Review Article

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Resuscitation of the Ischaemic Brain

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Abstract : *'Cerebral protection'* signifies strategies used to protect neural tissue from cellular events induced by deprivation of oxygen or glucose or both to the brain. Neurons are particularly susceptible to ischemic injury because they have a higher demand for energy and limited energy stores. Depletion of intrinsic central nervous system energy stores occurs within 2 to 4 minutes of anoxia. Protecting the brain from ischemia during neurosurgery is one of the most important concerns for Neuro anesthesiologists. Pharmacological brain protection may be employed to rest the brain while a temporary regional disruption in nutrient flow is expected to occur. Appropriate monitoring (EEG, evoked potentials, stump pressure, trans-cranial doppler) is needed to optimise therapy.

Cerebral protection may be initiated prior to the occurrence of brain ischaemia. Certain prophylactic measures can interfere with the cascade of events triggered by the injury. Such a salutary effect may be achieved by reducing demand for energy (using barbiturates or hypothermia) or blocking mediators of ischemic injury. In designing the anaesthetic plan for patients at high risk of cerebral ischaemia (e.g, carotid endarterectomy, open heart procedures), it is useful to consider the relative degree of protection provided by various agents. Treating patients with neuroprotective agents after cardiac arrest or a focal ischemic insult may be consideration in improving overall neurological outcome. Focal ischemia encompasses stroke subarachnoid haemorrhage (SAH) and trauma. With few exceptions, animal studies have shown that therapeutic efficacy is lost if treatment is delayed more than one hour after impact. Sooner the neuroprotective drug is given, the better is the outcome.

Keywords: brain protection, calcium channel blockers, hypothermia propofol

Introduction

Multimodality neuromonitoring facilitate tailoring of neuroprotection protocols to various clinical circumstances[1]. This permits rapid application of the most appropriate means for correcting an imbalance. Electroencephalography has been used to assess the electrical activity of the brain. Hypoxia and ischemia are commonly associated with changes in electrical activity. With EEG monitoring, barbiturate therapy can be titrated to the point of burst suppression[2]. Transcranial Doppler ultrasonography[3], which measures blood flow velocity, is finding usefulness for the identification of both low flow states and embolic phenomena. Reflectance oximetry, by using a fiberoptic catheter has allowed for 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[4]. 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. In vivo microdialysis may be performed intraoperatively and as a bedside monitoring the intensive case unit. Application of microdialysis in neurosurgery and neurointensive care is rapidly expanding in a number of clinical centres around the world. Many interstitial markers reliably reflect secondary brain ischaemia & infarction. pH is used for monitoring acidosis. Glutamate have been used as markers for excitotoxity. Increased lactate and decreased glucose, indicating accelerated glycolysis commonly occurs with cerebral ischaemia or hypoxia

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Current Cerebral Protection Strategies

Therapeutic options for intraoperative / perioperative cerebral protection

a) **Barbiturates :** The classic theory of cerebral protection is based on the concept that by decreasing cerebral metabolic demand, the neuronal survival will improve during periods of inadequate cerebral metabolism, it was the first drug to be considered as a potential cerebral protectant[5]. Barbiturates decrease cerebral metabolic activity in a dose-dependent manner, which produce a progressive decrease in EEG activity, a reduction in the rate of ATP depletion, and protection. Additional drug doses after an isoelectric EEG provide no additional

metabolic depression. Barbiturates provide cerebral protection in the face of incomplete ischemia, but not with complete cessation of CBF (complete ischemia).

b) **Etomidate :** Etomidate, an intravenous sedative-hypnotic, is similar to barbiturates in decreasing cerebral metabolism progressively until an isoelectric EEG appears[6]. Unlike barbiturates, etomidate has very little effect on blood pressure, and has a short duration of action. It must also be remembered that etomidate produces adrenal depression (inhibition of 11 – B – hydroxylase), which caused increased mortality when it was used as a continuous infusion for sedation in the ICU. This inhibition lasts 4-6 hours with a single dose, but is prolonged with continuous infusion or in elderly critically ill patients.

c) **Propofol :** Propofol introduced into clinical practice in the late 1980s, depresses cerebral metabolism in a dose dependent manner, similar to barbiturates, producing isoelectric EEG at clinically relevant doses[7]. Rapid emergence from burst suppression EEG may permit more accurate postanesthesia neurologic evaluation. Because propofol has significant negative inotropic activity in addition to vasodilatory properties, it can decrease cerebral perfusion pressure when a large dose is administrated over a short period of time. Additionally, propofol may afford cerebral protection by its antioxidant potential or by acting as a glutamate antagonist at the N-methyl-D-asparate (NMDA) receptor[7].

d) **Benzodiazepines :** Benzodiazepines also depress cerebral metabolism in a dose-response manner; however, they are not as potent as barbiturates and do not produce isoelectricity. Because they are unable to maximally suppress EEG activity, they have not been seriously considered for cerebral protection.

e) **Ketamine :** Ketamine is a controversial drug in neuroanesthesia because it has been shown to increase both cerebral metabolism and blood flow. Recently, however, Ketamine has been proposed as an anesthetic drug that may provide cerebral protection because it blocks the NMDA receptor, which is highly activated via enhanced excitatory neurotransmitter release during ischemia[8].

f) **Inhalation anesthetics :** Almost all of the inhalational anesthetic agents are similar to barbiturates in producing progressive EEG depression in a dose-dependent manner until obtaining electrical silence. This occurs at approximately 1.5 – 2 MAC. Because of this similarity to barbiturates, inhalational anesthetics are frequently used for cerebral protection. They produce less cardiovascular depression than the barbiturates and are more rapidly eliminated at the end of surgery. The exceptions are halothane and enflurane[9, 10].

g) **Temperature :** The beneficial effect of hypothermia is well known. Hypothermia has long been used during cardiopulmonary bypass and circulatory arrest surgery to provide protection from cerebral ischemia. Initially it was felt that hypothermic protection was based on a significant decrease in cerebral metabolism, allowing the neurons to exist in almost a suspended energy consumption state. For every degree Celsius decrease in temperature, cerebral metabolism is reduced by 5-7%. Therefore, a reduction in temperature from 37ºC to 34ºC produces a 15-20% reduction in cerebral metabolism, which is far less than the 50% decrease seen with EEG silence. Obviously hypothermia's protective effect is not mediated solely by metabolic depression. Proposed mechanisms include suppression of glutamate release, blunted nitric oxide production, which is involved in producing oxygen free radicals, formation of free fatty acids, reduced calcium influx, and increased gamma-aminobutyric acid (GABA) release is increased 10-fold when temperature is increased to 39ºC during ischemia[11].

Unfortunately, intraoperative cerebral temperature is usually not monitored. Instead, temperature is measured with esophageal, bladder, rectal, or tympanic membrane probes, even pulmonary artery catheter measurement may not be reflective of cerebral temperature. To compound this problem, brain temperatures during surgery varies from cortical surface to deep intracerebral. It is frustrating that a brain protectant therapy with few side effects is so difficult to correctly implement because of our inability to measure the temperature of the brain region at risk for ischaemia.

h) **Blood Pressure :** Control of blood pressure is possibly one of the most important aspects of preventing brain injury and promoting cerebral protection. The amount and direction of blood pressure control depends upon knowledge of the preoperative flow pattern (it is essential to review

the angiogram preoperatively) and the surgical approach, rather than a cookbook methodology.

j) **Glucose :** The deleterious effects of hyperglycemia have been well reported in both clinical and laboratory reports[12]. Hyperglycemia markedly increases damage in both global and focal ischaemia. Even moderately elevated serum glucose with an adequate oxygen supply converts aerobic to anaerobic metabolism, increasing brain lactic acid, which decreases brain pH. Buffering capacity is overwhelmed, free oxygen radicals are generated, neuronal pH decreases, and cell membrane rupture occurs, producing tissue necrosis.

Other Agents

a) **Glucocorticosteroids :** The use of glucocorticoids is not recommended for improving outcome or reducing ICP in patients with servere head injury. 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 bolus followed by 5.4 mg/kg for 23 hours) was of benefit in spinal cord injury if treatment was instituted within 8 hours of injury[13].

b) **Tirilazad mesylate™ :** Tirilazad Mesylate™ is a 21-aminosteroid (lazaroid) that was developed specifically to maximize the inhibition of lipid peroxidation by glucocorticoids such as methylprednisolone, but eliminate the unwanted glucocorticoids effects[13]. Its mechanism of action appears to be cell membrane preservation by inhibition of lipid per oxidation. There is also increasing interest in using tirilazad in combination with thrombolytic agents in the management of ischaemic strokes.

c) **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 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 serve head injury, treatment was a single bolus IV administration, with a mean time from injury to treatment of approximately 4 hours[14]. The % of time the ICP was above 20 mm Hg & the amount of mannitol required to control ICP were less in the moderative dose PEG-SOD (5000 µg) & high dose PEG-SOD (10000 µg) treated patients than in controls. Furthermore, outcome at 6 months was better in the high dose PEG-SOD treated patients.

d) **Nimodipine :** This drug antagonizes the entry of calcium into cells, which in turn ameliorates the lactic acidosis, which occurs during ischaemia[15]. Nimodipine probably increased CBF, particularly in regions of moderate ischemia. Nimodipine may be particularly effective at neuroprotection during hyperventilation, which is a common intervention during brain surgery. Neurological outcome was found to better in patients treated with nimodipine within 24 hours of the onset of ischemic stroke.

e) **Nicardipine :** This drug is a calcium antagonist. Cerebral Ischemia causes a rapid shift of calcium from the extracellular spaces into cells. Nicardipine directly reduces calcium entry into ischemic cells. Nicardipine has been administered into venous reservoir before DHCA[16].

f) **Lidocaine :** Neuropsychologic deficits remain vexing complications after both coronary artery & valve operations. Possible mechanisms for cerebral protection by lidocaine include deceleration of ischemic transmembrane ion shifts, reduction in CMR, modulation of leukocyte activity, & reduction of ischemic excitotoxin release[17].

g) **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[13].

h) **Insulin :** Elevated intracellular glucose concentration at the time of a cerebral ischaemic insult may result in increased cellular lactic acidosis, & this worsens ischemic injury. Insulin has been shown to have a neuroproctective effect and some observations in man are in keeping with these experimental findings[12].

j) **Tromethamine :** Tromethamine (THAM), a weak base which crosses the plasma membrane and acts directly on intracellular acidosis has been used with success in models of experimental head injury. THAM has been used in head injuries in man with

favourable effects on brain edema and intracranial pressure[18].

k) **Mannitol :** Mannitol is widely used in neurosurgical operations involving patients with cerebral oedema &/ or mass effect. Some of mannitol's potentially beneficial effects include osmotic diuresis, increased blood viscosity & free radical scavenging[13].

Mannitol is used for control of raised intracranial pressure (ICP) after brain injury. It may be given even before computed tomographic scanning, e.g., in patients who develop a fixed, dilated pupil or neurologic deterioration. This agent may also be used when high ICP is demonstrated in the intensive care unit. It should be given as a bolus intravenous infusion, over 10 to 30 minutes, in doses ranging from 0.25 to 1 g/Kg body weight. It is more effective and safer when administered in bolus infusion doses than as a continuous infusion.

In patients receiving mannitol, hypovolemia should be avoided, serum osmolarity should be kept below 320 mOsm & serum sodium should be kept below 150 mEq/ L.

Mannitol has been added to th venous reservoir before DHCA is employed. Mannitol is well known to reduce cerebral oedema after ischemia. Mannitol can also scavenge free radicals & thus reduce tissue damage caused by superoxide radicals.

Potential Cerebral Protective Mechanisms

The concept of providing cerebral protection in the future will probably not focus on decreasing cerebral metabolism, but rather on blocking the cascade of events that occur during ischaemia, which consists of:

a) Decrease cerebral metabolism
b) Increase cerebral blood flow
c) Mild hypothermia
d) Prevent hyperthermia
e) Maintain normoglycemia
f) Inhibit release of excitatory neurotransmitters (e.g., glutamate, aspartate)
g) Enhance release of inhibitory neurotransmitters (e.g., GABA)
h) Block neuronal calcium influx
i) Decrease nitric oxide formation
j) Decrease Neuronal free radical formation
k) Prevent apoptosis
l) Scavenge free radicals
m) Prevent Ca++ and Na + influx

Chemical Brain Retractor Concept

This concept includes the use of a total IV anaesthesia technique, mild hypocapnia & mannitol with strict monitoring & maintenance of the global cerebral homeostasis. This contributes to decrease brain volume & ICP. It allows the best possible access to the operative site, while avoiding excessive pressures under the surgical brain retractors. Prevention of ischemic cerebral insults during neurosurgical procedures includes maintenance of cerebral perfusion pressure & use of : 1) specific pharmacological agents, 2) chemical brain retractor concept, 3) hemodilution & 4) hypothermia.

The Ischaemic Cascade

During cerebral ischaemia large amounts of excitatory neurotransmitters (glutamate and aspartate) are released by presynaptic neurons. The amount released correlates with the severity of the ischemic insult and subsequent neuronal damage. Glutamate and aspartate activate postsynaptic receptors (NMDA, amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid [AMPA], kainite), resulting in an increase in intracellular calcium and stimulation of enzyme systems that produce ischemic damage and ultimately neuronal death. Nitric oxide synthase is stimulated, producing large amounts of neuronal nitric oxide. Lipid peroxidases, proteases, and phospholipases are activated, increasing intracellular free fatty acids and free radicals. Capsase, translocase, and endonuclease activity results in DNA fragmentation. Cell membranes become permeable, leading to oedema and additional calcium influx. ATP stores are depleted, energy-dependent membrane pumps fail, and neuronal death occurs.

New Concepts

Current philosophies of cerebral protection are focusing on these excitatory neurotransmitters and their receptors with the hope of finding ways to interrupt the cascade of neuronal damage. Some of the drugs that block glutamate release include inhalation anesthetics (70% reduction), adenosine A1 blockers, and Ü2 agonists. Inhalational anesthetics may also increase reuptake of neurotransmitters from the synaptic space. Drugs that competitively block postsynaptic receptors include barbiturates (primarily AMPA and Kainate receptors) and possibly inhalation anesthetics. Noncompetitive receptorantagonists include MK 801 (dizoclipine), phencyclidine, dextromethorphan, ketamine, and magnesium. Recently, sodium channel inhibition has been reported to decrease both potassium-evoked and spontaneous glutamate release. Examples of other

interesting approaches include aspirin, statins, and free radical scavengers. Recent work suggests that the statins, in addition to decreasing atheromatous plaque, may also possess beneficial effects during ischemic stroke and reperfusion. The proposed mechanisms include upregulation of endothelial nitric oxide synthesis. They also attenuate the inflammatory cytokine response to ischemia, possess antioxidant properties, and reduce ischemic oxidative stress.

Drugs that decrease free radical formation or enhance free radical scavenging are currently being evaluated as cerebral protectants. These include many well-known drugs such as mannitol and steroids in addition to some new ones. Although laboratory studies are promising, the human studies have not been very encouraging. Because cerebral ischemia is a complex event, a multifocal approach will probably be necessary, focusing at different steps in the pathway of ischemia.

REFERENCES

1. Schurr A, Payne RS, Levy RS, Rigor BM. Understanding cerebral energy metabolism : a key to successful Neuroprotection. In : Bailliere Tindall, editor.
Bailliere's Clinical Anesthesiology. International Practice and Research. UK : Saunders, 1996 : 409-25.

2. *Doyle PW and Matta BF*. Burst suppression or isoelectric encephalogram for cerebral protection : evidence from metabolic suppression studies.
British Journal of Anaesthesia 1999; 4 : 83 : 580-584.

3. Kahn RA, Slogoff FB, Reich DL, and Konstadt SN. Transcranial Doppler ultrasonography : what is its role in cardiac and vascular surgical patients?
Journal of Cardiothoracic and Vascular Anesthesia 1995; Vol 9, No. 5 : 589 97.

4. Owen-Reece H, Smith M, Elwell CE, Goldstone JC. Near infrared spectroscopy.
Br J Anaes 1999; 82 (3) : 418-26.

5. Hirotani T, KamedaT, Kumamoto T, Shirota S & Yamano M. Protective effect of thiopental against cerebral ischaemia during circulatory arrest.
Thorac Cardiovasc Surg 1999; 47 : 223-228.

6. Batjer HH, Frankfurt AI, Purdy PD et al. Use of etomidate, temporary arterial occlusion and intraoperative angiography in surgical treatment of large and small cerebral aneurysms.
J Neuosurg 1988; 68 : 234-240.

7. Stone JG, Young WL, Marans ZS, et al. consequences of electroencephalographic suppressing dose of propofol in conjunction with deep hypothermic circulatory arrest.
Anesthesiology 1996; 85 : 497-501.

8. Kirsch JR, Traystman RJ, Hurn PD. Anesthetics and Cerebroprotection : Experimental Aspects. In : Jaffe RJ, Giffard RG, eds. International Anesthesiology Clinics.
Topics in Neuroanesthesia 1996; Volume 34, No. 4 : 73-93.

9. Giffard RG, Jaffe RA. Anesthetic Agents for Neuroprotection. In : Andrews RJ, ed.
Intraoperative Neuroprotection. 1996, USA. Williams & Williams.

10. Michenfelder JD, Sundt TM, Fode N and Sharbrough FW. Isoflurane when compared to enflurane and halothane decreases the frequency of cerebral ischaemia during carotid endarterectomy.
Anesthesiology 1987; 67 : 336-40.

11. Svensson LG, Crawford ES, Hess KR, Coselli JS, Raskin S, Shenaq SA, Safi HJ. Deep hypothermia with circulatory arrest. Determinants of stroke and early mortality in 656 patients.
J Thorac Cardiovasc Surg 1993; 106 : 19-31.

12. Lam AM, Winn HR, Cullen BF, Sundling. Hyperglycemia and neurological outcome in patients with head injury.
J Neurosurg 1993; 75 : 545-551.

13. Andrews RJ, Giffard RG. Clinically useful nonanesthetic agents. In : Andrews RJ, editor. *Intraoperative Neuroprotection*, USA : Williams and Williams, 1996.

14. Muizelaar JP, Marmarou A, Young HF et al. Improving the outcome of severe head injury with the oxygen radical scavenger polyethyleneglycol-conjugated superoxide dismutase : a phase II trial.
J Neurosurg 1993; 78 : 375-82.

15. The European Study Group on Nimodipine in Severe head Injury : A multicenter trial on the efficacy of nimodipine on outcome after severe head injury.
J Neurosurg 1994; 80 : 797-804.

16. Hirotani Takashi, Tadashi Kameda, Kumamoto Takayuki, Shogo Siroto. Aortic arch repair using hypothermic circulatory arrest technique associated with pharmacological brain protection.
Eur J Cardio-thor Sur 2000; 18 : 545-49.

17. Mitchell SJ, Pellet Ora, and Gorman DF. Cerebral protection by lidocaine during cardiac operations.
Ann Thorac Surg 1999; 67 : 1117-27.

18. Wold AL, Levi L, Marmarou A, et al. Effect of THAM upon outcome in severe head injury : a randomised prospective clinical trial.
J Neurosurg 78 : 54-59.

19. Ravussin P, Moeschier O, Graftieaux JP, De Triolet N. Brain Protection and relaxation in the operating room,
Neurochirugrie. (French) 1994; 40/6 : 359 62.