Introduction

For brain metabolism, energy is derived from circulatory provision of oxygen and glucose. Surgery, anaesthesia, peri-operative stresses or other etiological factors can lead to decrease in oxygen supply leading to ischemia, with consequent interruption of metabolic process. This Ischemia stimulates active responses in the brain, which may persist long after substrate delivery has been restored. These responses include apoptosis and inflammation, inhibition of protein synthesis, sustained oxidative stress, and neurogenesis. All these factors culminate to ischemic brain damage, which may result in sub-clinical neurocognitive deficit to catastrophic neurological morbidity or death.

What is Cerebral Protection?

To tackle these problems, preemptive and resuscitation measures have to be taken, which is achieved by neuroprotection. This is a treatment protocol initiated before onset of ischaemia, with the objective of modifying intra-ischaemic cellular and vascular biological responses. Hence, during deprivation of energy supply, there is increased tolerance of tissue to ischaemia, resulting in improved outcome.

Following head trauma, secondary neuronal injury is triggered by physiological insults to the injured brain due to secondary ischemic episodes, which are major causes for bad outcome. Intensive care in acute head injury lies in the prevention, detection and reversal of secondary neuronal injury. Here, neuroresuscitation treatment protocol is instituted after the ischaemic insult due to TBI for prevention of secondary brain injury and optimization of reperfusion.

Historical notes

Cerebral protection was first attempted by Schafer and Hardin in 1952 for aortic arch surgery by insertion of small bore polyethylene tubes for circulatory support. Cooley in 1955 modified the process with mild-surface-induced-hypothermia and temporary shunts. First successful transverse aortic arch replacement was done by DeBakey and Crawford in 1957 by normothermic total cardiopulmonary bypass and cerebral protection by canulation and perfusion of both subclavian and both carotid arteries. Since then, much advancement has been done for brain protection by cerebral perfusion in both neuro and cardiac surgeries.

Pathophysiology (Ischaemic cascade)

In ischemic brain injury, energy supply falls short of the energy demand. It can be classified into three types:
a. Focal, characterized by the presence of surrounding non-ischemic region, e.g. embolic or thrombotic episodes or temporary arterial occlusion for surgical repair;
b. Incomplete global, e.g. hypotension or increased ICP;
c. Complete global, characterized by absent CBF e.g. cardiac arrest or hanging.

This ischemia can result in a spectrum of deficits, ranging from minor cognitive dysfunction to moderate focal functional deficits or catastrophic neurogenic death. High-risk groups include patients having carotid endarterectomy, cerebral aneurysm clipping, or cardiac surgery. In these planned surgical procedures, preventable procedures and therapies are attempted to protect the brain from injury.

In traumatic brain injury, the acceleration-deceleration forces can produce axonal dysfunction and injury, brain contusions, and axial and extra-axial hematomas. The microscopic changes are ischaemic cytotoxic oedema, astrocyte swelling with microvascular effacement and dysfunction, blood brain barrier disruption with vasogenic oedema, and inflammatory cell recruitment. Mechanisms involved in secondary neural injury include excitatory amino acid (EAA) release, intracellular calcium overload, free radical mediated injury and activation of inflammatory processes.

Following head injury, cerebral blood flow (CBF) shows a triphasic behaviour. Early, < 12 h, reduction of global CBF, sometimes to ischaemic levels. Between 12 h and 24 h, CBF increases and the brain may exhibit supranormal CBF, hyperaemia, with metabolism and blood flow often remaining coupled. After several days, CBF values begin to fall which may be associated with marked increases in large vessel flow velocity on transcranial Doppler ultrasound that suggest vasospasm.

**Modalities of cerebral protection**

The classic theory of cerebral protection is based on the concept that by decreasing cerebral metabolic demand as well as suppression of EEG, the neuronal survival will improve during periods of inadequate cerebral blood flow (CBF).

Hence, the protection strategies include:

- Decrease energy demand (cerebral metabolic rate): hypothermia, barbiturates, and other anesthetics.
- Increase energy supply (cerebral blood flow): induced hypertension, hemodilution, mannitol and thrombolysis.

Current modalities involving reduction of cerebral oxygen consumption and/or maintenance of cerebral blood flow includes:

☞ Deep Hypothermic Circulatory Arrest (DHCA)
☞ Retrograde Cerebral Perfusion (RCP)
☞ Antegrade Cerebral Perfusion (ACP)

**Deep Hypothermic Circulatory Arrest (DHCA)**

Hypothermia depresses cerebral metabolism, thereby, allow a safe period of total circulatory arrest. The relationship between cerebral metabolisms with temperature can be expressed according to van't Hoff's equation. Cerebral metabolism (CMR) is reduced
approximately 5% to 7% per each degree centigrade. Alpha-stat management maintains a better CBF to metabolism ratio during hypothermia than pH-stat management, but has the potential disadvantage of cerebral hypoperfusion because of low arterial carbon dioxide tension. Alternatively, pH-stat management with strongly uncoupled CBF and metabolism has the theoretical advantage of increasing cerebral perfusion and enhancing brain cooling, but possible drawbacks include raising intracranial pressure, increasing brain edema and brain embolism.

DHCA is a well established method of brain preservation during cardiovascular operations. However, periods of circulatory arrest greater than 40 minutes increases the risks of stroke and early mortality. At brain temperatures between 8-18°C there is loss of autoregulation resulting in “luxury perfusion” when cerebral blood exceeds metabolic demands with increased risk of brain embolism.

**Retrograde Cerebral Perfusion (RCP)**

RCP was first described as a treatment for massive air embolism during CPB by Mills and Ochsner in 1980. In 1982, Lemole and later on Ueda authenticated intermittent as well as continuous RCP for method of cerebral protection during aortic arch surgeries.

RCP neuroprotective mechanisms include maintaining of cerebral hypothermia, washout of embolic air or debris, cerebral perfusion and metabolic support. To improve neurological outcome, RCP has to be administered as an adjunct to DHCA.

After institution of CPB, a shunt line is set up between the arterial and venous lines. Central cooling is carried out to produce profound hypothermia to core temperatures ranging from 10°-20°C. After circulatory arrest, the arterial line is clamped while the shunt line is opened to allow the oxygenated blood to be diverted to the superior vena caval cannula. Desaturated venous blood is returned to the heart/lung machine via cardiotomy suction placed in the open thoracic aorta and via the inferior vena cava cannula. Flow (100-500 mL/min) is usually adjusted to maintain central venous pressure in the range of 15 to 25 mm Hg. RCP flow monitoring is usually carried out by either a central venous catheter or a jugular bulb catheter. Monitoring includes NIRS for cerebral oxymetry and TCD assessment of middle cerebral artery and central retinal artery flow.

Effectiveness of retrograde cerebral perfusion either via superior vena cava or even total body retrograde perfusion depends on competent valves in venous circulation and jugular vein as well as dominant collateral circulation via the azygos system.

During retrograde perfusion through SVC only 1/10’000 of flow reaches brain capillaries. (Ehrlich M. P. et al.; J Thorac Cardiovasc Surg 2001;122:331-338). Based on the capillary flow data, it is doubtful that RCP provides adequate perfusion to meet cerebral metabolic oxygen and substrates demand. RCP, in comparison to ACP, seems to be less affective but still providing some adjunctive brain preservation to DHCA.

**Antegrade Cerebral Perfusion (ACP)**

It is also known as antegrade selective cerebral perfusion (ASCP), regional low-flow cerebral perfusion (RLFP), selective cerebral perfusion (SCP), low-flow cerebral perfusion (LFCP), continuous cerebral perfusion (CCP) or regional cerebral perfusion (RCP).
addition to providing cerebral oxygenation, ACP can also provide blood flow to subdiaphragmatic organs as well.

First in 1986 spearheaded ACP for cerebral protection. Pigula et al in 1999 standardized its technique. Modern-day ACP has been evolved to a variety of cannulation techniques as well as separate arterial pump heads for cerebral and systemic circulations in order to provide individual hypothermic perfusion to each system. Cerebral perfusion is obtained by means of endo-luminal cannulation of the brachiocephalic and left common carotid arteries while the left subclavian artery is clamped or occluded with a Fogarty catheter to avoid the steal phenomenon or perfused separately. Other methods for antegrade brain perfusion are:

- Cannulation of the right axillary artery, via graft or cannula; perfusion to contra lateral hemisphere is via Circle of Wills
- Combined axillary and femoral artery perfusion.

The safe range of flow rates for cerebral perfusion during moderate hypothermia (22-25°C) is a perfusion pressure of no less than 30 mm Hg at a flow rate of 30ml/kg/min (20-94 ml/kg/min), with perfusion pressure of 40-70 mmHg, to provide > 50% of the physiologic flow rate of cerebral circulation.

In ACP, the moderate levels of hypothermia permit a shorter total perfusion time and thus a lower risk of microembolism, coagulopathy, hemorrhage, pulmonary and renal dysfunction.

**Physiological Approach**

**Temperature:**

In traumatic brain injury (TBI), reduction in brain temperature by only a few degree celsius provide major protection. Off-bypass hypothermia of out-of-hospital cardiac arrest patients, after restoration of spontaneous circulation, can appreciably improve outcome.

Peripartum neonatal asphyxial brain injury favourably responds to treatment with hypothermia. Here, total body cooling has more beneficial effect than selective head cooling.

Hypothermia reduces CMRO2 in a temperature dependent fashion, hence the hallmark of DHCA. Other mechanisms involved in its cerebral protective effect are suppression of glutamate release, blunted nitric oxide production, formation of free fatty acids, reduced calcium influx, and increased gamma-aminobutyric acid (GABA) release during ischemia. Hyperthermia worsens ischemic cascade and must be avoided.

**Ventilatory support:**

Patients with a GCS of ≤ 8 require intubation for airway protection and mechanical ventilatory support to ensure optimal oxygenation and PaCO2 control.

**Arterial carbon dioxide partial pressure (PaCO2)**

It was presumed that hyperventilation induced hypocarbia reduce arterial circulation and cerebral blood volume, thus offset increase in intracranial pressure. But, as documented in TBI by positron emission tomography, this phenomenon is actually detrimental as it
markedly increases volume of ischemic tissue. Maintenance of normocarbia is preferable. Hyperventilation is only indicated in refractory brain edema.

**Arterial oxygen partial pressure (PaO2)**

There is paucity of human data regarding the effects of normobaric hyperoxaemia in brain resuscitation. Reperfusion may increase formation of reactive oxygen species leading to secondary insults, thereby worsening outcome.

**Mechanical approach (Protection devices)**

Cerebral protection devices decrease the risk of perioperative stroke due to thromboembolism during CPB and interventional cerebro-vascular procedures. The accepted protected procedures are distal internal carotid artery occlusion balloon, filters or proximal occlusion devices, debris catchers and other balloon occlusion devices.

FDA-approved carotid stents, the Mo.Ma device, uses two balloons that are inflated in the external carotid artery and common carotid artery as well as act like endovascular surgical clamps. For procedural safety, the suspended blood is aspirated along with any particle. The Mo.Ma device also acts like a stent and provides an important alternative to surgery for stroke prevention.

Gaseous microembolization (GME) during cerebral circulatory support is associated with the occurrence of neurocognitive dysfunction and associated brain injury. Gas composition within the gaseous microemboli (GME), their volume and size also affects the severity of the neurological damage. As flow increases, the pressure difference over the filter screen will increase and air will be more compressed resulting in larger bubbles after the filter screen. Doppler and echographic techniques with acoustic GME counter are used to quantify GME and reduce the risk.

None of the devices or modifications has the ability to prevent embolization completely. An occlusion balloon leads to increased embolization into the external carotid artery. The effectiveness of the filter wire EX might be enhanced with design improvements. Neuroshield device is most effective for preventing polyvinyl alcohol particle embolization. Angioguard and GuardWire Plus devices have also been clinically used.

**Pharmacological approach**

**Barbiturates:**

Barbiturates are the only agents shown to be clinically useful in humans. It has been most extensively studied drug for cerebral protection. All other anaesthetic agents are evaluated for their activity vis-à-vis barbiturates.

In clinical doses, it reduces CMRO2 and brings about burst suppression leading to isoelectric EEC; resulting in decrease of neuronal energy consumption. Hence all metabolic energy is utilized for maintenance of cellular integrity. There is no further reduction in CMRO2 with increasing doses. Cerebral protection depends on free availability of active drug (not protein bound).

In incomplete ischemia, but not with complete cessation of CBF (complete ischemia), barbiturates provide cerebral protection. Thus, it reduces the detrimental effect of acute or
chronic hypoxia on the brain as long as the brain is actively functioning. It also protects even when the hypoxic event has depleted most of the brain energy stores. This protection may be related to a more basic subcellular mechanism such as free radical scavenging.

**Anaesthetics:**

These drugs depress cerebral metabolic rate (CMR), EEG burst suppression, cerebral blood flow (CBF) and flow-metabolism coupling to varying degrees in a nonlinear fashion. Factors such as blood glucose, brain temperature, and perfusion pressure are important determinants of ischaemic outcome and that anaesthetics independently modulate these factors.

All currently used potent volatile anaesthetics protect against both focal and global ischaemia. However, the improvement in outcome is transient in global ischaemia, whereas it is persistent in focal ischaemia.

**Isoflurane** causes a larger MAC-dependent depression of CMRO2. Because of this greater depression in neuronal activity, isoflurane abolishes EEG activity at clinically used doses. It modulates release of excitatory neurotransmitters and delay apoptosis, which may provide a window of opportunity for the administration of other cerebral protective agents.

**Desflurane** increases and maintains brain tissue PO2 to a greater extent than thiopental during temporary cerebral artery occlusion during cerebrovascular surgery.

**Sevoflurane**, at normal CO2 and blood pressure may be neuroprotective. However, high, long-lasting concentrations of sevoflurane (1.5 to 2.0 MAC) or sudden increase in cerebral sevoflurane concentrations as well as hypocarbia can trigger EEG abnormalities and may be proconvulsant. Hence, it is not used in epilepsy.

**Propofol:** It also possesses potential intra-ischaemic neuroprotection properties. It depresses cerebral metabolism in a dose dependent manner producing isoelectric EEG at clinically relevant doses. It may also afford cerebral protection by its antioxidant potential or by acting as a glutamate antagonist at the N-methyl-D-aspartate (NMDA) receptor.

**Etomidate:** Due to EEG burst suppression, in the past, it was the standard regimen for cerebral protection at several institutions. However, currently it is not used cerebral protection. Paradoxically, it may exacerbate ischemic injury by inhibiting nitric oxide synthase.

**Ketamine**, an N-methyl-D-aspartate (NMDA) receptor antagonists offer little or no protection against global insults. Protection against focal insults is substantial, but only if the drug is given before ischaemia onset. However, it is not recommended for neuroprotection in the clinical practice.

**Biochemical Interventions**

**Glucose:** In the absence of oxygen, glucose amplifies the severity of deleterious cascades initiated by the ischaemic insults. Rigid glycemic control is mandatory for better outcome.

**Steroids:** Steroids such as dexamethasone reduce oedema surrounding brain tumours. Methylprednisolone may improve outcome from acute spinal cord trauma. However, concomitant hyperglycemia may exacerbate injury from global ischaemia.
Intraoperative Cerebral Protection: The two main goals of intraoperative management are to protect the brain and to protect the heart, yet these two goals often conflict. Mild intraoperative hypothermia (32 to 34°C) during aneurysm surgery enhances the brain's ability to tolerate ischemia. Thiopental has been the drug of choice for intra-operative cerebral protection during aneurysm surgery.

Monitoring Cerebral Protection

Besides routine vital sign monitoring, cerebral protection protocols require specialized monitoring like ICP, EEG, NIRS, TCD, SjVO2, CT, MRI, PET etc. to aids in evaluation and modulation of instituted therapy.

Intracranial pressure monitoring: Ventriculostomy with intraventricular catheter remains the gold standard. This also aids in CSF drainage for high ICP. Other methods for ICP are Intraparenchymal micromanometers or fibre-optic probes.

Transcranial Doppler (TCD) ultrasonography: It is the non-invasive monitor for cerebral perfusion pressure to guide cerebral perfusion. TCD measures the velocity of red blood cells (RBCs) flowing through the large vessels at the base of the brain. Flow velocity (FV) in these vessels provides an index of flow (Pulsatility index – PI). Reduction in MCA FV denotes critically reduced cerebral perfusion. Episodic rises in ICP can also be diagnosed by increases in TCD FV. TCD for the anterior and middle cerebral artery usually ensures monitoring of larger territory of the brain.

Exaggerated transmission of the arterial pressure waveform to the intracranial waveform by TCD indicates compromised intracranial compliance.

Cerebral oxygenation is assessed by jugular bulb oximetry. Bilateral jugular bulb catheterization and oximetry is preferred due to less lateralization of supratentorial venous drainage. Normal jugular bulb oxygen saturations (SjvO2) tend to run at 65-70%. Reductions in SjvO2 or increases in arteriojugular differences in oxygen content (AJDO2) to greater than 9 ml/dl provide useful markers of inadequate CBF. SjvO2 value below 50% is associated with poor outcome in head injury. Grossly elevated SjvO2 denotes cerebral hyperaemia.

Near infra-red spectroscopy (NIRS), a non-invasive method, not requiring calibration, shows real time cerebral oxygenation. Bifrontal NIRS shows regional oxygen saturation (rSO2). On bilateral NIRS, perfusion has to target rSO2 of 90–95% on both sides. If the left side decreases to >10% below the right, or <80–85%, higher flows and hematocrits may increase left sided rSO2. Monitoring a small frontal cerebral sample volume with NIRS, may result in inadequate regional flow in unmonitored areas of brain.

Direct tissue oximetry measures oxygenation in a very small volume of tissue.

Tissue microdialysis presents the opportunity of directly sampling brain ECF composition, with opportunities for the measurement of glucose, lactate/pyruvate ratios and glutamate. This also provides 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 133Xe washout techniques at the bedside. CBF reductions <18 ml/100 g/min is the accepted ischaemic threshold.
Imaging physiology and metabolism in head injury: Reporting by conventional X-ray CT or conventional MRI shows delayed irreversible changes due to ischemia. Stable xenon CT studies are used for measurement of regional CBF (rCBF).

**Positron Emission Tomography (PET)** provides the opportunity to access brain metabolic parameters like cerebral glucose, oxygen utilisation and radioligand binding. Recent interest has focused on increased uptake of the PET tracer 18F-deoxyglucose around contusions and adjacent to haematomas.

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

**Prospects:**

The concept of providing cerebral protection in the future will probably not only focus on decreasing cerebral metabolism, but also on the excitatory neurotransmitters and their receptors with the hopes of finding ways to interrupt the cascade of neuronal damage. Methods to block the ischemic cascade include:

- **Inhibit release of excitatory neurotransmitters e.g. glutamate & aspartate),**, e.g. hypothermia, inhalational anaesthetics, adenosine A1 receptor blockers, a2 agonists, sodium channel inhibitors, lamotrigen, etomidate,

- **Enhance release of inhibitory neurotransmitters e.g. GABA**

**The futuristic drugs under evaluation are:**

- **NMDA (N-methyl-D-aspartate) receptor blockers / antagonists:** To reach the binding site, these drugs require an ion channel to be opened up and the voltage-dependent Mg$^{2+}$ block to be released by postsynaptic membrane depolarization.
  - MK-801 (Dizoclipine): widely studied, but not clinically accepted due to hippocampal neurotoxicity;
  - NPS-1506: Less neurotoxic than MK-801;
  - Selfotel (CGS 19755): clinical trial abandoned due to excess mortality;
  - Dextromethorphan and its analogue AHN649 are relatively selective, and have been experimentally shown to have neuroprotective efficacy;
  - Aptiganel (CNS 1102): more selective and has been shown to be neuroprotective in neonatal lambs after HCA;
  - Remacemide hydrochloride and its principal active desglycinyl metabolite: shown to be neuroprotective in animal model in hypoxia and ischaemic stroke;
  - 7-Chlorokynurenic acid and its derivatives ACEA-1021 (Licostinl-safer and better tolerated), ACEA-1031 and ACEA-1416: reduce infarct volume in focal ischaemia models;
  - Felbamate: an anticonvulsant that binds to the glycine site of the NMDA receptor, has been shown to have neuroprotective properties in higher doses;
Eliprodil (Synthelabor, France) and CP-101-606 (Pfizer, USA): most promising NMDA antagonist under clinical evaluation

Voltage-gated Sodium Channel Blockers:

- Lamotrigine (3,5-diamino-6-(dichlorophenol)-1,2,4-triazine) inhibits ischaemia induced release of glutamate. It is a commercially available, orally administered anticonvulsant. However, side effects include rashes and Stevens-Johnson syndrome;
- Riluzole (2-amino-6-trigluoromethoxy benzothiazole): Used clinically in neurodegenerative diseases;
- Lubeluzole: Inhibit release of glutamate from ischaemic neurons, reduce postsynaptic excite-toxicity and inhibit postsynaptic nitric oxide synthetase activity;
- Lifarizine: Neuroprotectant in an experimental setting, but clinically abandoned due to cardiac side effects such as hypotension and arrhythmia;
- BW619C87 [4-amino-2-(4-methyl-1-piperazinyl)-5-(2,3,5-trichlorophenyl) pyrimidine]: neuroprotectant in animal experiment at a dose of 50 mg/kg;

Calcium channel antagonists e.g. nimodipine improve outcome in TBI with subarachnoid haemorrhage; SNX-111 is a presynaptic Ca\(^{2+}\) channel blocker can reduce the influx of Ca\(^{2+}\) and the subsequent release of neurotransmitters;

Decrease nitric oxide formation, scavenge free radicals and inhibit lipid peroxidation: Lazariods (tirilazad mesylate), mannitol, statins, hypothermia, ARL17477 (selective NOS inhibitor);

Calpain inhibitors: MDL 28,170 and Cbz-Val-Phe-H reduce infarct volume in rodents;

Gelsolin analogue: Cytochalacin D, stabilize Ca\(^{2+}\) influx and can reduce ischaemic injury, although this can lead to apoptosis;

The pan-caspase inhibitor: boc-aspartyl(OMe)-fluoromethylketone significantly improved neuroprotection when injected into brain ventricles 3 h after cerebral hypoxic-ischaemia, and systemic injections of this molecule given in a delayed fashion resulted in significant neuroprotection;

Reduce inflammatory cytokinins: statins, aspirin, cox-2/3 inhibitors, estrogen;

Prevent apoptosis: isoflurane, desflurane

Potassium channel blockade: Tetrodotoxin (TTX), no clinically beneficial effect

Cerebral Preconditioning

It can be Genomic Preconditioning or Ischemic Preconditioning

Genomic studies by Stenzel-Poore and colleagues documented that ischemic preconditioning in a homeothermic mammal elicits “an evolutionarily conserved endogenous response to decreased blood flow and oxygen limitation as in hibernators”. Documentation of the specific human genetic codes and their future successful clinical application will eventually lead to brain protection during protracted periods of ‘ischemic’ CBF and induce circulatory arrest in different surgical scenario and cerebral resuscitation.

Clinically acceptable and applicable means of accomplishing cerebral preconditioning are preoperative hyperbaric oxygen, normobaric 100% oxygen exposure, electroconvulsive shock, and the potassium channel opener diazoxide.
Role of endogenously produces erythropoietin (EPO) in human in the brain protection has also recently been elucidated. Ehrenreich and others have noted that in ischemic stroke patients, within 8 hours of the onset of symptoms, intravenous injection of recombinant EPO once daily for 3 days led to 60- to 100-fold increases of EPO in the CNS and improved recovery. In clinical practice, intravenous EPO may be used as an effective prophylactic brain protectant 24 to 48 hours pre-surgery with follow up in ICU.

However, EPO increases hematocrit along with its potentially deleterious effect in ischemic injury. Non-hematopoietic analogues of EPO, asialoEPO, may have better therapeutic acceptance.

**Neurogenesis and Diaschisis**

There is a mis-conception that neurogenesis occurs only for the young. Recent studies have noted that adult neurogenesis is possible by activated neural stem cells; being facilitated by administration of growth factors. Drugs that nonselectively impede programmed cell death or apoptosis may be the futuristic therapies.

**Conclusion**

The notion that reduced cerebral metabolism is associated with cerebral protection has been challenged. Postoperative neurologic deficits may be due to inadequate collateral flow. Assessment cerebral ischemic damage by multimodal monitoring should guide the treatment.

Control of physiological variables, avoidance of hyperthermia, rigid glycemic control, volatile anesthetic agents, control of ICP by osmodiuretics, prophylactic administration of magnesium in patients at risk of vasospasm and of statins in patients with cerebrovascular risk factors are currently the most important strategies to reduce neuronal injury.

Protection of brain is related to the complex pathophysiology of cerebral ischemia. Hence, a single pharmacological intervention cannot result in tenable neuroprotection. Multifocal approach focusing at different steps in the pathway of ischemia is necessary. In practice, the center of attention should not be on a single method or drug, but rather a cocktail of options has to be used to inhibit the harmful effects of the ischemic cascade.

**References:**

2. Cerebral Protection with Barbiturate: Relation to Anesthetic Effect; PA Steen & JD Michenfelder; Stroke (published by American Heart Association), 1978; 9: 140-142.
6. Cerebral Protection in Severe Brain Injury: Physiological Determinants of Outcome and their Optimization; David K Menon; British Medical Bulletin 1999; 55 (No. 1) 226-258.

8. New Cerebral Protection Device Prevents Stroke During Treatment to Clear Blocked Carotid Arteries; Published on March 16, 2010 at 3:49 AM; Source: Society of Interventional Radiology; http://www.sirweb.org/


