Risk Factors and Characteristics of Seizures during Awake Craniotomy

The incidence of intraoperative seizures (IOS) during awake craniotomy (AC) varies between 3 and 30% and is associated with significant morbidity. Several risk factors for IOS during AC have been reported in the literature. The influence of specific anesthesia drugs on seizure incidence during AC is poorly defined. Paquin-Lanthier et al conducted a single-center retrospective study of 581 patients to analyze and identify risk factors that may predispose them to seizures during ACs for elective resection of a space-occupying brain lesion. Their data showed that the incidence of IOS was 5% (29/581) and the majority were focal seizures (93%). However, they did not limit planned intraoperative stimulation mapping or failure of AC. In the multivariable analysis, variables that showed to be independently associated with IOS were the frontal location of the tumor (adjusted odds ratio [aOR]: 5.68, 95% confidence interval [CI] [2.11–15.30]) and intraoperative dexmedetomidine use (aOR: 2.724, 95% CI [1.24–6.00]). Though the frontal location of the tumor has been a well-established risk factor for IOS, an association between intraoperative dexmedetomidine use and IOS was an interesting new finding. Though the exact mechanism behind this is not clear, lower propofol use might be an important contributor. Authors have acknowledged that inadequate sample size (29 IOS) limited their ability to construct a multivariable model including all potential confounders. Further research should investigate the effect of dexmedetomidine in IOS as a potentially modifiable risk factor.

Scalp Blocks for Craniotomy

Previous research showed that after craniotomy up to 50% of patients experience moderate-to-severe postoperative pain in the first 2 days after surgery and up to 30% even develop chronic headaches. The most efficacious methods for postoperative pain control after craniotomy remain unknown. Luo et al conducted a systematic review and meta-analysis of 24 randomized controlled trials (RCTs) (1,361 patients) comparing the efficacies of different strategies (scalp nerve block [SNB] and scalp infiltration [SI]) in postoperative pain in patients undergoing craniotomy. SNB using ropivacaine was found to be the most efficacious method for pain control (success rate of 91%) and reduced postoperative opioid consumption in the first 24 hours compared with control (mean difference [MD] = −11.91, 95% CI [−22.42, −1.4]; low quality). SNB using ropivacaine reduced postoperative (24-hour) pain score when compared with control (mean difference [MD] = −2.04, 95% CI [−3.13, −0.94]; low quality), and when compared with SI using ropivacaine (MD = −1.77, 95%
CI [−3.04, −0.51]; low quality) or bupivacaine (MD = −1.96, 95% CI [−3.65, −0.22]; low quality). This study showed that different methods of SNB/SI have slightly different efficacies after craniotomy and concluded that SNB with ropivacaine might be superior to other methods for postcraniotomy pain control; however, due to the high heterogeneity of included studies, the overall quality of evidence was low.

**Effect of Inotropes and Vasopressors on Cerebral Oxygen Saturation**

Cerebral hypoperfusion is of major concern during anesthesia, especially with intraoperative hypotension. Treatment of intraoperative hypotension usually consists of a combination of drugs (inotropes and/or vasopressors) and fluids. However, the preferred drug of choice is not known. Bombardieri et al conducted a Bayesian network meta-analysis of available RCTs comparing the effect of various inotropes and/or vasopressors used to treat intraoperative hypotension on cerebral oxygen saturation (ScO2) measured by cerebral oximetry. Nine RCTs were included (6 studies were in non-neurological surgeries, 2 in carotid endarterectomy, and 1 in craniotomy) and pooled analysis showed that dopamine, ephedrine, and norepinephrine had the lowest probability of decreasing ScO2. The suggested rank order to use to maintain ScO2 during perioperative hypotension, from higher to lower, was respectively dopamine, ephedrine, norepinephrine, and phenylephrine. This systematic review and meta-analysis suffers from inherent imprecision due to direct/indirect comparisons of different drugs. Further studies on direct comparison of different drugs are needed.

**Dexmedetomidine in the Prevention of Delirium after Cranial Neurosurgery**

Delirium after neurosurgery is a common complication and typically occurs in the initial days after surgery. It is characterized by acute onset attention disorders and fluctuating changes in the mental state of the patient. Though dexmedetomidine has been shown to improve delirium after non-neurological surgeries, it remains unclear if dexmedetomidine is effective in preventing delirium in patients having brain tumor resection. Li et al conducted a double-blind, placebo-controlled RCT to evaluate the effect of dexmedetomidine administration during intracranial tumor resection on the incidence of postoperative delirium. A total of 260 patients were randomized to either a dexmedetomidine (130 patients) or a placebo (130 patients). All patients had a standardized balanced anesthesia. In the dexmedetomidine group, a loading dose of dexmedetomidine 0.6 µg/kg over 10 minutes was given, followed by a continuous infusion at 0.4 µg/kg/hour till the start of dural closure. The incidence of delirium during the initial 5 postoperative days was lower in the dexmedetomidine group when compared with the placebo (22 vs. 46%, relative risk [RR] 0.51, 95% CI [0.36, 0.74]; p < 0.001). Further, postoperative pain scores with movement, recovery, and sleep quality were improved by dexmedetomidine (p < 0.001). Hemodynamic changes were similar between the groups. Limitations of the study included a relatively young patient population (45 ± 12 years), inclusion in only two centers, no perioperative depth-of-anesthesia monitoring information was analyzed (combined volatile and intravenous [IV] anesthesia), and no long-term follow-up was done.

**Updates in the Use of Tranexamic Acid in Neurosurgical Patients**

Tranexamic acid (TXA) is an antifibrinolytic agent that has been demonstrated to have a significant impact on reducing blood loss within major trauma and surgery, with no increased risk of vasoco-occlusive events. TXA may prove a promising therapeutic intervention to decrease blood loss during the resection of intracranial tumors. Clynch et al performed a systematic review and meta-analysis to assess the effect of TXA use in meningeal surgery in reducing blood loss, transfusion requirement, and postoperative complications. Four studies with 281 participants (141 receiving TXA) were included and evaluated key outcomes namely intraoperative blood loss, transfusion requirement, and postoperative outcomes (hospital stay, seizures, disability, thromboembolic events, and hematoma). Of the four studies, three (181 participants) utilized the same TXA protocol: 20 mg/kg IV loading dose prior to incision and 1 mg/kg/hour until conclusion of surgery. In the fourth study, single dose of 2 g of TXA in 50 mL of saline was administered prior to incision. TXA use significantly reduced intraoperative blood loss (mean difference 315.7 mL, 95% CI [−532.8, −98.5]) but not the transfusion requirements (OR = 0.52; 95% CI [0.27, 0.98]) or other postoperative outcomes. Of the included studies, only three (a total of 181 patients) patients reported intraoperative blood loss. Differences in blood loss did not translate into observed differences in transfusion requirements. The latter could reflect that 300 mL may not be a meaningful difference in the circulatory volume for an average adult (< 10%). The key limitations of this review were the small sample size, limited data for secondary outcomes, and a lack of a standardized method for measuring blood loss. Hematoma expansion (HE) complicates up to 25% of intracerebral hemorrhages (ICH) and is associated with significant morbidity and mortality. High-quality evidence from Tranexamic acid for hyperacute primary Intra Cerebral Hemorrhage (TICH-2) trial demonstrated that while TXA may be modestly effective in reducing early death and limiting HE, particularly when administered early (within 8 hours of ICH) in patients at high risk for HE. However, this does not translate into improvement in functional status or 90-day mortality. However, patients with anticoagulation-associated hemorrhage were excluded from the trial. Novel, nonvitamin K antagonist oral anticoagulants (NOACs: Direct thrombin and Xa inhibitors) are of concern to clinicians managing patients with ICH, as reversal agents for these drugs are expensive and inaccessible. The role of TXA, in
minimizing hematoma expansion (HE), has been interrogated in the Tranexamic Acid for Intracerebral Hemorrhage in Patients on Non-Vitamin K Antagonist Oral Anticoagulants (TICH-NOAC) trial.\(^\text{15}\) This trial investigated the effect of TXA on HE among patients with NOAC-associated ICH in addition to standard medical care. This trial was prematurely terminated due to lack of funding, so only 67 of the planned 109 patients were included in the analysis; hence, it is impossible to ignore the possibility of a type 2 error. Interestingly, none of the patients randomized in this study were receiving a direct thrombin inhibitor, which limits the generalizability of this study to all patients on NOACs. The study failed to find a significant difference between those that did and did not receive TXA (38 vs. 45%, \(p = 0.40\)), but there was a signal for interaction with onset-to-treatment time (\(P_{\text{interaction}} = 0.024\), favoring TXA when administered within 6 hours of symptom onset. Similarly, none of the secondary outcomes reached significance (symptomatic HE, modified Rankin Scale [mRS] score, in-hospital death, death at 90 days, major thromboembolic events, or neurosurgical intervention). Given the limitations of this trial, the question of TXA’s use or futility remains unanswered.

**Prediction Score for Extubation Readiness after Cranial Neurosurgery**

Neurosurgical patients admitted to the intensive care unit (ICU) often require prolonged ventilation for multiple reasons.\(^\text{16}\) No consensus exists on the optimal weaning and extubating strategies for this patient population, leading to heterogeneity in clinical practices and high rates of delayed extubation and extubation failure-related complications. Xu et al conducted a single-center prospective observational diagnostic study on mechanically ventilated neurosurgical patients with extubation attempts who were consecutively enrolled over 1 year.\(^\text{17}\) The responsive ICU physicians (20 ICU physicians and 30 neurosurgeons) were surveyed on the reasons for delayed extubation for every patient. Based on the gathered reasons, a scoring system was designed to predict extubation success rate based on five items: Swallowing, Tongue protrusion, Airway protection reflected by spontaneous and suctioning cough, and Glasgow Coma Scale Evaluation (STAGE). A total of 226 patients were enrolled in this study. The rates of delayed extubation and extubation failure were 25% (57 of 226) and 19% (43 of 226), respectively. While weak airway-protecting function and poor consciousness were the main reasons for delayed extubation, upper airway obstruction, excess airway secretions, and decreased consciousness were the reasons for extubation failure. The area under the receiver operating characteristics curve of the total STAGE score associated with extubation success was 0.72 (95% CI [0.64–0.79]). When the cutoff point of the STAGE score was set at 6, it could predict extubation success and exclude extubation failure with an acceptably overall value (59% sensitivity, 74% specificity, 90% positive predictive value, and 30% negative predictive value). However, a STAGE score higher than 9 might have a better probability of predicting extubation success (100% specificity and 100% positive predictive value). Overall, this study is an interesting study, and the STAGE score is an effort to predict the success of extubation in neurosurgical patients, who already meet the general extubation criteria. However, the STAGE scoring system was not validated externally, the definition of delayed extubation was not well determined in advance, and a lack of sample size power calculation making it a preliminary study needing external validation on a larger sample size.

**Blood Pressure Management for Patients Undergoing Endovascular Thrombectomy (EVT)**

**Blood Pressure Management before EVT**

Evidence demonstrating causation between high admission BP and poor stroke outcomes is lacking.\(^\text{18}\) This relationship has been frequently observed in observational data, but in the absence of randomization causality cannot be inferred. Samuels et al conducted a systematic review to evaluate whether admission systolic blood pressure (SBP) level modified the effect of EVT on outcomes in pooled data from the seven RCTs within the Highly Effective Reperfusion Using Multiple Endovascular Devices (HERMES) collaboration.\(^\text{19}\) A total of 1,753 patients, for whom admission SBP data was available, were included. The primary outcome of this meta-analysis was a mRS score at 90 days. The seven original trials involved patients who have been randomized to undergo EVT or thrombolysis. The post-hoc analysis of this dataset demonstrated a J-shaped association between thrombectomy outcomes and admission SBP, with the inflection point occurring at 140 mm Hg. Patients with an admission BP of less than 140 mm Hg were more likely to have functional independence than those presenting with SBP more than 140 mm Hg (55 vs. 43%, \(p = 0.0002\)). This relationship was also observed in the control (thrombolysis/medical management) group. Higher BPs on presentation were associated with early neurological deficit and larger follow-up infarct volume. Significantly, no association was seen between symptomatic ICH and SBP of 140 mm Hg or higher. Presentation BP did not modify the success of the EVT procedure. However, the results of this study should be interpreted cautiously. This study fails to answer whether high SBP should be treated as a prognosticator or a therapeutic target to minimize morbidity.

**Blood Pressure Management after EVT**

Observational data has previously suggested that an association exists between high SBP after thrombectomy and poor functional recovery.\(^\text{20}\) BP management after EVT has thus been the subject of two further RCTs in 2023.

Intensive vs Conventional Blood Pressure Lowering After Endovascular Thrombectomy in Acute Ischemic Stroke: the OPTIMAL BP trial was a multicenter, randomized, open-label, controlled trial involving 306 patients who underwent EVT for large vessel occlusion.\(^\text{21}\) Inclusion criteria mandated patients have partial or complete reperfusion (modified thrombolysis in cerebral infarction score \(\geq 2b\)) and elevated BP postprocedurally (SBP \(\geq 140\) mm Hg) on at least two...
measurements. Patients were randomized to intensive BP management (SBP < 140 mm Hg, n = 155) or conventional management (SBP 140–180 mm Hg, n = 150). The primary outcome was functional status at 3 months (mRS score 0–2), with primary safety outcomes being symptomatic ICH within 36 hours or death related to primary stroke within 3 months. This trial was terminated early due to observed harm in the intervention group. In posthoc analysis, the intensive management group had a lower proportion of achieving functional independence (39.4%) than the conventional management group (54.4%), with a significant risk difference (−15.1%, 95% CI [−26.2% to −3.9%]) and aOR (0.56, 95% CI [0.33−0.96]; p = 0.03). Malignant cerebral edema was also more common in the intensive SBP group as were deaths related to the index stroke, but the latter was not statistically significant. The rate of any ICH was the same in both treatment arms (53.5 vs. 52.3%, p = 0.93). In post-hoc analysis, there was a J-shaped relationship between mean SBP and OR of dependence or death. Several methodological issues with this study limit its internal and external validity, but overall, these findings are suggestive of morbidity with iatrogenic BP lowering for patients who have had successful reperfusion.

Blood Pressure Management After Endovascular Therapy for Acute Ischemic Stroke (BEST II) was a futility design RCT. This trial assessed whether lower SBP targets after successful anterior circulation thrombectomy are harmful. The 120 patients enrolled in the study were randomized to one of three treatment arms: SBP less than 140 mm Hg, SBP less than 160 mm Hg, and SBP less than 180 mm Hg. Primary outcomes were infarct volume measured at 36 ± 12 hours and utility-weighted mRS score at 90 days. The investigators utilized expert consensus and linear regression to determine what a “meaningful” infarct volume change should be for every 10 mm Hg decrease in SBP. The minimal clinically important difference was used to determine a similar metric for the mRS score. There was a 0.29 ml reduction in infarct volume for every mmHg SBP lowered (95% CI [ −0.81 : futility p = 0.99]). A Small decrease in utility-weighted mRS scores was observed, with the upper limit of the CI suggesting a small benefit (−0.0019, 95% CI [−infinity to 0.0017]; futility p = 0.93) Across both outcomes, results did not meet the predefined threshold for futility. Hence, the findings suggested a low probability of benefit from lower SBP targets after EVT.

On a related topic, Sharma has written a focused review on periprocedural management of BP after acute ischemic stroke. This focused review aims to provide an update on the recent evidence around periprocedural BP management after acute ischemic stroke, highlighting its implications for clinical practice while identifying gaps in current literature.

**General Anesthesia versus Sedation for Patients undergoing EVT**

**Anterior Circulation Stroke**

The debate regarding optimal anesthetic techniques for patients undergoing EVT continues. The most recent, the Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial, reiterates that anesthesia technique does not inform outcomes. Patients were randomized to either a sedation technique of the anesthesiologists’ choice or general anesthesia (GA). Regarding the primary outcome, 28.2% of patients in the GA group versus 36.2% of the procedural sedation patients achieved functional independence (mRS score 0–2) at 90 days. AMETIS is the first of the EVT trials to evaluate periprocedural medical complications between patients undergoing GA versus sedation; there were no differences observed between the two cohorts (34.1 vs. 32.6%, p = 0.8). Rates of hypotension were more common in the GA group (RR, 0.51, 95% CI [0.42, 0.63], p = 0.001). Puncture to reperfusion time was 6 minutes faster in the GA group but no analysis was done to determine if this was statistically significant.

The findings of this study in are step with recent systematic reviews and meta-analyses by Geraldini et al. in this study, 1,342 patients from nine RCTs were included in the analysis. No significant differences were detected between GA or sedation with regard to functional independence post-EVT (mRS score 0–2), procedure duration, stroke onset to reperfusion time, mortality, and hospital or ICU length of stay. However, GA was associated with a greater rate of successful reperfusion (OR, 1.86, 95% CI [1.12, 3.0]) (moderate heterogeneity), but puncture to reperfusion time was longer in the GA group (−6.7 minutes; 95% CI [−11.3 to −2.1 minutes]). However, this systematic review was accepted for publication in mid-2022; the complete data from the AMETIS trial was not included in the statistical calculations of this meta-analysis. In this study, the 95% CIs for puncture to perfusion time were 2 to 11 minutes. If the AMETIS trial had been included, this mean difference would have been lower. Irrespective of the statistical significance, it seems unlikely that a difference of this magnitude would be clinically significant. In summary, this study further stresses the point that anesthetic technique probably is not a significant modifier of outcome for patients undergoing EVT.

**Posterior Circulation Stroke**

EVT is not consistently superior to medical management in the treatment of patients with posterior circulation occlusion. It is unclear from the current, largely retrospective evidence if the type of anesthesia is a significant factor in the long-term neurological outcome in patients with posterior circulation stroke undergoing EVT. Choice of Anesthesia for Endovascular Treatment of Acute Ischemic Stroke (CANSAS II) represents the first RCT interrogating this relationship. The primary outcome was functional independence at 90 days (mRS score 0 or less) in patients who underwent GA versus conscious sedation. This trial failed to show a statistically significant difference in functional independence between patients in either arm (48.8% vs. 54.5%; RR, 0.89; 95% CI [0.58, 1.38]). Failure to detect a difference in the primary outcome occurred despite GA being associated with a greater probability of successful reperfusion (95.3 GA vs. 77.3% conscious sedation, OR, 6.03, 95% CI [1.24, 29.40]). This indicates the complex interplay of factors that contribute to neurological recovery following a stroke.
On the same topic, Wang et al recently published a systematic review and meta-analysis comparing GA and non-GA on clinical outcomes in patients with posterior circulation stroke undergoing EVT. Eight studies including 1,777 patients were identified. Although GA was associated with lower odds of functional independence at 90 days (OR, 0.55; 95% CI [0.38, 0.81]; p = 0.009), substantial heterogeneity was noted (I² = 65%). Subgroup analysis showed that GA was associated with higher odds of mortality than conscious sedation (OR, 1.83; 95% CI [1.30, 2.57]; I² = 0%), but there was no difference between GA and local anesthesia (I² = 0%). Interestingly, subgroup analysis did not identify a relationship between functional independence and GA compared with local anesthesia (OR, 0.90; 95% CI [0.64, 1.25]; p = 0.919; I² = 0%). This meta-analysis demonstrates that GA is associated with worse outcomes in patients with acute posterior circulation stroke undergoing EVT based on current studies.

### Intensive Care Management of Traumatic Brain Injury

Traumatic brain injury (TBI) is still a major cause of global death and disability despite high-quality research that has become available in recent years. In patients with TBI, increased intracranial pressure (ICP) is one of the most important modifiable and immediate threats to critically ill patients. In the clinical practice management of elevated ICP, two hyperosmolar agents, mannitol, and hypertonic saline (HTS), are routinely used. The Collaborative European Neuro Trauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study group investigated whether a preferrable approach to multimodal brain monitoring only (160 patients) or both ICP and PbtO₂ monitoring (158 patients). Their study showed that after severe non-penetrating TBI, combined ICP and PbtO₂ monitoring did not reduce the proportion of patients with poor neurological outcomes at 6 months. Moreover, the complication of intracerebral hematoma was more frequent in the combined monitoring group compared with the ICP monitoring group (4% vs. 0%, p = 0.030). Further research is needed to assess whether a targeted approach to multimodal brain monitoring could be useful in specific TBI subgroups.

### Guideline for the Management of Patients with Aneurysmal Subarachnoid Hemorrhage

Patients with aneurysmal subarachnoid hemorrhage (aSAH) require expert care to minimize morbidity and mortality. The American Heart/Stroke Association (AHA) has recently published a new iteration of their guidelines for best practice management. Important updates for the anesthesia relate to perioperative hemodynamic management of patients. Lowering BP on presentation to the hospital to minimize rerupture has been cautioned. Previous (2013) guidelines drew on data from cohort studies to suggest that SBP more than 160 mm Hg was associated with harm. The AHA now emphasizes that evidence is of insufficient quality to support a specific BP target for lowering as there are no randomized trials that have assessed the relationship between BP lowering following aSAH and the risk of rebleeding and morbidity. BP augmentation remains topical after definitive intervention for aSAH. The 2023 guidelines suggest that iatrogenic increasing the SBP to defend cerebral perfusion may be reasonable (Class of Recommendation 2b); however, prophylactic augmentation of BP to prevent vasospasm is associated with harm (Class of Recommendation 3).
Minimizing the risk of rebleeding and management of the subsequent medical complications of aSAH remain the cornerstone in minimizing death and morbidity. Surgical intervention should be performed within 24 hours, but no evidence that expedited interventions (<6 hours) is associated with better outcomes. Medical therapies to reverse anticoagulation where possible remain important, but the results of the Ultra-early TXA after subarachnoid hemorrhage (ULTRA) trial failed to demonstrate any long-term benefit of TXA. The AHA reiterates support for early initiation of nimodipine and euvolemic fluid management in improving patient outcomes.

The Neurocritical Care Society (NCS) has also published an updated consensus statement for aSAH. The recommendations are largely the same as those from AHA. Of note, while AHA has supported the use of BP augmentation for patients with vasospasm and Delayed Cerebral ischemia DCI, the NCS feels that clinical evidence is of insufficient quality to unequivocally support this practice, given the risk of harm.

**Narrative Reviews of Interest**

Several excellent review papers focused on topics of particular interest to neuroanesthesiologists were published over the last year. Jha et al have published a neurocritical care update in cerebrovascular disease. They summarized key research advances in cerebrovascular neurocritical care over the past year. Abdulazim et al have published a review on current modalities used for monitoring patients after aSAH, on the diagnosis of delayed cerebral ischemia, and putative triggers for intervention. Adrogue and Madias have published a comprehensive review (case-based discussion) on the Syndrome of Inappropriate Antidiuresis (SIADH). Mazzoleni et al have published a review that provides an update on the etiological diagnostic workup, acute treatment, and prognosis of ICH. Ma et al have published a focused review of the clinical evidence of the pharmacological interaction of certain multimodal analgesics with routine intraoperative neuromonitoring modalities. Di Filippo et al have published an observational prospective cohort study on the use of ICP and EVD for management of postoperative delirium in patients admitted to the ICU after elective intracranial surgery: a prospective cohort study. EJ Anaesthesiol 2020;37(01):14–24


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