Protecting the brain during neurosurgical procedures: strategies that can work

Hossam El Beheiry[a,b]

Purpose of review
The quest for neuroprotection strategies during periods of neuronal vulnerability persists despite decades of basic and clinical research. This review will focus on the latest developments in the area of clinical brain protection with the major emphasis on strategies that can be beneficial during neurosurgical procedures.

Recent findings
Brain protection in neurosurgical patients may be achieved by nonpharmacological and pharmacological strategies. Pharmacological neuroprotection including anaesthetic administration have not been recently shown to be successful. Alternatively, nonpharmacological strategies including maintenance of cerebral perfusion by adequate control of mean arterial pressure (≥80 mmHg), liberal normoglycaemia (7.8–10 mmol/l), adequate haemoglobin levels (preoperative ≥120 g/l and intraoperative ≥90 g/l) and induction of hypertension (20–40% of preoperative values) in certain neurosurgical situations can be beneficial as neuroprotectants during neurosurgery. Mild hypothermia (32–35°C) failed to achieve neuroprotective effects in several situations of brain injury.

Summary
The findings of this review suggest that the anaesthesiologist is compelled to use nonpharmacological strategies sometimes based on empiric evidence to protect the brain during neurosurgical procedures. These strategies are simple, have high benefit/risk ratios and are inexpensive. Rigorous controlled clinical studies are needed to investigate the neuroprotective efficacy of these commonly used nonpharmacological methods.

Keywords
neuroanaesthesia, neuroprotection, neurosurgery, perioperative

INTRODUCTION

A special situation that always faces anaesthesiologists is the surgically induced brain injury during the administration of anaesthesia for neurosurgical procedures. Such inevitable injury exists in many forms and affects normal brain structures whilst eliminating pathological tissue [1] (Table 1). Therefore, the onus is on the anaesthesiologist to provide the patient with neuroprotective measures that will reduce poor neurological outcomes, that is, motor and sensory deficits and cognitive dysfunction. The available presumed effective neuroprotective strategies can be passive involving the avoidance of a deleterious intervention or active including the application of a beneficial strategy [2]. Collectively, neuroprotective strategies can be classified into nonpharmacological and pharmacological [3,4] (Table 2).

The current review will focus on the recent evidence that shows the potential for specific neuroprotective strategies to prevent or reduce brain damage and improve neurological outcomes following neurosurgical procedures. Some of the strategies may be 'empiric', meaning that these strategies are guided by practical experience including observation and experimentation rather than precepts or theory.

NONPHARMACOLOGICAL STRATEGIES

Nonpharmacological strategies indicate the manipulation of physiological variables in a manner that

[a]Department of Anaesthesia, Trillium Health Centre, Mississauga and [b]University of Toronto, Toronto, Ontario, Canada

Correspondence to Hossam El Beheiry, MBBCh, PhD, FRCPC, Trillium Health Centre, 100 Queensway West, Mississauga, Ontario, Canada. Tel: +1 905 848 7628; e-mail: h.el.beheiry@utoronto.ca

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KEY POINTS

- Protecting the brain during neurosurgical procedures may be achieved by nonpharmacological and pharmacological strategies.
- Reported clinical trials failed to show any benefit of pharmacological agents in achieving neuroprotection.
- The anaesthesiologist is compelled to use nonpharmacological strategies by manipulating the physiological variables to protect the brain and improve the neurologic outcomes in the neurosurgical patient.
- Important physiological variables that can be easily manipulated perioperatively with low risk and high benefit include body temperature, cerebral perfusion pressure, blood glucose level and haemoglobin concentration as well as brain tissue oxygen tension, arterial CO_2 partial pressure and brain size.
- Future clinical studies will continue in the area of brain protection focussing on improving clinical outcome, using multimodal approaches and rationalizing the treatment strategies according to the cause of brain injury.

can have neuroprotective effects. These include body temperature, cerebral perfusion pressure (CPP), blood glucose concentration, haemoglobin concentration, brain tissue oxygen tension, arterial CO_2 partial pressure and brain size (Table 2). The subsequent paragraphs examine the strategies that have the potential for protecting the brain during neurosurgical procedures based on recent evidence.

Mild hypothermia

Clinicians were hopeful that induction of mild hypothermia (32–35°C) will have neuroprotective effects during brain surgery [5]. Such hope originated from many laboratory reports showing the efficacy of mild hypothermia in preserving the neuronal units during acute ischaemic insults [6,7]. The mechanisms of mild hypothermia neuroprotection are complex. Hypothermia maintains the integrity of the blood–brain barrier after ischaemic insults; reduces the metabolic demands of neurons; constricts cerebral blood vessels causing a reduction of cerebral blood volume, brain oedema and intracranial pressure; decreases the destructive effects of intracellular calcium overload; depresses the programmed cell death apoptotic cascade; inhibits the inflammatory pathway that leads to delayed cell necrosis; and ameliorates secondary neuronal injury by inhibition of the deleterious genetic-induced proteomic response [7] (Fig. 1).

Unfortunately, the hope of establishing the efficacy of mild hypothermia as a neuroprotective strategy in humans is still elusive. In a recent carefully conducted meta-analysis on the subject of cooling for cerebral protection during brain surgery, mild hypothermia was found to be ineffective as a neuroprotectant [8▪▪]. Four randomized controlled studies were included in the meta-analysis from 33 eligible clinical trials investigating mild hypothermia during neurosurgical procedures [9–12]. The primary outcomes analysed were mortality during treatment or follow-up period and Glasgow Outcome Scale (GOS) 3 or less, that is, persistent vegetative state, severe disability or death. The odds of dying or having a poor GOS ($\leq$3) were not statistically significant if mild hypothermia is compared to normothermia. Analysing the secondary outcomes (incidence of neurological and cardiac morbidities) showed that mild hypothermia is safe. It is noted that the clinical trials included in the meta-analysis comprised patients who underwent clipping of cerebral aneurysm [10,12], surgery following traumatic brain injury [11] or hemicraniotomy for malignant supratentorial infarction [9].

In keeping with the above observations, major trials for the application of mild hypothermia after traumatic brain injury did not show any benefit pertaining to mortality or morbidity when compared to normothermia [13,14▪]. In fact, The National Acute Brain Injury Study: Hypothermia II trial was terminated prematurely because of the ineffectiveness of the intervention [14▪]. In contrast, mild hypothermia might be beneficial in the case of

Table 1. Forms of inevitable brain injury during neurosurgical procedures

Brain tissue manipulation	Brain vasculature manipulation	Global haemodynamic changes
Predetermined cortical incisions to access deeper pathological tissue	Localized surgical bleeding and brain contusion	Brain hypoperfusion resulting from major air embolism or surgical bleeding
Retraction of brain tissue with brain retractors	Temporary or permanent vascular occlusion	
Thermal and ultrasonic energy induced injury during cutting, coagulation and dissecting		

Table 2. Neuroprotective strategies

Nonpharmacological	Pharmacological
Mild hypothermia	Agents targeting molecular sites of action
Normoglycaemia	Antiexcitotoxic
Arterial blood pressure control	Anti-O2 free radicals
Induced hypertension	Anti-inflammatory
Optimum haemoglobin concentration	Antiapoptosis
PaO2 optimization	Agents with indeterminate site of action
PaCO2 manipulation	Erythropoietin
Limit ischaemic time	Cell membrane stabilizer
Embolic load reduction	Antithrombotics
Osmotherapy	Anaesthetics
	Volatile, intravenous, other

comatose survivors of out-of-hospital cardiac arrest [15,16] and peripartum neonatal asphyxia brain injury [17,18].

But there is no convincing evidence yet that mild hypothermia can be used routinely during neurosurgical procedures as a neuroprotective strategy. However, it may be used by some anaesthesiologists because of its relative safety and presumed efficacy in nonoperative situations of global brain injury. If mild hypothermia is used, several precautions should be considered: core body temperature should be monitored at two sites to avoid inadvertent excessive cooling, the target temperature has to be reached before opening the dura, rewarming should start after manipulating the brain tissue has ended and rewarming should continue in the immediate postoperative period until tympanic temperature normalizes. Hyperthermia should be diagnosed and treated promptly because of its adverse effects on the ischaemic and vulnerable brain.

Arterial blood pressure control

Intracranial procedures compromise regional cerebral blood flow (CBF) and regional CPP leading

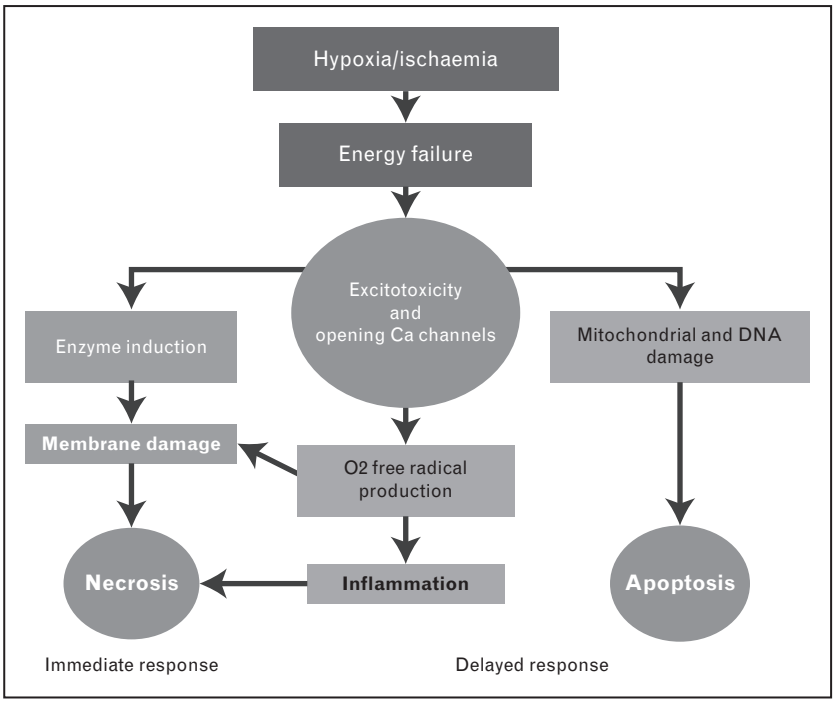

FIGURE 1. The immediate and delayed pathways that are activated after an ischaemic insult to the brain. The pathways lead to cell death by necrosis or apoptosis.

to localized brain ischaemia (see list above). Additionally, global brain hypoperfusion has been shown to be common during neurosurgery [19▪] and can lead to brain injury and unfavourable outcomes [20▪▪]. A reduction in mean arterial pressure (MAP) decreases CPP and hence CBF; this reduction is further enhanced by raised intracranial pressure (ICP). In a healthy brain with intact autoregulation, CBF is maintained in the MAP range of 50–150 mmHg. During neurosurgery and in the diseased brain, cerebral autoregulation is frequently impaired. Unfortunately, the degree of impairment is unknown and the relationship between CBF and CPP may become linear. Hence, in our clinical practice any drop of MAP below 80 mmHg should be recognized and treated promptly to keep the CPP near 70 mmHg. Elevation of MAP is achieved by adequate volume resuscitation, use of alpha-agonists or ephedrine and decrease in anaesthetic depth. Interestingly, recent reports showed that acute reductions in MAP caused decreased diffusion of cerebral tissue on MRI (a surrogate measure of cerebral ischaemia) and was associated with disability and death in patients with intracerebral haemorrhage (ICH) [21]. In contrast, increasing CPP improved clinical outcomes in patients who suffered aneurysmal subarachnoid haemorrhage [22] and head injury [23]. Taking it together, moderate or severe hypotension should be avoided and MAP should be maintained close to the patient's baseline pressure during neurosurgical procedures.

Normoglycaemia

Clinical studies in the last decade reported that hyperglycaemia in diabetic and nondiabetic patients enhances brain injury during periods of vulnerability, that is, stroke, traumatic brain injury, cardiac and neurologic surgery, sepsis and critically ill patients in ICU [24,25]. These investigations are mainly retrospective correlative research that associates a trend of poor neurologic outcomes in patients with increased blood glucose levels. Most recently, a retrospective study in children with severe traumatic brain injury showed that hyperglycaemia beyond the initial 48 h is associated with poor outcome [26]. Additionally, Pasternak and the team of the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) investigators concluded that blood glucose levels greater than 7.2 mmol/l (129 mg/dl) and greater than 8.4 mmol/l (152 mg/dl) at the time of clipping of a ruptured cerebral aneurysm are associated with long-term changes in cognition and gross neurologic dysfunction, respectively [25]. Finally, Godoy *et al.* [27▪▪] reviewed the clinical studies (mostly retrospective) that included a wide variety of neurosurgical patients including those suffering from aneurysmal subarachnoid and ICH, severe traumatic brain injury, spinal cord and spine pathology, intracranial masses and tumours and patients undergoing interventional neuroradiology. The review concluded that high blood glucose levels are associated with various unfavourable neurological outcomes as well as increased surgical infection rate.

Although there is a consensus about the deleterious effects of hyperglycaemia on neurological outcome during brain surgery, the recommended target for blood sugar control is still unclear. There are clues in the literature that tight blood sugar control may itself be harmful to patients and offsets the benefits of treating hyperglycaemia. For example, the large, international, randomized NICE-SUGAR study [28] found that intensive insulin therapy (IIT) with a target blood sugar 4.5–6 mmol/l (81–108 mg/dl) increased mortality amongst surgical and nonsurgical adult patients in the ICU compared to the more conventional blood glucose target of 10 mmol/l (180 mg/dl). Moreover, severe hypoglycaemia where blood glucose levels were 2.2 mmol/l or less ($\leq$40 mg/dl) was much more frequently reported in the IIT group (6.8%) compared to the conventional control group (0.5%). Similar results were described in other investigations [29–32], particularly in cardiac surgery patients who had an increased incidence of stroke and death when intraoperative IIT was used to control hyperglycaemia [33]. In fact, measuring markers of glucose utilization (glucose and lactate/pyruvate ratio) in brain tissue by microdialysis in neurocritical care patients showed that IIT may impair cerebral glucose metabolism by reducing cerebral extracellular glucose availability. This will lead to brain energy crisis, which correlates with increased mortality [34].

Hence, the above evidence and other reports [35–37,38▪▪] do not advocate tight glucose control using IIT during the perioperative period in neurosurgical patients. Consequently, the American Diabetes Association and the American Association of Clinical Endocrinologists [39] set an upper limit of 10 mmol/l at which insulin therapy should be started. The guidelines also propose to maintain blood glucose levels between 7.8 and 10 mmol/l (140–180 mg/dl) in the subgroup of patients vulnerable for brain injury [39]. Finally, therapy for hyperglycaemia should be individualized relating to the speed of achieving conventional normoglycaemia and the insulin regimen used.

Induced arterial hypertension

Induced hypertension, that is, raising the arterial blood pressure by 20–40%, may increase collateral CBF through the leptomeningeal circulation and

other pathways given that the Circle of Willis is incomplete in 21% of patients [40]. The specific intraoperative situations in which induced arterial hypertension might be beneficial include:

(1) interventional neuroradiology, that is, endovascular obliteration of cerebral aneurysms, cerebral angioplasty/stenting and intra-arterial thrombolysis;
(2) transient vessel occlusion during clipping of cerebral aneurysm and carotid endarterectomy;
(3) extracranial to intracranial bypass surgery;
(4) surgery in patients with cerebral vasospasm after subarachnoid haemorrhage;
(5) in patients with a change in the cerebral autoregulation relationship, that is, intracranial pathology with mass effect, systemic hypertensive disease and traumatic brain injury.

Although there is no direct evidence for the benefits of induced hypertension, most recent reports point to potential benefits of such a strategy. Indeed, increased middle cerebral artery flow velocity by induced hypertension during dissection of the carotid artery in carotid endarterectomy prevented the postoperative development of new cerebral ischaemic lesions detected by MRI diffusion-weighted imaging [41▪]. Additionally, two new reviews [42,43] analysed the different components of triple-H therapy (hypervolemia, haemodilution and hypertension) and their effects on cerebral perfusion and neurologic outcome in patients with subarachnoid haemorrhage. The reviews concluded that the hypertensive component was more effective in increasing CBF than haemodilution and hypervolemia and was associated with neurological symptoms reversal seen in two-thirds of patients.

Increase in arterial blood pressure is more reasonably achieved by vasoconstriction rather than by increasing the cardiac output because changes in cardiac output do not affect CBF. Therefore, in the intraoperative situation the alpha-agonist, phenylephrine is commonly used. If bradycardia occurs because of the presence of active baroreflex activity, anticholinergic agents can be administered to neutralize the baroreceptor induced vagotonic effect [40]. Other sympathomimetics namely dopamine, dobutamine and vasopressin can be used to induce hypertension and increase CBF particularly in the ICU.

Optimum haemoglobin concentration

There is a paucity of clinical studies that showed an association between preoperative anaemia or low intraoperative haemoglobin and adverse neurological outcomes in neurosurgical patients. However, retrospective [44] and prospective [45,46] cohort studies of patients with nontraumatic, supratentorial ICH have shown that low haemoglobin levels were associated with poor functional neurological outcome and increased mortality, respectively. Additionally, anaemia requiring transfusion (haemoglobin <90 g/l) was an independent predictor for severe global cognitive impairment in subarachnoid haemorrhage patients [47]. This is in agreement with the investigations showing increased incidence of stroke in patients having on-pump cardiac surgery, in which the haemoglobin during cardio-pulmonary bypass was less than 70 g/l [48,49]. The mechanism of acute anaemia-induced cerebral injury emanates from decreased O_2 delivery leading to the activation of deleterious hypoxic cell signalling pathways [50]. However, Hare and his team have identified the upregulation of neuronal molecules that represent adaptive and hopefully neuroprotective responses to severe acute anaemia. These are neuronal nitric oxide synthase (nNOS), hypoxia-inducible factor-1α and vascular endothelial growth factor [51]. The increase in nNOS is necessary for hypoxia-inducible factor to stimulate cellular responses to anaemia in the form of increased vascular endothelial growth factor (enhances angiogenesis), erythropoietin (promotes erythropoiesis), glucose transporter 1 (increases cellular glucose) and mitochondrial pyruvate dehydrogenase kinase isozyme 1 (prompts glycolytic anaerobic metabolism) [52▪▪,53▪▪]. Moreover, the same group recently reported a novel finding that methaemoglobin (MetHb) may be a marker of anaemic stress associated with reduced tissue perfusion during acute anaemia in humans [54▪]. Accordingly, if increasing MetHb is shown to be associated with adverse outcomes, a MetHb threshold level may prompt the initiation of perioperative blood transfusion.

The haemoglobin threshold for brain tissue injury during neurologic procedures leading to poor outcomes is not precisely known. On the basis of the available evidence, it is recommended that preoperative and intraoperative haemoglobin levels should be maintained at at least 120 and 90 g/l, respectively, in neurosurgical patients [44–47,55]. Despite the previous conclusion, the Transfusion Requirements in Critical Care (TRICC) trial found increased mortality in critical care patients with a target haemoglobin of 100–120 g/l compared to patients with a target of 70–90 g/l [56]. Nonetheless, the results of the TRICC trial cannot be applicable to patients with neurosurgical pathology because neurosurgical patients are much more vulnerable to neurologic adverse events compared to other surgical and medical populations that were included in the TRICC trial.

Table 3. Current status of perioperative neuroprotection during neurosurgery

Strategies that can work	Strategies that do not work*
Liberal normoglycaemia (7.8–10 mmol/l or 140–180 mg/dl)	Mild hypothermia
Mean arterial pressure close to preoperative baseline or ≥80 mmHg	Pharmaceutical agents
Induced hypertension (~20%) in special situations	Volatile anaesthetics during brain ischaemia including xenon
Preoperative haemoglobin ≥120 g/l	Preconditioning and postconditioning with volatile anaesthetics
Intraoperative haemoglobin ≥90 g/l	Intravenous anaesthetics including lidocaine and α2-agonists
	Agents targeting specific molecular sites, examples:
	NMDA antagonist: gavestinel [GAIN trial], Mg2+ [IMAGES & FAST-MAG trials]
	Ca2+ channel antagonist: Flunatrizine [FIST trial]
	Na+ channel antagonist: Fosphenytoin
	$GABA_A$ receptor agonist: Clomethiazole [CLASS trial]
	Free radical-trapping agent: NXY-059 [CHANT trial], Trilazad [RANTASS trial]
	Agents with nonspecific action, examples:
	Cell membrane stabilizer: Citicoline trial
	Haemopoietic agent: Erythropoietin [German Multicenter EPO Stroke Trial]

*These strategies have been tested in single centre clinical trials or large phase II and III clinical trials and did not show favourable results for the treatment.

PHARMACOLOGICAL STRATEGIES

Ischaemic brain injury triggers a cascade of pathophysiologic processes that culminates in cell death because of necrosis (premature cell death caused by progressive enzymatic degradation) or apoptosis (spontaneous genetically directed process of cell self-destruction that is marked by the fragmentation of nuclear DNA). Many pharmacological strategies for neuroprotection has been tested in the laboratory and aimed at inhibiting or reversing of the pathways that leads to ischaemic cell death (Fig. 1). Unfortunately, the successes achieved in the laboratory have not been translated yet to the bedside. First, there are no randomized controlled trials either completed or ongoing that studied the efficacy of pharmacological agents as neuroprotectants in neurosurgical patients undergoing intracranial procedures. Second, clinical trials conducted to test certain drugs for protecting the brain during acute neurosurgical catastrophes, that is, traumatic brain injury, ICH, ischaemic stroke and subarachnoid haemorrhage [57–60], failed to show any benefit from the studied treatments (Table 3). The reasons for such negative results were reviewed and specific recommendations were suggested for improving the quality of future neuroprotection clinical trials [61,62].

Anaesthetics and neuroprotection

There has been a resurgence of the concept of intravenous and volatile anaesthetics as neuroprotectants. However, recent clinical studies were disappointing pertaining to efficacy of anaesthetics in protecting the brain. Hindman *et al.* [63] performed a post hoc analysis of data obtained from 441 patients who participated in the IHAST study in whom temporary arterial occlusion was used. Multiple linear logistic regressions showed that the intraoperative use of intravenous anaesthetic drugs did not impact the odds of good neurological outcomes. In line with these results, there is very limited clinical data suggesting a neuroprotective effect of volatile anaesthetics during neurosurgical procedures assessed by improved neurological outcome [64,65]. Regarding the concepts of volatile anaesthetics preconditioning and postconditioning, there are no clinical data supporting that the application of volatile agents prior or after neurosurgery and ischaemic or traumatic insults will provide any form of intraoperative brain protection. Finally, the re-emergence of interest in inert gases as anaesthetics lead to the conduction of clinical trials looking at xenon as neuroprotectant in cardiopulmonary bypass, neonatal asphyxia and following cardiac arrest and resuscitation. To date, none of these trials have been completed. However, small phase II trials of xenon did not elicit any indication that the inert gas can decrease the incidence of postoperative cognitive dysfunction [66].

CONCLUSION

It is clear that neuroprotectant pharmaceutical agents do not currently exist despite decades of

'bench' research claiming different forms of successes. Thus, the anaesthesiologist will be compelled to use nonpharmacological strategies sometimes based on the empiric evidence that 'makes sense' physiologically and pharmacologically to protect the brain during neurosurgical procedures (Table 3). Cerebral perfusion should be maintained by adequate control of MAP at values more than 80 mmHg. Blood glucose should be kept within a liberal normal range (7.8–10 mmol/l). Tight control with IIT as well as hyperglycaemia should be avoided. Achievement of adequate haemoglobin levels preoperatively (≥120 g/l) and intraoperatively (≥90 g/l) is important to sustain sufficient oxygen delivery to the brain. Induced hypertension may be used in certain neurosurgical situations in which there is a vessel occlusion (temporary clipping/clamping, vasospasm) or a change in the cerebral autoregulation relationship (intracranial pathology with mass effect, hypertensive disease and traumatic brain injury). Mild hypothermia (32–35°C) may be used if the anaesthesiologist chooses to extrapolate the data showing a degree of neuroprotection by mildly lowering body temperature in asphyxiated neonates and postcardiac arrest patients to the neurosurgical situation.

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Conflicts of interest

There are no conflicts of interest.

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