Pharmacological prevention and modulation of cerebral ischemia and neurological dysfunction during cardiac surgery

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Neurologic complications, a well-recognized source of morbidity and mortality, continue to be the concern of both patients undergoing cardiac surgery, and those caring for them (1). Without question, advancements in the conduct of surgery and bypass have been made that have worked to mitigate the risk of neurologic injury. However, to some extent, the neurologic advantages that these advancements have allowed have been masked somewhat by allowing surgery to be offered to patients who are now older and possess many more comorbidities. The overall effect is that neurologic injury persists as a frequent complication. Indeed, multiple technologic advancements in the surgical and cardiopulmonary bypass (CPB) technologies formed the early basis for non-pharmacologic methods to decrease some of the neurologic injury that was being observed. The search for a pharmacologic solution, one that could be offered in addition to various surgical modifications (such as optimized atheroma detection and management), has been ongoing for decades.

Early efforts to identify pharmacologic neuroprotectants (such as with barbiturates) were based on assumptions of the importance of metabolic suppression to protect the ischemic brain. However, the over-simplified concept that pharmacologically reducing cerebral metabolism in order to offset the depletion of high energy substrates and destruction of brain tissue that rapidly follows ischemia, has now been replaced by a considerably more complex temporal, topographic and molecular picture of ischemic brain injury. Advanced imaging techniques have discovered spatial gradations of residual blood flow in the downstream territory of an occluded cerebral vessel producing an ischemic „penumbra“, where blood flow is critically reduced but still sufficient to prevent immediate cell death. There is a marked difference in the temporal association between the ischemic insult and eventual cell death. There is a „therapeutic window“ in which potential pharmacologic intervention may reduce infarct size. This „window“ differs between the profoundly ischemic core and the penumbra. In the ischemic core, restoration of oxygen and glucose supplies is essential in this area of severe ischemia where high-energy phosphates have been severely depleted. In contrast, in the penumbra, the decrease in oxygen and glucose delivery is insufficient to kill cells directly. In these regions, pharmacologic agents with little or no ability to modify cerebral blood flow (CBF) have been demonstrated experimentally to effectively reduce cerebral infarct volume, even if administered after the onset of permanent focal ischemia.

An ischemic cascade of intracellular events is triggered by reductions in CBF, either globally or regionally, to the point at which the demands of cerebral metabolism (CMRO2) can no longer be met (2). This depletion in cerebral energy stores leads to membrane ionic pump failure resulting in a cascade of injurious events mediated by the influx of sodium, the opening of voltage-dependent calcium gates, a release of stored intracellular calcium and overall membrane depolarization. Membrane depolarization results in the release of excitatory amino acids (glutamate, aspartate), with subsequent dramatic increases in intracellular calcium. This increase in cytoplasmic calcium propagates the cascade through the activation of a number of calcium-dependent enzymes, including endonucleases, nitric oxide synthase, various proteases, protein kinases, and phospholipase. If left unabated, these enzymes will result in neuronal death.

Although some of these events are potentially reversible if reperfusion is quickly re-established, reperfusion itself initiates a number of other destructive pathways. The re-establishment of oxygen delivery provides substrate for the production of reactive oxygen species (ROS), so-called free radicals. In addition, reperfusion initiates a number of other damaging

extracellular events including blood brain barrier breakdown, endothelial swelling, and localized thrombosis that together may culminate in microvascular occlusion and further ischemia. Independent of these direct ischemic related events, is the discreet inflammatory milieu that is initiated and propagated by the contact of blood elements with the foreign surfaces of the CPB circuit. Each of these pathways in the ischemic cascade, as well as bypass-mediated inflammatory pathways, represent distinct potential targets for neuroprotection.

From the outset, it should be stated that there are currently no pharmacologic therapies that can be definitely recommended. Despite that, an understanding of what has been studied previously identifies important fertile, and some many futile, directions for continued and future research. Some of the most relevant cardiac surgery pharmacologic neuroprotection strategies, past and present, will be reviewed below.

Barbiturate anesthetic agents were among the first compounds investigated as neuroprotectant agents in cardiac surgery. In an early study by Nussmeier et al., **thiopental** was administered, to an EEG isoelectricity end-point, prior to cannulation and continued until separation from CPB (3). Neurologic complications on post-operative day 10 were significantly reduced in the thiopental group *versus* controls. Based on these encouraging results, high-dose thiopental was frequently used for valvular and other open ventricular procedures. The mechanism of this effect related to the suppressive effects of barbiturates on cerebral metabolism. This mechanism, along with experimental data reporting the beneficial effects of the barbiturates (4), made it a logical choice for cardiac surgery. However, further investigations of the use of thiopental were not as positive. A study by Zaidan et al and one by Pascoe et al, failed to support a beneficial effect of thiopental on neurologic outcome after cardiac surgery (5,6). These negative trials and the side-effects of prolonged sedation with barbiturates served to quell the optimism for barbiturates. Retrospectively examining the initial Nussmeier study, the beneficial effects of the thiopental, although not demonstrated in longer-term follow-up, may not have been related to a direct neuroprotective effect per se, but due to an indirect effect on reducing emboli-containing CBF. The well-known cerebral vasoconstricting effects of thiopental (in which CBF is reduced via a matching with a barbiturate-induced reduction in $CMRO_2$) may have resulted in a reduction in embolic load to the brain during CPB and as a result, a beneficial effect on neurologic outcome.

Propofol has similar effects on $CMRO_2$ and CBF as thiopental and has also been demonstrated to possess antioxidant and calcium-channel antagonist properties (7). Along with supportive data from the experimental cerebral ischemia studies (8-10), propofol underwent evaluation as a neuroprotectant in the setting of cardiac surgery. A prospective randomized clinical trial by Roach et al. (11) to determine whether propofol-induced EEG burst-suppression would reduce the incidence or severity of cerebral injury during valvular surgery was performed (11). In 109 of 215 patients randomized to receive burst-suppressive doses of propofol, there was no beneficial cognitive effect at two-months. The authors concluded that EEG burst-suppressive doses of propofol provided no neuroprotection during valvular cardiac surgery. No other studies in non-valvular cardiac surgery have assessed the effects of propofol on the brain.

The γ-aminobutyric acid (GABA) receptor antagonist **clomethiazole** has been evaluated in CABG surgery. GABA has repeatedly been shown to be an important neuroprotective target, both in focal and global experimental ischemia (12,13). However, in a relatively large well-designed and conducted study, it failed to decrease neurocognitive dysfunction after cardiac surgery (14).

The adenosine-regulating agent, **acadesine**, was studied in the early 1990s with the aim of improving myocardial outcome; stroke was examined as a secondary outcome (15). Compared to placebo, both high and low dose infusions of acadesine resulted in a lower stroke rate ($p = 0.016$). There are a number of other adenosine-like agents that in pre-clinical experimental settings have provided neuroprotection (16,17). Despite this positive (albeit indirect) clinical data and supportive experimental data, no further clinical neuroprotection indication for acadesine has been pursued (18).

Aprotinin is a non-specific serine protease inhibitor that was first used in the 1950s for the treatment of pancreatitis. Its most recent indication in cardiac surgery was for the prevention of blood loss and transfusion. In several large multi-center trials of aprotinin for primary or redo CABG and valvular surgery evaluating aprotinin's blood loss reducing effects, the high-dose aprotinin group also had a lower stroke rate compared to placebo ($p = 0.032$) (19,20). Similarly, Frumento et al. retrospectively examined patients at

high risk for stroke (due to the presence of significant aortic atheroma); those who received aprotinin had a significantly lower stroke rate (21). In a recent small (n = 36) study examining the effect of aprotinin on cognitive deficit following CABG surgery, the incidence of cognitive deficit was reduced in the aprotinin group (58%, aprotinin vs. 94% placebo; p = 0.01) (22). However, the high rate in the placebo group, the small size of the study, and methodologic concerns limit the applicability of these results to broader populations (23). Animal investigations in the setting of cerebral ischemia failed to show any direct benefit on either functional or neurohistologic outcome following cerebral ischemia (24).

There has been considerable discussion and investigation as to the potential mechanism for any aprotinin-derived neuroprotection. Initial enthusiasm focused upon its anti-inflammatory effects potentially preventing some of the adverse inflammatory sequelae of cerebral ischemia. However, aprotinin may have had its beneficial effects independent of any direct neuroprotective effect through an indirect effect of modulating cerebral emboli. Brooker et al. have identified the cardiotomy suction as a major source of cerebral emboli during CPB (25). One could extrapolate that if a drug reduces the amount of particulate-containing blood returning from the operative field to the cardiotomy reservoir (by decreasing overall blood loss), then cerebral emboli (and the resulting neurologic consequences) might also be decreased.

More recently, the neurologic effects of aprotinin have been re-examined in a publication by Mangano et al. (26). Contrary to the previous data which suggested, albeit weakly, that aprotinin may have some neuroprotective effects, the Mangano observational study outlined a significant increase in the stroke rate. The mechanism responsible for this potential side effect may be related to a net prothrombotic effect. In summary, the data suggesting that aprotinin had any neuroprotection was somewhat indirect and weak; however, the data suggesting that it is neurologically detrimental is similarly weak. The true effects of aprotinin on the brain during cardiac surgery remain incompletely understood, and with its recent withdrawal from the market due to renewed safety concerns, will likely remain unknown.

Calcium plays a central role in propagating cerebral ischemic injury. For this reason, as well as a demonstrated beneficial effect of the calcium channel blocker **nimodipine** in subarachnoid hemorrhage and experimental cerebral ischemia, a randomized double-blind placebo, single center trial to access the effect on nimodipine on neurologic, neuro-opthalmologic and neuropsychologic outcomes after valvular surgery was undertaken (27-29). The trial was not completed after safety concerns regarding an increased bleeding and death rate in the nimodipine group prompted an external review board to suspend the study (after enrolling 150 of 400 patients planned to be studied). There was also no neuropsychologic deficit difference between the placebo or nimodipine groups at this interim review. As a result, the true effect of this drug, or similar calcium trial blockers, may never be fully known in this setting.

The monosialoganglioside, **GM1-ganglioside** has been investigated as a potential neuroprotectant during cardiac surgery (30). In addition to the potential beneficial effects of this type of compound on preserving neuronal membranes, there is also some data to suggest that it has a potential beneficial effect on reducing excitatory amino acid transmission (31). In a preliminary (but underpowered) cardiac surgery study, there was no beneficial effect demonstrated. However, the authors used this pilot trial to describe useful statistical methodology needed to measure differences in neurocognitive outcome, thereby constituting a template for later trials. This trial highlights one of the biggest difficulties in this investigative field – the interpretation of negative but underpowered studies.

Several antagonists to the N-methyl-D-aspartate (NMDA) receptor, known to play a major role in cerebral ischemic injury (2), have been studied. Although human stroke trials have been limited by distressing psychomimetic side effects, there is a wealth of experimental data pointing towards NMDA receptor antagonists being robust neuroprotective agents. It has also been postulated to play a potential role in CPB-associated cerebral injury (32). **Dextromethorphan**, known for its antitussive activity has been demonstrated to have some nonspecific NMDA antagonism properties. A small pilot study examined dextromethorphan in the setting of pediatric cardiac surgery and used both EEG and MRI end points to determine a difference between treatment groups, but saw no difference (likely due to the small size of the study) (33). There have been no other studies examining NMDA receptor antagonism in the setting of pediatric cardiac surgery.

A second NMDA receptor antagonist that has been evaluated for neuroprotection during CABG surgery is **remacemide**. In a well-designed and executed study by Arrowsmith et al. remacemide was given orally for four days prior to CABG (32). A neurocognitive bat-

tery was performed one week before and eight weeks after CABG. A deficit was defined as a decrease in one standard deviation in two or more of the 12 tests within the neurocognitive battery. In addition, the patients were evaluated for their learning ability by subtracting the post-operative neurocognitive score from the pre-operative score (thus formulating a Z score). Although there was no difference between groups with respect to the dichotomous outcome of cognitive deficit ($p = 0.6$), examination of a continuous measure of learning ability showed there was a beneficial cognitive effect in the patients who received remacemide ($p = 0.028$). Despite these apparently beneficial results, due to the length of time that it took to perform this single center trial, initial non-beneficial preliminary results, as well as a prolonged period of data analysis and review for publication, this drug was not further pursued for this indication. It has, however, highlighted the potential utility of this class of drugs for this indication and ongoing investigations examining other NMDA receptor antagonists continue (34-36).

Recently, the neuroprotective effects of S(+)-**ketamine**, a frequently used anesthetic that is also an NMDA-receptor antagonist, was evaluated in a small ($n = 106$) study in cardiac surgery patients (37). The incidence of neurocognitive dysfunction 10 weeks after surgery trended towards being lower in the ketamine group (20%, ketamine vs. 25%, controls; $p = 0.54$), but as the study was underpowered, it was not a significant change. There are no other published trials evaluating ketamine for neuroprotection in this setting.

Lidocaine, a sodium channel-blocking agent, that also possesses potential anti-inflammatory actions, has been investigated several times as a neuroprotectant in cardiac surgery. In a study of 55 patients undergoing valvular surgery, a lidocaine infusion (in an anti-arrhythmic dose of 1 mg/min) was begun pre-induction and maintained for 48 hours following surgery (38). Neurocognitive testing was performed pre-operatively, then eight days, two and six months post-operatively. Compared to placebo, neurocognitive outcome eight days following the surgery was significantly better in the lidocaine group ($p = 0.025$). However, a much larger double blind randomized trial in cardiac surgery failed to replicate the finding (39). Currently, lidocaine cannot be recommended as a clinical neuroprotective agent in cardiac surgery. Interestingly, not only did lidocaine not confer any benefit, but in diabetic patients, it actually worsened neurocognitive outcome.

Although **betablocker** use in patients with cardiac disease has been predominately directed towards the prevention of adverse myocardial events, their relationship to neurologic outcomes following cardiac surgery has also been studied (40). In a retrospective study of nearly 3000 patients, stroke, and encephalopathy were studied. Patients receiving beta-blocker therapy had a significantly lower incidence of neurologic deficit versus those not receiving beta-blockers. Although the reasons for this potential benefit are not clear, there are several potential reasons why they may be efficacious, including the modulation of both cerebrovascular tone and CPB-related inflammatory events. Supporting this observational effect of a potential neuroprotective effect from beta-blockers is a study of carvedilol, which is known to have mixed adrenergic antagonist effects as well as acting as an antioxidant and inhibitor of apoptosis (41).

The generation of reactive oxygen species (ROS) is a well-described pathophysiologic mechanism of ischemic reperfusion injury. This, combined with the whole-body inflammatory response associated with CPB (with its own ROS generation), has opened the field of neuroprotection in cardiac surgery to antioxidant therapies. Superoxide dismutase (SOD) is involved in the catabolism of free radicals, and SOD mimetics have had beneficial results in the setting of experimental ischemia. **Pegorgotein**, a covalently linked monomethyoxypolyethyleneglycol to SOD has been shown to be protective against reperfusion-mediated cardiac and neuronal injury in animal studies (42). One small study examined whether pegorgotein would be associated with a reduced number of neurocognitive deficits following cardiac surgery (43). In this study of 67 patients undergoing primary elective CABG surgery were studied ($n = 22$-23 in each of three groups: placebo, 200 IU/kg pegorgotein or 5000 IU/kg pegorgotein), no difference in neurocognitive outcome was found.

The activation of complement is central to the inflammatory response seen as a response to CPB (44). In a small ($n = 18$) study using a simple assessment of cognitive function, patients receiving an inhibitor to C5 (h5G1.1-scFv; **pexelizumab**), demonstrated fewer visuospatial deficits at hospital discharge (45). Further large-scale (phase III) investigations of this compound to more adequately delineate any potential longer-term neuroprotective effects from this drug in this setting have been performed. Mathew et al. studied pexelizumab in a 914-patient study aimed at evaluating its effect on both myocardial outcome and mortality (45). A secondary endpoint of neurocognitive outcome demonstrated that pexelizumab, although having no

effect on global measures of cognition, appeared to have a benefit with respect to the visuospatial domain.

Platelet activating factor (PAF) antagonists have demonstrated neuroprotective effects in experimental models of cerebral ischemia (46). Platelet activating factor is thought to modulate postischemic injury via the release of cerebral cellular lipids and free fatty acids that may result in cellular injury and cerebral edema (47). In a recent investigation of 150 cardiac surgery patients (receiving either placebo or one of two different doses of **Lexiphant**) however, no protective effects were found in neurocognitive outcome three months after cardiac surgery. This study was significantly underpowered, which is a recurring and troublesome feature of many studies in this field (48).

Corticosteroids have long been considered as potential cerebroprotective agents in part due to their ability to reduce the inflammatory response. Inflammation is considered an important factor in propagating ischemia mediated brain injury (49,50). However, with the exception of spinal cord injury (51), they have never been demonstrated to possess any significant clinical neuroprotective properties. Furthermore, the administration of steroids has actually worsened cerebral outcome in a recent large (n = 10,000) trial. The CRASH trial demonstrated an increased relative risk of death (1.18 [95% CI, 1.09 – 1.27], p = 0.0001) in those receiving high dose steroids with 8 hours of injury (52,53). Part of their lack of effect may be due to the hyperglycemia that generally follows their administration. Hyperglycemia, in animal models and several human studies of cerebral injury, has been associated with worsened neurologic outcome (54,55). Hyperglycemia has also been shown to increase the incidence of cognitive deficits after CPB (56). The administration of steroids with the intent of conferring some degree of neuroprotection during cardiac surgery cannot be recommended.

Future neuroprotective drug trials

Despite the failure thus far to discover a robust pharmacologic neuroprotectant, there continue to be efforts in this investigative field. Most of these drug trials are using neurocognitive dysfunction, or mild cognitive impairment, as primary endpoints, though stroke is assumed (albeit with little evidence) to be on the same brain injury continuum. Dexanabinol is one such potential neuroprotective compound that is synthetic non-competitive NMDA receptor antagonist. It also possesses some TNF-α antagonist properties. Its neuroprotective potential has been evaluated extensively experimentally in the setting of various models of cerebral ischemia (57,58). It is currently being evaluated in early phase clinical trials in CABG for the prevention of neurocognitive dysfunction. In addition to the dexanabinol trial, other peptides are also under investigation. One of these, AL-208, is an 8-amino acid activity dependent neurotrophic factor that is secreted by allele cells in response to stimulation by vasoactive intestinal protein. Augmenting its to anti-apoptotic activity, it has also been shown to promote neurite outgrowth and stabilize microtubules. It is currently underway in a Phase II trial in coronary artery bypass graft surgery.

Another growth factor related peptide, Glypromate® (glycine-proline-glutamate) is an insulin-like growth factor that has completed a small Phase II trial (n = 30) and has advanced to larger clinical trials. Furthermore, a small Phase I CABG trial (n = 20) was undertaken with the energy substrate providing ketone body drug, KTX-0101 (sodium β-hydroxybutyrate), but the results have not been reported. Several other proprietary compounds are also undergoing evaluation and have yet to be reported.

In summary, despite decades of work and the investigations of dozens of drugs, the prospect of having a robust pharmacologic neuroprotective agent does not appear promising. However, with a better understanding of the etiology and mechanisms of neurologic injury, investigations will continue to be undertaken. Clearly, when it comes to neuroprotection, the search continues, but the answers have thus far remained elusive.

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Management of the Renal Patient: Clinical Algorithms on Vascular Access for Haemodialysis

This manual summarises the results of the latest research in the field of vascular access of the haemodialysis patient. It contains a series of algorithms designed to guide the nephrologist through the different options for the patients' vascular access. The handbook shows the various problems that may occur with the specific access and demonstrates how to deal with one of these particular situations.
The comprised flow-charts offer a fast overview of the most important steps, while the accompanying text provides more detailed background information, evaluating the results of research and supporting the recommendations on the patient's management. In addition the evidence level for the literature enforcing those recommendations is shown.

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