

# Pharmacologic Neuroprotection

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**Abstract:** Considerable progress has been made in the understanding of the consequences of brain anoxia/ischaemia and reperfusion on metabolism and neuronal viability. Neurons are particularly susceptible to ischemic injury because they have a higher demand for energy and limited energy stores that get depleted within 2 to 4 minutes of anoxia. Neuroprotection involves provision of the means to prevent or minimize injury to neurons using treatments used to protect neural tissue from cellular events induced by deprivation of oxygen or glucose or both to the brain. When confronted with the need for neuroprotection, a clear understanding of the underlying mechanisms of both injury and treatment are required to decide on the best approach. Neuronal tissue injury processes continue over a prolonged period of time, implying that neuroprotective therapies may be initiated beyond the acute post-injury phase. Drugs targeting prolonged injury mechanisms, such as mitochondrial dysfunction, axonal injury, and neuro inflammation have a better chance of limiting irreversible damage. Barbiturates, etomidate, propofol, isoflurane, methylprednisolone, tirilazad mesylate, nimodipine, nicardipine and mannitol have all been used for neuroprotection, combining physiologic (oxygen, hypothermia), pharmacologic (erythropoietin derivatives), thrombolytic and anesthetic therapies. The concept of an ischemic penumbra and the chemical brain retractor concept have aided the emergence of neuroprotective strategies that play important roles in perioperative situations such as cardiopulmonary bypass, deep hypothermic circulatory arrest, carotid surgery, and cerebral aneurysm surgery. Pharmacological neuroprotection is also exhibited in subarachnoid haemorrhage, stroke, brain trauma, spinal trauma, induced hypotension, and post cardiac arrest resuscitation. Important strategies in neuroprotection include maintenance of normoxia, adequate cerebral perfusion pressure, maintenance of mild hypothermia and timely surgical intervention.

**Keywords:** Pharmacology; neuroprotection

## 1. Introduction

Traumatic brain Injury (TBI) as well as cardiac and neurointerventional procedures often result in devastating individual neurological disability and a significant burden on society.

Neuroprotective pharmacological agents can be used to reduce or eliminate secondary brain injury. While there is currently no single pharmacological therapy that will unequivocally improve clinical outcomes, several agents have demonstrated promising clinical benefits. The pharmacological approach to neuroprotection against ischemic brain injury aims at blocking the biochemical, metabolic and cellular cascades leading to cell death.

The concept of an ischemic penumbra following vascular occlusion results in a central focus of infarct unless reperfusion is quickly established. The penumbra contains electrically inexcitable but essentially viable cells and, with time, the infarct grows in size because the perifocal tissues are recruited into the infarction process. Hence, there exists a 'therapeutic window' during which time perifocal tissues may be salvaged by reperfusion or by exhibiting pharmacological agents that support cells at risk over a critical period.

The primary goal is to limit the devastating consequences of no flow or low flow in the penumbra and prevent reperfusion-induced secondary insults. Almost all steps leading to cellular death represent putative targets for neuroprotective agents. The main strategies are decreasing ischemia duration, blocking ionic Na<sup>+</sup>, Ca<sup>2+</sup> glutamate receptor-channel-mediated flux, eliminating free oxygen

radicals, inhibiting apoptosis, decreasing the inflammatory secondary phenomena, promoting tissue growth and repair.

Cerebral protection may be initiated prior to the occurrence of brain ischemia by reducing demand for energy (using barbiturates) or blocking mediators of ischemic injury. Therapeutic efficacy is lost if treatment is delayed more than 1 hour after an event /impact. Sooner the neuroprotective drug is given, the better is the outcome. However, the requirement for informed consent in the clinical situation (such as road accident) may preclude administration of neuroprotectants within the laboratory-defined therapeutic window of efficacy.

## 2. Pathophysiological Aspects of Neuronal Injury

The cascade of events leading to excitotoxic cell death are as follows:

- 1) As the blood or oxygen supply to the brain is impaired, the ATP content falls due to a decrease in its production.
- 2) Subsequently, energy-dependent processes such as Na/K ATPase transporter activity decreases.
- 3) Activation of ATP-dependent K<sup>+</sup> channels (K<sub>ATP</sub>) and opening of calcium-activated K<sup>+</sup> channels are interrupted, which leads to neuronal hyperpolarization and then electrical silence just after the onset of ischaemia.
- 4) Loss of activity of the Na/K ATPase transporter leads to the accumulation of K<sup>+</sup> outside neurons and subsequent slow depolarization. Once a threshold is reached,

depolarization with massive  $\text{Na}^+$  and  $\text{Ca}^{2+}$  entry into cells leads to a complete loss of membrane potential.

- 5) This depolarization triggers the release of excitotoxic glutamate from nerve terminals, which activates both *N*-methyl-D-aspartic acid (NMDA) and  $\alpha$ -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors enhancing  $\text{Na}^+$  and  $\text{Ca}^{2+}$  entry and  $\text{K}^+$  extrusion from neurons through the glutamate receptor-coupled cationic channels.
  - 6) During ischaemia,  $\text{Ca}^{2+}$  cytosolic concentration markedly increases, due to activation of both NMDA receptors and voltage-gated  $\text{Ca}^{2+}$  channels and the blockade of the Na/Ca transporter and release of  $\text{Ca}^{2+}$  from intracellular stores.
  - 7) This significant increase in cytosolic calcium concentration plays a prominent role in the development of ischaemic injury and neuronal death by necrosis and/or apoptosis.
  - 8) Detrimental effects occur during reperfusion also as a result of excessive production of superoxide and generation of free radicals. Reactive oxygen species cause lipid and protein oxidation and DNA damage.
  - 9) Necrosis causes disintegration of the cell, which spreads to adjacent neurons due to the release of cytochrome C
- 10) This leads to activation of caspase 3 and then programmed cell death. Apoptosis is tightly regulated by both antiapoptotic factors (bcl-2) and proapoptotic factors (bax, bad).
  - 11) Tyrosine phosphorylation, triggered by brain-derived nerve growth factor (BDNF) and nerve growth factor (NGF), plays a major role in the inhibition of neuronal apoptosis.
  - 12) At the early stage, peri-infarction depolarization may contribute to increased neuronal damage triggered by excitotoxic injury.
  - 13) Inflammatory mediators such as i-NOS, Cox-2, IL-1 and monocyte chemo-attractant protein-1 (MCP-1) are generated by microglia, macrophages, leukocytes, as well as astrocytes and neurons in the ischaemic area.
  - 14) In the minutes following initial vessel occlusion, there is an increase in the expression of transcription factors such as c-fos, c-jun followed by a second wave of heat shock genes (HSP-70) that increase their expression in the 1–2 h to 1–2 day period. An increase in chemokine expression (IL-1, IL-6, Il-8, TNF- $\alpha$ , etc.) is observed in the first 24 h after occlusion. (Fig 1)

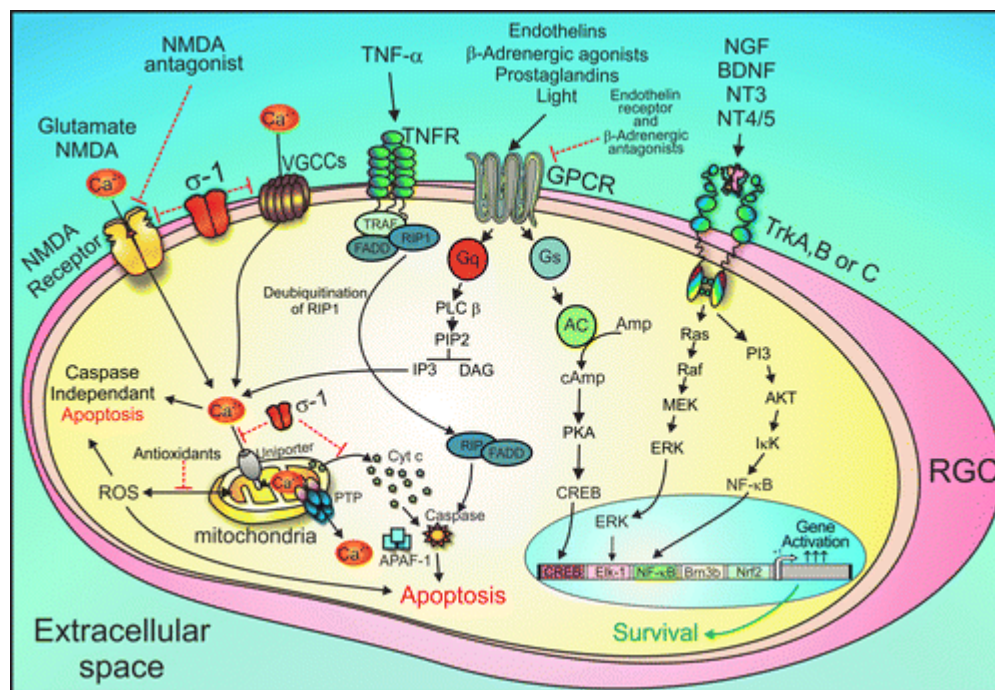


Figure 1: Targets of Neuroprotection

The major mechanisms of ischemic cell death include excitotoxicity, oxidative stress and peri-infarct depolarization in the early stages, and inflammation and apoptosis later. However, specific repair processes are also triggered by the anoxic/ischemic injury in the brain.

The relative involvement of grey versus white matter in the ischemic zone has an impact on outcome, as ischemia in deep white matter is generally severe due to the lack of collateral blood supply in this area. In addition to neurons, stroke injury also involves endothelial and smooth vascular cells, astrocytes and microglial cells and associated tissue matrix proteins. Plasminogen activator and matrix metalloproteases (MMPs) are the most important factors that

contribute to matrix proteolysis after disruption of the neurovascular matrix by ischemic injury.

Inflammation may promote repair through the ability of T cells to produce neurotrophic factors such as BDNF, NGF and neurotrophins 3, 4 and 5, which facilitate neural cell proliferation and differentiation. Macrophages also play a role in this process through secretion of cytokines (IL-1 $\beta$  and IL-6), chemokines and TNF- $\alpha$ . Cellular repair by remyelination and reorganization of compensatory pathways, such as increased activity of contralateral or undamaged adjacent brain areas, may attenuate the long-term effects of ischemic injury on outcome.

### 3. Monitoring Neuroprotection

Transcranial Doppler ultrasonography, which measures blood flow velocity can identify both low flow states and embolic phenomena.

Reflectance oximetry, by using a fiberoptic catheter, permits continuous jugular venous oxygen saturation monitoring. This saturation is a measure of global cerebral oxygenation and the normal value is about 55 to 75%.

Continuous near-infrared spectroscopy (NIRS) monitoring may prove useful in determining episodes of impaired cerebral oxygenation. NIRS continues to examine the oxygenation state of capillary hemoglobin even during deep hypothermic circulatory arrest (DHCA).

Neurochemical monitoring is the use of microdialysis for sampling of chemical substances from the interstitial fluid of the brain. Many interstitial markers reliably reflect secondary brain ischemia & infarction. pH is used for monitoring acidosis, glutamate levels serve as markers for excitotoxicity. Increased lactate and decreased glucose, indicates accelerated glycolysis commonly occurs with cerebral ischemia or hypoxia.

### 4. Neuroprotection Strategies

#### 4.1 Pharmacological Neuroprotection in Head Injuries

Traumatic brain injury (TBI) is a major cause of death and disability worldwide. Neurological injury after TBI can be mechanistically classified into two stages: primary and secondary injury. Primary brain injury occurs at the moment of focal impact. In the hours following the trauma, secondary brain injury may result from changes in cerebral blood flow and intracranial pressure (ICP), hypoxemia, systemic hypotension, and cerebral edema. These deleterious effects of secondary brain injury may be attenuated by early pharmacological therapy in the emergency room and intensive care unit (ICU, aimed at reducing intracranial pressure (ICP) and optimizing cerebral perfusion. The initiation of neuroprotective strategies target specific and limited steps in the extensive chemical cascade to prevent mortality and improve neurological outcomes. Monitored pharmacological brain protection provides rest the brain during a temporary regional disruption in nutrient flow. EEG, evoked potentials, stump pressure, trans-cranial Doppler have to be monitored to optimize therapy, as this permits rapid application of the most appropriate means for correcting an imbalance.

Of the clinically available anaesthetics, barbiturates have the greatest potential to protect the brain from ischemic injury mediated via reduced metabolic demand. Barbiturate neuroprotection is likely to be most marked in focal ischemia where there remains a marginally perfused penumbral zone in which oxygen supply is reduced but synaptic activity is still going on. Greatest efficacy has been observed when EEG activity remains present during the ischemic period (e.g. focal ischemia) and little efficacy was observed when the EEG is ablated during ischemia (e.g. complete transient global ischemia). In global total ischemia

or global total anoxia, barbiturates only reduce the rate of ATP fall for the first 20 to 30 seconds. This is because profound ischemia flattens the EEG in 15 to 20 seconds, after which time the rate of ATP fall will be the same regardless of the presence or absence of barbiturates. Deep barbiturate anaesthesia can reduce CMR to the same extent as hypothermia to 30°C. 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. Inhibition of the release of excitatory neurotransmitters (aspartate, taurine, glutamate & GABA) has been demonstrated even if barbiturates are administered after the period of ischemia, suggesting that at least some of the benefit occurs after reperfusion. In patients with intracranial hypertension, barbiturate therapy would be expected to reduce CMRO<sub>2</sub>, 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 (cerebral perfusion pressure = mean arterial pressure - ICP). Barbiturates appear to be protective in the setting of focal and incomplete ischemia, but not complete, global cerebral ischemia. Protection during focal ischemia may be due to decreased production of free fatty acids during ischemia or inhibition of excitotoxic mechanisms. Barbiturates appear to be only effective at brain protection, when ischemia is incomplete, i.e. there is still some electrical activity.

High-dose barbiturate therapy should only be considered for haemodynamically stable salvageable severe head injury patients with intracranial hypertension refractory to maximal medical and surgical ICP lowering therapy.

Pentobarbital has been used extensively for high dose barbiturate therapy because of the predictability of metabolic clearance (serum half life 21 hours), the availability of serum drug levels, and the lack of active metabolites. Serum drug levels of 25 to 40 mg/l are associated with barbiturate induced coma, electrically silent EEG, and a maximal reduction in cerebral metabolic rate (CMR). A loading dose of 10 mg/kg of pentobarbital over 30 minutes, with 5 mg/kg every hour for 3 doses, and maintenance dose of 1 mg/kg/hr is recommended. Pentobarbital dose should be adjusted to avoid systemic complications like cardio-respiratory collapse by supporting cardiac output and cerebral perfusion pressure during the loading process. Vasoconstrictors, inotropes and volume expansion may be required to support CPP. Once, a therapeutic barbiturate effect has been achieved, a maintenance infusion of 1 to 3 mg/kg/hour is usually sufficient to cover clearance of the drug and to achieve an EEG pattern of burst suppression. (1)

Continuous EEG monitoring is useful in tracking the depth of barbiturate therapy. Monitoring of blood level and maintaining it at 25 to 40 mg/ml range may prevent excessive recovery times from barbiturate coma. (2,3)

Thiopentone is a rapidly acting barbiturate, which is often used if the desired effect is necessary immediately. In this context, doses of 3 to 5mg/kg IV will produce transient (<10minutes) 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 ischaemia. Loading dose consists of 25 to 50mg/kg. This is followed by an infusion 2 to 10mg/kg/hr to give plasma concentration of 10 to 50mg/L. Accumulation occurs and recovery may be prolonged over a period of days before neurological assessment can be made. Nitrous oxide (N<sub>2</sub>O) is not used when barbiturates are used for providing brain protection. This regimen is usually reserved for high-risk cases. The potential benefit should outweigh the necessity for postoperative ventilator and circulatory support. It is preferable that barbiturates be administered prior to vessel occlusion so that it can circulate to the area which is to become ischemic. There appears to be a narrow therapeutic window post-insult, during which therapy may be effective. Treatment upto 2 hours post-insult may be beneficial, but after this time, it may actually be harmful.
- 2) Low initial dose followed by infusion. This regimen is used to control ICP. A dose of 1 to 3 mg/kg IV is followed by an infusion of 0.06 to 0.2mg/kg/min and useful in head injuries to decrease raised ICP. Intermittent low doses of thiopentone (1 to 3 mg/kg) will lower ICP & 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. This time is much shorter than the probable period of surgically induced reversible focal ischemia (carotid surgery or extracranial-intracranial bypass or temporary clamping during surgery for management of intracranial aneurysm). It is suggested that the drug may be delivered to the area that may become ischemic after clamping. When ischemia is induced after this, the level would remain high in severely ischemic areas since the drug would not be washed out of the area. Local protective effects could thus continue longer than the general EEG suppression.
- 4) 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 and cerebral edema peaks at 48 hours after an ischemic injury.
- 5) Timing of barbiturate therapy: Cerebral protection is best initiated prior to the occurrence of brain ischemia. Barbiturate therapy appears to provide some benefit even if administered after a focal ischemic insult. Barbiturates have been shown to diminish infarct size when administered after focal ischemia and a beneficial effect can be seen when barbiturates are given upto 120 minutes after middle cerebral artery occlusion. (4)

Methohexitone is less frequently used because of the possibility of exacerbation of seizure disorders.

#### 4.2 Pharmacological Neuroprotection During CPB

With EEG monitoring, barbiturate therapy can be titrated to the point of burst suppression. If thiopental is administered shortly before the onset of circulatory arrest, adequate blood and brain tissue levels will be present when bypass flow is restarted because no redistribution or hepatic metabolism will occur during arrest. Thus, the brain should benefit from barbiturate neuroprotection throughout the rewarming period and potentially into the early post bypass period, when it is no longer protected by hypothermia.

There are 2 reasons why thiopental should not be administered early in the cooling phase.

- 1) At normothermia & hypothermia, barbiturates cause cerebral vasoconstriction and reduce cerebral blood flow to nearly half of control values.
- 2) If barbiturate is administered before the onset of CPB or early during the cooling process, it may impair effective brain cooling because effective global cooling is dependent on cerebral blood flow.

Barbiturates prevent the increase in high-energy phosphate stores and intracellular pH in the brain that normally occurs during cooling. The onset of circulatory arrest should be delayed by 5 minutes after barbiturate administration to allow effective circulation to the brain. A thiopental dose of 10 mg/kg is hemodynamically well tolerated when administered before circulatory arrest and does not seem to be associated with difficulty in weaning. Burst suppression or isoelectric EEG for cerebral protection is not required to elicit maximum neuroprotection as there is a greater reduction in cerebral blood flow with a completely isoelectric EEG than with 50% burst suppression. Reduction in EEG activity is associated with a significant reduction in middle cerebral artery flow velocity (VMCA), but complete EEG silence may give more protection than 50% burst suppression especially when deep hypothermic cardiac arrest (DHCA) time lasts less than 60 minutes.

#### A. Pharmacological Neuroprotection During Carotid Endarterectomy

The main cause of ischemic damage during carotid endarterectomy is the formation and migration of emboli from the plaques. A decrease in cerebral perfusion during clamping can also lead to brain ischemia. When cerebral protective drugs are employed, they must be given prior to the carotid cross clamping. If drug treatment is initiated after cross clamping, areas of lowered cerebral perfusion may not get adequate doses of the drug (for maximum protection) from collateral flow. Continuous IV infusions are better than intermittent infusions for cerebral protection. Intermittent boluses of thiopental give protection for approximately 15 minutes. Continuous infusions of IV anaesthetics have the benefit of maintaining their cerebroprotective effect over the duration of the carotid occlusion period. Infusions also allow the anesthesiologist to titrate the infusion rate carefully to maintain burst suppression while minimizing the flat-line periods that occur with the bolus technique. Etomidate may be used for cerebral protection in patients with a significant cardiac history.

**Monitoring parameters:** Intraoperative measurement of common carotid stump pressure, monitoring of somatosensory evoked potentials or homolateral cerebral blood flow have been used to guide the decision to use a temporary bypass shunt. Pharmacological brain protection may be employed during carotid endarterectomy if electrophysiologic or clinical evidence of ischemia does not resolve with conventional therapy such as increasing circulating volume, increasing BP and shunt insertion. During carotid surgery, barbiturate-induced burst suppression consistently induces significant inverse steal to such an extent that very significant increases in stump pressure (up to 50mmHg) may be seen. Increases of stump pressure of this magnitude explains a significant part of the ‘protective’ effect seen with barbiturates in carotid endarterectomy. Thiopental and drugs that decrease CBF similar to thiopentone have the potential to decrease the number of emboli delivered to the cerebral circulation by decrease in cerebral metabolism. Inverse steal does not occur with sevoflurane. Barbiturates, mild hypothermia, mild hypocarbia and hypertension are recommended for protection during regional ischemia in carotid surgery.

### B. Pharmacological Neuroprotection during Cerebral aneurysm surgery

During cerebral aneurysm surgery, temporary clamping of feeder vessel may become necessary to control bleeding or for proper placement of the final clip. Though a valuable technique, this practice is complicated by a risk of focal infarction, particularly in sensitive areas of the brain such as that territory supplied by the middle cerebral artery (MCA). In this situation, pharmacological brain protection may be used to protect against ischemic sequelae. Barbiturates have been widely used for the protection of brain during cerebral aneurysm surgery. After induction of burst suppression, patients routinely tolerate 14 minutes of temporary focal occlusion during clip ligation of cerebral aneurysms. An anesthetic protocol of mannitol & pentobarbital bolus prior to and during temporary ischemia, permits 8 minutes of maximal occlusion time without immediate postoperative neurological deficit. A protocol of hypothermia, induced hypertension, and intravenous mannitol gives 20 minutes maximum occlusion time. Propofol and etomidate provide adequate brain protection by EEG burst suppression. After cerebrovascular surgery, if an ischemic deficit is found which can be surgically corrected (intimal flap, thrombus, or malpositioned aneurysm clip), pharmacological brain protection may be employed while preparations are made to reoperate.

### C. Pharmacological Neuroprotection In Spinal Trauma

In patients treated within 8 hours of injury with high doses of methyl prednisolone (30 mg/kg bolus and 5.4 mg/kg/hr for 23 following hours), a certain degree of increased recovery of neurological function was observed at 6 weeks & 6 months and confirmed at 1 year follow up (The National Acute Spinal Cord Injury Study).

### D. Pharmacological Neuroprotection in Subarachnoid Hemorrhage

Subarachnoid haemorrhage: The most conspicuous cause of brain ischemia following subarachnoid haemorrhage (SAH) is secondary ‘vasospasm’. The use of nimodipine (60 mg

every 4 hours for 3weeks) has shown some benefit in the management of vasospasm. The risk of cerebral infarction is reduced by 34% and the incidence of poor outcome by 40%. Nimodipine is widely accepted as a standard treatment in SAH patients in the acute stage. Those with moderately severe deficits at the beginning of the study obtain the greatest benefit.

### 4.3 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. It is sometimes necessary to correct hypovolemia and provide pharmacologic inotropic support with invasive cardiovascular monitoring. Cerebral protection with barbiturates may be limited in patients with a reduced cardiac function.
- 2) The profound respiratory depressant effect of barbiturates may need transient respiratory support, hence continuous monitoring of SpO<sub>2</sub> and ETCO<sub>2</sub> is advisable.
- 3) Long-term barbiturate therapy is associated with hypothermia and depression of immune responses. This increases susceptibility to infections.
- 4) Neurologic evaluation of the patient in induced barbiturate coma is difficult. The use of intracranial pressure monitoring devices and electrophysiologic monitoring (e.g. evoked potentials, which can be monitored even when the EEG is isoelectric), coupled with early CT scan, MRI or angiography can help identify adverse developments.
- 5) Since 99% of administered thiopental is metabolized in the liver, special attention is required in patients with hepatic dysfunction. A sophisticated intensive care setting is required to support patients who are selected to benefit from this mode of therapy.

### 4.4 Alternatives to Barbiturates

#### a) Etomidate

Like barbiturates, etomidate produces EEG burst suppression and reduces CMR for glucose and oxygen. Clinically, etomidate decreases CBF, CMRO<sub>2</sub> and ICP whereas carbon-dioxide (CO<sub>2</sub>) reactivity, haemodynamic stability and cerebral perfusion pressure (CPP) are maintained. It inhibits release of excitatory neurotransmitters. It may be useful for neuroprotection when temporary vessel occlusion is required. It is routinely used in some centers to increase safety during temporary arterial occlusion employed for surgery of complex cerebral aneurysms. Doses of 0.4 to 0.5 mg/kg-1, causes burst suppression in less than 2 minutes in the majority of patients, with a maximum drop in BP of 5%. Consciousness is usually regained in 3 to 5 minutes due to redistribution. Additional doses in increments of 0.1mg/kg-1 may be given as electrical activity returns. Etomidate 1 mg/kg-1 can also be administered as a bolus followed by an infusion of 10 mg/kg-1min-1 to maintain burst suppression during temporary arterial occlusion for complex intracranial aneurysms. This regimen is well tolerated. Etomidate has good hemodynamic stability 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 anaesthetic care but not its utility in neurosurgical cases in which patients are routinely administered high doses of steroids. EEG excitation, abnormal movements & vomiting are other adverse effects that can occur. Etomidate has been associated with renal failure secondary to the propylene glycol vehicle.

#### b) Propofol

The metabolic changes resulting from propofol anaesthesia closely resemble the homogenous depression of CMR caused by barbiturates and etomidate. Propofol reduces cerebral metabolism with a consensual reduction in EEG activity, O<sub>2</sub> consumption & 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 of the drug (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-1hr-1) in humans, resulted in 55% depression in CMR for glucose, as measured using positron emission tomography. An EEG suppressive dose of propofol does not depress cardiovascular performance or excessively prolong emergence from anaesthesia when administered in conjunction with DHCA. Before initiating bypass, propofol is administered first as a 1 mg/kg-1 bolus, and then by a 100 mg/kg-1min-1 infusion, with dose increased every few minutes until the EEG displays a burst suppression pattern with a 1:5 ratio within 20 minutes, at a propofol infusion rate of between 200 & 300 mg/kg-1min-1 and continued at that rate until circulatory arrest, even though the EEG became isoelectric during bypass cooling. When CPB is resumed, the propofol infusion is restarted at the rate that provided pre bypass normothermic burst suppression and continued until the end of surgery.

#### c) Ketamine

Following ischemia, the pathological mechanism which results in cerebral infarction involves the release of a number of neurotransmitters a major one being N-methyl-D-aspartate (NMDA). Ketamine is a non-competitive antagonist at NMDA receptors & may therefore offer protection from the adverse effects of cerebral ischaemia.

#### d) Inhalational agents

1) **Isoflurane:** It 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<sub>2</sub> 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. The majorities of human studies indicate that isoflurane below 1 % has little effect on ICP. Isoflurane at inspired concentrations of 0.6 to 1.1 MAC does not alter CBF although 1.6 MAC doubles CBF. Isoflurane-anaesthetized patients demonstrated fewer ischaemic EEG changes during carotid surgery than patients anaesthetized with enflurane or halothane. The critical cerebral blood flow (CBF) below which ischaemic EEG changes occurred is 10 ml/100g-1min-1 during isoflurane anaesthesia versus 15 ml/100g-1min-1 during enflurane anaesthesia. The ischaemic threshold (cerebral blood flow at which ischaemic EEG changes occur) was higher in halothane-anaesthetized patients (18 to 20 ml/100 g-1 min-1, observed in a previous study) as compared to patients anaesthetized with isoflurane (8 to 10 ml/100g-1min-1). These results suggest some beneficial effect of isoflurane during transient incomplete regional ischaemia in humans.

- 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. Sevoflurane not only reduces brain damage following focal ischaemia but also improves neurological outcome following incomplete global ischaemia.
- 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 at the end of surgery. Desflurane treatment for cerebral protection significantly increases brain tissue oxygenation & pH above control levels. Desflurane attenuates hypoxic changes during brain artery occlusion. It also attenuates ischaemic lactic acidosis & decreases in pH during brain artery occlusion. Thiopental produced no change in tissue gases or pH, but temporary artery clipping in thiopental-treated patients decreased PO<sub>2</sub> by 30%. Significant increases in tissue PO<sub>2</sub> & pH and decreases in PCO<sub>2</sub> were observed during desflurane treatment for brain protection. During brain artery occlusion, tissue PCO<sub>2</sub> & pH returned to baseline levels & tissue oxygenation remained elevated in the desflurane group. The enhanced tissue oxygenation & CO<sub>2</sub> clearance that is observed with desflurane may be caused by the cerebral vasodilating effect of desflurane compared with thiopental.
- 4) **Nitrous oxide:** Some forms of cerebral protection may be adversely affected by the presence of nitrous oxide (N<sub>2</sub>O). In general, barbiturates have limited efficacy as cerebral protectants when nitrous oxide is part of the anaesthetic management. However, barbiturates are efficacious in those studies that did not employ nitrous oxide as part of the anaesthetic management. Nitrous oxide decreases isoflurane's efficacy as a neuroprotectant. (5)

#### e) Non-anesthetic agents as neuroprotectants

- 1) **Glucocorticosteroids:** Their efficiency in reducing vasogenic peritumoral edema is well documented. The

Second National Acute Spinal Cord Injury Study (NASCIS II) demonstrated that high dose methylprednisolone (30 mg/kg-1 bolus followed by 5.4 mg/kg-1 for 23 hours) was of benefit in spinal cord injury if treatment was instituted within 8 hours of injury. At these doses, methylprednisolone inhibits lipid peroxidation of neuronal, glial, and vascular membranes caused by O<sub>2</sub> free radicals. Lipid peroxidation is a process implicated in the pathophysiology of secondary central nervous system (CNS) injury. Lower doses had proven ineffective in the NASCIS I study. Similar high doses of methylprednisolone are of benefit in humans with severe head injury. The major mechanism for the neuroprotective effect of corticosteroids is probably inhibition of lipid peroxidation. This effect is extremely dose-dependent, which can account for methylprednisolone's effect at high doses (30mg/kg-1) but not low dose. Methylprednisolone's possible efficacy in subarachnoid haemorrhage induced vasospasm has also been ascribed to inhibition of lipid peroxidation. The anti edema effect of methylprednisolone may at least in part be a result of other actions that are not so dependent on high dose administration. Gastrointestinal bleeding and infection are two complications attributed to corticosteroids use. Glucocorticosteroids such as dexamethasone and methylprednisolone cause or exacerbate hyperglycemia. Hyperglycemia has been shown to increase brain injury in ischaemia. When corticosteroids are used it is essential to maintain precise control of blood glucose levels. The use of glucocorticoids is not recommended for improving outcome or reducing ICP in patients with severe head injury

- 2) **Tirilazad mesylate** (TM): It is a 21-aminosteroid (lazaroid) that was developed specifically to maximize the inhibition of lipid peroxidation by glucocorticoids such as methylprednisolone and eliminate the unwanted glucocorticoids effects. The lazarooids are potent antioxidants, 100 times more potent than the corticosteroids, & therefore may be efficacious in the clinical management of acute CNS injury. TM has been of benefit in both focal and global ischaemia with reperfusion. Its mechanism of action appears to be cell membrane preservation by inhibition of lipid peroxidation. Brain levels of the antioxidants vitamin E and, to a lesser extent, vitamin C are preserved in ischaemia-reperfusion, when TM is used. Post ischaemic recovery of extracellular calcium is more rapid with TM use, as is the recovery of intracellular pH and somatosensory evoked potentials. In subarachnoid haemorrhage, 6mg/kg-1day-1 (given in divided doses, 6 hourly) tirilazad administered for 10 days gives good result. The effect was most marked in men in whom mortality was reduced from 20% to 6%. Multicentre studies of high dose (15 mg/kg-1day-1) tirilazadin women reduces the incidence of vasospasm associated with aneurismal subarachnoid haemorrhage and the mortality in patients who were neurological grade IV or V on admission. There is also increasing interest in using tirilazadin combination with thrombolytic agents in the management of ischaemic strokes.
- 3) **Superoxide dismutase** (SOD): It is a specific scavenger of superoxide anion. Superoxide anion is

capable of producing significant biological injury. It is generated on reperfusion of post ischaemic tissues. Because superoxide dismutase (SOD) has a biological half-life of only 5 minutes, it has been conjugated with polyethyleneglycol (PEG-SOD) for use in humans. In a trial of PEG-SOD in patients with severe head injury, treatment was a single bolus IV administration, with a mean time from injury to treatment of approximately 4 hours. The % of time the ICP was above 20mmHg & the amount of mannitol required to control ICP were less in the moderate-dose PEG-SOD (5000 U/kg-1) & high-dose PEG-SOD(10000 U/kg-1) treated patients than in controls. Furthermore, outcome at 6 months was better in the high-dose PEG-SOD treated patients (i.e., fewer vegetative or dead)

- 4) **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. Nimodipine may be particularly effective at neuroprotection during hyperventilation, which is a common intervention during brain surgery. Alkalosis is particularly detrimental to neuronal survival during ischaemia. The protection provided by nimodipine during brain retraction ischaemia is not surprising, in light of its amelioration of hyperventilation alkalosis. Nimodipine is particularly effective in focal cerebral ischaemia, & thus would be expected to offer protection for intraoperative focal ischaemia such as temporary vessel occlusion and brain retraction. In light of nimodipine's safety as well as its efficacy when given prior to injury, it appears reasonable to consider nimodipine for intraoperative use, particularly where focal ischaemia can be anticipated (e.g., brain retraction or temporary vessel occlusion). Nimodipine has a beneficial effect on neurological outcome in patients recovering from aneurismal subarachnoid haemorrhage and has become a standard prophylactic therapy in such patients. This effect is thought to be mediated by nimodipine's effect on small vessel cerebral vasospasm. Treatment with Nimodipine decreases BP, decreases systemic vascular resistance & increases cardiac output. Nimodipine produced equivocal preservation of memory function 6 months postoperatively in a small controlled cardiac surgical trial. Nimodipine is a cerebral vasodilator, conferring a physiologic effect of increased embolic load and obliterating any protective effect at the cellular & biochemical level. Neurological outcome was found to be better in patients treated with nimodipine within 24 hours of the onset of ischaemic stroke.
- 5) **Naloxone**: Treatment, at a dose of 0.8mg, improved outcome in patients with acute ischaemia & is markedly effective in hyperacute ischaemia. Intravenous naloxone treatment may be used in the evaluation of acute cerebral ischaemia to determine the potential reversibility of such injury.
- 6) **Nicardipine**: This drug is a calcium antagonist. Cerebral ischaemia causes a rapid shift of calcium from the extracellular spaces into cells. Nicardipine directly reduces calcium entry into ischaemic cells. Nicardipine can be administered into venous reservoir before DHCA

- 7) **Lidocaine:** As sodium influx is the first step in the ischaemic cascade, truncating  $\text{Na}^+$  influx represents a potential target for drugs to achieve neuroprotection. Several lines of evidence suggest that the local anaesthetic lidocaine, a blocker of voltage-gated  $\text{Na}^+$  channels, protects the brain against ischaemic damage. The ability of local anaesthetic agents to block the hypoxia-induced changes in  $\text{Na}^+$  influx rather than blocking propagation of action potential is predictive of their neuroprotective effects. Prophylactic infusion of lidocaine, substantially improves neuropsychologic outcome at 10 days, 10 weeks, and 6 months compared to a placebo control. Lidocaine infusion was begun at induction of anaesthesia & continued for 48 hours. Following a 1 mg/kg-1 'bolus' over 5 minutes, followed by 240 mg over the first hour, 120mg over the second hour, and then 60 mg/hour-1 to target plasma concentration of 6 to 12 mmol litre-1 is selected. Possible mechanisms for cerebral protection by lidocaine include deceleration of ischaemic trans membrane ion shifts; reduction in CMR; modulation of leukocyte activity; and reduction of ischaemic excitotoxin release.
- 8) **Gabapentin:** It is neuroprotective against focal cerebral ischemia related to expression of Hsp70. The ischemic pathway overlaps greatly with seizure processes and therefore anticonvulsants have been proposed as possible neuroprotective agents. High-dose gabapentin decreases acute seizure frequency and reduce brain atrophy. Low-dose gabapentin also has a neuroprotective effect apart from anti-seizure activity. Gabapentin directly inhibits necrotic responses to focal ischemia but fails to inhibit apoptosis that is concurrently stimulated, with the net result being neuroprotective in 24 hours. (6)
- 9) **Growth Hormone:** Patients with TBI-induced damage to the anterior pituitary often demonstrate behavioral and cognitive impairment, which may be related to GH deficiency. GH deficiency is defined as peak GH values below 7.5 ng/mL in response to the GH-releasing hormone-arginine test is commonly observed after TBI and may contribute to cognitive and behavioral dysfunction in these patients. Furthermore, GH is thought to facilitate neurogenesis, neuronal differentiation, and survival of neurons after TBI, and may play a role in facilitating neuronal recovery in TBI patients without GH deficiency. The initial dose of GH replacement therapy is 0.3 mg/day for 15 days, and progressively titrated to 0.8-1.0 mg/day to achieve an insulin-like growth factor (IGF)-1 plasma level between 0 and +2 standard deviations (SDs) of the normal range for age. After 1 year of GH replacement therapy, the treatment group demonstrate a significant improvement ( $p < 0.05$ ) in most cognitive functions, such as attention and executive function, and a non-significant trend ( $p < 0.07$ ) towards improvement in spatial orientation and verbal memory test. Similar improvements were also demonstrated in ADL and four areas of QoL, including intellectual, psychological, functional, and personal domains.(7,8)
- 10) **Statins:** Statin therapy results in long-lasting improvements in functional outcomes after TBI, and enhances neuronal survival in the hippocampus. Statins induce neurogenesis and angiogenesis after brain . Rosuvastatin 20 mg/day initiated within 24 h of moderate-to-severe TBI reduces inflammatory cytokines and improves functional outcomes in humans. The levels of TNF- $\alpha$  are significantly reduced. Statins reduce proinflammatory mediators and improve functional outcomes after TBI in humans. Patients who discontinued statin therapy had a fourfold higher mortality rate compared with patients who continued statins following TBI. Abrupt, unintended discontinuation of statin therapy is associated with an increased risk of mortality in the elderly TBI population. (9)
- 11) **Marijuana:** Cannabinoid analogs have been shown to have neuroprotective by a reduction in glutamate neurotoxicity, free radical damage, and inflammation. The cannabinoid analog dexanabinol is highly neuroprotective, and may improve the control of ICP. The mortality rate in the THC-positive group was 2.4 % compared with 11.5 % in the THC-negative group ( $p < 0.05$ ), and a THC-positive screen was independently associated with survival after TBI. (10,11)
- 12)  **$\beta$ -Blockers:** Severe TBI is often associated with a tremendous catecholamine surge, known as 'paroxysmal sympathetic storm', which may result in worsening secondary brain damage and multi-organ failure. The increased sympathetic activity reflects abnormally elevated plasma concentrations of the catecholamines epinephrine and norepinephrine in the first week after TBI, which subsequently leads to a pathologic vasoconstriction of cerebral vessels, reduced perfusion to the brain, and subsequent worsening of the brain injury. In-hospital treatment with  $\beta$ -blockers improves survival in patients after TBI. It has been hypothesized that the beneficial neuroprotective effects of  $\beta$ -blockers result from a downregulation of the catecholamine surge that occurs after TBI. Patients exposed to  $\beta$ -blockade and no  $\beta$ -blockade had a mortality rate of 13 and 22 %, respectively ( $p = 0.01$ ). The absence of  $\beta$ -blockade exposure was a significant risk factor for mortality. Pre-injury  $\beta$ -blockade improved survival following isolated severe TBI. (12,13)
- 13) **N-acetyl-l-cysteine:** The neuroprotective benefits of NAC have been demonstrated in stroke and TBI, mediated by its antioxidant and anti-inflammatory properties. 4 g loading dose followed by 4 g for 4 days and 3 g for 3 days is trial worthy.(14)
- 14) **Enzogenol:** Enzogenol is a pine bark extract from New Zealand that has been shown to have antioxidant and anti-inflammatory properties. Enzogenol (1000 mg/day) results in a significant reduction in cognitive failures after 6 weeks, with improvements in the frequency of self-reported cognitive failures.(15)
- 15) **Cerebrolysin:** Cerebrolysin is a neurotrophic agent that mimics the endogenous actions of neurotrophic factors on neuroprotection and repair after injury. It has been successful in improving cognitive function in Alzheimer's dementia and after stroke. (16)
- 16) **Nitric Oxide Synthase Inhibitor:** NO is an important compound in promoting secondary brain injury after TBI by causing cerebral dilation and induction of the production of reactive nitrogen species, and inhibition



of NO-mediated cascade has been shown to decrease ICP and improve outcomes.

- 17) **Furosemide**: It is a sulfonamide that inhibits distal tubular reabsorption and decreases ICP effectively without the transient ICP increase seen with mannitol. The drug reduces cerebrospinal fluid formation. The dose of furosemide may be upto 1 mg/kg-1, depending on the degree of diuresis required.
- 18) **Mannitol**: It is widely used in neurosurgical operations involving patients with cerebral edema and /or mass effect. Some of mannitol's potentially beneficial effects include osmotic diuresis, increased blood viscosity & free radical scavenging. Mannitol is used for control of raised intracranial pressure (ICP) after brain injury when high ICP is demonstrated. Given as a bolus intravenous infusion, over 10 to 30 minutes, in doses ranging from 0.25 to 1g kg-1 bodyweight. Hypovolemia should be avoided, serum osmolarity should be kept below 320 mOsm & serum sodium should be kept below 150mEq/L. Mannitol is added to the venous reservoir before DHCA is employed. Mannitol is well known to reduce cerebral edema after ischemia. Mannitol can also scavenge free radicals & thus reduce tissue damage caused by superoxide radicals. (17)
- 19) **Papaverine**: It is a smooth muscle relaxant that works by blocking calcium channels. It is used for topical application on arteries to reverse vasoconstriction resulting from manipulation (mechanical 'vasospasm'). It has also been given as intra-arterial injection. Dose used is 30mg in 9cc saline. It is applied on to vessels with gelfoam or cotton pledget soaked in this mixture & left in contact with vessels for 2 minutes. The solution can directly be applied to the vessels with a syringe & left in contact with them. Local application of controlled-release papaverine drug pellets have been safely used in preventing vasospasm. During cerebral aneurysm surgery, drug pellets are placed in cisterns over arterial segments
- 20) **Insulin**: Elevated intracellular glucose concentration at the time of a cerebral ischaemic insult may result in increased cellular lactic acidosis. This worsens ischaemic injury. Insulin has a neuroprotective effect.
- 21) **Glibenclamide**: The administration of glibenclamide, a sulfonylurea medication commonly used to treat hyperglycemia in patients with type II diabetes mellitus (DM), has been shown to improve neurological outcomes after stroke in humans, reduce secondary brain injury, and improve functional outcomes by blocking the sulfonylurea receptor 1 (SUR1), a nonspecific water channel that plays an important role in the development of cytotoxic cerebral edema following TBI. (18)
- 22) **Progesterone**: Progesterone rapidly crosses the blood-brain barrier and has several properties that make for a potentially useful pharmacological therapy after TBI, including antioxidant, anti-inflammatory, and remyelination effects after injury. medroxyprogesterone tablets (treatment) at a dose of 1 mg/kg 12 hourly by NGT for 5 days can be tried. (19,20)
- 23) **Erythropoetin**: possess anti-inflammatory and anti-apoptotic properties, and has neuroprotective effects 10,000 s/c for 7 consecutive days or 40,000IU s/c weekly for 3 doses. (20,21)

- 24) **Tromethamine (THAM)**: It is a weak base which crosses the plasma membrane and acts directly on intracellular acidosis has been used with in TBI with favorable effects on brain edema and intracranial pressure. (22)
- 25) **Perfluorocarbons**: Decreases cerebral emboli associated with cardiac surgery. These compounds have high gas affinity and decrease cerebral gaseous microemboli and improve flow characteristics in areas of decreased perfusion.
- 26) **Aprotinin**: High-dose aprotinin has anti-inflammatory properties and is neuroprotective.
- 27) **Acadesine**: Is an adenosine-regulating agent that decreases excitatory transmitter release or reduces granulocyte accumulation, thus protecting against stroke induced neuronal injury.
- 28) **Cyclosporin**: ciclosporin confers neuroprotection by inhibiting calcineurin, thereby inhibiting NO-mediated glutamate neurotoxicity. (23)

## 5. Conclusions

Although many drugs show promising neuroprotective effects in experimental models of focal or global ischaemia, to date not a single so-called 'neuroprotective' pharmacologic agent has demonstrated efficacy in a clinical phase III stroke trials.

The great majority of clinical trials testing neuroprotectants for the treatment of acute ischaemic stroke have failed to demonstrate any benefit on any major outcome endpoint.

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