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Cerebral protection during neurosurgery and stroke

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Abstract

Purpose of review—This article reviews the recent evidence on perioperative neuroprotection in patients undergoing brain surgery and in patients with acute stroke.

Recent findings—With varying degrees of success, numerous pharmacological and nonpharmacological therapies have been employed to provide neuroprotection for patients during the perioperative period and after acute ischemic stroke (IAS). Recent studies have failed to demonstrate neuroprotective effects of intraoperative remifentanyl or propofol use, although hypertonic saline may provide better brain relaxation than mannitol during elective intracranial surgery for tumor. Magnesium sulfate offers no improvement in neurological outcome at 90 days after stroke. Medical management alone may be superior to medical management with interventional therapy for the prevention of death or stroke in unruptured arteriovenous malformations. In patients with IAS with a proximal vessel occlusion, small infarct core, and moderate-to-good collateral circulation, rapid endovascular treatment resulted in improved functional outcomes and reduced mortality. For endovascular clot evacuation after IAS, conscious sedation may be safer than general anaesthesia.

Summary—Recent evidence provides insufficient evidence of neuroprotective strategies to guide clinical management, and more randomized clinical trials are needed to optimize patient care.

Keywords

Neuroanaesthesia; neuroprotection; stroke

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INTRODUCTION

Patients undergoing brain surgery are at high risk for developing new neurological deficits because of disease and procedure-related complications. Studies have demonstrated that up to 50% of patients with acute subarachnoid hemorrhage (SAH) suffer from some degree of neurological impairment after aneurysm clipping [1,2]. In patients with acute stroke who have a high rate of neurological morbidity, therapies that provide neuroprotection are the mainstay of clinical management [3,4]. With varying degrees of success, numerous pharmacological and nonpharmacological therapies have been employed to provide neuroprotection in the perioperative period [5,6].

Neuroprotection is a central focus of neuroanaesthesia and neurocritical care [7]. Although more than 1473 completed clinical trials are included in the Internet Stroke Trials Registry, few studies have demonstrated reproducible results that reliably improve outcomes in the acute care setting [8]. However, promising preclinical laboratory studies justify the enormous time and expense of conducting clinical trials. In this review, we present the recent evidence on perioperative neuroprotection in patients undergoing brain surgery and after acute stroke.

PERIOPERATIVE NEUROPROTECTION IN PATIENTS UNDERGOING BRAIN SURGERY

A recent retrospective observational study evaluated the role of intraoperative remifentanyl in patients undergoing surgical clipping of intracranial aneurysms (ICAs) [9]. From 3 million patients in the registry, 6186 patients who underwent craniotomy for surgical clipping of ruptured or unruptured ICA were identified. Patients who died within 3 days of the operation were excluded from the data analysis. The 4502 patients who met the inclusion criteria were categorized into one of two groups: the first group received fentanyl alone ($n = 1809$) and the second group received both remifentanyl and fentanyl ($n = 2693$). Although the authors demonstrated a difference in hospital mortality (4.7 vs. 7.7%; $P < 0.001$), this evidence was limited to patients with ruptured aneurysm. There were no differences in postoperative length of stay or the incidence of postoperative neurological, cardiovascular, and respiratory complications. A major drawback of this study was its retrospective and observational design. To adjust for differences in baseline characteristics and reduce the potential bias related to nonrandomization, the statistical analysis was done using a propensity score matching. The study failed to demonstrate neuroprotective effects of intraoperative remifentanyl use.

In a prospective randomized study, 74 patients with ASA-PS I to III scheduled to undergo craniotomy for intracranial tumors were enrolled with the purpose of comparing the effects of equivolume, equiosmolar solutions of mannitol, and hypertonic saline on brain relaxation and postoperative complications [10]. Patients received a 3.75 ml/kg of intravenous infusion of either 3.2% hypertonic saline ($n = 36$) or 20% mannitol ($n = 38$). The surgeon assessed the condition of the brain using a 4-point scale after opening the dura. Recorded measures included the duration of surgery, blood loss, urine output, volume and type of infused fluids, hemodynamic variables, electrolytes, glucose, creatinine, predefined

postoperative complications (including postoperative Glasgow Coma Scale and focal neurological deficits), and length of ICU and hospital stays. Patients who were administered hypertonic saline had more brain relaxation compared with patients who received mannitol ($P < 0.05$). There were no significant differences in postoperative complications or in lengths of ICU or hospital stays observed between the groups. These results suggest that hypertonic saline may provide better brain relaxation than mannitol during elective intracranial surgery for tumor.

In another prospective randomized study, 66 patients with good-grade aneurysmal SAH undergoing temporary aneurysm clipping evaluated the neuroprotective effects of propofol on postoperative cognition [11]. Patients in the treatment group received propofol in titrated doses to attain a burst suppression ratio of $75 \pm 5\%$ on a bispectral index monitor. The cognitive function was assessed by the Hindi-language modification of the mini-mental state examination preoperatively, 24 h after surgery, and at discharge from the hospital. A score of 23 or below was indicative of cognitive dysfunction. Twenty-four hours after surgery, eight patients in the control group and 12 in the propofol group had cognitive dysfunction. At the time of discharge, five patients in each group had cognitive dysfunction. In both groups, there was a trend toward a decline in cognition at 24 h followed by improvement at the time of discharge. Neurological outcome at discharge (measured by the Glasgow Outcome Score) in both groups was comparable. The results suggest that propofol at the time of temporary aneurysm did not result in preservation of cognition.

PERIOPERATIVE NEUROPROTECTION IN PATIENTS WITH STROKE

Acute stroke is the second leading cause of death worldwide and the leading cause of long-term disability. Anaesthetic management of the acute stroke patient demands consideration of the penumbra as the central focus. The Society of Neuroscience in Anaesthesiology and Critical Care (SNACC) created a task force to provide expert consensus recommendations on anaesthetic management of endovascular treatment of acute ischemic stroke (IAS) [12]. Therapy should be quickly initiated after stroke because ‘time is brain’.

A multicenter, randomized, double-blinded, placebo-controlled, phase 3 clinical trial (FAST-MAG study) evaluated whether the prehospital initiation of magnesium sulfate by paramedics improves long-term functional outcomes in patients with acute stroke [13]. A total of 1700 patients were randomized to receive either magnesium sulfate ($n = 857$) or placebo ($n = 843$). There was no significant difference in 90-day disability outcomes using the global modified Rankin scale between groups. Furthermore, there was no significant difference between groups with respect to mortality or serious adverse events. These results suggest that although prehospital initiation of magnesium sulfate therapy is well tolerated, it offers no improvement in neurological outcomes at 90 days after stroke.

Another multicenter, prospective, randomized, open-label, blinded-end-point study (EXTEND-IA trial) evaluated whether more advanced imaging and earlier interventions improve outcomes after ischemic stroke [14]. Patients with ischemic stroke were administered 0.9 mg/kg of alteplase less than 4.5 h after the onset of ischemic stroke, and were subsequently randomized to either undergo endovascular thrombectomy with the

solitaire flow restoration stent retriever or continue receiving alteplase alone. All patients had an internal carotid or middle cerebral artery occlusion, and evidence of salvageable brain tissue and ischemic core of less than 70 ml on computed tomographic (CT) perfusion imaging. The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). The percentage of ischemic territory that underwent reperfusion at 24 h was greater in the endovascular therapy group than in the alteplase-only group (median 100 vs. 37%, $P < 0.001$). Endovascular therapy initiated at a median of 210 min after the onset of stroke increased early neurologic function at 3 days (80 vs. 37%, $P < 0.005$). Furthermore, the functional outcome was improved at 90 days with more patients achieving functional independence (score of 0–2 on the modified Rankin scale, 71 vs. 40%, $P < 0.05$). There were no significant differences in the rates of death or symptomatic intracerebral hemorrhage. These results suggest that in patients with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging, early thrombectomy with the Solitaire flow restoration stent retriever improved reperfusion, early neurologic recovery, and functional outcome compared with alteplase alone.

A multicenter, nonblinded, randomized clinical trial (ARUBA) compared the risk of death and symptomatic stroke in patients with an unruptured brain arteriovenous malformation who received either medical management alone or medical management with interventional therapy [15■]. Patients were randomized to medical management with interventional therapy (including surgery, embolization, and stereotactic radiotherapy) or symptomatic medical management alone. Randomization was stopped on April 15, 2013, when a data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health observed that the medical management group was highly superior. At that time, the outcome data were available for 223 patients with a mean follow-up of 33.3 months (SD 19.7), with 114 patients assigned to interventional therapy and 109 to medical management. The primary endpoint of death or symptomatic stroke was reached by 11 (10.1%) patients in the medical management group compared with 35 (30.7%) in the interventional therapy group. The risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group [hazard ratio 0.27, 95% confidence interval (CI) 0.14–0.54]. Thus far, the ARUBA trial showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured brain arteriovenous malformations. The trial is continuing its observational phase to establish whether these differences will persist after an additional 5 years of follow-up. At this time, it is difficult to conclude that conservative management is superior to interventional treatment for unruptured brain arteriovenous malformations (bAVMs) due to limited long-term comparative data.

A phase 3, multicenter, open-label treatment, blinded end-point evaluation, randomized clinical trial (MR CLEAN) assessed whether intra-arterial treatment (IAT) plus standard medical care is more effective than standard care alone within 6 h after symptom onset from a proximal arterial occlusion in the anterior cerebral circulation [16■]. Patients were randomly assigned to receive IAT plus medical management or standard medical care alone. A total of 500 patients were enrolled at 16 medical centers in the Netherlands, with 233

assigned to IAT and 267 to medical management alone. A total of 445 patients (89.0%) were treated with intravenous alteplase before randomization. Retrievable stents were used in 190 of the 233 patients (81.5%) assigned to IAT. The adjusted common odds ratio was 1.67 (95% CI, 1.21–2.30). There was an absolute difference of 13.5 percentage points (95% CI, 5.9–21.2) in the rate of functional independence (modified Rankin score, 0–2) in favor of the intervention group (32.6 vs. 19.1%). There were no significant differences in mortality or the occurrence of symptomatic intracerebral hemorrhage. This study suggests that IAT administered within 6 h after stroke onset was effective and well tolerated in patients with AIS caused by a proximal occlusion of the anterior circulation.,

Similarly, another multicenter, prospective, open-label, randomized control trial (ESCAPE trial) with blinded outcome evaluation (PROBE design) evaluated rapid endovascular treatment alone or in addition to standard medical care in patients with AIS with a small infarct core, a proximal intracranial arterial occlusion, and moderate-to-good collateral circulation [17■]. Within 12 h of symptom onset, patients were randomly assigned to receive standard medical care (control) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention). The trial was stopped early because of efficacy. Three hundred and sixteen patients were enrolled in 22 centers worldwide, and 238 of these patients received intravenous alteplase (120 in the intervention group and 118 in the control group). In the intervention group, the median time from undergoing a head-CT to the first reperfusion was 84 min. The rate of functional independence (90-day modified Rankin score of 0–2) was increased in the intervention group (53.0 vs. 29.3% in the control group, $P < 0.001$). The primary outcome favored the intervention (common odds ratio, 2.6; 95% CI 1.7–3.8, $P < 0.001$), and the intervention was associated with reduced mortality (10.4 vs. 19.0% in the control group, $P < 0.05$). There was no difference in symptomatic intracerebral hemorrhage between patients in the intervention group and the control group (3.6 vs. 2.7%, respectively). This study suggests that in patients with AIS with a proximal vessel occlusion, a small infarct core, and moderate-to-good collateral circulation, rapid endovascular treatment resulted in improved functional outcomes and reduced mortality.

A retrospective observational study evaluated whether the use of general anaesthesia or conscious sedation during endovascular clot evacuation in patients with AIS influenced patient outcomes in 109 patients undergoing emergent intra-arterial therapy [18■]. Thirty-five patients had general anaesthesia and 74 patients had conscious sedation (Ramsay Sedation Score of 2–3, described as cooperative, oriented, calm, and responsive to commands only). The duration of the procedure and the time-to-revascularization from symptom onset were significantly longer in the general anaesthesia group. The mortality was higher in the general anaesthesia group compared with the conscious sedation group (40 vs. 22%, $P < 0.05$). A multivariate analysis was done to control for confounding variables, and identified general anaesthesia and elevated postprocedure blood glucose concentrations as significant predictors of mortality. However, this study has some important limitations including its retrospective study design and lack of data regarding stroke severity, size, and location, all of which may impact patient outcome. Consequently, at this point, there is

insufficient evidence to suggest a change in practice, and the decision for or against general anaesthesia should be based on other clinical considerations.

Furthermore, another retrospective cohort study from the MR CLEAN trial investigated the association between type of anaesthesia and clinical outcome in a large cohort of patients with AIS treated with IAT [19]. Three hundred and forty-eight patients were included in the analysis; 70 patients received general anaesthesia and 278 patients did not receive general anaesthesia. General anaesthesia was associated with a significantly worse clinical outcome (odds ratio 2.1, 95% CI 1.02–4.31). After adjusting for prespecified prognostic factors, the point estimate remained similar; however, the statistical significance was lost (odds ratio 1.9, 95% CI 0.89–4.24). This study suggests that patients with AIS of the anterior circulation undergoing IAT with general anaesthesia have a higher probability of a poor clinical outcome compared with patients treated without general anaesthesia.

Other areas of research have shown potential, but are lacking sufficient data. The promising role of the herbal medication ginseng in providing neuroprotection in AIS has long been a topic of great interest to researchers; however, few comprehensive double-blinded clinical trials have been performed with standardized ginseng extracts [20]. Blood glucose management in the perioperative period and in patients with critical illnesses has the potential to play an important role in the prevention of acute brain dysfunction and long-term cognitive impairment in survivors [21]. There is no evidence at this time to suggest that induced hypothermia is associated with a significant reduction in mortality or severe neurological disability, or an increase in harm in patients undergoing neurosurgery [22].

CONCLUSION

In this review, we presented the recent evidence on perioperative neuroprotection in patients undergoing brain surgery and in patients with AIS. Perioperative brain damage is among the most serious adverse complications of surgery and anaesthesia, resulting in new postoperative neurological deficits including transient ischaemic attack, stroke, and postoperative cognitive decline [23,24]. Pharmacological perioperative neuroprotection has yielded conflicting results [25], and based on the recent studies we reported, remifentanyl, mannitol, hypertonic saline, and propofol have all failed to demonstrate neuroprotective effects. For patients with AIS, recent studies have demonstrated that patients who receive general anaesthesia for endovascular therapy have worse outcomes than patients who do not receive general anaesthesia. Prehospital initiation of magnesium sulfate therapy failed to demonstrate neuroprotective effects, and currently there are no proven neuroprotective drugs for use in AIS. The absence of reliable biomarkers to guide clinical management and research are considerable obstacles for developing neuroprotective agents. Despite these challenges, many researchers argue that we are indeed making significant progress in this area [26]. Recent evidence provides conflicting results, and more randomized control trials are needed to draw significant conclusions that guide clinical management.

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KEY POINTS

- Perioperative brain damage is among the most serious adverse complications of surgery and anaesthesia, resulting in new postoperative neurological deficits including transient ischemic attack, stroke, and postoperative cognitive decline.
- Perioperative neuroprotection in patients undergoing brain surgery and after acute stroke is controversial, and there are currently insufficient data to guide clinical management.
- Acute stroke is the second leading cause of death worldwide and the leading cause of long-term disability.
- After acute stroke, therapy should be initiated quickly because ‘time is brain’; rapid endovascular treatment has been shown to improve functional outcomes and reduce mortality.
- For endovascular therapy for acute ischaemic stroke, general anaesthesia may worsen outcomes; more evidence is needed before definitive conclusions can be drawn.