

Brain Protection in Neurosurgery - Dos and Don'ts

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After an official *Decade of the Brain* that followed two decades of searching for the same prize, one might ask "Why is it taking so long?" Most of the answer to that question is straightforward and simple: M&M rates for elective neurosurgery are so low that daunting sample sizes would be required to detect a major improvement in morbidity, detecting lesser improvements would require even larger samples, and mortality is so rare that detecting a decrease is virtually out of the question.

It follows that our difficulty in finding neuroprotection may be one of camouflage rather than mirage. Protective drugs and techniques may be at hand, but we may not have been able to see them clearly. Indeed, we may have already lost interest in several therapies that would have evidenced reliable protection if more sensitive outcome measures had been employed and if those interventions had been tested in CABG and valve replacement patients. That is, if we had looked harder and if we had looked in places where adverse events are frequent enough to make improvements detectable. The good news is that we are making progress in the methodology of making progress, so there are new reasons for hope.

Standard-of-care prophylactic cerebral protection has not arrived, but if we put our ears to the track, two trains can be heard. One has been on its way for a long time and may prove to be as good as it is late. Two techniques are onboard - intraoperative mild hypothermia and postoperative low normothermia. The other train just started heading our way, but it is picking up speed and may contain the stuff of magic bullets. Its load is cerebral preconditioning. Also promising are some more conventional bullets. Remacemide and lidocaine appear to have improved cardiac patients' neuropsychological function in clinical trials, and magnesium is being

tested in the heart room **and in the** field for "prehospital" neuroprotection in stroke patients.

At the same time, some of yesterday's trains were pulling empty cars, so we need to clear the tracks. For that purpose, we will weigh laboratory and clinical evidence regarding the disappointing effects of some anesthetic and adjuvant drugs that are currently in use: including nitrous oxide, ketamine, nimodipine, tirilazad and etomidate. On the technique side, we will consider evidence that post-ischemic mild hypothermia in the ICU is less neuroprotective than initial reports suggested.

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Nitrous Oxide

In 1938 C.D. Courville published "The pathogenesis of necrosis of the cerebral gray matter following nitrous oxide anesthesia" -- an article which presents photographs of vacuolated cortical neurons from patients who died subsequent to administration of nitrous oxide (N₂O).¹ Sixty years later, Jevtovic-Todorovic and coauthors published compelling evidence that N₂O causes vacuolation of both the endoplasmic reticulum and mitochondria of neurons in the posterior cingulate and retrosplenial cortices of rats. Are we on our way to where we might have been if Courville's work had received more sustained attention?^{cf3}

Nitrous oxide's mechanism of action appears to be NMDA receptor antagonism, and like other NMDA antagonists, N₂O has been shown to reduce damage from excessive glutamate release. Unfortunately, however, because NMDA also excites inhibitory neurons, NMDA blockade causes inhibition of GABA release, and thus general disinhibition. This is probably a component of the mechanism by which N₂O, like other NMDA antagonists (e.g., ketamine, phencyclidine, dextrophan, MK-801), can cause neural damage.^{2,4}

In patients with folic acid deficiency, a single exposure to N₂O can cause spinal cord degeneration.⁵ Less direct, but also less rare, exposure to N₂O causes a substantial increase in plasma homocysteine,⁶ which can increase coagulation,⁷ decrease flow-mediated vasodilation⁸ and increase postoperative myocardial ischemia⁹ - all of which complicate recovery in the neuro ICU. Prolonged hyperhomocystenemia is also an independent risk factor for cerebrovascular disease."

The question of N₂O's effect on the neuroprotective efficacy of primary anesthetics has been addressed by several investigations. Following Arnfred and Secher's demonstration that thiopental more than doubles survival time in mice subjected to hypoxia while N₂O used alone reduces survival,^{1,12} we found that co-administration of N₂O virtually eliminates the protective effect of thiopental in the same model." Two years later, Baughman and coauthors found that 0.5

MAC N₂O added to either 1 MAC or 0.5 MAC isoflurane cut the protective effect of isoflurane in half relative to the effect of 0.5 MAC N₂O alone during moderate forebrain ischemia." Sugaya & Kitani subsequently reported that N₂O attenuates the protective effect of isoflurane on preservation of a critically important neuronal cytoskeletal protein during forebrain ischemia in the rat.¹⁵ More recently, Jevtovic-Todorovic and coauthors found that N₂O converts a non-toxic dose of ketamine into a substantially toxic dose in rats."

Evidence that the above clinical and laboratory findings resulted in part from a direct neurotoxic effect of N₂O is bolstered by our findings in the hippocampal slice model, where nitrous oxide markedly reduced electrophysiological recovery from severe hypoxia without affecting fundamental biochemical parameters like ATP concentration, Ca influx, K efflux and Na influx."

Direct neurotoxicity aside, N₂O has been repeatedly shown to increase cerebral metabolic rate (CMR), cerebral blood flow (CBF) and intracranial pressure (ICP) when used alone, but these effects are variable when N₂O is used as an adjunct anesthetic, with or without hypocapnia, and with or without EEG burst suppression."

Perhaps the most pressing question regarding the use of N₂O in neurosurgical patients was recently framed by Enlund, Edmark and Revenas: "It is no consolation for the patient who suffers from an irreversible neurological sequela after nitrous oxide exposure that he happens to be the first one at your clinic for the last five years. For those like us who administer drugs, or for the regulatory authorities, such an incident might nevertheless be acceptable provided that a great number of patients receive indispensable benefits, which outweigh a severe side effect. Are there such pros [benefits] from nitrous oxide?"¹⁹

Tirilazad, Nimodipine and Etomidate

Clinical application of the 21-amino steroid tirilazad looked promising. Unfortunately, more substantive results from a North American trial in subarachnoid hemorrhage patients failed to reach statistical significance,²⁰ and a follow-up study of high dose tirilazad

in women depended upon an idiosyncratic grouping of data to reach statistical significance." A detailed commentary on that analysis concluded that "any eventually proven therapeutic efficacy is likely to be modest,"²³ and a systematic review of tirilazad use in 1,757 stroke patients concluded that "Tirilazad mesylate increases death and disability by about one fifth when given to patients with acute ischemic stroke.

Several clinical trials and two meta-analyses suggest that calcium channel blockers nimodipine, nifedipine and AT877 reduce the frequency of vasospasm subsequent to subarachnoid hemorrhage and/or improve outcome.^{25,26} The most favorable finding of the most recent meta-analysis suggests that nimodipine improves outcome, on average, by preventing one poor outcome in one out of every 13 patients treated. Whether the reduction in blood pressure that accompanies these Ca blockers improves outcome relative to hypertensive, hypervolemic, hemodilution remains controversial. Neither meta-analysis was able to detect a statistically significant reduction in mortality. Two subsequently published clinical trials, one which administered nimodipine within 24 hours of acute stroke, and one which administered nimodipine within 6 hours of stroke,²⁸ failed to detect a beneficial effect.

The most disturbing reports yet published about nimodipine, disturbing for medical research in general, are two systematic reviews which reveal a lack of evidence to justify Phase 3 clinical trials. Contrary to conventional assumption, published laboratory experiments found as many negative as positive results, and animal experiments and clinical studies ran simultaneously.²⁹ Making matters worse, several methodologically sound clinical studies of calcium antagonists in ischemic stroke patients remained unpublished. In each of those unpublished studies, results were significantly worse for patients in the treatment groups.³⁰

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paucity of supportive clinical evidence, and the presence of troubling laboratory results,'^{g 3'} etomidate is still used for cerebral protection at some institutions. We now have clinical evidence that the standard propylene glycol formulation of etomidate induces more cerebral tissue hypoxia, tissue acidosis, and neurological deficits than an EEG-equivalent dose of desflurane."

Postoperative Hypothermia

Results from the multi-institutional study of post-operative mild hypothermia in head injury patients have been published.¹⁴ The trial was terminated in May of 1998 by its Safety Monitoring Board after enrollment of 392 patients. A decrease in the number of hypothermic patients with ICP >30 mmHG (59% vs. 41%) did not produce a difference in mortality (28% vs. 27% in the normothermic group) and normothermic patients experienced fewer bouts of critical bradycardia and hypotension, and fewer medical complications.

These findings accord well with results from a clinical study of the effect of prolonged mild hypothermia on electrolyte balance. Polderman and coauthors found that serum magnesium, phosphate and potassium fell to critical levels "despite the fact that moderate and, in some cases, substantial doses of electrolyte supplementation were given."³⁵ More generally, some of the most competent laboratory studies indicate that hypothermia administered subsequent to an ischemic event only delays neuronal death,^{36,37} and recent laboratory work suggests that if there is a window of opportunity for inducing protective post-ischemic hypothermia, it is very narrow.³⁸

Indeed, the narrowness of that window may account for recent reports of neuroprotective effects from mild hypothermia after cardiac arrest. In both major studies,^{39,40} most patients were mildly hypothermic upon admission, and it is reasonable to speculate that their brains began to cool as soon as they lost CBF. Patients assigned to the hypothermic groups were cooled further for 12-24 hours, while those assigned to the normothermic groups were passively warmed to normothermia or above over a 6-8 hour period, such that the hypothermic groups began to cool immediately and were kept cool for

a substantial period of time while patients in the normothermic groups began to cool immediately but did not remain hypothermic for a substantial period of time. Put differently, both groups of patients became hypothermic within the window of opportunity, but the opportunity for a protective effect was lost shortly thereafter in the normothermic patients.

Evidence that the above consideration might be critically important comes from the definitive head injury study: "Among the patients who had normothermia on admission, the outcomes were similar in the two treatment groups... [But] among the patients who had hypothermia on admission and were treated with hypothermia, 61 percent had poor outcomes, as compared with 78 percent of those with hypothermia on admission who were in the normothermia group (P=0.09) ... [and] among patients 45 years of age or younger who had hypothermia on admission, 52 percent of those assigned to the hypothermia group had poor outcomes, as compared with 76 percent in the normothermia group (P=0.02).",³⁴

The other major possibility regarding hypothermia subsequent to cardiac arrest is that, as with the head injury studies, early optimism obscured objectivity.^{41,42} The statistical significance of the primary outcome in the Australian study⁴¹ depends upon a clearly inappropriate analysis (Chi square without Yate's correction). A proper analysis (Fisher Exact) renders that result statistically non-significant. In the European study⁴² more than 20% of patients assigned to the normothermia group were allowed to go above 38° C for 75% of the 48 hour period subsequent to restoration of spontaneous circulation. It may be the case that mild hypothermia would not have improved outcome relative to a control group that did not experience mild hyperthermia.

Low Normothermia

A promising development in ICU temperature control is the concept of "Low Normothermia" - keeping non-ventilated patients servo-controlled at 36 °C in order to provide substantial assurance against bouts of fever. In vitro results indicate that just as

hypothermia preserves ATP, reduces Ca^{2+} influx and improves electrophysiologic recovery from hypoxia, so hyperthermia depletes ATP, increases Ca^{2+} influx and impairs recovery.^{44,45}

Fever in the neuro^{146,47} and cardiac⁴⁸ ICU associates strongly with poor outcome. For example, Schwarz and coauthors found that 90% of intracerebral hemorrhage patients experience hyperthermia in the ICU, with severity and duration providing an independent prognostication of poor outcome.⁴⁹ Nevertheless, in a preliminary trial of moderate hypothermia (33° C) for such patients, 11 out of 24 (44%) died from "herniation caused by a secondary rise in ICP after rewarming," and 10 of 25 (40%) contracted pneumonia.⁵⁰ If the benefit of postoperative mild hypothermia is limited to avoidance of hyperthermia, a better cost/benefit ratio could be obtained by maintaining low normothermia. In distinction, if post-operative mild hypothermia is utilized to extend the therapeutic window of an intervention,⁵¹ it may prove useful even in the absence of a direct therapeutic effect.

Prophylactic Hypothermia

In contrast to post-ischemic hypothermia, laboratory studies overwhelmingly evidence a neuroprotective effect of prophylactic mild hypothermia. A survey conducted in '93-'94 indicates that 40% of neuroanesthesiologists already used mild to moderate intraoperative hypothermia, 26% used hypothermia in every patient, and 14% thought it would be unethical to use normothermia." Nevertheless, we need a prospective, randomized clinical trial of intraoperative mild hypothermia. Fortunately, such a trial is underway.⁵³

Data from a recent comparison of normothermic versus hypothermic (35.5-36.5 vs. 28-30° C) cardiopulmonary bypass patients failed to detect a benefit of hypothermia.¹⁴ Fortunately, however, this investigation in conjunction with another study by the same group,⁵⁵ may have revealed a variable which explains why several such studies have failed to find a therapeutic effect: rewarming overshoot. Patients rewarmed with perfusate 4-6° C

higher than nasopharyngeal temperature experienced more hyperthermic overshoot and greater decrement in cognitive function than patients who were rewarmed with perfusate which was not more than 2° C higher than nasopharyngeal temperature. Perhaps the ideal rewarming protocol would bring patients to low normothermia without any hyperthermic overshoot.

Until empirical evidence is definitive, we can only guess about the future of intraoperative mild hypothermia. My guess is that it will prove beneficial. Likewise, for head injury and stroke patients, moderate hypothermia in the ambulance may be within the window of opportunity for neuroprotection - because early cooling has the potential to prophylactically reduce ischemic injury that is still in the initial stages of development.

Looking In The Right Place With The Right Tools

Remacemide is not a powerful neuroprotectant. Its mechanism of action, glutamate antagonism through NMDA channel blockade, works too far downstream in the ischemic cascade to have magic-bullet potential, 56 and remacemide has not been shown to reduce morbidity or mortality in coronary artery bypass patients. Nevertheless, evidence for a beneficial effect of this NMDA blocker was gleaned by combining scores from nine neuropsychological tests. Those data allow the inference ($p < 0.03$) that in exchange for a higher risk of dizziness during nine days of drug administration, patients in the treatment group retained more of their ability to learn. 57

How much optimism does this single, modest result justify? More than the result itself would indicate, I think, for two reasons. First, the study looked in the right place. It was conducted in cardiopulmonary bypass patients, where unlike elective neurosurgical cases, morbidity and mortality rates are high enough to allow detection of a positive effect" - and yet unlike head trauma and stroke, where M&M rates are so high and patient conditions are so variable that positive effects are lost in a low signal-to-noise ratio. Second, Arrowsmith and coauthors used the right tools. Outcome measures in the remacemide study included a battery of psychological tests that are more sensitive than perception of pinpricks, presence or

absence of paralysis, ability to follow simple commands, and other standard indicators of neurological deficits. Future investigations should add neurobiochemical markers of neurobehavioral damage.⁵⁹

Barbiturates, Magnesium and Lidocaine

As with hypothermia, reducing CMR is the mainstay of brain protection. Although an intellectual backlash has challenged the operating hypothesis that lowering CMR has a substantial protective effect," all known means of lowering CMR entail simultaneous negative effects, with the continuum of drugs, techniques, and toxins that reduce CMR ranging, on balance, from protective to damaging. Nakashima and coauthors found that for similar reductions of CMR obtained with hypothermia, pentobarbital or isoflurane, hypothermia resulted in substantially longer times to depolarization of cerebral cortex subsequent to cardiac arrest." Concomitantly, Verhaegen and coauthors found that hypothermia reduces CMR during ischemia proportionately more than does pentobarbital or isoflurane."

Accordingly, we find mild hypothermia near the most protective end of the continuum, followed at some distance by anesthetics (reversible neurotoxins), then moving to the damaging end, we find nonreversible neurotoxins followed at some distance by blunt trauma - all of which lower cerebral metabolism. My point here is that the benefit of reducing CMR remains constant while the cost of doing so varies from minor to lethal. From this perspective it seems rash to challenge the efficacy of reducing CMR in and of itself.

Some of the proximate mechanisms by which barbiturates lower CMR include reduction of calcium influx, sodium channel block, inhibition of free radical formation, potentiation of GABAergic activity, and inhibition of glucose transfer across the blood-brain barrier. All of these mechanisms are consistent with Goodman and coauthors' report that pentobarbital coma markedly reduces lactate, glutamate and aspartate in the extracellular space of head injured patients with severely increased ICP.⁶³ An in vitro investigation suggests that thiopental also delays the loss of transmembrane electrical gradients caused by application of NMDA and AMPA. This

stands in marked contrast to the effect of propofol, which can aggravate glutamate excitotoxicity and increase neuronal damage.'

Magnesium blocks both ligand and voltage dependant Ca entry and has shown considerable promise in animal experiments." The fact that magnesium is also powerfully protective in vitro ⁶⁶ suggests that it may critically reduce calcium influx in addition to improving CBF subsequent to cerebrovascular dilation.

Magnesium loading for clinical cerebral protection is receiving renewed attention ⁶⁵ A meta-analysis of results from four small trials in acute ischemic stroke patients suggests improved functional outcome, and a study designed to test efficacy in 2,700 patients is ongoing. ⁶⁷ Recent laboratory work indicates that magnesium deficiency exacerbates traumatic brain injury while magnesium loading shortly subsequent to trauma reduces injury. ⁶⁸ If the same holds for stroke patients, efficacy is most likely to be realized by the FAST-MAG trial (Field Administration of Stroke Treatment - Magnesium). A preliminary report on the first 20 FAST-MAG patients indicates that paramedics can deliver a 4 g loading dose of magnesium sulfate en route to the hospital without substantial complications.

Unfortunately, laboratory evidence indicates that pre-ischemic magnesium administration is much more protective than post-ischemic administration, ⁷⁰ suggesting that magnesium's efficacy in stroke and head trauma patients may be limited to patients who are fortunate enough to enter a VERY FAST-MAG trial. Fortunately, a prospective, randomized trial of prophylactic magnesium in cardiac surgery patients is underway."

Sodium influx is the first step in the ischemic cascade. Blocking initial events in the cascade, events which do not directly cause neuronal damage, will reduce the damage done by downstream events. It follows that truncating initial steps of the ischemic cascade, as distinct from blocking glutamate receptors and scavenging free radicals, will reduce the probability of interfering with endogenous mechanisms of repair. Acting more directly on post-necrotic injury, recent in vitro data also "suggest that [Na channel blocker] lidocaine

may reduce ischemic damage in the penumbra by blocking the apoptotic cell death pathways that involve cytochrome C release and caspase-3 activation." These appear to be some of the mechanisms by which experimental, prophylactic, low-dose lidocaine has demonstrated neuroprotective properties both in vitro ^{73,74} and in vivo. ^{75,76,77}

Looking for neuroprotection in cardiac valve patients, Mitchell and coauthors found that lidocaine infusion begun at induction of anesthesia and continued for 48 hours with a target plasma concentration between 6 and 12 mol/L increased scores in 6 of 11 neuropsychological tests and in patients' memory inventory.⁷⁸ A second trial of lidocaine neuroprotection in cardiac patients is scheduled for completion this year.⁷⁹

Cerebral Preconditioning

Among the most promising prospects currently under investigation is the possibility of inducing cerebral preconditioning prior to elective surgery. Using the retina as a model for the CNS, Barbe and coauthors found that subjecting rats to heat shock (15 min at 41°C) protected neurons from high intensity light damage if the rats were allowed to recover for 18 hours subsequent to heat exposure.⁸⁰ This phenomenon was soon replicated in a model of cerebral ischemia,⁸¹ and the induction of endogenous proteins of repair is now well documented."

Evidence in humans suggests that TIA's **induce ischemic preconditioning.**^{81,84,81} Congruent with experimental preconditioning, patients whose TIA's lasted 10-20 minutes and occurred a week or less prior to their cerebral infarction were more strongly protected than patient whose prior TIA lasted less than 10 minutes (insufficient stimulus) or longer than 20 minutes (damaging stimulus) and whose CI occurred more than one week later.

Clinically acceptable means of accomplishing cerebral preconditioning are being sought. Experimental results suggest the possibility of pre-op hyperbaric oxygen,^{86,87} electroconvulsive shock¹⁸ and the potassium channel opener diazoxide" among other candidates,

but the first human trial of a known preconditioning agent employs a substance that is endogenously produced in the brain after lethal hypoxic or ischemic insults - erythropoietin. 90 Preliminary results in stroke patients are encouraging," but for reasons outlined above, one would expect cerebral preconditioning to be most effective when given prior to anticipated ischemia - i.e., prior to cardiac bypass or elective neurosurgery.

Conclusion

I recommend caution in the use of nitrous oxide, etomidate, tirilizad, nimodipine and postoperative moderate hypothermia in neurosurgical patients. On the positive side, my guess is that if looking in the right place with the right tools can detect the cerebral protective effects of an NMDA blocker," similar methodology will detect stronger effects with more promising drugs and techniques - for example, cerebral preconditioning, prophylactic mild hypothermia, pre-op magnesium loading, intra and post operative lidocaine infusion, and servo-controlled low normothermia in the neuro ICU.