excitotoxicity concerns only cells equipped with EAA(excitatory amino acids) linked receptor channels which are essentially neurons. According to the excitotoxic concept a rise in the EAA concentration is the main cause of calcium entry via specific glutamate operated calcium channels. The immediate consequence of extracellular glutamate elevation is an enhanced stimulation of post-synaptic receptors. Different types of these receptors are currently described. These are:

a) the ionotropic receptors : NMDA

b) the quisqualate or AMPA receptors and

c) the kainate receptors.

In pathological conditions with high extracellular glutamate concentration , two processes take place: an immediate entry of sodium via the quisqualate kainite receptor accompanied by chloride and water which creates a sudden intracellular edema and can kill neurons very rapidly, and entry of calcium via the NMDA receptor associated channel which is a slower process and would be responsible for a delayed type of neuronal death[1,2].

ii) Perioxidative damage

Free radical reactions production is the consequences of the arachidonic acid cascade triggered by calcium-activated

phospholipase A2. In brain tissue, arachidonic acid and other PUFAS (polyunsaturated fatty acids) induce the production of superoxide anion and provoke a parallel swelling of the tissue. The activation of nitric oxide (NO) synthetase is another possible calcium-dependent mechanism of free radical production. It has been postulated that liberation of NO could account in part for glutamate-mediated neurotoxicity. NO produced in excess functions as a powerful neurotoxin. NO combines with superoxide anion O_2^- produced by xanthine oxidase activation to yield the peroxynitrite anion, which is an extremely potent free radical.

3) Acidotic damage

In anerobic conditions not only is there a breakdown of ATP production but also intracellular acidosis. Main features of acidosis related brain damage include edema, widespread neuronal necrosis and complete tissue destruction. In the anerobic conditions, the cell sacrifices its volume to save its pH. Acidosis is inevitably linked to ischemia and it is not possible to prevent acidosis if ischemia itself cannot be avoided[4].

There is, however, new and emerging interest in the role of *cerebral inflammation* following acute brain injury from a variety of causes[5]. There is good evidence now that there is a local inflammatory response in the human brain following a variety of insults, with production of pro-inflammatory cytokines (including IL-6 and IL-8) and adhesion molecule up regulation (including ICAM-1, ICAM-2 and Eselectin). These changes result in early neutrophil influx, and later recruitment of lymphocytes and macrophages and a chronic inflammatory response which may be associated with the laying down of amyloid. Indeed, head injury is a recognised risk factor for amyloid deposition in the brain and for Alzheimer's disease. Further, the risk of these outcomes is related to an individual's apolipoprotein E (ApoE) genotype, with an increased risk conferred by possession of the ApoEe4 genotype[6]. Even more intriguingly, the ApoEe4 genotype has been shown to affect outcome directly in patients admitted with a severe head injury. This may be the first recognition of many genotypic influences that modulate the severity of secondary neuronal injury mechanisms, and elucidation of these processes may enable us, in the future, to select high risk patients for intensive neuroprotection strategies.

C.Change in cerebrovascular hemodynamics

Following head injury, cerebral blood flow (CBF) is shows a triphasic behaviour[2,3]. Early after head injury (within 12 hours), global CBF is reduced, sometimes to ischemic levels. Between 12 and 24 hours post injury, CBF increases and the brain may exhibit supranormal CBF (while many reports refer to this phenomenon as hyperemia, the absence of consistent reductions in cerebral oxygen extraction suggest that metabolism and blood flow often remain coupled, and a more appropriate label would be hyperperfusion). Thereafter CBF values begin to fall several days following head injury, and, in some patients, these reductions in CBF may be associated with marked increases in large vessel flow velocity on transcranial Doppler ultrasound that suggest vasospasm. Immediately after head injury there is no vascular engorgement and, though a transient blood-brain-barrier (BBB) leak has been reported in the immediate period after impact in animals, there is no evidence of BBB disruption at this stage in humans. Apart from surgical lesions (*e.g.* intracranial haematomas), ICP elevation during this phase is commonly the consequence of cytotoxic oedema, usually secondary to cerebral ischemia. Increases in CBF and cerebral blood volume (CBV) from the second day post injury onward make vascular engorgement an important contributor to intracranial hypertension. The BBB appears to become leaky between the second and fifth days post trauma, and vasogenic edema then contributes to brain swelling.

MONITORING IN ACUTE HEAD INJURY

Monitoring modalities are selected based on their ability to measure physiological endpoints that have been shown to influence outcome as well those which can be modulated by therapeutic interventions[2].

Monitoring systemic physiology

Monitoring of direct arterial blood pressure along with measurement of ICP is essential for calculating and manipulating CPP. The need to manipulate mean arterial pressure will also require the measurement of central venous pressure, or left atrial pressure using pulmonary artery catheterization, wherever appropriate. Similarly, the maintenance of systemic oxygenation requires the continuous monitoring of this variable (by pulse oximetry, supported by arterial blood gas measurement). The need to measure core body temperature and regular blood sugar estimation cannot be overemphasized.

Intracranial pressure monitoring

The need to optimise CPP predicates the requirement of monitoring ICP in all patients with severe head injury. Clinical signs of intracranial hypertension are late, inconsistent and non-specific. Further, it has been shown that episodic rises in intracranial pressure may occur even in patients with a normal X-ray and CT scan. Majority of the devices used to monitor ICP can be placed under local anesthesia at the bedside. A ventriculostomy with an intraventricular catheter

remains the gold standard, and provides a means of treating high ICP with drainage of CSF. Intraparenchymal micro-manometers or fibreoptic probes are increasingly being used instead of ventriculostomies. While these present a lower infection risk, they are more expensive and do not permit CSF drainage for the reduction of elevated ICP. A more complete assessment of intracranial fluid dynamics may be obtained by assessing the intracranial compliance, where changes in ICP are observed following the infusion into or removal of fluid from ventricular catheter. The arterial pulse produces a small increase in intracranial volume with every cardiac contraction, and an exaggerated transmission of the arterial pressure wave form to the intracranial wave form (which normally has a pulse pressure of a few mmHg) suggests that intracranial compliance may be compromised.

Transcranial Doppler (TCD) ultrasonography

TCD measures the velocity of red blood cells (RBCs) flowing through the large vessels at the base of the brain using the Doppler shift principle. Although many of the intracranial arteries may be studied, the middle cerebral artery (MCA) is most commonly insonated because it is easy to detect, receives a substantial proportion of the blood flow from the internal carotid artery and allows easy probe fixation. Marked reductions in MCA flow velocity (FV) may provide a useful marker of critically reduced cerebral perfusion in the setting of intracranial hypertension in acute head injury, but episodic rises in ICP may also be caused by hyperemia, which may be diagnosed by increases in TCD flow velocity. Transcranial Doppler ultrasonography can also be used as a non-invasive monitor of cerebral perfusion pressure. As the ICP increases and cerebral perfusion pressure correspondingly decreases, a characteristic highly pulsatile flow velocity pattern is seen. Continuing increases in ICP result first in a reduction and then loss of diastolic flow, progressing to an isolated systolic spike of flow in the TCD waveform, and eventually to an oscillating flow pattern, which signifies the onset of intracranial circulatory arrest. The pulsatility index (PI) is one way of mathematically describing the waveform pattern, and correlates with cerebral perfusion pressure than with ICP. This form of monitoring may become particularly useful in centres where ICP measurement is not routinely used or in patients in whom ICP monitoring is unavailable or may not be clearly indicated (*e.g.* mild closed head injury). Loss of cerebral pressure autoregulation and vasoreactivity to carbon dioxide are indicators of poor prognosis after head-injury. Classical tests of autoregulation involve recording TCD responses to induced changes in mean arterial pressure. Cerebral autoregulatory reserve is also assessed by the transient hyperemic response test (THRT). More recent algorithms constantly assess autoregulation by on-line calculation of changes in MCA flow velocity in response to small spontaneous alterations in MAP. Such analysis permits the on-line calculation of indices of cerebrovascular reactivity and compensatory reserve, which may allow prediction rather than recording of physiological behaviour, and facilitates the selection of patients for intensification of therapy[5].

Jugular venous oximetry

The superior sagittal sinus is thought to drain primarily into the right internal jugular vein, and it is common practice to place jugular bulb catheters on this side in order to monitor the oxygenation in the supratentorial compartment. More recent data suggest that supratentorial venous drainage is less lateralised, and hence bilateral jugular bulb catheterization is better than unilateral measurements. Normal jugular bulb oxygen saturation ($SjvO_2$) is around 65–70%. Reductions in $SjvO_2$ or increases in arterio-jugular differences in oxygen content ($AJDO_2$) to greater than 9 ml/dl suggest inadequate CBF and can guide therapy. $SjvO_2$ values below 50% have been shown to be associated with a worse outcome in head injury. Conversely, marked elevations in $SjvO_2$ may provide evidence of cerebral hyperemia. While $SjvO_2$ monitoring has been widely used in head injury, it is technically difficult to setup and monitor.

Newer techniques for brain oximetry

The major deficiencies of jugular venous oximetry are its invasiveness and the poor reliability of signal obtained. Other techniques that have been employed in acute head injury include near infra-red spectroscopy (NIRS), direct tissue oximetry and cerebral microdialysis. Some authors were able to demonstrate that during 1–5 days after head injury, NIRS was better than SjvO2 at detecting periods of abnormal physiology as defined by multimodality monitoring

An entirely opposite approach is taken by the technique of direct cerebral oximetry, which uses a combined pO_2, pCO_2, pH and temperature microsensor implanted in the brain. This technique has been used in several clinical studies, and results are beginning to emerge that relate tissue oxygen levels to outcome. However, it measures oxygenation in a very small volume of tissue, and it remains to be established whether this is representative of the large bulk of brain that requires monitoring. Tissue microdialysis presents the opportunity of directly sampling brain ECF composition, with opportunities for the measurement of glucose(which tends to parallel perfusion), lactate/pyruvate ratios (which provide information regarding ischemia) and glutamate (which tends to be elevated after physiological

insults). In addition to insights into brain physiology, this technique may provide a method of measuring local pharmacokinetics of drugs in head injury.

Cerebral blood flow measurement

Global cerebral blood flow measurements in acute head injury have commonly used ^{133}Xe washout techniques at the bedside and documented the phasic changes in CBF after head injury.

Imaging physiology and metabolism in head injury

The best established technique for physiological imaging is the use of stable xenon CT studies for measurement of regional CBF (rCBF). Positron emission tomography (PET) and magnetic resonance imaging have been also used for the purpose. In addition, PET provides the opportunity to image cerebral glucose and oxygen utilization, and radio ligand binding. Recent interest has focused on increased uptake of the PET tracer 18F-deoxyglucose around contusions and adjacent to hematomas, which are probably unaccompanied by increases in oxygen metabolism.

Multimodality monitoring

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

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I. GENERAL MEASURES

A. Brain oriented life support:

Basic physiological premises suggest the benefit of maintaining cerebral blood flow and oxygenation, and these assumptions are confirmed by data from the Traumatic Coma Data Bank (TCDB) and from other sources which demonstrate the detrimental effects of hypotension (systolic blood pressure below 90 mmHg) and hypoxia (PaO_2 levels below 60mmHg [8 kPa]) in the early and later phases of head injury on outcome[8]. Hypotension and low cardiac output are deleterious to an already compromised brain. CVP should be maintained within 8–10 cms of water, and hypotension should be treated expeditiously by administering IV fluids, blood or ionotropes as appropriate in a given situation. Hypoxia and hypercapnia cause further cerebral injury and need to be strictly avoided. Mechanical ventilation and PEEP is generally required to optimize oxygenation. Normal acid base balance is desirable. Metabolic acidosis and respiratory alkalosis are the common disturbances that need to be treated. Normovolemia should be maintained: hypervolemia increases brain edema while excessive dehydration decreases CBF. Normal serum osmolality and oncotic pressure should be maintained. Hyponatremia aggravates brain edema and precipitates seizures and should be promptly corrected. Hyperglycemia is associated with worsening of neurological injury in head injury[9]. Normothermia should be achieved by measures such as cold sponging, cooling blankets and antipyretics, since hyperthermia aggravates neurological injury. Systemic infections should be appropriately treated[8].

B. Fluid therapy

Fluid replacement should be guided by clinical and laboratory assessment of volume status and by invasive hemodynamic monitoring, but generally involves the administration of 30–40 ml/kg of maintenance fluid per day. The choice of hydration fluid is largely based on inconclusive results from animal data. Unlike other vascular beds, capillaries in the brain are impermeable to most small molecules, and fluid flux across the normal BBB is governed by osmolarity rather than oncotic pressure. Consequently, hypotonic fluids are avoided and serum osmolality is maintained at high normal/levels (290–300 mosm/l in our practice) to minimise fluid flux into the injured brain. Dextrose containing solutions are avoided since the residual free water after dextrose metabolism can worsen cerebral edema, and because the associated elevations in blood sugar may worsen outcome[10]. Hypertonic saline has been shown to raise plasma sodium and osmolality with reduction in ICP and reduction of midline shift in head injuries[11,12]. Simma *et al* reported that 1.6% saline, when compared to lactated Ringer's solution as maintenance fluid in head injured children, resulted in lower ICP values, less need for barbiturate therapy, a lower incidence of acute lung injury, fewer complications and a shorter ICU stay[13]. Maintenance of oncotic pressure with albumin supplements is one of the cornerstones of the Lund protocol, and other authors have discussed the advantages of colloid use in this setting [13]. Both albumin and gelatins have been used, but hetastarch should be used with caution, since its effects on hemostasis may potentiate intracranial haemorrhage. There is some evidence indicating that certain colloids (pentastarch) may be effective in reducing the

cerebral oedema associated with cerebral ischaemic and reperfusion injury [10,14]. Agents which 'plug leaks' by acting as oxygen free radical scavengers and or by inhibiting neutrophil adhesion may be the resuscitation fluids of the future.

C.Nutrition

Head injured patients have high nutritional requirements and feeding should be instituted early (within 24 h), aiming to replace 40% of resting metabolic expenditure (with 15% of calories supplied as protein) by the seventh day post trauma[15]. Enteral feeding is preferred as it tends to be associated with a lower incidence of hyperglycemia and because of its protective effect against gastric ulceration, the incidence of which may be increased in these patients. Impaired gastric emptying is a common finding in head injury, and can be treated with prokinetic agents. In those who cannot be fed enterally, parenteral nutrition should be considered together with some form of prophylaxis against gastric ulceration (H2 antagonists or sucralfate) and rigorous blood sugar control.

D.Antiepileptic therapy

Seizures occur early (before 7 days) or late (after 7 days) following head injury, with a reported incidence of between 4–25% and 9–42%, respectively[15]. Seizure prophylaxis with phenytoin or carbamazepine can reduce the incidence of early post-traumatic epilepsy, but has little impact on late seizures, neurological outcome or mortality. The incidence of posttraumatic seizures is greatest in patients with a GCS below 10, and in the presence of an intracranial haematoma, contusion, penetrating injury or depressed skull fractures. Since it is important to balance the possible benefit from seizure reduction against the side effects of anti epileptic drugs, such patients may form the most appropriate subgroup for acute (days to weeks) seizure prophylaxis following head injury[8,16].

II. CEREBRAL BLOOD FLOW PROMOTION TECHNIQUES

The ultimate object is to provide brain cells with the amount of oxygen and glucose which covers their energy requirements for both functional needs and to circumvent the crisis. Against energy failure we have two lines of protection: hemodynamic and metabolic. Hemodynamic protection composes attempts at restoring circulation or at improving its efficiency via manipulation of blood pressure, vasoreactivity and blood rheology[17,18]. The alternative strategy is to reduce the needs by lowering $CMRO_2$ [19].

Available oxygen = CBF x Hb x sO_2/100.

Available oxygen can thus be improved by

a) Increasing CBF essentially by improving CPP

b) Improving Hb

c) Improving sO2 : Intentional hyperoxia has been documented to reverse the cerebral oxygen desaturation and anerobic metabolism in head injured patients[20,21].

A. MAP Targeted treatment : CPP = MAP - ICP

When cerebral autoregulation is intact the cerebral blood flow is kept constant despite changes in CPP between 60 mm and 140 mm. The controversy centers on the minimum level of CPP that is adequate in TBI. Most centres would agree on the need to maintain cerebral perfusion by keeping CPP well above 60–70 mmHg, either by decreasing ICP or by increasing MAP. Despite this large body of data that supports the maintenance of high CPP values in head injury, there is some concern that relatively high perfusion pressures may contribute to oedema formation post head injury. A recent study comparing CBF targeted management (CPP more than 70, pCO_2= 35) with ICP targeted therapy (ICP below 25, pCO_2 upto 25, CPP below 50) found no difference in the outcome[5]. There are however, data that show that ICP is an independent, albeit weaker, determinant of outcome in severe head injury. A recent study in fact concluded that CPP has correlation with outcome only when CPP was below 60 mm; above 60 mm CPP had no correlation with outcome suggesting that higher CPP does not always translate itself into better outcome[1,2,18]. The different schools of thought on CPP targeted therapy can be summarized as follows

Optimising cerebral perfusion by CPP management[22]: This approach is based on the concept that normal autoregulatory response to reduced CPP causes dilatation of the cerebral blood vessels .This results in an increase in ICP causing further reduction in CPP, thus setting up a cycle that leads to ever reducing CPP. Under these circumstances an increase in arterial blood pressure would break the cycle and reduce ICP. This approach is widely practiced and recommended.

Lund Therapy approach[2,18,22,23]: This approach centers on reduction in microvascular pressures to minimize edema formation in the brain. Colloid osmotic pressure is maintained near normal values using infusion of albumin and erythrocytes and capillary hydrostatic pressure is decreased by reducing systemic blood pressure using betablockers and clonidine. In addition, low dose thiopental and dihydroergotamine are used to reduce cerebral blood volume by contricting precapillary resistance vessels.

Miller et als balanced approach [23,24]: This approach attempts to direct the treatment to the underlying

pathophysiology.

Zero-flow pressure (remodeling of cerebral circulation)[24]: The concept of zero-flow pressure (ZFP) and the critical closing pressure has been introduced recently and is still being debated. There is increasing evidence that the traditional view of CPP = MAP – ICP is rather simplistic. Vascular tone, compliance and other physical properties may play an important role in determining the effective downstream pressure in cerebral circulation. Estimation of ZFP allows estimation of changes in the downstream pressure noninvasively. More work is required to ascertain its importance in TBI but there may be exciting opportunities to manipulates the downstream pressure in TBI it increase CPP without having to raise MAP.

B.Decreasing ICP: This involves

i) Drainage of CSF and surgical decompression (whenever possible): Data quoted in the Brain Trauma Foundation guidelines for the management of severe head injury provide circumstantial evidence supporting the increased use of CSF drainage for ICP control

ii) Hyperventilation

iii) Hypersomolar therapy

iv) Use of CNS depressants (typically barbiturates) have all been used to reduce ICP.

Hyperventilation

Hyperventilation, once the mainstay of ICP reduction in severe head injury, is now the subject of much debate[25]. The aim of hyperventilation is to reduce cerebral blood volume and hence ICP, but this is accompanied by a reduction in global and regional cerebral blood flow, which may drop below ischaemic thresholds. In addition to concerns regarding ischemia, hyperventilation may have only short-lived effectiveness in decreasing ICP[26,27].

The drawback with hyperventilation is that with prolonged use, compensatory reductions in cerebral extracellular fluid (ECF) bicarbonate levels rapidly restore ECF pH and over time, attenuate the effect of low PaCO2 levels on vascular tone. This can be overcome with the use of the diffusible hydrogen ion acceptor, tetra-hydro-aminomethane (THAM), which may restore ECF base levels and restore the reactivity of the cerebral circulation to carbon dioxide. Similarly with associated hyperoxia the effects of hyperventilation can be sustained longer. Thus hyperventilation with concomitant use of THAM and hyperoxia is again being considered in the treatment of cerebral protection.

Hyperosmolar therapy

In the setting of clinical, radiological or measured evidence of intracranial hypertension, mannitol (0.25–1 g/kg, usually as a 20% solution) has traditionally been used to elevate plasma osmolarity and reduce brain oedema [28]. In addition to its osmotic effects, mannitol probably reduces ICP by improving CPP and microcirculatory dynamics. Some of mannitol's potentially beneficial effects include increased blood viscosity and free radicals scavenging and antioxidant activity. Side effects include secondary increases in ICP when the BBB is disrupted, fluid overload from initial intravascular volume expansion, and renal toxicity from excessive use. These can be minimized if its use is discontinued when it no longer produces significant ICP reduction, volume status is monitored and if plasma osmolality is not allowed to rise above320 mOsm/L (although there is little objective evidence to support this threshold). In addition to their use as maintenance fluids, hypertonic saline solutions (7.5%) are being used for small volume resuscitations, and may provide improve outcome in comatose patients suffering from multiple trauma. Recent reports also highlight the successful use of 23.4% saline for treatment of intracranial hypertension refractory to mannitol[12]. While more studies are required, it appears hypertonic saline will find a place in the treatment of brain swelling.

Sedation and neuromuscular blockade

Intravenous sedating agents preserve autoregulation and the cerebrovascular response to CO2, even at doses sufficient to abolish cortical activity, and decrease cerebral blood flow, cerebral metabolism and ICP. The reduction in flow is secondary to a reduction in metabolism (flow-metabolism coupling). Barbiturates are now less commonly used in the head injured patient for routine sedation, owing to the availability of other agents, such as propofol, which possess similar cerebrovascular effects but better pharmacokinetic profiles. However, propofol is not without side effects. At high doses, propofol can induce hypotension and decrease in cerebral perfusion pressure. Midazolam is often used in combination with fentanyl and propofol for sedating the patient with head injury. Midazolam reduces $CMRO_2$, CBF and CBV with both cerebral autoregulation and vasoreactivity to carbon dioxide remaining intact. However, these effects are inconsistent and transient, and even large doses of midazolam will not produce burst suppression or an isoelectric EEG. Opioids generally have negligible effects on CBF and CMRO2. However, the newer synthetic opioids fentanyl, sufentanil and alfentanil, can increase ICP in patients with tumors and head trauma.

Neuromuscular blockade in the head injured patient receiving intensive care is currently the subject of much debate. The use of neuromuscular blockers can play an important role in the head injured patient. Coughing and 'bucking on the tube' can result in an increase in ICP, and the administration of non-depolarising muscle relaxants prevents such rises in ICP. However, despite facilitation of ICP control, use of these agents is not associated with better outcomes, perhaps because of increased respiratory complications. Further, long term use of neuromuscular blockade has been associated with continued paralysis after drug discontinuation and acute myopathy, especially with the steroid-based medium to long acting agents. However, atracurium is non-cumulative and has not been associated with myopathy, and theoretical concerns about the accumulation of l audanosine, a cerebral excitatory metabolite of atracurium, in head injured patients have not been shown to be clinically relevant[2,18].

III.REDUCING CEREBRAL METABOLISM

1. Hypothermia

One of the interventions which has never lived up to the theoretical promise it offered is the reduction of brain metabolism in order to reduce the production of cytotoxic radicals, penumbral ischemia and brain swelling. The well designed National Acute Brain Injury study (NABIS) trial in conjunction with the similar Japanese trial seems to settle the matter and has shown fairly conclusively that mild hypothermia applied following head injury does not reduce mortality or dysfunction. It is important however not to entirely dismiss the role of hypothermia in achieving cerebral protection and may still be used in patients with cardiac arrest, pediatric head injury etc[1,2,18,29,30] .

Hypothermia progressively depresses the cerebral metabolism which has been reported to decrease linearly from 6 to 10% for each one degree decrease in temperature in the range 35 to 25º. The protective mechanism may not entirely be due to decrease in metabolism but also due to its membrane stabilization action, influence on blood flow, reduction in excitatory amino acids and sustained suppression of cytokines, particularly interleukin[1].

One of the early studies on hypothermia, the NABIS study by Clifton et al [29] in 1994 was halted after 392 patients as the treatment was not effective. Some important points from the study are that older patients not only do not benefit from the hypothermia , they also do worse than normothermics. Also if patients are hypothermic on admission it is not advisable to warm them to normothermia. The timing of initiation might also be important with early induction of hypothermia giving better results. Similarly it was shown that hypothermia did have a beneficial effect on the proportion of patients with high intracranial pressure.

The Cochrane review analyzing 12 trials with 812 patients could not find a statistical reduction in mortality in patients receiving mild hypothermia either early or deferred. The patients receiving hypothermia seemed to give an increase in ventilator associated pneumonia, which negate any beneficial effect. Two ongoing trials (IHAST) and (HyP – HIT) should however provide information on the role of hypothermia in post SAH and pediatric head injury respectively.

2. Barbiturate narcosis

Intravenous barbiturates have been used in the setting of acute head injury for ICP reduction since 1937 when the utility of barb narcosis in decreasing ICP was described by Shapiro[31]. Among the other possible indications were, control of ICP intraoperatively , focal and global ischemia and in decreasing the incidence of neuropsychiatry complications following cardiopulmonary bypass.

Barbiturate can reduce the rate of energy depletion (ATP depletion and lactate accumulation), and prolong the time for energy failure in case of ischemic injuries. Deep barbiturate anesthesia can reduce cerebral metabolic rate to the same extent as hypothermia to 30ºC. Barbiturate therapy would be expected to reduce $CMRO_2$, which limits cell energy demand at a time when blood flow may be compromised. In these patients, barbiturates may increase perfusion pressure through reduction of ICP (CPP = MAP - ICP). Other potential beneficial effects of barbiturates are reduction of elevated intracranial hypertension, producing favorable redistribution of blood towards ischemic tissue by constricting the vessels in the non-ischemic cortex and suppression of abnormal or seizure-like activity. It has also been suggested that barbiturates exert neuroprotective effects through anti-oxidant or free radical scavenging actions. Barbiturates may also reduce ischemia induced neurotransmitter release.

Dosage: Pentobarbital may be used for elective induction of barbiturate coma. It has a serum half-life (elimination) of about 30 hours. It is administered by a loading dose (3 to 10 mg/kg) at 1 mg/kg/min, followed by continuous infusion at 1 to 2 mg/kg/hour. Monitoring of blood level and maintaining it at 25 to 40 mg/ml range may prevent excessive recovery times from barbiturate coma. Thiopentone is a rapidly acting barbiturate, which is often used if the desired effect is necessary immediately. In this context, doses of 3 to 5 mg/kg intravenously will produce transient burst suppression and blood thiopentone levels of 10 to 30 mg/ml. Following are the various regimens used:

1) High initial dose to produce burst suppression on EEG, which may or may not be followed by an infusion. This use is applicable to situations of focal ischemia. Loading dose consists of 25 to 50 mg/kg. This is followed by an infusion 2 to 10 mg/kg/hr to give plasma concentration of 10 to 50 mg/L. Accumulation occurs and recovery may be prolonged over a period of days before neurological assessment can be made.

2) Low initial dose followed by infusion: this regimen is used to control ICP. A dose of 1 to 3 mg/kg intravenously is followed by an infusion of 0.06 to 0.2mg/kg/min. This regimen is useful in head injuries to decrease raised ICP. Intermittent low doses of thiopentone (1 to 3 mgkg-1) will lower ICP and brain bulk during intracranial operations.

3) Small bolus dose for short-term protection. A dose of 4 mg/kg over 3 minutes produces EEG burst suppression for about 6 minutes.

Duration of therapy: When used prophylactically, therapy is usually discontinued when the period of potential or actual insult is over. The duration of therapy when instituted after an insult is controversial and has varied from bolus doses to infusions for 24 to 72 hours or more. The long duration has been advocated because post-insult injury may last for this period & cerebral edema peaks at 48 hours after an ischemic injury.

Problems during barbiturate therapy

1) Barbiturate therapy may cause depression of cardiac output and cerebral perfusion pressure, and even frank cardiovascular collapse in poorly hydrated patients as well as in those with a reduced cardiac function.

2) The profound respiratory depressant effect of barbiturates makes controlled mechanical ventilation mandatory.

3) Long-term barbiturate therapy is associated with hypothermia & depression of immune responses. This introduces the risk of pulmonary infectious complications.

4) Neurologic evaluation of the patient in barbiturate coma is difficult.

5) Ninety nine percent of administered thiopental is metabolized in the liver. Therefore special attention is required inpatients with hepatic dysfunction.

6) A sophisticated intensive care setting is required to support patients who are going to benefit from this mode of therapy.

Two randomized control trials compared barbiturate narcosis to mannitol as initial therapy in head injury patients with GCS less than 8. The important message form the Schwartz and Ward studies were

i) Barbiturate narcosis is associated with a high incidence of hypotension.

ii) As a first line of therapy mannitol is superior to pentobarbital in ICP control.

iii) In some case barbiturate narcosis can cause oligemic hypoxia to the brain because of decrease in CPP. Nordstorms group from Sweden suggested that response to barbiturate narcosis in severe head injures may be related to the response of cerebral circulation to $PaCO_2$. Patients who responded to hypocarbia with decrease in CBF and ICP are the ones who respond to barbiturate narcosis with decrease in ICP. In these patients (intact cerebral vasoreactivity), 50% had a good outcome and 25% died. In patients with absent cerebral vasoreactivity barbiturate narcosis was associated with a mortality of 64%.

The best source of review for this subject is the guidelines for the management of severe traumatic brain injury patients – a joint venture of the BTF, AANS and the joint section of the neurotrauma and critical care. The guidelines say that "high dose barbiturate therapy can be considered in hemodynamicaly stable salvageable severe head injury with increased ICP, refractory to conventional medical/surgical management". Two laboratory studies and one clinical study have clarified the role of barbiturate in ischemia once and for all – barbiturate narcosis is of no benefit in global ischemia and may be of variable use in some cases of focal ischemia and in reducing neuropsychitaric complications in CPB[1,2,18,32,33].

3) Etomidate

Like barbiturates, etomidate produces EEG burst suppression and reduces CMR for glucose and oxygen. Clinically, etomidate decreases CBF, $CMRO_2$ and ICP whereas carbon-dioxide reactivity, hemodynamic stability and cerebral perfusion pressure (CPP) are maintained. It inhibits release of excitatory neurotransmitters. Etomidate has a low incidence of hemodynamic instability at doses sufficient to depress the EEG. In this respect, it has a major advantage over thiopental. However, etomidate has been associated with significant adrenocortical suppression, even when administered as a single injection. This effect of the drug has greatly limited its utility in usual anesthetic care but not its utility in neurosurgical cases in which patients are routinely administered high doses of steroids[32].

4) Propofol

The metabolic changes resulting from propofol anesthesia closely resemble the homogenous depression of CMR caused by barbiturates and etomidate. Propofol reduces cerebral metabolism with a consensual reduction in EEG activity, oxygen consumption and cerebral blood flow. Propofol also reduces voltage-activated sodium channel conductance at concentrations within the clinical range. Its antioxidant properties may also be of benefit. High doses may produce hypotension, which reverses rapidly upon discontinuation (usually within 5-10 minutes). Administration of propofol to head injured patients with elevated ICP has been associated with a reduction in ICP but also of CPP. Propofol infusion titrated to produce unresponsiveness (8 mg/kg/hr) in humans, resulted in 55% depression in CMR for glucose, as measured using positron emission tomography. There are reports of possible anaphylactic reaction with angioneurotic edema of the airways. Seizure-like activity has been reported after anesthesia with propofol. The high doses of propofol required to achieve burst suppression (up to 200 mg/kg/min), necessitate the delivery of high lipid loads with resultant abnormalities in plasma lipid status. The availability of 2% preparations of propofol may substantially ameliorate this problem[1,2,32,34].

D. PHARMACOLOGICAL NEUROPROTECTION

Mechanism of action of neuroprotectant drugs

Conventionally pharmacological neuroprotection was considered to be the domain of anesthetic drugs and that was considered in terms of their ability to modify cerebral metabolic rate. There are many other pharmacological effects, which may contribute to neuroprotection. These include reduction of intracranial pressure (ICP), anti-convulsant action, free radical scavenging, drug-induced inverse steal, antagonism at voltage-sensitive calcium or sodium channels or ligand gated calcium channels, potentiation of GABAergic transmission or attenuation of ischemia induced neurotransmitter release. Drug-induced inverse steal requires reduction in cerebral metabolism (usually to the point of EEG burst suppression) with an agent, which maintains flow metabolism coupling. This will result in reductions in blood flow in well perfused regions with subsequent increases in upstream perfusion pressures leading to the redistribution of this 'excess' flow down pressure gradients to more ischemic areas. Thiopental & drugs that decrease CBF similar to thiopentone have the potential to decrease the number of emboli delivered to the cerebral circulation. Presumably, for such a mechanism to provide protection, there must also be an accompanying decrease in cerebral metabolism. [19,32,35]

A.Anesthetic agents as neuroprotectants

a) Intravenous anaesthetic agents

1) Barbiturates See earlier section
2) Etomidate
3) Propofol
4) Ketamine16

Ketamine is a noncompetitive antagonist at NMDA receptors and may therefore offer protection from the adverse effects of cerebral ischemia

b) Inhalational agents

1) Isoflurane

Isoflurane offers a similar level of metabolic depression as barbiturates at a concentration less likely(than barbiturates) to be accompanied by severe cardiovascular depression or prolonged recovery. Isoflurane can suppress brain electrical activity to the point of isoelectricity at clinically useful concentrations(<2MAC). Isoflurane is a potent inhibitor of CMR and$CMRO_2$ in all species studied. In addition to its GABAergic effects, isoflurane has also been shown to inhibit multiple voltage-gated calcium currents in hippocampal pyramidal neurons. Isoflurane has been shown to significantly inhibit glutamate receptor activation and ischaemia induced calcium influx. [32,35,36]

2) Sevoflurane

In common with isoflurane and barbiturates, sevoflurane produces a dose- dependent decrease in CMR. Autoregulation appears to be well maintained in patients with cerebrovascular disease undergoing sevoflurane anaesthesia. [32,35]

3) Desflurane

Although thiopental treatment for brain protection is effective in decreasing ischaemic injury, the doses required for EEG suppression prolong recovery times. Inhalation anaesthetics such as desflurane can also produce EEG silence but allow a more rapid recovery. Desflurane treatment for cerebral protection significantly increases brain tissue oxygenation and pH above control levels. Significant increases in tissue pO_2 and pH, and decreases in pCO_2 were observed during desflurane treatment for brain protection. The enhanced tissue oxygenation and carbon dioxide clearance that is observed with desflurane may be caused by the cerebral vasodilating effect of desflurane compared with thiopental[36].

B. Non-anesthetic agents as neuroprotectants

In the past ten years , published reports of clinical trials on the treatment of head injury have included one large trial on the use of a corticostreoid (triamcinolone), three trials on the use of nimodipine , three trials on the use of free radical scavenging agents (PEGSOD and tirilazad) and three trials on the use of NMDA antagonists. Four of these studies were halted prematurely, and only six were completed.

Corticosteroids

Their efficiency in reducing vasogenic peritumoral edema is well documented. Use of glucocorticoids is not recommended for improving outcome or reducing ICP in patients with severe head injury. The ability of steroids to stabilize membranes, prevent lipid peroxidation and their anti-inflammatory property can be expected to protect ischemic/ injured brain. Early studies using various types of steroids both in high and low doses did not provide any benefit. A recent trial using triamcinolone showed increase in the number of patients with good recovery and decrease in mortality. A recent Cochrane review[39] concluded that neither moderate benefit nor moderate adverse effect of steroid can be confirmed and a large randomized controlled trial is justified to explore the benefits of steroids in severe head injury. After performing a meta analysis of the results of all identified steroid trials in head injury both published and unpublished it was concluded that a 2% reduction in mortality is possible and to confirm or exclude this a prospective trial of 20000 patients is necessary[1,2,8,32].

Novel neuroprotective interventions

Although none of these have been accepted as standard therapy in acute head injury, a variety of novel pharmacological neuroprotective agents are currently under investigation. Disappointingly, none of the agents that have been tested thus far in Phase III trials have proved to provide benefit on an intention to treat basis.

a. Calcium anatagonists:

The vital role played by calcium in ischemic and traumatic injury raised the possibility of utilizing calcium entry blockers for cerebral protection[37,38]. Lidoflazine was one of the first calcium entry blockers to be tried but the most studied drug is nimodipine. This drug antagonizes the entry of calcium into cells, which in turn ameliorates the lactic acidosis, which occurs during ischemia. Nimodipine probably increases CBF, particularly in regions of moderate ischemia. Major human trials in head injury also documented very limited role for nimodipine. The two major European trials HIT 1 and HIT II showed no statistically significant improvement in favorable outcome at the end of six months with the use of nimodipine. HIT III however reported a 10% improvement in favorable outcome in a sub group of patients who had evidence of traumatic SAH. A recent Cochrane data base review on the subject of calcium blockers in head injury was uncertain about the ability of these agents to decrease death and disability. However there seems to be a trend towards improved outcome in a subgroup of patients with traumatic SAH.

Treatment with Nimodipine decreases BP, decreases systemic vascular resistance and increases cardiac output. The lack of a neuroprotective effect was disappointing & may be attributable to the fact that nimodipine is a cerebral vasodilator, conferring a physiologic effect of increased embolic load and obliterating any protective effect at the cellular &biochemical level. Nicardipine, another calcium antagonist has been administered into venous reservoir before deep hypothermic circulatory arrest but has not been extensively studied in head injury

b. Magnesium:

By virtue of its ability to antagonize the actions of calcium , anatagonism of glutamate release and NMDA receptor blockade magnesium has been proposed to protect the ischemic brain. Though the results of small trials have not been encouraging they have provided the sample for large ongoing randomized trial (IMAGES- intravenous magnesium efficacy in Stroke), the results of which are expected.

c. Glutamate antagonist:

Recent microdialysis experiments have shown association between brain glutamate levels and neurological deterioration. Major effects of glutamate are mediated through NMDA receptors. Competitive NMDA antagonists, selfotel and non competitive antagonist like dizocilpine dexanibol and aptiganel have been subjected to phase III trials. The Selfotel study was prematurely terminated because of concerns relating to increased mortality[38]. Human studies in head injury with non competitive NMDA antagonist dizocilpne and aptiganel also had to be prematurely terminated because of unacceptable side effects. A trend towards beneficial effect in head injury has been seen in a trial with dexanabinol. Lubeluzole is an agent that inhibits glutamate release or glutamate initiated nitric oxide toxicity. Modest beneficial effect has been reported with this drug in patients with stroke. Dextromethorphan and its metabolite dextrorphan are also non-competitive NMDA antagonists useful in focal cerebral ischemia. So is dexmedetomidine, an alpha 2 agonist, but they all need to be tried in head injury.

d.Antioxidants

Although initial clinical trials of polyethylene glycol conjugated superoxide dismutase (pegorgotein) were encouraging, a more recent large randomized outcome study has failed to demonstrate any benefit, and large Phase III trials of the novel antioxidant, tirilazad (which had proven efficacy in experimental models) have shown no improvement in outcome in clinical head injury.

Tirilazad mesylate (TM): Tirilazad mesylate (TM) is a 21-aminosterid (lazaroid) that was developed specifically to maximize their inhibition of lipid peroxidation by glucocorticoids such as methylprednisolone, but eliminate the unwanted glucocorticoids effects. The lazaroids are potent antioxidants, 100 times more potent than the corticosteroids, therefore may be efficacious in the clinical management of acute CNS injury. The mechanism of action appears to be cell membrane preservation by inhibition of lipid peroxidation.

Superoxide dismutase: Superoxide dismutase (SOD) is a specific scavenger of superoxide anion. Superoxide anion is capable of producing significant biological injury. It is generated on reperfusion of post ischemic tissues. Because, superoxide dismutase (SOD) has a biological half-life of only five minutes, it has been conjugated with polyethyleneglycol (PEG-SOD) for use in humans.

e. Lidocaine

Possible mechanisms for cerebral protection by lidocaine include deceleration of ischemic transmembrane ion shifts, reduction in CMR, modulation of leukocyte activity, and reduction of ischemic excitotoxin release.

f. Furosemide

It is a sulfonamide that inhibits distal tubular reabsorption. It has been shown to decrease ICP effectively without the transient ICP increase that can be seen with mannitol. An additional action of furosemide, which may be of benefit, is its reduction of cerebrospinal fluid formation. The dose of furosemide may be upto 1 mg/kg, depending on the degree of diuresis required.

g. Tromethamine

Tromethamine (THAM), a weak base which crosses the plasma membrane and acts directly on intra cellular acidosis has been used with success in models of experimental head injury. THAM has been used in head injuries in man and is reportedly useful along with hyperventilation to reduce brain edema and intracranial pressure .

h. Perfluorocarbons

Perfluorocarbons have been mainly used in decreasing cerebral emboli associated with cardiac surgery, and no controlled trial is available on its use following head injury. These compounds have high gas affinity, hence may decrease cerebral gaseous microemboli. They may improve flow characteristics in areas of decreased perfusion.

i. Other drugs

Other drugs used include high dose aprotinin and acadesine, an adenosine-regulating agent. The mechanism of action is unknown; however it is tempting to speculate that the anti-inflammatory properties of aprotinin may be responsible. Again, the possible mechanism of action of acadesine is unknown, but may involve decreased excitatory transmitter release or reduced granulocyte accumulation[32,36].

However despite an extensive understanding of the pathophysiology of traumatic brain injury and convincing success in experimental animals, success with pharmacological cerebral protection has been very limited.

CONCLUSION

Pathophysiology of traumatic brain injury is multifaceted, wherein multiple mechanisms are simultaneously operative. It is unlikely that a single treatment aimed at a single mechanism will be successful. The existence of these mechanisms and the relative importance of each of these mechanisms have never been satisfactorily demonstrated in human studies and most of our inference is from animal studies.

Hemodynamic and physiological manipulations for cerebral protection, though theoretically sound have not been practically successful. Following the relative failure of barbiturates and hypothermia the possibilities and limits of metabolic brain protection seems to be restricted. The balance of hopes and actual achievements in pharmacological brain protection is not satisfactory. Nearly all the compounds of proven efficacy in animal models have failed to demonstrate consistent usefulness in clinical trials,

To quote Cohadon[1] "The present concept of brain protection brings together in a unique piece of mechanism thinking, facts, hypothesis and hopes. The investigation of biochemical cascades allows a scientific description of facts: the assumption that specifically these biochemical events are a major aspect of the secondary evolution of brain insult is for a large part hypothesis: the proposal that appropriate drugs could oppose this evolution in a clinically meaningful manner is as yet only a hope. Such a mixture of solid data, nice ideas and dreams for a better world is typical of ideological thinking and to some extent brain protection

is a medical ideology".

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