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SASA MAIN CONFERENCE

Neuroprotection: fact and fantasy

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Introduction

Neuroprotection refers to strategies that prevent, antagonise, interrupt or slow the biochemical and molecular events which have the potential to cause the injury and death of brain cells.

Brain injury is an important adverse complication of anaesthesia and surgery, with variable clinical manifestation from postoperative cognitive decline, transient ischaemic attacks to cerebrovascular accidents (CVAs). Incidences vary according to the type of surgery, with up to 80% being reported in cardiac surgery.[1] Although the injury mechanisms differ between neurosurgical and non-neurosurgical procedures, the common denominator is failure of glucose and oxygen supply, which triggers the cascades of inflammation, oxidative stress, mitochondrial dysfunction and excitotoxicity that lead to neuronal death by apoptosis and necrosis.

In the past 40 years, our understanding of the pathophysiology of brain injury has grown. Numerous trials have been conducted on pharmacological and physiological brain protection strategies. Some have been useful in animal (mostly rodent) and preclinical studies, but have failed to show benefit in clinical human studies. Reasons for this might be discrepancies with regard to the experimental duration of ischaemia compared to that in human studies,[2] a limited understanding of apoptosis, its triggers and antagonists, and other undefined pathophysiological mechanisms that might not be addressed by a single strategy. Importantly, the impact of any neurological deficit in humans is likely to be significant in terms of quality of life for which cognitive, gross motor and fine motor capabilities are required. Hence, relatively acceptable outcomes in animals might not be adequate in humans.

This review will differentiate between the interventions by comparing acceptable evidence from human trials ("fact") and those without ("fantasy").

Fact

The maintenance of arterial blood pressure to within 30% of preoperative values is beneficial in the prevention of perioperative CVAs in non-cardiac and non-neurosurgical procedures, as is the maintenance of blood pressure in the immediate postoperative period. Two important studies support this; the 2008 Perioperative Ischemic Evaluation (POISE) trial, where the use of metoprolol was associated with hypotension, death and strokes,[3] and a retrospective study carried out by Bijker et al, of 48 241 patients who underwent non-cardiac non-neurosurgical procedures, where hypotension was associated with CVAs.[4] Although the overall incidence of perioperative CVAs is low at 0.05-7.4%,[5] and the evidence linking perioperative CVAs to hypotension is not based on good-quality randomised trials, the expert opinion of members of the Society for Neuroscience in Anaesthesiology and Critical Care is that hypotension should be prevented. This includes avoiding the initiation of beta blockers immediately preoperatively, or carefully titrating new beta blockers.

Equally, numerous retrospective studies on neurosurgical procedures have demonstrated the association of intraopeartive hypotension with poor neurological outcomes, suggesting that cerebral perfusion pressure near 70 mmHg is safer.[6-8]

Furthermore, induced hypertension that targets blood pressure increases of 20-40% on pre-existing values improves neurological outcomes in cerebral aneurysms during endovascular coiling, clipping and vasospasm, and in carotid endarterectomies.[9] The benefit is also found in patients with intracranial pathology that has resulted in intracranial hypertension, who have concomitant systemic hypertension, and a shift in the autoregulatory relationship.

Normoglycaemia, with blood sugar targets of 7.8-10.0 mmol/l for neurosurgical and cardiac procedures, is safer than tight control, although hyperglycaemia has been associated with brain injury when the brain is vulnerable to ischaemia. This is supported by the results of the Normoglycaemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study on surgical and non-surgical intensive care unit patients, which showed intensive insulin therapy, with targets of 4.5-6 mmol/l, to be associated with hypoglycaemia, strokes and death.[10] Intensive insulin therapy was demonstrated to impair glucose utilisation and cause brain energy failure in the neurocritical care population.[11]

As brain ischaemia is caused by the failure of oxygen delivery, anaemia is a focus of research in neuroprotection. There is evidence of improved outcomes in patients with subarachnoid

haemorrhage and a higher haemoglobin.[12,13] Since haematocrit has the opposite effect on cerebral blood flow and oxygen delivery, the optimal haematocrit level which balances the two needs to be achieved. Lee et al showed the optimal haematocrit for maximum oxygen delivery and maintenance of cerebral blood flow to ischaemic brain tissue to be around 30% in a canine model of focal brain ischaemia.[14] More recently, a haematocrit of less than 33% was shown to be a cause of morbidity and mortality in elective cranial neurosurgery in a wide variety of indications; a threefold higher postoperative mortality risk than that for non-anaemic patients.[15]

Fantasy

Induced hypothermia during neurological surgery as a neuroprotective strategy has had disappointing results. A Cochrane meta-analysis of four randomised controlled trials on mild hypothermia used during neurosurgical procedures failed to show benefit in terms of mortality and disability, although the hypothermia had no adverse effects.[16] The subjects were a mix of patients undergoing cerebral aneurysm clipping, craniotomies for traumatic brain injury and hemicraniotomies for malignant supratentorial infarction. Mild hypothermia may be used because it is relatively safe. Hyperthermia should be avoided. Outside theatre, it is an established evidence-based neuroprotective strategy for comatose patients post out-of-hospital cardiac arrest and in neonatal peripartum hypoxic ischaemic encephalopathy.

Volatile anaesthetics have been studied for many years. Although their neuroprotective effects are based on sound physiological principles, the clinical benefit has not been realised. It has been proposed that they work through reducing cerebral metabolism and intracranial pressure, anti-seizure activity, the inhibition of glutamate release, the activation of gamma-aminobutyric acid and glycine receptors, and by minimising intracellular calcium and free radical accumulation. Isoflurane delayed, but did not prevent, infarction, after a period of ischaemia in a mouse experiment by Kawaguchi et al, presumably because it failed to inhibit post-ischaemic neuronal apoptosis.[17] Human clinical trials have also not been able to show meaningful positive outcomes in both neurosurgery and non-neurosurgical procedures. A difference in stroke occurrence at 30 days post surgery was not shown in a widely cited, multicentre randomised controlled trial in which stroke incidence was compared in patients undergoing carotid endarterectomy under general anaesthetic with volatile anaesthetic, versus patients undergoing carotid endarterectomy under local anesthesia.[18] The noble gas, xenon, is still the subject of ongoing research. The protective effects of xenon given 15 minutes after injury in an animal model of traumatic brain injury was demonstrated in a recent study by Campos-Pires et al.[19] This study adds to our knowledge on the subject by providing a time frame after the insult within which xenon neuroprotection can still be applied. Xenon has been safely used in humans, although the costs are prohibitive. Human clinical trials on its neuroprotective effects will probably follow soon.

Intravenous anaesthetics, propofol and dexmedetomidine, have neuroprotective effects in animal models of brain ischaemia. Propofol is the subject of ongoing research in which new mechanisms of cerebral preservation have been uncovered, including changes in neurotransmitter activity, protein expression, the inhibition of apoptosis and the upregulation of haeme-oxygenase 1 expression that attenuates ischaemic injury by immunomodulation.[20] Unfortunately, these benefits need to be established in human trials.

Pharmacological experimental interventions that target the pathways of neuronal damage have been studied, including anti-excitotoxic, anti-inflammatory, antioxidant, and pre- and post-ischaemic conditioning, but have not yielded results that can be translated to clinical benefit.

The neuroprotective effect of drugs in non-neurosurgical procedures was reported in a recent systematic review of randomised trials by Bilotta et al, whereby the majority underwent cardiac surgery.[21] Twenty-five randomised controlled trials in which pharmacological perioperative neuroprotection was used were included, particularly when neurological and cognitive status was evaluated preoperatively. Atorvastatin and magnesium sulphate were associated with a reduced incidence of new postoperative deficits, although there was no effect on postoperative cognitive decline or mortality. Other agents, such as lidocaine, thiopental, S(+)-ketamine, propofol, nimodipine and erythropoietin, had no effect on new postoperative deficits or postoperative cognitive dysfunction. This review, which included single-centre, randomised controlled trials, with a heterogeneous mix of surgical procedures, provides hope for magnesium and atorvastatin, although magnesium studied in subarachnoid haemorrhage had conflicting results. In conclusion, the neuroprotective effects of pharmacotherapies remain controversial.

At present, the literature on neuroprotection is open to misinterpretation. Interventions that appear to be based on sound physiological principles, and which are beneficial in animal models, have not been translated to clinical benefit in human trials. More trials need to be conducted using higher functioning primates to accurately quantify the impact of neuroprotective strategies. It seems that maintaining homeostasis, with an emphasis on normocarbia, normoxia, blood pressure, glycaemic control and adequate haemoglobin concentration, is the only proven neuroprotective strategy at present.

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