Neuroanesthesiology Update

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Abstract: This review summarizes the literature published in 2020 that is relevant to the perioperative care of neurosurgical patients and patients with neurological diseases as well as critically ill patients with neurological diseases. Broad topics include general perioperative neuroscientific considerations, stroke, traumatic brain injury, monitoring, anesthetic neurotoxicity, and perioperative disorders of cognitive function.

Key Words: perioperative neuroscience, neuroanesthesiology, stroke, traumatic brain injury, brain monitoring, spine surgery, delirium, postoperative cognitive dysfunction, anesthetic neurotoxicity

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PERIOPERATIVE NEUROSCIENTIFIC CONSIDERATIONS

Coronavirus and the Nervous System

Severe acute respiratory syndrome associated coronavirus 2 is a single strand positive-sense ribonucleic acid virus that emerged from Wuhan, China and has resulted in the coronavirus disease 2019 (COVID-19) pandemic. Global medical systems have been radically impacted by this pandemic, not only related to the direct care of infected patients, but also by changing the care, processes, and access to care by patients for non–COVID-19-related medical needs. The Society for Neuroscience in Anesthesiology and Critical Care (SNACC) developed recommendations that are specific to the care of neurosurgical patients and those requiring electroconvulsive therapy (ECT) during the COVID-19 pandemic.[1] These recommendations address general considerations, including case prioritization, use and conservation of personal protective equipment, airway management, and patient transport. They also provide recommendations for specific procedures. For those having transnasal procedures, all personnel should be wearing full personal protective equipment throughout the surgical procedure due to the high risk for aerosolization of nasal secretions during surgery.[2] Awake craniotomy should still be considered if it may optimize patient outcome, unless the patient has tested positive for COVID-19. The recommendations discuss specific options for awake craniotomy management in the context of minimizing or avoiding unnecessary airway manipulations during the procedure. For those who may be a candidate for ECT, optimization of other treatments for depression before considering ECT and avoiding this treatment in those acutely infected with COVID-19 is recommended. During ECT treatments, personnel in the room should be the minimum required, and mask ventilation, coughing, and generation of secretions should be minimized. The authors of the recommendations also provide suggestions to support health care worker wellness during the pandemic.

Although respiratory symptoms generally predominate, COVID-19 can also result in systemic aberrations that can affect multiple organ systems, including the nervous system.[3] Mao et al[4] characterized neurological manifestations among 214 patients who were hospitalized with COVID-19 in Wuhan, China. Among these patients, 41% had severe respiratory manifestations of COVID-19[5] and 36% developed neurological manifestations that included dizziness (17%), headache (13%), impaired consciousness (8%), acute cerebrovascular disease (3%), seizures (<1%), impairment of taste (6%) or smell (5%), nerve pain (2%), and evidence of skeletal muscle injury (11%). Skeletal muscle injury was diagnosed in those complaining of muscle pain and who also had elevated serum creatine kinase. Nervous system manifestations were more common among those with severe (46%) versus nonsevere (30%) COVID-19 respiratory manifestations ($P = 0.02$).

Matschke et al[6] report on neuropathologic findings from 43 patients who died after COVID-19 infection. Median age of this cohort was 76 years old (interquartile range [IQR] 70 to 86 y). Acute territorial ischemic lesions were identified in 6 (14%) patients and astrogliosis was identified in all brain regions assessed in 37 (86%) patients. Microglial activation and infiltration by T lymphocytes was most prominent in the brainstem and cerebellum. T-lymphocyte infiltration was also commonly noted in meninges, frontal cortex, and basal ganglia. COVID-19 virus could be detected in 53% of brains, especially in the brainstem and cranial nerves. The authors conclude that direct injury to the brain by COVID-19 virus is possible, but adverse effects may be more likely mediated by the immune response in the brain generated in response to the virus.

Radmanesh et al[7] report on brain imaging findings among 242 patients within 2 weeks of testing positive for

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COVID-19. The 3 most common indications for brain imaging (either computerized tomography [CT] or magnetic resonance imaging [MRI]) were altered mental status (42%), syncope (33%), and new focal neurological deficits (12%). The most common abnormal findings were nonspecific white matter angiopathy (55%), chronic infarcts (19%), new infarcts (5%), and acute hemorrhage (5%). No patient imaged for altered mental status had evidence of new ischemic or hemorrhagic stroke. Yoon et al[8] report on CT or MRI brain imaging findings from 150 patients with COVID-19 infection. Among this cohort, 26 (17%) had abnormal imaging findings, most commonly hemorrhage (11/26, 42%), infarction (13/26, 50%), and leukoencephalopathy (7/26, 27%).

In addition to gross neurological signs and symptoms, disorders of cognitive function have also been reported to be associated with COVID-19 infection. Helms et al[9] reported delirium in 118 of 140 (84%) patients with COVID-19 admitted to the intensive care unit (ICU). In those with delirium, 87% exhibited hyperactive delirium and 9% inappropriately self-extubated. Zhou et al[10] performed neurocognitive testing on 29 patients who had recovered from COVID-19 (as demonstrated by 2 negative polymerase chain reaction tests) and compared their performance to matched persons who were never infected by COVID-19. Compared with those without prior infection, patients with prior COVID-19 infection had lower scores in tests of selective attention and impulse; greater impairment correlated with increased serum C-reactive protein concentrations. Unfortunately, the authors did not report the time interval between infection and cognitive assessment in those with prior COVID-19 infection, or assess if the severity of COVID-19 manifestations impacted cognitive performance.

Multiple review articles in 2020 addressed neurological manifestations of COVID-19. Two thorough reviews were published by Zubair et al[11] and Nepal et al[12] and address not only stroke, but other neurological disorders in those with COVID-19 infection, including encephalitis, transverse myelitis, Guillan-Barre Syndrome, Bell palsy, and skeletal muscle manifestations.

Minimizing Adverse Outcomes in Neurosurgical Patients

External ventricular drains (EVDs) are used to measure intracranial pressure (ICP), treat hydrocephalus, administer therapeutic drugs, and obtain cerebrospinal fluid (CSF) samples for analysis. Mismanagement of EVDs can result in potentially life-threatening complications. For those unfamiliar with, or with questions about, EVD management, SNACC developed guidelines and management principles for the care of patients with an EVD.[13] To assess the degree of familiarity with EVDs among anesthesiologists, Lele et al[14] conducted the EVD Aware Study, administering a survey among anesthesiologists at 27 institutions in North America, Europe, and Asia. There were 599 respondents (33% response rate) of whom 143 were neuroanesthesiologists. Although survey respondents were rarely personally involved in transporting patients with EVDs, 51% did assure that the EVD was clamped during transport although only 13% monitored ICP via the EVD during transport. Neuroanesthesiologists were more likely than non-neuroanesthesiologists to ascertain CSF output, CSF color, ICP trends, and findings of EVD clamp trials preoperatively in patients with an EVD in place. Collectively, EVD complications included CSF over draining, CSF leakage, contamination of the EVD system, and inadvertent injection of medications into the EVD system.

The time of day that a surgical procedure is performed can potentially impact outcome as resources may be less available and team fatigue may be greater when procedures are performed at night. Qadri et al[15] retrospectively compared outcome following 304 emergent neurosurgical procedures in patients 18 years old and above stratified by time of day. Of these procedures, 199 started during the hours of 7 AM to 7 PM (ie, daytime) and 105 started between 7 PM to 7 AM (ie, nighttime). Demographics were similar between groups, although aneurysm clipping and burr holes for hematoma evacuation were more common during the day, whereas craniotomy for hematoma evacuation was more commonly performed during the night hours. The groups did not differ in rates of medical or surgical complications or rates of poor outcome at discharge (defined as a Glasgow Outcome Score [GOS] of 3 to 5 where a GOS of 1 is a good outcome). Logistic regression identified increasing age, lower preoperative Glasgow Coma Score (GCS), surgical procedure type, surgical case acuity, and intraoperative complications, but not timing of surgery, as independent factors associated with increased odds for poor outcome.

The prevalence of obstructive sleep apnea is increased in those with acromegaly or Cushing disease.[16] Continuous positive airway pressure (CPAP) can decrease airway obstruction in those with obstructive sleep apnea but may increase risk for pneumocephalus or intracranial infection if used following transsphenoidal surgery. Rieley et al[17] retrospectively identified 427 patients who underwent transsphenoidal resection of a pituitary tumor during an 11-year period. In this cohort, 64 (15%) had obstructive sleep apnea. Acromegaly, but not Cushing disease, was more common in those with obstructive sleep apnea. Of those with obstructive sleep apnea, 29 (45%) used CPAP preoperatively. Eight patients required CPAP to be instituted while in the postanesthesia recovery room and continued into the ICU. No cases of symptomatic pneumocephalus or CSF leak were subsequently identified. The reader should interpret these findings with caution as data were retrospectively obtained, only 8 patients had CPAP employed postoperatively, and there was no formal before-and-after assessment of intracranial air volume.

Anesthetic Techniques

Inhalational anesthetics have been associated with an increase in the proliferation of various cancers.[18–20] Dong et al[21] retrospectively identified patients who had glioma resection where anesthesia was maintained with either propofol alone (n = 154) or propofol plus sevoflurane (n = 140). Demographics, tumor pathology, and hospital course were similar between groups. Median progression free survival was

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similar (10 mo, IQR 6 to 18 mo and 11 mo, IQR 6 to 20 mo in the propofol only and propofol plus sevoflurane groups, respectively; $P=0.674$) as was overall survival following surgery (18 mo, IQR 11 to 39 mo and 18 mo, IQR 10 to 44 mo in the propofol only and propofol plus sevoflurane groups, respectively; $P=0.759$). However, among patients with greater preoperative disability (ie, those with a Karnofsky Performance Status <80) sevoflurane use was associated with a significantly shorter median survival following surgery (11 mo, IQR 6 to 16 mo) compared with that observed in patients who only received propofol for maintenance of anesthesia (15 mo, IQR 8 to 39 mo; $P=0.017$). These findings may warrant further study in a prospective manner where anesthetic technique is controlled and randomized.

The trigeminocardiac reflex can lead to severe hypotension in patients undergoing trigeminal nerve decompression.[22–24] To determine if anesthetic depth influences the severity of the trigeminocardiac reflex, Wang et al[25] randomized patients having balloon compression of the trigeminal ganglion with general anesthesia to have balloon inflation performed while the bispectral index (BIS) was either in the range 40 to 60 (ie, lighter anesthesia) or <40 (ie, deeper anesthesia). In both groups, general anesthesia was maintained with 2% inspired sevoflurane, 0.15 μg/kg/min remifentanil, and a propofol infusion that was titrated to maintain BIS 40 to 60. In the deep anesthesia group, additional propofol boluses were administered to decrease the BIS to <40 before needle puncture of the skin at the start the procedure. The trigeminocardiac reflex was defined to have occurred if either heart rate was <60 beats per minutes or heart rate decreased by ≥20% from basline. With balloon entry through the foramen ovale, the trigeminocardiac reflex occurred in 70% and 67% of those maintained with light and deep anesthesia, respectively ($P=0.34$). With balloon inflation, the trigeminocardiac reflex occurred in 87% and 75% of those maintained with light and deep anesthesia, respectively ($P=0.10$). Mean arterial blood pressure (MAP) was significantly lower in the deep anesthesia group at both balloon entry into the foramen ovale and upon balloon inflation, by ~5 to 6 mm Hg in both instances. This difference likely represents propofol-induced vasodilation. Thus, deepening anesthesia with propofol did not attenuate the trigeminocardiac reflex in patients having trigeminal balloon compression.

During cerebral bypass surgery, maintenance of adequate cerebral perfusion via the anastomosis is critical to protect vulnerable brain. Use of vasoconstricting drugs may increase systemic blood pressure but could lead to vasoconstriction of the graft, thus impairing cerebral perfusion distal to the graft. Akkermans et al[26] performed a prospective, randomized cross-over study to evaluate the effects of systemic dobutamine and phenylephrine on graft flow in 10 patients undergoing cerebral bypass surgery. All patients received a standardized general anesthetic. After the bypass was complete, patients were randomly allocated to receive either dobutamine then phenylephrine or phenylephrine then dobutamine, with adequate time in between drugs to allow for wash-out. Dobutamine was titrated to increase cardiac index measured with a FloTrac device (Edwards Lifesciences, Irvine, CA) via a radial arterial catheter by 10%, and phenylephrine was titrated to increase MAP by 10%. Graft blood flow was measured with an ultrasonic flow meter (Transonic Systems, Ithaca, NY). Graft flow increased by a median rate of 4.1 mL/min (IQR 1.7 to 12.0 mL/min) with dobutamine and 3.6 mL/min (IQR 1.3 to 7.8 mL/min) with phenylephrine, with no significant difference in the magnitude of increase in graft flow between drugs ($P=0.44$) and no significant carry-over effect. Of note, Thorup et al[27] provide a review of the physiology and effects of 4 vasopressors (ie, phenylephrine, ephedrine, norepinephrine, and dopamine) on cerebral hemodynamics in both the healthy brain and following traumatic brain injury (TBI).

Approximately half of patients report moderate or severe pain following craniotomy.[28] Opioids and adjuvants, such as gabapentin, may reduce pain scores but can be associated with other adverse side effects such as nausea, vomiting, and sedation.[29,30] Scalp blocks offer the possibility for pain control with a favorable side effect profile. Rigamonti et al[31] randomized adult patients having supratentorial craniotomy to receive either directed scalp blocks with 0.5% bupivacaine with 1:200,000 epinephrine (n=44) or saline injections (n=45) postoperatively before emergence from anesthesia. All patients received a standardized general anesthetic with sevoflurane, remifentanil infusion, and hydromorphone (0.4 to 1.2 mg). Scalp injections were performed bilaterally and focused on 6 nerves on each side. Visual analog pain scores at 1, 2, 4, 8, 12, 24, and 48 hours postoperatively were similar between groups, as was total hydromorphone consumption at 24 hours, rates of nausea and vomiting, and rates of severe pain at 5, 30, and 60 days postoperatively. The authors performed a post hoc linear mixed effect model analysis of visual analog pain scores and found that mean pain scores were significantly lower in those who received scalp blocks only until 12 hours following surgery. Gaudray et al[32] prospectively randomized 134 patients having supratentorial craniotomy to receive either bilateral scalp blocks with 0.75% ropivacaine at 6 nerves on each side or no scalp blocks. Patients received a standardized general anesthetic and standardized postoperative analgesic management. Systolic blood pressure (SBP) was significantly lower at the time of Mayfield head-holder placement in those who received scalp blocks. Although there was no difference in verbal analog pain scores in the postanesthesia recovery unit and at assessment intervals during the first 48 hours following surgery, fewer patients among those who received scalp blocks required rescue analgesic during the first 48 hours (39%) compared with those who did not receive scalp blocks (65%; $P=0.006$), with the majority of this difference accounted for within the first 6 hours following surgery. These findings support other data that suggest that the benefit of scalp blocks may only be early in the postoperative period.[31,33–35] It was unclear if investigators or patients were blinded to group assignments or if sham injections were performed in those randomized to not receive scalp blocks.

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Dexmedetomidine is an alpha-2 adrenergic receptor agonist that has pharmacological properties that make it appealing for use in the perioperative period for patients having neurosurgical procedures.[36] Koo et al[37] performed a meta-analysis of 17 trials that randomized adult patients having supratentorial craniotomy to receive either dexmedetomidine or either placebo, fentanyl, remifentanil, or propofol prior to skull pin head-holder application. Dexmedetomidine was associated with lower MAP and lower heart rate following head-holder application versus placebo and fentanyl. Dexmedetomidine had a similar effect at attenuating blood pressure and heart rate changes during head-holder application as both propofol and remifentanil.

Kang et al[38] prospectively randomized 46 patients having transsphenoidal resection of nonfunctioning pituitary adenomas to receive either dexmedetomidine (1 μg/kg over 10 min followed by an infusion at 0.2 to 0.7 μg/kg/h) or saline intraoperatively. Anesthesia was maintained with propofol titrated to maintain BIS 40 to 60, and remifentanil titrated to maintain MAP and heart rate within 20% of preoperative values. Serum norepinephrine concentrations decreased in both groups during surgery but the decrease was significantly greater in those who received dexmedetomidine. Serum epinephrine concentrations increased similarly during surgery in both groups, but may be confounded by absorption of epinephrine applied to the nasal mucosa as part of the surgical procedure. Thus, increases in serum epinephrine concentration may not reflect an increase in endogenous epinephrine production. Serum glucose concentration increased during surgery in both group, but the increase was greater in those who received dexmedetomidine. The increase in serum glucose concentration may be due to stimulation of postsynaptic α2 adrenergic receptors on pancreatic islet cells that result in a decrease in insulin secretion.[39] In addition, the increase in serum epinephrine concentration may have also contributed to the increase in serum glucose concentration. Dexmedetomidine was also associated with higher rates of intraoperative bradycardia without differences in rates of hypotension, and also associated with decreased need for rescue analgesics in the postanesthesia recovery room.

Despite prior concerns that ketamine significantly increases ICP, a recent systematic review of the cerebral hemodynamic effects of ketamine demonstrated minimal effect on ICP and a favorable effect on systemic hemodynamics that maintained cerebral perfusion pressure in patients with acute brain injury.[40] In addition to having analgesic properties, ketamine has also been associated with improvement in mood and a decrease in depressive symptoms.[41] Wang et al[42] used a mouse model for pain and depression to assess the mechanism that may mediate analgesia and a reduction in depressive symptoms by ketamine. Male mice were divided into 4 group based on 2 parameters: (1) injection of either saline or complete Freund adjuvant into the right tibiotarsal joint cavity, and (2) injection of saline or ketamine (10 mg/kg intraperitoneally) 7 days following joint injection. Animals that received complete Freund adjuvant injection and did not receive ketamine exhibited mechanical hyperalgesia and subsequent depressive behaviors. Although ketamine did not affect hyperalgesia, it was associated with an attenuation of depressive behaviors in animals that received complete Freund adjuvant. Caveolin-1 is a membrane protein that is increasingly expressed in the brain with increased pain but is also associated with depressive symptoms.[43,44] Messenger ribonucleic acid expression for caveolin-1 was increased in prefrontal cortex and nucleus accumbens both ipsilateral and contralateral to the injected joint in animals that received complete Freund adjuvant. The increase in caveolin-1 messenger ribonucleic acid expression was significantly attenuated by ketamine. Caveolin-1 may, in part, modulate both analgesia and an antidepressant effect by ketamine but further study will be required to confirm this finding and potentially demonstrate a cause and effect relationship.

ICP Management

Mannitol is an osmotic diuretic that has a long history of being used to treat intracranial hypertension.[45] Li et al[46] prospectively randomized 204 patients with midline shift who were undergoing supratentorial craniotomy for tumor resection to receive 200 mL of 0.9% sodium chloride or 3 different doses of 20% mannitol (0.7, 1.0, or 1.4 g/kg) at incision. Mannitol was associated with a dose dependent decrease in dural tension at bone flap removal, and a dose dependent improvement in brain relaxation. However, patients who received 1.4 g/kg of mannitol had a higher rate of moderate or severe postoperative cerebral edema on MRI imaging based on the Steinhoff criteria.[47] Specifically, rates of moderate or severe postoperative cerebral edema were 53%, 51%, and 53% in those who received 0.9% sodium chloride and 0.7 and 1.0 g/kg of mannitol, respectively, versus 78% in those who received 1.4 g/kg of mannitol ($P = 0.018$). There were no other differences between groups with respect to rates of complications. The authors concluded that a mannitol dose of 1.0 g/kg was optimal as it produced the greatest brain relaxation while minimizing risk for significant postoperative cerebral edema.

Hypertonic saline increases serum sodium concentration and can be used to decrease brain water content. Mangat el al[48] identified patient data from those with severe TBI in the New York State TBI-trac database (Brain Trauma Foundation, New York, NY) who received either hypertonic saline (n = 27) or mannitol (n = 477). All patients in the mannitol group received 20% mannitol, and all patients in the hypertonic saline group received 3% sodium chloride except one who received 23.4% sodium chloride. Using these prospectively collected data, the authors matched 25 patients in each group 1:1 and 24 to 48 patients in the hypertonic saline and mannitol groups 1:2. Patients were matched based on time of onset of intracranial hypertension, age, admission GCS, pupillary reactivity, presence of intracranial abnormalities on CT, and presence of extracranial surgical lesions. Cumulative median osmolar doses were similar between groups in 1:1 and 1:2 matching. The primary outcome was the collective burden of intracranial hypertension (defined as ICP > 25 mm Hg) and cerebral hypoperfusion (defined as cerebral perfusion pressure <60 mm Hg). In the 1:1

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cohort, compared with those treated with mannitol, those who received hypertonic saline had fewer days with either intracranial hypertension or cerebral hypoperfusion (0.6 ± 0.8 vs. 2.4 ± 2.3 d, respectively; $P < 0.01$) and a lower total duration with either intracranial hypertension or cerebral hypoperfusion (11 ± 14 vs. 31 ± 32 h, respectively; $P = 0.01$). These findings were similar when comparing groups that were matched 1:2. There were no differences between groups with either matching paradigm with respect to vasopressor use, duration with MAP <80 mm Hg, or Injury Severity Scores. Unfortunately, the authors did not report on complications that may have been related to these treatments, or patient outcomes stratified by treatment.

Biomarkers

Elevated CSF lactate concentration is associated with poor outcome in patients following subarachnoid hemorrhage or TBI.[49,50] CSF is not easily sampled in all patients, although concentrations of lactate in serum do correlate with CSF concentrations. Lactic acidosis occurs when anaerobic metabolism of glucose ensues, and is a marker for ischemia. However, hyperlactatemia without acidosis is frequently identified in neurosurgical patients and has an unclear relationship to patient outcome.[51] De Smalen et al[52] retrospectively identified 496 patients who underwent intracranial tumor biopsy or resection with general anesthesia at a single institution over a 2-year period. Of these, 257 (52%) had an elevated serum lactate concentration (lactate >2.0 mmol/L), 86 (17%) had acidosis (pH < 7.35), and 38 (8%) had both elevated serum lactate and acidosis. Elevated lactate was associated with a statistically significant increase in length of hospital stay (by a median difference of 1 d), but no difference in the rate of postoperative neurological deficits, need for rehabilitation after discharge, or survival at 6 months following surgery. Factors found to be independently associated with elevated serum lactate concentration were increased surgical duration, use of dexamethasone, and glioblastoma pathology, whereas use of a total intravenous anesthesia was independently associated with decreased serum lactate concentration. Acidosis was not associated with hospital length of stay, postoperative neurological deficits, nor survival at 6 months following surgery. High body mass index and elevated serum glucose concentration were associated with acidosis. Corticosteroids, such as dexamethasone, inhibit lactate dehydrogenase and may contribute to increased serum lactate without acidosis due to decreased lactate metabolism.[53] Likewise, propofol has been associated with lower brain lactate than volatile anesthetic exposure.[54,55] Thus, hyperlactatemia, especially in the absence of acidosis, may be associated with various periprocedural factors and not necessarily a biomarker for anaerobic metabolism or adverse outcome.

Patients having revascularization procedures for Moyamoya disease are at significant risk for periprocedural cerebral ischemic events.[56,57] During cerebral ischemia, nitric oxide is produced in response to decreased cerebral blood flow (CBF) and causes vasodilation in an attempt to increase blood flow.[58] Although nitric oxide has a very short half-life, its metabolite, nitrite, has a serum half-life of 42 minutes[59] and is a more durable biomarker for increased nitric oxide production. In 9 patients undergoing revascularization procedures for Moyamoya disease with a standardized anesthetic and standardized hemodynamic and physiologic goals, Silver et al[60] measured baseline serum nitrite concentration with a nitric oxide-specific electrode (Innovative Instruments, Tampa, FL) after stoichiometric reduction of nitrite to nitric oxide, and then repeated these measurements immediately before and following middle cerebral artery occlusion. Serum nitrite concentration was slightly increased before middle cerebral artery occlusion compared with baseline concentrations, a finding attributed to occlusion of the superficial temporal artery before obtaining the measurement. Serum nitrite concentration was significantly increased following middle cerebral artery occlusion and increased even further following reperfusion, likely due to nitrite wash out from ischemic tissue. This technique may need further refinement but could be a simple and low risk technique to monitor for cerebral hypoperfusion.

FACTORS AFFECTING OUTCOME FOLLOWING SPINE SURGERY

Regional Anesthesia

Some lumbar spine procedures can be performed with regional anesthesia. Baenziger et al[61] prospectively randomized 100 patients undergoing elective single or multilevel lumbar discectomy or decompression for spinal stenosis to have surgery with either general or regional anesthesia. General anesthesia was maintained with propofol and remifentanil target controlled infusions; the only analgesic that was administered intraoperatively was fentanyl 4 to 6 μg/kg at induction of anesthesia. Regional anesthesia was conducted with an intrathecal injection of 15 to 20 mg of 0.5% hyperbaric bupivacaine and 25 μg of fentanyl. Patients who received regional anesthesia also had sedation during the procedure either with a propofol infusion or intermittent doses of midazolam. Patients were well matched for demographics, surgery, and preoperative pain scores. The primary endpoint, mean total morphine consumption during the first 24 hours following surgery, was similar between groups (34 ± 26 vs. 41 ± 22 mg in the regional and general anesthesia groups, respectively; $P = 0.197$). Mean pain scores were significantly lower in the regional anesthesia group only upon admission to the postanesthesia recovery room; pain scores were similar at 24 hours, 48 hours, at hospital discharge, and at 6 weeks postoperatively. Rates of postoperative nausea and vomiting were also similar between groups. Anesthesia and surgical durations were both shorter in the regional anesthesia group (99 ± 14 and 49 ± 13 min) than in the general anesthesia group (125 ± 24 and 56 ± 16 min; $P < 0.05$ for both comparisons). Overall patient satisfaction was higher among those who received regional anesthesia.

Perioperative Stroke and Spine Surgery

Perioperative ischemic stroke is most commonly associated with cardiovascular and intracranial neurosurgery.

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In a retrospective analysis by Ishak et al,[62] 13 (0.26%) of 5029 patients who underwent elective spine surgery at a single institution over a 3-year period for noninfectious or non-neoplastic etiologies suffered a perioperative ischemic stroke. Of these 13 ischemic strokes, 7 occurred intraoperatively. It was unclear how the authors identified intraoperative stroke during general anesthesia. The authors focused only on the 7 patients who suffered an intraoperative stroke. Six were female, one, three and three had cervical, thoracic, and lumbar surgery, respectively, and 2 underwent decompression without fusion with the remaining having spinal fusion. Three patients required both intraoperative inotropic support and allogenic blood transfusion. Two patients had pontine strokes and one patient each had a stroke in the left caudate, left posterior cerebellar artery distribution, left internal capsule, left middle cerebral artery distribution, and multiple supratentorial locations. Overall, 3 patients had no improvement in neurological deficits related to the stroke, 2 completely recovered function, and 2 died.

Intraoperative Hypotension

Although hypotension may not always cause ischemic stroke, it can increase risk for critical organ hypoperfusion including the brain, heart, kidney, and optic nerve. Yoon et al[63] retrospectively identified 179 adult patients who underwent elective surgery on the lumbar spine in the prone position during a 10-month period at a single institution. All patients had general anesthesia maintained with propofol and remifentanil infusions titrated to maintain BIS 40 to 60 and MAP within 20% of preoperative values, respectively. All patients had intra-arterial blood pressure monitoring. Blood pressure before placement of the patient in the prone position was compared to blood pressure after placement in the prone position. Hypotension was defined as a MAP decrease of $>20\%$ with change from supine to prone position. Overall, 16 (9%) patients exhibited hypotension with position change. There was no significant difference in demographics, comorbidities, or site of surgery on the spine between those with and without hypotension. Three factors were found to be independently associated with increased odds for hypotension with change to the prone position: (1) higher effect site concentration of remifentanil at the time of position change; (2) preoperative use of beta-adrenergic receptor antagonists, and; (3) higher MAP before placement into the prone position. The authors attribute the association between higher MAP and subsequent hypotension to a higher MAP activating the baroreceptor reflex leading to greater peripheral vasodilation and a greater decrease in MAP with position change. Chalo et al[64] measured cardiac output noninvasively during induction of anesthesia with propofol and placement of the patient in the prone position in 20 patients having spine surgery. Cardiac output significantly decreased both upon induction of anesthesia and with placement of the patient in the prone position. The decrease in cardiac output with placement of the patient in the prone position may be due, in part, to decreased preload due to an increase in intrathoracic pressure.

Acute Kidney Injury

Acute kidney injury can occur in patients having neurosurgical procedures.[65–67] Oh et al[68] retrospectively identified 6520 adult patients without pre-existing end-stage renal disease who underwent elective spine surgery at a single institution during an 8-year period. Postoperative acute kidney injury occurring during the first 3 days after surgery was diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[69] Patients were stratified into 3 groups based on their mean core body temperature: (1) normothermia (36.5 to 37.5°C); (2) mild hypothermia (35.0 to 36.5°C), and; (3) hypothermia (<35°C). Overall, 248 (4%) patients developed acute kidney injury within 3 days of surgery. Those with hypothermia, but not mild hypothermia, had a significantly lower odds of developing acute kidney compared with those with normothermia (odds ratio [OR] = 0.68, 95% confidence interval [CI] = 0.53-0.87; $P = 0.002$) and OR = 0.85, CI = 0.69-1.05; $P = 0.139$ for hypothermia and mild hypothermia groups compared with the normothermic group, respectively). Unfortunately, the authors did not report on other outcomes stratified by mean core temperature as hypothermia may be associated with renal protection but it may increase odds for other adverse outcomes.

Airway Management

In patients with known or suspected cervical spine injury, one of the goals during tracheal intubation is to minimize movement of the cervical spine. Romito et al[70] used fluoroscopy to assess maximum cervical spine movement during tracheal intubation with 4 techniques using a cadaveric model with a maximally destabilized cervical spine. In 2 cadavers, the anterior and posterior longitudinal ligaments, anterior and posterior disc annuli, supraspinous and intraspinous ligaments, ligamentum flavum, and facet capsules were all surgically destabilized or transected. Fluoroscopy was used to assess maximum cervical spine movement at each upper cervical level to the fifth cervical vertebra during intubation facilitated by 4 devices with appropriately sized blades: direct laryngoscopy with a Macintosh blade, Glidescope, Storz C-MAC, and McGrath laryngoscope. Each cadaver was intubated 8 times via each technique with the head rigidly fixed in position with a Mayfield headholder. All attempts with the Glidescope, C-MAC, and McGrath laryngoscopes resulted in an adequate view of the glottic opening and successful tube placement, whereas direct laryngoscopy with a Macintosh blade was associated with poor or absent glottic view and successful tube placement in only 1 of 16 attempts. Compared with the 3 other techniques, direct laryngoscopy with a Macintosh blade was associated with the greatest degree of cervical spine distraction; the greatest magnitude of distraction occurred at the level of the first and second cervical vertebrae. There was no significant difference in the degree of cervical spine distraction at any level during intubation among the Glidescope, C-MAC, and McGrath laryngoscopes. It is important to note that, although distraction was greater with direct laryngoscopy with a Macintosh blade,

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laryngoscopy and intubation with the Glidescope, C-MAC, and McGrath laryngoscopes were all associated with some degree of cervical spine distraction. For example, cervical distraction was greatest at the level of the first cervical vertebra and the degree of distraction was 5.7 ± 0.5, 2.0 ± 0.5, 2.1 ± 0.5, and 1.4 ± 0.5 mm with direct laryngoscopy, Glidescope, C-MAC, and McGrath laryngoscopes, respectively.

Dutta et al[71] compared the degree of motion at the junction of the first and second cervical vertebra and at the junction of the second and third cervical vertebrae during tracheal intubation via an awake fiberoptically facilitated technique or the McGrath video laryngoscope following induction of anesthesia in 46 patients having cervical spine surgery for cervical instability. Lateral fluoroscopic images of the neck were obtained prior to intubation, during entry of the tube into the trachea, and following the procedure. Intubation with the McGrath laryngoscope was associated with significantly greater cervical spine distraction during and following intubation at the junction of the first and second cervical vertebrae but not at the junction of the second and third cervical vertebrae. However, as with the findings of Romito et al,[70] even intubation via an awake fiberoptically-mediated technique was associated with some motion at the junction of the first and second cervical vertebrae.

Swain et al[72] compared cervical spine distraction, measured with fluoroscopy, during intubation of 40 patients with normal cervical spines using the C-MAC laryngoscope or a Fastrach laryngeal mask airway-guided fiberoptic intubation. All patients were intubated using both techniques but the first technique used was randomly allocated. Cervical spine range of motion was assessed down to the fifth cervical vertebra. Cervical spine distraction spanning the occiput to the fifth cervical vertebra was 62% less during a Fastrach laryngeal mask airway-guided fiberoptic intubation compared with that measured during intubation with a C-MAC laryngoscope. The degree of movement was greatest at the level of the atlanto-occipital joint and the atlanto-axial joint, with Fastrach laryngeal mask airway-guided fiberoptic intubation associated with a 65% and 52% decrease in the degree of distraction at these levels, respectively. Even though Fastrach laryngeal mask airway-guided fiberoptic intubation was associated with decreased distraction, cervical distraction did still occur during intubation with this technique.

The incidence of reintubation following anterior cervical fusion currently reported in the literature is based primarily on smaller case series. Wilson et al[73] retrospectively identified patients who underwent anterior cervical fusion in 3 databases: (1) those that underwent surgery at a single institution between 2005 and 2014, (2) those contained in the National Surgical Quality Improvement Program Database between 2006 and 2016, and (3) those contained in the Premier Database having surgery between 2006 and 2016. Reintubation rates within 24 hours following surgery were: (1) 6 of 3056 (0.20%) cases at the single institution, (2) 100 of 47,525 (0.21%) cases in National Surgical Quality Improvement Program Database, and (3) 482 of 234,115 (0.21%) cases in the Premier database. Based on the National Surgical Quality Improvement Program database, increased age and higher American Society of Anesthesiology Physical Status Classification scores were independently associated with increased risk for reintubation. Factors associated with increased risk for reintubation based on data in the Premier database were male sex, Medicaid, surgery at a large hospital, urgent surgery, high comorbidity burden, and use of anticoagulants, whereas perioperative use of steroids and delayed extubation at the end of the procedure were associated with decreased risk for need for reintubation within 24 hours of surgery. Unfortunately, the authors did not report on whether side of approach to the cervical spine (ie, right vs. left) impacted risk for reintubation. The right recurrent laryngeal nerve is not protected within the tracheoesophageal groove[74] potentially increasing risk for nerve injury during retraction of the airway in the setting of a right-sided approach.[75]

In addition to the side of surgical approach potentially impacting risk for recurrent laryngeal nerve injury in those having anterior spine fusion, endotracheal tube management can also impact risk. Specifically, the endotracheal tube is fixed in 2 places—in the trachea by the inflated cuff and externally. Once the airway is retracted during surgery, the fixed endotracheal tube can compress the convex inner surface of the trachea and injure submucosal branches of the recurrent laryngeal nerve. Huang et al[76] prospectively randomized 110 patients having anterior cervical fusion via a right-sided approach to receive tracheal intubation either orally or nasally. Tracheal tube cuff pressure was maintained at 15 mm Hg following intubation. Once the airway was retracted to expose the cervical spine, if cuff pressure increased to ≥ 25 mm Hg, air was removed from the cuff until the pressure was <25 mm Hg. Patient demographics, surgical details, and airway anatomy findings were similar between groups. Mean cuff pressure immediately following airway retraction was also similar between groups (30 ± 12 and 28 ± 12 mm Hg in those nasally and orally intubated, respectively; $P = 0.463$). Air was removed to decrease cuff pressure to <25 mm Hg in 60% and 58% of those nasally and orally intubated, respectively ($P = 0.841$). However, dysphonia scores were significantly lower in those who were nasally intubated, especially immediately following surgery. There was a significantly higher proportion of patients who were intubated with a tube with a diameter <7 mm Hg in those nasally intubated (84%) compared with those orally intubated (56%; $P = 0.003$). Despite correcting for tube size, those who were nasally intubated still had lower dysphonia scores. Unfortunately, the authors did not report whether the endotracheal tubes used in this investigation contained low volume or high volume cuffs. Also, the maneuver following airway retraction did not involve complete deflation of the cuff of the tube to allow the tube to displace superiorly so as to minimize the pressure of the tube on the convex surface of the retracted airway.

Blood Conservation During Spine Surgery

Increases in intrathoracic pressure, as occur during mechanical ventilation, can impair venous return, increase

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venous pressure, and can potentially contribute to increased operative site bleeding.[77] Dunn et al[78] retrospectively identified 822 adults who underwent spine surgery in the prone position of whom 794 and 28 received volume-controlled and pressure-controlled ventilation during surgery, respectively. Neither ventilatory mode nor specific ventilator parameters (ie, mean tidal volume, mean peak inspiratory pressure, mean plateau pressure, mean airway driving pressure, mean estimated static compliance) were associated with estimated intraoperative or postoperative blood loss, fluid administration, postoperative drain output, or any postoperative adverse outcome. Airway driving pressure was calculated as the difference between peak and plateau pressure whereas static compliance was estimated from the ratio of tidal volume and airway driving pressure.

Intraoperative cell salvage is a widely used technique to potentially minimize the need for allogenic blood transfusion during a variety of surgical procedures, including spine surgery. Cheriyan et al[79] performed a meta-analysis of both prospective and retrospective studies that evaluated the utility of intraoperative cell salvage to decrease allogenic transfusion rates in patients having spine surgery. This meta-analysis included 18 investigations and data from a total of 2815 patients. Intraoperative cell salvage did not decrease intraoperative, postoperative, or total (ie, intraoperative plus postoperative) transfusion rates, but did decrease the mean number of allogenic units transfused by 0.81 units (CI = 0.48-1.15). There was no significant difference in operative time or in rates of perioperative complications between those who did and did not have cell saver during spine surgery.

Nemani et al[80] randomized 70 adults who underwent spinal fusion procedures of ≥ 6 levels to either have the output from postoperative subfascial drains discarded or salvaged with the Ortho-PAT autotransfusion system (Haemonetics, Fort Myers, FL) and reinfused intravenously. Patients received an allogenic transfusion if hemoglobin concentration was $\geq$ 8 g/dl. Drains were removed when drain output decreased to <50 mL over 4 hours. Patient groups were well matched for demographics and surgical procedure characteristics. Total drain output was greater in those who had salvaged drainage material (1901 ± 924 mL) compared with those from whom drain material was discarded (1304 ± 665 mL; $P = 0.005$). Mean salvaged drain output transfused was 208 ± 225 mL. Rates of patients receiving allogenic blood were similar (41% vs. 60% in the salvaged and discarded groups, respectively; $P = 0.17$), although blood hemoglobin concentration was higher on postoperative day 2 in those who received salvaged drain output (10.1 ± 1.2 vs. 9.4 ± 0.8 g/dL; $P = 0.01$). Although postoperative blood salvage did not significantly decrease postoperative allogenic transfusion, it was associated with higher blood hemoglobin concentration despite also being associated with increased drain output.

Pain Management for Spine Surgery

Enhanced recovery pathways provide an evidence-based management framework with the intent to improve pain control, facilitate faster mobility, shorten hospital stay, and improve patient satisfaction.[81,82] Soffin et al[83] randomized 51 adult patients undergoing lumbar spinal fusion of 1 to 2 levels to receive perioperative care with (n = 25) or without (n = 26) an enhanced recovery pathway. The enhanced recovery pathway included the following:

- Focused preoperative education.
- Preoperative gabapentin and acetaminophen.
- Oral consumption of a carbohydrate-containing beverage preoperatively.
- A risk-adjusted protocol for antiemetic drugs.
- Maintenance of anesthesia with a protocol that consisted of propofol, ketamine, dexmedetomidine, up to 0.3 minimum alveolar concentration of inhaled anesthetics, and no nitrous oxide.
- Specific goals to maintain normothermia.
- Goal-directed fluid management protocols to maintain euvolemia.
- A perioperative analgesic plan focusing on opioid-sparing multimodal options.
- Early ambulation and early nutrition.

The primary outcome was quality of recovery, assessed on postoperative day 3, via the Quality of Recovery-40 (QoR40) score, a 40 item questionnaire that assesses comfort, emotions, degree of physical independence, patient support, and pain where scores range from 40 (ie, extremely poor recovery) to 200 (ie, best recovery).[84] On postoperative day 3, mean QoR40 score was 9 points higher in those managed with the enhanced recovery pathway compared with those managed without the pathway ($P = 0.041$); this difference was mostly attributed to better scores on questions about patient comfort. However, the investigators estimated that a difference in QoR40 scores of at least 12 points would be required for a clinically significant difference. Those managed with the enhanced recovery pathway also had a shorter duration of patient-controlled analgesic use, decreased opioid consumption during the first 24 hours following surgery, and lower pain scores during physical therapy. There was no difference between groups in rates of postoperative nausea and vomiting, ileus, mental status changes, or infection, nor was there a difference in hospital length of stay. Therefore, the authors concluded that, although statistically significant differences were noted, these differences likely were not associated with a clinically significant difference in outcomes.

Methadone is not only a mu-opioid receptor agonist with a very long half-life but also an antagonist of the n-methyl-D-aspartate receptor.[85] Methadone also inhibits the re-uptake of the neurotransmitters serotonin and norepinephrine.[86] Murphy et al[87] report the findings of a survey of patients enrolled in two trials to assess the utility of methadone at treating postsurgical pain following spine and cardiac surgery; only the findings in patients who underwent spine surgery are discussed in this review. Patients undergoing posterior spine fusion having a standardized anesthetic and postoperative analgesic plan were randomized to receive either 0.2 mg/kg methadone (n = 62) at induction of anesthesia or 2 mg hydromorphone (n = 53) at

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surgical closure. Patients received questionnaires at 1, 3, 6, and 12 months following surgery with respective response rates of 65%, 57%, 64%, and 57%. Methadone was associated with a significant decrease in the frequency of postsurgery pain at 1, 3, 6, and 12 months and also with a decrease in analgesic medication use, the degree of pain during sleep and with activities, and the presence of chronic postsurgical pain at 3 months but not at 1, 6, or 12 month after surgery. The degree of back pain, and less so leg pain, was lower in those who received methadone, and fewer patients among those who received methadone were requiring opioid analgesics at 3 months (10%) compared with those who received hydromorphone (41%, $P = 0.009$). Thus, methadone potentially has a durable effect at decreasing long-term pain following spine surgery.

Ultrasound-guided deposition of local anesthetic solution between the transverse process and erector spinae muscle (ie, the erector spinae block) allows for blockade of dorsal and ventral rami of spinal nerves. Erector spinae blocks have been used to decrease pain following rib fracture and various surgical procedures on the hip, abdomen, and chest wall.[88] Singh et al[89] randomized 40 patients having lumbar laminectomy to receive either erector spinae block or no block. In patients receiving a block, the erector spinae block was performed bilaterally at the level of T10 with 20 mL of 0.5% bupivacaine injected on each side. After receiving an erector spinae block, patients were observed for 30 minutes and block effectiveness was assessed via checking sensation to pin prick in the T6-L3 dermatomes. If loss of sensation was not noted bilaterally, the block was considered a failure. All patients received a standardized general anesthetic with 0.1 mg/kg morphine administered intravenously with induction of anesthesia and a standardized postoperative analgesic regimen. Demographics and surgical duration were similar between groups. Patients who received erector spinae blocks had significantly lower 24 hour mean cumulative intravenous morphine utilization (1.4 ± 1.5 vs. 7.2 ± 2.0 mg; $P < 0.001$) with 55% and 0% of patients in the block and no-block groups requiring no morphine during the first 24 hours following surgery ($P = 0.002$). Patients who received a block were more satisfied with their periprocedural experience than those who did not receive a block. There were no block failures, nor complications attributed to the erector spinae block.

STROKE

Stroke and COVID-19

Li et al[90] reported a 4.5% rate of ischemic stroke among 219 patients with COVID-19 infection in Wuhan, China. To investigate whether COVID-19 infection is associated with an increased risk of ischemic stroke compared to other significant respiratory illnesses, Merkler et al[91] retrospectively identified patients with COVID-19 and those with influenza A and compared rates of ischemic stroke. Among 1,916 patients with COVID-19 infection, 31 (1.6%) subsequently developed an acute ischemic stroke. Those with ischemic stroke had a higher median serum D-dimer concentration and a higher in hospital mortality compared with those with COVID-19 infection but without ischemic stroke (1.93 μg/dL; IQR = 0.56 to 5.29 vs. 0.68 μg/dL, IQR 0.34 to 1.99 μg/dL; $P = 0.01$ and 32% vs.14%; $P = 0.003$, respectively). Ischemic stroke rate among those with influenza A infection was 0.2%. Those with COVID-19 infection had a 7 (CI = 2.3-25.2) fold increased odds of developing an ischemic stroke compared with those with influenza A. This association between increased risk for ischemic stroke in those with COVID-19 is supported by Belani et al[92] who found that COVID-19 increased the odds of acute ischemic stroke by 3.9 (CI = 1.7-8.9; $P = 0.001$).

Despite this increased rate of acute ischemic stroke associated with COVID-19, earlier in the pandemic many centers reported a 30% to 40% decrease in the rate of patients presenting to hospital with acute ischemic stroke but no difference in patient demographics or stroke severity compared with those with stroke prior to the COVID-19 pandemic.[93–95] The authors hypothesize that this may be due, in part, to reluctance by patients to seek medical care for fear of acquiring COVID-19 while in hospital. Patients with COVID-19 infection who suffer an ischemic stroke were more likely to have a worse neurological outcome and higher risk for death compared with those without COVID-19 infection.[96,97] In addition, patients with COVID-19 infection who suffer an ischemic stroke and undergo mechanical thrombectomy may be at higher risk for reocclusion.[98]

Sharma et al[99] developed a consensus statement on behalf of SNACC for the management of revascularization procedures in patients with acute ischemic stroke during the COVID-19 pandemic. They review viral transmission and protective measures for health care workers. The authors suggest that monitored anesthesia care can still be considered during the pandemic but that, in an effort to reduce the chance for intra-procedural conversion to general anesthesia, there should be a lower threshold to consider general anesthesia, especially in patients with respiratory signs and symptoms, worse stroke severity, and altered mental status. In those receiving general anesthesia, staff presence should be minimized during airway management, and coughing and circuit disconnects should also be minimized. During monitored anesthesia care, the patient should wear a mask, high flow oxygen should be avoided, and sedation should be minimized. The authors also discuss extubation and patient disposition. A similar guidance statement was also developed on behalf of the Society of Vascular and Interventional Neurology.[100]

Periprocedural Factors and Outcome Following Ischemic Stroke

Anesthetic considerations for patients having mechanical thrombectomy were recently reviewed by Businger et al.[101] Retrospective and post hoc analyses of prospectively collected data where anesthetic technique was not randomized suggested that general anesthesia, compared with monitored anesthesia care, when used to facilitate thrombectomy was associated with worse outcome.[102,103] However, prospective randomized trials and one prospective nonrandomized trial failed to demonstrate increased risk for poor

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outcome or complications with general anesthesia.[104–107] Sun et al[108] report on the result of a randomized controlled pilot trial—Choice of Anesthesia for Endovascular Treatment of Acute Ischemic Stroke (CANVAS). Forty-three patients with acute anterior circulation stroke treated at a hospital in Beijing, China were randomized to receive either general anesthesia maintained with propofol and remifentanil or monitored anesthesia care facilitated with propofol and sufentanil. Rates of hypotension (ie, episodes where MAP decreased by >20% from baseline) were more common in the general anesthesia group but rates of severe hypotensive episodes (ie, MAP decrease by >40% from baseline) were similar between groups. Four patients randomized to receive monitored anesthesia care required conversion to general anesthesia. Rate of successful reperfusion (modified Thrombolysis in Cerebral Ischemia score 2b-3) was higher in the general anesthesia group (95%) compared with that among those who received monitored anesthesia care (65%; $P=0.048$). However, there was no difference in National Institutes of Health Stroke Scale scores at 24 hours or 7 days, or in modified Rankin Scale score (mRS) at 30 days after randomization between groups.

Intraprocedural conversion to general anesthesia during mechanical thrombectomy is not uncommon. Flottmann et al[109] retrospectively identified 254 patients who underwent mechanical thrombectomy, of whom 94 received local anesthesia, 76 monitored anesthesia care, 59 general anesthesia, and 25 either local anesthesia or monitored anesthesia care initially but required intraprocedural conversion to general anesthesia. Reasons for conversion included excessive movement (n=18; 72%), neurological deterioration (n=4; 16%), emesis (n=1; 4%), intracranial hemorrhage (n=1; 4%), and need for stenting of an intracranial vessel (n=1; 4%). The time interval between hospital admission and flow restoration was significantly longer in both those who received general anesthesia from the onset or required intraprocedural conversion to general anesthesia compared with those who received local anesthesia or monitored anesthesia care. The odds of successful reperfusion were similar between those who required conversion to general anesthesia and the remaining 3 groups. There was no difference among the groups in mRS at discharge and at 90 days following the procedure. Collectively, intraprocedural conversion to general anesthesia may not be associated with poor outcome.

Blood pressure changes are common during endovascular treatment of ischemic stroke and may modulate outcome.[110–112] Rasmussen et al[113] performed a post hoc analysis of data from 365 patients with acute ischemic stroke who were enrolled in 3 prospective randomized trials that assessed the impact of anesthetic technique on outcome following endovascular therapy.[104–107] In this cohort, 50% had general anesthesia and the remainder had monitored anesthesia care with or without sedation. Preprocedural blood pressure was similar between groups based on anesthetic technique, although intraprocedural blood pressure was generally lower in those who received general anesthesia. In the entire cohort, every 10 min of cumulative time with MAP <70 mm Hg increased the odds of a shift in mRS toward worse outcome by 30% (OR=1.30, CI=1.03-1.65; $P=0.03$) and every 10 min of continuous time with MAP <70 mm Hg increased the odds of a shift in mRS toward worse outcome by 62% (OR=1.62, CI=1.15-2.27; $P=0.005$). Every 10 minutes cumulative time with MAP >90 mm Hg was associated with an 8% increased odds of a shift in mRS toward worse outcome (OR=1.08, CI=1.04-1.11; $P<0.001$). Vasopressor use was not found to be a modulator of outcome in this cohort. The association of hypotension with poor outcome was also supported by Valent et al.[114] In this retrospective study involving 371 patients with acute stroke, odds of poor outcome, defined as a mRS>2 at 90 days, was increased by 11% for every 10 minutes that MAP was >10% lower than the MAP before starting the procedure (OR=1.11, CI=1.02-1.21; $P<0.05$).

Petersen et al[115] prospectively studied cerebral autoregulation and used that information to calculate an MAP where autoregulation was optimized in a cohort of 90 patients following mechanical thrombectomy for ischemic stroke. A cerebral oximetry index (COx) was calculated as the moving Pearson correlation coefficient between MAP and regional cerebral oxygen saturation (rSO_2) determined by near infrared spectroscopy. Data were collected for up to 48 hours following mechanical thrombectomy. As higher values of COx indicate greater impairment of cerebral autoregulation, the MAP associated with optimal cerebral autoregulation was determined by calculating the MAP associated with the lowest COx. The upper and lower limits of autoregulation were determined as the MAP above and below which COx was >+0.3. Greater time spent with MAP greater than the upper limit of autoregulation was associated with worse mRS scores at 90 days, whereas the duration of time spent with SBP >160 or 180 mm Hg were not significantly associated with outcome; this suggests that blood pressure targets should be individualized, if possible. Increased duration of time above the upper limit of autoregulation was significantly associated with increased risk for hemorrhagic transformation, whereas increased duration below the lower limit of autoregulation was associated with infarct progression (ie, increasing infarct size on imaging).

Blood pressure may not be the only factor that influences risk for hemorrhagic transformation of ischemic stroke. Patients with hyper-attenuated regions on CT of the brain following thrombectomy may be particularly susceptible to hemorrhagic transformation.[116] Ding et al[117] retrospectively identified 148 patients with anterior circulation stroke and hyper-attenuated brain lesions on noncontrast CT of the head immediately following mechanical thrombectomy. Each increase in maximum SBP by 10 mm Hg was independently associated with increased odds of poor outcome (defined as mRS >2 at 90 d) during the procedure (OR=1.43, CI=1.10-1.86; $P=0.008$) and during the first 12 hours (OR=1.40, CI=1.08-1.81; $P=0.005$) and second 12 hours (OR=1.39, CI=1.06-1.81; $P=0.017$) following the procedure. Each increase in maximum SBP by 10 mm Hg was also independently associated with increased

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odds of subsequent hemorrhagic transformation during the procedure (OR = 1.03, CI = 1.01-1.48; $P = 0.044$) and during the first 12 hours following the procedure (OR = 1.24, CI = 1.02-1.51; $P = 0.03$). The optimal cut-off value of maximum SBP with the highest Youden index for predicting risk for hemorrhagic transformation was 155 mm Hg (area under the curve 0.638; $P = 0.006$) with a sensitivity and specificity of 69% and 66%, respectively.

Remote ischemic conditioning refers to the institution of temporary ischemia to an anatomic structure that results in the attenuation of ischemic injury to a different anatomic structure. For example, temporary limb ischemia induced by inflation of a blood pressure cuff has been show to attenuate ischemic brain injury in animals.[118,119] Pico et al[120] randomized 188 patients with anterior circulation ischemic stroke to standard management with or without remote ischemic conditioning. Remote ischemic conditioning was induced by maintaining a pressure of 110 mm Hg greater than SBP for 5 minutes in a blood pressure cuff placed on the patient's thigh within 6 hours of stroke onset. The cuff was then deflated for 5 minutes for 4 cycles. In this cohort, 87% and 34% of patients received intravenous thrombolytics and mechanical thrombectomy, respectively. There was no difference between groups in infarct size following stroke, the proportion with mRS ≤ 1 at 90 days, 90-day mortality, or rate of hemorrhagic transformation indicating that remote ischemic conditioning may not be beneficial at attenuating focal ischemic brain injury in humans.

Nerinetide is a neuroprotective drug that reduces excitotoxicity and attenuates ischemic injury *in vitro* and in animal models of ischemic stroke.[121,122] Hill et al[123] performed a prospective, multicenter trial in adults with acute ischemic stroke who were randomized to receive either nerinetide (2.6 mg/kg up to 270 mg intravenously, n = 549) or placebo (n = 556) within 60 minutes of initial brain imaging. The primary outcome, the proportion of patients who achieved a mRS = 0 to 2 at 3 months, was similar among those who did or did not receive nerinetide (59.2 vs. 61.4%, respectively; $P = 0.35$). All secondary outcome measures, including rate of patients with a National Institutes of Health Stroke Scale 0 to 2 at 90 days, mRS 0 to 1 at 90 days, 90-day mortality, and infarct volume at 24 hours, were also similar between groups. Although there were no differences among prespecified subgroups, use of alteplase appeared to attenuate a beneficial effect from nerinetide. Specifically, among patients who did not receive alteplase, rates of patients with mRS 0 to 2 at 3 months was significantly higher among those who received nerinetide (58.9% vs. 49.8% in those who did not received nerinetide; $P < 0.05$). In addition, median infarct volume at 24 hours was lower (26.7 mL, IQR 6.3 to 88.0 vs. 39.2 mL, IQR 9.2 to 132.9 mL; $P < 0.05$) and 90-day mortality rate was lower (12.8% vs. 20.3%; $P < 0.05$) in those who did versus did not receive nerinetide, respectively. Nerinetide did not impact any outcome measure in those who received alteplase. Since nerinetide has an amino acid sequence that would be cleaved by plasmin, a serine protease, and alteplase increases circulating plasmin concentrations, nerinetide may be inactivated as a consequence of alteplase.[124]

Perioperative Stroke

Ischemic perioperative stroke is most commonly associated with cardiovascular and neurological surgery, although patients having other procedures are not immune to this complication. Vlisides at al[125] published guidelines on behalf of SNACC for the perioperative care of patients at high risk for stroke following noncardiovascular or neurologic surgery. The authors review and provide recommendations for risk stratification and preoperative and perioperative medication management of drugs such as anticoagulants, antiplatelet agents, statins, and beta-adrenergic antagonists. They address intraoperative strategies to potentially reduce the risk of stroke, including hemodynamic and respiratory management, glycemic control, and blood transfusion. In addition, they review postoperative stroke identification and management.

Roughhead et al[126] surveyed 673 patient presenting to 2 perioperative clinics before noncardiac and non-neurologic surgery to assess perceptions about perioperative stroke. Overall, 600 patients completed the survey and 479, 104, and 15 were classified as being at low, moderate, and high risk for perioperative stroke based on risk factors published by Mashour et al,[127] although Roughhead et al[126] also included atrial fibrillation as a risk factor. The authors estimated the overall perioperative stroke risk in the entire cohort to be ~0.2%. However, 57% of the cohort self-predicted their risk as 0.01%. Only 14% and 20% of those at medium and high risk for stroke, respectively, did not significantly underestimate their risk for stroke. Lower educational status and presence of chronic renal disease were independently associated with significant underestimation of stroke risk. Only 15% of patients remember having a discussion about perioperative stroke risk with their surgeon or primary physician.

Delayed Cerebral Ischemia and Vasospasm Following Subarachnoid Hemorrhage

Various biomarkers and monitors can be used to detect and stratify prognosis following vasospasm and delayed cerebral ischemic after subarachnoid hemorrhage.[128,129] Aoun et al[130] assessed the role of pupillometry for predicting and detecting cerebral vasospasm. Neurological pupillary index (NPI) was measured every 4 hours in 56 patients admitted to the ICU following subarachnoid hemorrhage. The Neuroptics Pupillometer NPI-200 (Neuroptics Inc., Laguna Hills, CA) employs a proprietary algorithm to calculate the NPI which estimates the appropriateness of pupillary reactivity. When calculating the NPI, the pupillometer measures variables such as pupillary contraction rate and maximum degree of contraction with light exposure, and compares these values to normative values to quantify the integrity of the pupillary light reflex. NPI ranges from 0 to 5, where NPI of 5 indicates normal pupillary function and a value of 0 indicates unreactive pupils. In the study by Aoun et al,[130] decreases in NPI were not associated with sonographic evidence of vasospasm. However, 12 patients developed delayed cerebral ischemia defined as a development of new focal neurological deficit or sudden deterioration in level

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of consciousness. Seven patients with delayed cerebral ischemia exhibited decreases in NPI to values <3, with 71% initially occurring > 8 hours before the onset of clinical manifestations of delayed cerebral ischemia. These decreased NPI values normalized in all patients with delayed cerebral ischemia following treatment. Thus, pupillometry may have utility in predicting delayed cerebral ischemia.

Vasodilators can be used to treat cerebral vasospasm but may impact systemic hemodynamics.[131] Sriganesh et al[132] prospectively evaluated the effect of directed intra-arterial nimodipine on cerebral oxygenation (measured by near infrared spectroscopy) and systemic hemodynamics in 20 patients undergoing treatment for cerebral vasospasm. Patients received 3 mg of nimodipine over 30 minutes delivered directly into the spastic cerebral vessel. Despite a significant increase in spastic vessel diameter and a decrease in contrast transit time, there was no change in rSO_2 on the side ipsilateral and contralateral to the injected vessel. Nimodipine was associated with a significant decrease in MAP (114 ± 16 to 102 ± 19 mm Hg; $P < 0.001$), increase in cardiac index (3.7 ± 1.0 L/min/m^2 to 4.3 ± 0.3 L/min/m^2; $P < 0.001$), and decrease in total peripheral resistance index (2714 ± 985 dynes×s/cm^5/m^2 to 2040 ± 711 dynes×s/cm^5/m^2; $P < 0.001$); the latter 2 variables were measured with a NICOM noninvasive cardiac output monitor (Cheetah Medical, Tel Aviv, Israel). The authors hypothesize that a decrease in systemic blood pressure may have offset the effects of cerebral vasodilation leading to no significant change in rSO_2. In addition, whether or not the vasospastic segment perfused the region of brain interrogated by the oximeter probe could have also impacted this finding.

Anesthetic drugs have been shown to attenuate cerebral vasospasm in animals.[133–137] Athiraman et al[138] retrospectively identified 157 patients who received general anesthesia for cerebral aneurysm treatment by clipping (n = 66) or radiologically guided coiling (n = 91). Patients were stratified into those who had general anesthesia maintained for these procedures with inhalational anesthetics only (n = 119) or those who received inhalational anesthetics in combination with propofol infusion (n = 34). Overall, 97 (62%) developed angiographic evidence of vasospasm and 63 (40%) developed delayed cerebral ischemia diagnosed by criteria similar to those used by Aoun et al.[130] Use of an inhalational anesthetic only technique was independently associated with a significantly decreased odds for patients to develop angiographic vasospasm during hospitalization (OR = 0.35, CI = 0.14-0.89; $P < 0.05$) but no effect on risk for delayed cerebral ischemia or outcome at discharge. The authors hypothesize that this effect may be due to exposure to higher concentrations of inhaled anesthetics in those who received inhalational anesthetics only.

Sharma[139] reviewed perioperative management of patients with aneurysmal subarachnoid hemorrhage. He discusses and provides recommendations for preoperative management and stabilization, intraoperative anesthetic management, and discusses cerebral vasospasm and delayed cerebral ischemia.

TBI

Factors Potentially Affecting Outcome

Decompressive craniectomy has been used to treat refractory intracranial hypertension following TBI. The Decompressive Craniectomy (DECRA) Trial was a prospective investigation that included 155 patients under 60 years old with diffuse TBI and intracranial hypertension refractory to other treatments.[140] Patients were randomized to either undergo or not undergo bilateral decompressive craniectomy, and outcome was worse after 6 months in patients who were randomized to receive decompressive craniectomy. Cooper et al[141] now report on 12 month outcome among patients enrolled in the DECRA Trial. The primary outcome, rate of unfavorable functional outcome (those with extended GOS <5), was now not different between groups following correction for factors thought to influence outcome. There was also no difference in rates of survivors in a vegetative state (extended GOS 2) or those survivors with severe disability (extended GOS 2 to 4). However, fewer patients randomized to decompressive craniectomy had a good outcome (extended GOS 7 to 8) than those not randomized to receive decompressive craniectomy (10% vs. 26%, respectively; adjusted $P = 0.04$). Given these data and the outcome data from the RESCUEicp Trial,[142] the Brain Trauma Foundation has updated their recommendations for using decompressive craniectomy in those with refractory intracranial hypertension following TBI.[143] The recommendations now include:

- Secondary decompressive craniectomy is recommended for late, but not early, refractory intracranial hypertension to improve odds for favorable outcome and decrease mortality.
- If decompressive craniectomy is to be performed, a larger sized decompressive craniectomy is recommended.
- Decompressive craniectomy for early or late refractory intracranial hypertension is suggested to reduce ICP and duration of ICU stay, but has an unclear impact on odds of favorable outcome.

Mannitol and hypertonic saline can both be used to treat intracranial hypertension. Anstey et al[144] retrospectively identified patients with severe TBI from 14 ICUs in Australia and Europe who received either mannitol only (n = 46) or hypertonic saline only (n = 46) for the treatment of intracranial hypertension. Patients who received mannitol were older and had higher Injury Severity Scores and IMPACT-TBI-predicted 6 month mortality but similar mean and maximum ICP during the first 96 h following injury. The concentrations of hypertonic saline used varied among institutions. All but one center used 20% mannitol and the remaining center used 15% mannitol. Median total osmotic load was significant higher among patients who received hypertonic saline (629 mOsm, IQR = 322 to 965 mOsm) compared with those who received mannitol (447 mOsm, IQR = 238 to 745 mOsm) during the first 96 hours following injury. Although in-hospital mortality rate was higher among those who received mannitol (24% vs. 10% in those

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who received hypertonic saline; $P = 0.002$), this difference was no longer statistically significant when correcting for center, Injury Severity Score, extended IMPACT-TBI score, and mean ICP during the first 96 hours following injury ($P = 0.06$).

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 3 (CRASH-3) Trial findings were published in 2019 showing that patients with mild or moderate, but not severe, TBI who received tranexamic acid within 3 hours of injury had decreased odds of head trauma-related mortality.[145,146] Rowell et al[147] report on a multicenter trial where 966 patients above 15 years of age with moderate or severe TBI were randomized to receive either: (1) tranexamic acid administered as 1 g in the prehospital setting and 1 g over 8 hours upon arrival to the hospital, (2) 2 g of tranexamic acid administered only in the prehospital setting, or (3) no tranexamic acid. The primary outcome, the rate of favorable outcome defined as an extended GOS of 5 to 8 at 6 months, was achieved in 65% and 62% among those who did and did not receive tranexamic acid, respectively (adjusted $P = 0.16$). Rates were not different when the three groups were compared separately. There was also no difference in mortality rate at 6 months or the rate of patients who developed intracranial hemorrhage. These findings were similar to that of the CRASH-3 trial when all patients were collectively considered. Unfortunately, Rowell et al[147] did not perform a subgroup analysis that evaluated the effect of tranexamic acid in only patients with moderate TBI.

Airway and Ventilation Management

Tracheal intubation following traumatic injury can be life-saving. Gravesteijn et al[148] characterized intubation practices in patients with TBI using data from 3843 patients with all severities of TBI from 61 centers in Europe included in the Collaborative European Neurotrauma Effectiveness Research in TBI Database.[149] Overall, 839 (22%) were intubated before arriving at hospital and 483 (13%) where intubated following hospital arrival. The rates of prehospital intubation varied from 2% to 56% across European countries, with France having the highest rate of prehospital intubation. Rates of in-hospital intubation varied from 1% to 41% across countries, with Sweden having the highest rate of in-hospital intubation. Collectively, factors associated with higher rates of tracheal intubation either before or following arrival at the hospital were younger age, lower GCS, higher Injury Severity Score, and at least one nonreactive pupil. Gravensteijn et al[150] also found that, following correction for confounders, intubation either before or following arrival at the hospital was not associated with increased odds for poor outcome.

Picetti et al[151] performed a survey of members of the European Society of Intensive Care Medicine to assess respiratory and ventilator management practices in patients with TBI with or without respiratory failure. There were 687 respondents of whom 472 (69%) were from a country in Europe with 328 (48%) and 206 (30%) of respondents being intensivists or anesthesiologists, respectively. In patients with arterial partial pressure of oxygen (PaO_2)/inspired fraction of oxygen (FiO_2) ≥ 150 mm Hg, most respondents used a tidal volume of 6 to 8 mL/kg; a tidal volume of 4 to 6 mg/kg was most frequently used for patients with $PaO_2/FiO_2 < 150$ mm Hg. Independent of PaO_2/FiO_2 ratio, a maximum positive end expiratory pressure that would be employed was 15 cm H_2O in those without intracranial hypertension and 10 cm H_2O in those with intracranial hypertension. Also independent of PaO_2/FiO_2 and independent of the presence or absence of intracranial hypertension, the target arterial partial pressure of carbon dioxide and PaO_2 used most commonly by clinicians were 36 to 40 mm Hg and 81 to 100 mm Hg, respectively. The 3 most common rescue strategies employed for refractory respiratory failure were the use of muscle relaxation, recruitment maneuvers, and prone positioning.

Monitoring

Zeiler et al[152] identified patients included in the Collaborative European Neurotrauma Effectiveness Research in TBI Database[149] who had both invasive ICP monitoring and brain tissue oxygen partial pressure ($PbtO_2$) monitoring following TBI. Patients also had an extended GOS recorded at 6 months following injury. Among the 43 patients identified, 35 were male. Although the authors did not report median admission GCS, the cohort included in this investigation likely consisted mostly of those with moderate or severe TBI. Collectively, 6%, 19%, and 61% of measurements consisted of an ICP > 20 mm Hg, $PbtO_2 < 20$ mm Hg, and pressure reactivity index > 0, respectively. The pressure reactivity index was calculated as the moving Pearson correlation coefficient between ICP and MAP and can be used to estimate the integrity of cerebral autoregulation. Ranging from −1 to +1, more positive values of pressure reactivity index indicate greater impairment of cerebral autoregulation. The authors report that most episodes of autoregulatory impairment (where pressure reactivity index was > 0) occurred when ICP and $PbtO_2$ were normal, likely suggesting that elevated ICP and local cerebral hypoxia are not the only factors contributing to impairment of autoregulation following TBI. Increased duration of time with higher values of pressure reactivity index was a strong predictor of increased odds of death within 6 months of injury, but had limited utility at predicting rates of unfavorable outcome (extended GOS <5) at 6 months. Increased duration of time with ICP > 20 mm Hg or $PbtO_2 < 20$ mm Hg were not predictive of death or rates of unfavorable outcome at 6 months, although this study may not be powered to detect an effect of ICP or $PbtO_2$ on outcome.

Zeiler et al[153] review cerebral autoregulation monitoring in patients with moderate or severe TBI, including the physiology of cerebral autoregulation, how autoregulation is estimated, how it is affected by various diseases states of the brain, and its relation to outcome. Mathieu et al[154] provide a qualitative review of the literature pertaining to the use of cerebral near infrared spectroscopy in patients with TBI. Including an analysis of

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42 studies, the authors summarize the relationship between rSO_2 and ICP, cerebral perfusion pressure, $PbtO_2$, and outcome. They also discuss the utility of cerebral near infrared spectroscopy as a tool to estimate the integrity of cerebral autoregulation.

MONITORING

ICP

Elevated ICP can result from increased cerebral blood volume, intracranial masses, and hematomas, cerebral edema, or disorders related to CSF production, flow, or absorption.[155] Various noninvasive techniques have been described to estimate ICP and cerebral perfusion pressure.[156] Cardin et al[157] prospectively compared ICP measured via either an intraparenchymal probe or ventriculostomy to that estimated by a method employing transcranial Doppler sonography in 100 patients with TBI. Transcranial Doppler measurements were made via insonation of middle cerebral arteries bilaterally; right and left values were averaged. ICP was estimated using the following formula[158]:

$$\mathrm{ICP} = \mathrm{MAP} - \left(\mathrm{MAP} \times \frac{\mathrm{DFV}}{\mathrm{MFV}} + 14\right),$$

where ICP and MAP are expressed in mm Hg and diastolic flow velocity and mean flow velocity are measured with transcranial Doppler sonography and expressed in cm/s. Decreases in diastolic flow velocity results in higher calculated values of ICP. In this cohort, median measured ICP was 13 mm Hg (IQR = 10 to 17 mm Hg). The correlation between measured and calculated ICP was not significant ($R = -0.17$, CI = −0.35 to +0.03; $P = 0.097$). Bland-Altman mean difference in measured and calculated ICP was 1.3 mm Hg, but 95% limits of agreement ranged from −28 mm Hg to +30 mm Hg. Estimation of ICP was not able to discriminate between measured ICP of ≤20 mm Hg versus >20 mm Hg; area under the received operating characteristic curve was 0.34 (CI = 0.23-0.46) with a sensitivity and specificity of 0% and 74%, respectively. These findings confirm earlier data that use of this noninvasive transcranial Doppler technique to estimate ICP may be limited.[159] The authors also measured optic nerve sheath diameter in this cohort and found that optic nerve sheath diameter was the only noninvasive parameter that could effectively discriminate between normal and elevated ICP. Of note, Hajat at al[160] describe a model consisting of a table tennis ball, 3.0 mm endotracheal tube, and gelatin to represent the globe, optic nerve and sheath, and soft tissue, respectively, that can be used to train people to measure optic nerve sheath diameter with ultrasound.

Nearinfrared Spectroscopy

Nearinfrared spectroscopy can be used to measure rSO_2 and to assess the effectiveness of various therapies and the effect of systemic hemodynamic changes on cerebral well-being.[161,162] Thiele et al[163] report on a joint consensus statement developed by the American Society for Enhanced Recovery and the Perioperative Quality Initiative, and provide recommendation for the perioperative use and utility of cerebral near infrared spectroscopy as summarized in Table 1.

Induced circulatory pause can be helpful during cerebral aneurysm clipping to decrease risk for rupture or to assist in the management of intraoperative aneurysm rupture. This may be accomplished with rapid ventricular

TABLE 1. Summary of Recommendations for the Perioperative Use of Cerebral Oximetry

Statement	Strength of Evidence	Quality of Evidence
We recommend interpreting perioperative cerebral oximetry measurements in the context of a pre-induction baseline value	Strong	B
We recommend interpreting perioperative cerebral oximetry measurements in the context of the physiologic variables that affect them	Strong	B
We recommend caution in comparing cerebral oximetry values between different manufacturers	Strong	B
We recommend the use of preoperative cerebral oximetry to identify patients at increased risk for adverse outcomes after cardiac surgery	Weak	B
We recommend intraoperative cerebral oximetry indexed to preinduction baseline to identify patients at increased risk for adverse outcomes after cardiac surgery	Weak	C
We recommend using cerebral oximetry to identify and guide management of acute cerebral mal-perfusion during cardiac surgery	Weak	D
We recommend using an intraoperative cerebral oximetry-guided interventional algorithm to reduce ICU length of stay after cardiac surgery	Weak	C
There is insufficient evidence to recommend using intraoperative cerebral oximetry to reduce mortality or organ-specific mortality after cardiac surgery	NA	NA
There is insufficient evidence to recommend using intraoperative cerebral oximetry to improve outcome after noncardiac surgery	NA	NA

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria and consensus were used to quantify the strength of evidence and level of evidence. Level of evidence was stratified into the following categories:

A. High quality: further research is not likely to change this recommendation.

B. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

C. Low quality: further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

D. Very low quality: any estimate of effect is uncertain.

ICU indicates intensive care unit; NA: not applicable.

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pacing or with intravenous adenosine. Saldien et al[164] report on changes in rSO_2 and $PbtO_2$ in 5 patients who received rapid ventricular pacing. Measurements were performed while patients inspired either 30% or 100% oxygen. rSO_2 was measured on the side contralateral to the craniotomy site with a Foresight monitor (CAS Medical, Branford, CT), $PbtO_2$ and CBF were measured invasively with probes placed into white matter with an IMC probe kit and a CC1SB oxygen probe (Integra, Plainsboro, NJ) and a QFlow 500 Probe (Hemedex, Cambridge, MA), respectively. Rapid ventricular pacing was performed for 40 seconds. With pacing, median SBP decreased from 86 (IQR = 82 to 89 mm Hg) to 34 mm Hg (IQR = 30 to 39 mm Hg) within 3 seconds of the start of pacing. CBF, rSO_2, and $PbtO_2$ all decreased significantly with pacing and eventually returned to baseline with reperfusion during inspiration of both FiO_2 30% and 100%. Figure 1 illustrates the changes in CBF, rSO_2, and $PbtO_2$ over time. CBF was lower and both rSO_2 and $PbtO_2$ were higher with FiO_2 of 100% versus 30%. CBF decreased quickly with the start of pacing and recovered quickly following pacing. However, rSO_2 and $PbtO_2$ required time to decrease after the onset of pacing and were much slower to recover with reperfusion.

Cerebral oximetry can be used to assess cerebral autoregulation and may predict changes in neurologic function and stratify outcome.[165] Rivera-Lara et al[166] utilized cerebral near-infrared spectroscopy to estimate cerebral autoregulatory function in 88 comatose patients. They calculated COx as the moving Pearson correlation coefficient between MAP and rSO_2 in 10 seconds nonoverlapping epochs; COx values can vary between −1 and +1. With intact autoregulation, decreases in MAP should correlate with cerebral vasodilation and increases in rSO_2, thus COx should be lower than in the setting of autoregulatory impairment. At hospital discharge, 89% of subjects had a mRS ≥ 4 and in-hospital mortality rate was 51%. Cox ≥ 0.05 was independently associated with higher odds of mRS ≥ 4 at 6 months (OR = 4.4, CI = 1.1-17.8; $P = 0.04$) and in-hospital mortality (OR = 2.9, CI = 1.2-7.3; $P = 0.024$).

Montgomery et al[167] report on a modification to the standard COx method for estimating the integrity of cerebral autoregulation. Instead of calculating the COx, the authors use a method referred to as "co-trending" that can more quickly and easily estimate the integrity of cerebral autoregulation. In the co-trending method, 50 seconds of rSO_2 and MAP data are compared (as opposed to > 300 s as is typically used to calculate COx). In 69 patients undergoing cardiac surgery, the first estimate of cerebral autoregulatory status was obtained in a mean of 63 seconds producing reliable results 99.4% of the time. The estimated lower limit of autoregulation determined via the co-trending method was similar to that obtained via transcranial Doppler sonography by determining the relationship between MAP and the correlation coefficient between MAP and middle cerebral artery blood flow velocity.

Das et al[168] measured rSO_2 and tissue oxygen saturation (StO_2) from the thenar eminence of the hand in 45 patients in a neurological ICU who were subsequently diagnosed with sepsis or septic shock. rSO_2 and StO_2 were measure at prespecified intervals for 48 hours following the diagnosis of sepsis or septic shock. Mean StO_2 was significantly higher among those who survived to hospital

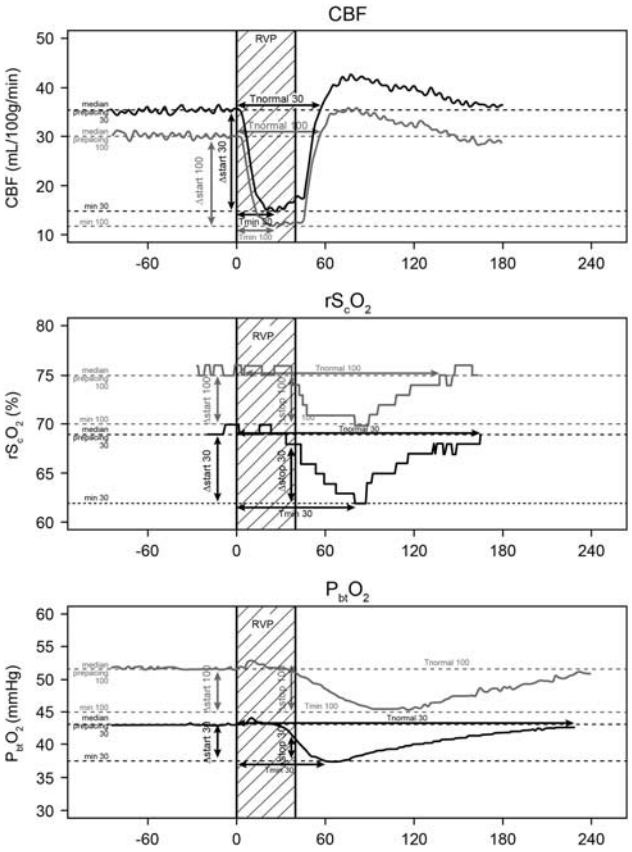


FIGURE 1. Cerebral blood flow and brain oxygenation during rapid ventricular pacing in a single patient. The graphs illustrate cerebral blood flow (CBF), regional cerebral oxygen saturation (rS_cO_2), and brain tissue oxygen partial pressure ($P_{bt}O_2$) with respect to time, measured in seconds, on the x-axis. Time = 0 denotes the start of pacing and the gray hashed region represents the duration of rapid ventricular pacing (RVP). In each graph, the black line and gray line represent data obtained while patients inspired an oxygen fraction of 30% and 100%, respectively. Median prepacing and minimum values of each parameter are illustrated by horizontal hashed lines for each inspired oxygen concentration. T_{min30} and T_{min100} represent the duration of time required to reach minimum values of each parameter from the onset of RVP while patients inspired 30% and 100% oxygen, respectively. $T_{normal30}$ and $T_{normal100}$ represent the duration of time required for each parameter to return to its pre-pacing median value while patients inspired 30% and 100% oxygen, respectively, after RVP is terminated. Δstart30 and Δstart100 represent the absolute value difference at the start of RVP and the minimum reached for each variable while patients inspired 30% and 100% oxygen, respectively. Δstop30 and Δstop100 represent the absolute value difference at the termination of RVP and the minimum reached for each variable while patients inspired 30% and 100% oxygen, respectively. From Saldien et al, with permission.[164]

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discharge (68% ± 6%) compared with those who died during hospitalization (63% ± 7%; $P = 0.03$)., but there was no difference in mean rSO_2 among survivors (65% ± 8%) and nonsurvivors (63% ± 10%; $P = 0.58$). StO_2 also had a stronger correlation with serum lactate concentration than rSO_2. The authors suspect that cerebral autoregulation may partially compensate for hypotension and acidosis associated with sepsis and septic shock thus attenuating changes in rSO_2 but not in StO_2.

Pupillometry

As noted earlier, a pupilometer is a noninvasive monitor that can be used to quantify pupillary size and reactivity. Abnormalities in pupillary reactivity can be used to stratify the severity of neurological disease and may offer some prognostic information.[169] Using the Neuroptics NPI-200 Pupillometry (Neuroptics, Irvine, CA), Riker et al[170] measured pupil size and reactivity in 55 patients following cardiac arrest who received targeted temperature management. All patients with nonreactive pupils (NPI 0) 6 hours following return of circulation died before discharge. Static pupillary size was not significantly associated with odds of poor outcome (defined as a Cerebral Performance Score of 3 to 5 at discharge). However, low NPI, decreased percent pupillary constriction with light exposure, and decreased contraction velocity, measured within 6 hours of return of circulation, were all found to be significantly predictors or poor outcome.

Iatrogenic Horner syndrome can occur following carotid endarterectomy or stenting due to disruption of the sympathetic fibers that travel from the superior stellate ganglion to the eye.[171] Weerakoon et al[172] utilized a Neuroptics NPI-200 Pupillometer (Neuroptics) to characterize pupillary changes following carotid revascularization procedures. This study was conducted in 7 patients who each underwent either carotid endarterectomy or carotid stenting and 14 patients who did not undergo carotid revascularization. There was no difference in static pupil size, dilation velocity, contraction velocity, or NPI, between the side ipsilateral and contralateral to the revascularized vessel in those who had endarterectomy or stenting. There was also no difference in these parameters among those who had right sided endarterectomy, right sided stenting, or who did not undergo revascularization. However, those who underwent stenting of the left carotid artery, but not left endarterectomy, had a significantly slower dilation velocity and slower contraction velocity compared to those who did not undergo a carotid revascularization procedure. The authors did not offer any explanation to account for this finding. However, it is possible that the small study sample did not represent a reliable random sample of patients who develop pupillary abnormalities following carotid revascularization. Further, the duration of time between the end of the procedure and acquisition of pupillometric measurement was not stated, nor was anesthetic technique or drugs that were administered that could impact pupillary function. Thus, these latter parameters may have contributed to the findings of this investigation.

Robba et al[173] compared pupillary parameters measured with 2 different pupilometers: the Neurolight Algiscan (ID-MED, Marseille, France) and the a Neuroptics NPI-200 Pupillometer (Neuroptics) in 112 critically ill patients. Overall, there was very good agreement in measurement of static pupillary diameter, percent pupillary constriction with light exposure, and pupillary constriction velocity with light exposure. Although average pupillary contraction latency was similar, latency measured with the two pupilometers did not have a strong correlation with one another. Clinical assessment of the presence of pupillary reactivity was underestimated compared with rates of patients with reactive pupils measured with both pupilometers.

Electrophysiological Monitoring

Intraoperative awake language mapping is used to guide resection of masses near regions of brain responsible for language. This technique requires an awake patient and thus may not be suitable for all patients such as those with developmental delay, cognitive disorders, or various psychiatric diseases. Martin et al[174] describe the use of electroencephalography (EEG) to demonstrate that language processing can be measured in patients during general anesthesia. The authors recruited 5 volunteers and 11 patients undergoing intracranial tumor surgery. Anesthesia was maintained in those having surgery with total intravenous anesthetic consisting of propofol and sufentanil infusions. The EEG was recorded from subdermal needle electrodes in the volunteers. Cortical strip electrodes were used to record from locations within the craniotomy site in those having surgery; at least 3 electrodes were placed at the anticipated locations of Broca's area and Wernicke's area. Earphones were placed in the patient's or volunteer's ear and the repetitive syllable sound "pa" was produced with intermittent production of the syllable sound "po." EEG signals were recorded during production of the "pa" sound and compared with waveforms obtained while the "po" sound was produced in the earphones. EEG could adequately discriminate between the 2 sounds in the 5 volunteers. In those having intraoperative monitoring, inadequate recording quality prevented analysis of waveforms in 4 of 11 patients due to very deep anesthesia or excessive waveform artifact. Among the remaining 7 patients, waveform analysis was able to discriminate the "po" syllable in 5 patients.

In 12 patients undergoing tumor resection near Broca's area, Aydinlar et al[175] investigated whether cortical stimulation could result in evoked potential signals detected in contralateral cricothyroid muscles. All patients had left sided tumors and underwent preoperative functional MRI to confirm left sided language dominance. The cerebral cortex was electrically stimulated and responses were detected via hook electrodes placed in the cricothyroid muscles. Anesthesia was maintained with propofol and remifentanil infusions without muscle relaxation. Broca's area was successfully identified in 9 of 12 patients; evoked potential signals could be detected in the contralateral cricothyroid muscle with a mean latency and

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amplitude of 50 ± 11 ms and 117 ± 67 μV, respectively. In these 9 patients, the region of brain that resulted in detectable evoked potential was avoided during resection. Of the 12 patients, 4 had decreased speech fluency at 2 days following surgery of whom 3 patients had Broca's area identified with evoked potentials. No patient had speech deficits at 3 months postoperatively. Although both methods currently have limitations, the techniques described by Martin et al[174] and Aydinlar et al[175] suggest some opportunities for speech mapping during general anesthesia. However, both techniques will need to be further refined to increase sensitivity to correctly map cortical regions responsible for language.

ANESTHETIC NEUROTOXICITY AND PERIOPERATIVE DISORDERS OF COGNITIVE FUNCTION

Anesthetic Neurotoxicity in the Developing Brain

Exposure of the developing brain to commonly used anesthetic drugs has been associated with increased apoptosis, alterations in tau protein phosphorylation, and alterations in synapse structure in laboratory and animal models, whereas prospective studies in humans have failed to show a consistent detrimental effect of anesthetics on learning and behavior.[176–178] Using the Avon Longitudinal Study of Parents and Children Birth Cohort, Walkden et al[179] assessed cognitive outcome in children who either did or did not receive a general anesthetic before the age of 4 years. The Avon Longitudinal Study of Parents and Children Birth Cohort followed pregnant women in the Avon area of England that comprised 75% of women pregnant in the region with expected delivery dates between April 1, 1991 and December 31, 1992. After excluding children with birth asphyxia, and neurodegenerative, cardiac, or genetic disorders, of the remaining 13,433 children, 110 had a single exposure and 212 had multiple exposures to general anesthesia prior to the age of 4 years. Neurodevelopmental outcome was assessed at 7 to 16 years of age. Exposed children were more commonly male, the product of a multiple gestation pregnancy, born at an earlier gestational age and had mothers who were older, had more medical comorbidities, underwent induction of labor, and underwent nonroutine fetal screening compared with unexposed children. The investigators did not find evidence of global neurocognitive deficits among children exposed to general anesthesia. However, there were some differences in specific neurodevelopmental metrics among the groups. Although there was no difference among groups in educational outcomes or performance on tests of intelligence, 20.3%, 23.1%, and 28.0% of children among those unexposed, those with a single exposure, and those with multiple exposures had special educational needs provisions during schooling, respectively ($P = 0.001$). Among those singly and multiply exposed to anesthesia, there was a small but statistically significant higher rate of motor impairment (ie, heel-to-toe walking, performance on peg placement tests) and impairment in pragmatic communication skills compared with those who did not receive anesthesia. Those with multiple exposures had increased odds for behavioral difficulties at a mean age of 8.6 years but not at a mean age of 6.8 years or 11.2 years. The above associations were true even following correction for variables that may influence outcome, including type of surgical procedure. These findings support earlier prospective human trials that did not demonstrate significant global cognitive and developmental disorders in children exposed to general anesthesia at an early age.

Early exposure to general anesthesia has been shown to be associated with increased odds for the development of attention deficit/hyperactivity disorder.[180] Using data from children enrolled in Medicaid in Texas and New York from 1999 to 2010, Ing et al[181] identified those who received a single general anesthetic before the age of 5 years for 1 of 4 common procedures performed in the pediatric population. They also identified a cohort of similar children who did not receive general anesthesia before the age of 5 years. Using propensity matched cohorts, use of medications to treat attention deficit/hyperactivity disorder was 37% higher among those who received general anesthesia. Similarly, use of sedative/anxiolytics, antidepressants, antipsychotics, and mood stabilizers were higher among those exposed to anesthesia. For comparison, use of amoxicillin, azithromycin, and diphenhydramine were similar between groups.

Binding of γ-amino butyric acid (GABA) to GABA-A receptors can lead to neuronal depolarization or hyperpolarization depending on the direction of the intracellular-to-extracellular chloride gradient. During development, increased expression of the NKCC1 transporter by GABA-ergic neurons results in high intracellular chloride concentrations and neuronal depolarization upon binding of GABA to the GABA-A receptor. Later, increased expression of the KCC2 transporter and decreased expression of the NKCC1 transporter causes low intraneuronal chloride ion concentration and neuronal hyperpolarization with GABA binding to the GABA-A receptor. Ju et al[182] recently showed that sevoflurane led to behavioral changes and decreased expression of the KCC2 transporter not only in male rats exposed at an early age to sevoflurane but to male offspring of rats exposed to sevoflurane. This effect may be due to hypermethylation of the promotor of the KCC2 gene upon exposure to sevoflurane.[183] Xu et al[184] showed that exposure of male rats on postnatal day 5 to sevoflurane resulted in increased expression of DNA methyltransferases and decreased expression of KCC2 in the hypothalamus along with behavioral changes in adulthood. These effects were attenuated by prior administration of decitabine, a nonspecific DNA methyltransferase inhibitor. Male rats that were either exposed on postnatal day 5 to sevoflurane, sevoflurane with prior decitabine treatment, or neither drug were mated with females not exposed to sevoflurane or decitabine. Paternal sevoflurane exposure resulted in increased expression of DNA methyltransferases and decreased expression of KCC2 in the hypothalamus along with behavioral changes in offspring. These effects were attenuated in offspring by prior administration of decitabine in male parents.

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In rats, the transition of decreased expression of NKCC1 and increased expression of KCC2 occurs at an earlier age in female rats compared with male rats making female rats potentially lose their susceptibility of the neurotoxic effects of GABA-ergic anesthetics at an earlier age.[185,186] Chinn et al[187] showed that male rats exposed to isoflurane on postnatal day 7 exhibited deficits in spatial and recognition memory tasks in adulthood. This effect was attenuated by administration of flutamide, an androgen receptor antagonist, prior to isoflurane exposure. Administration of flutamide alone resulted in an increase in KCC2 expression and a decrease in NKCC1 expression in cerebral cortex. Administration of bumetanide, an NKCC1 inhibitor, also attenuated the spatial and recognition memory deficits. Thus, endogenous sex steroids may play a role in mediating the expression of neuronal chloride transporters and, potentially, susceptibility to anesthetic toxicity.

Cabrera et al[188] provide a narrative review of the literature pertaining to differences in neurotoxicity among males and females. They review multiple reasons why the brain may be differentially affected by anesthetics based on the sex of the organism. These include high expression of aromatase, the enzyme responsible for the synthesis of estradiol from testosterone, in the developing brain, and differential effects of sex steroids on neuroapoptosis. They review differential manifestations of early anesthetic exposure based on sex, specifically noting that female animals generally exhibit problems with special memory and attention-deficit hyperactivity behaviors, whereas male animals exhibit anxiety-like behaviors after anesthesia exposure. Therefore, appropriate tests for anesthetic neurotoxic effects should be chosen based on the sex of animals included in specific investigations.

Gangliosides are glycosphingolipid derivatives that are abundant in the brain and appear to play a role in neurodifferentiation, neuroplasticity, and stimulate the release of growth factors such as brain derived neurotrophic factor (BDNF).[189] Meng et al[190] administered ketamine 20 mg/kg intraperitoneally for 5 doses every 90 minutes, monosialotetrahexosylganglioside (GM1) 30 mg/kg intraperitoneally, or both ketamine and GM1 to rat pups on postnatal day 7. Ketamine was associated with visual spatial learning deficits as rats had increased escape latency and decreased platform crossings on the Morris water maze when tested on postnatal day 36 after daily learning trials. These deficits were attenuated by co-administration of GM1 with ketamine. Ketamine was associated with increases apoptosis in the hippocampus, and co-administration of GM1 with ketamine attenuated this effect. To determine if the effects of GM1 on BDNF expression played a role in mediating the attenuation of ketamine neurotoxicity, cohorts of rats received either ketamine alone, ketamine plus GM1, or ketamine plus both GM1 and antibodies to BDNF on postnatal day 7. Ketamine alone was associated with increased BDNF expression in the hippocampus and this expression was attenuated by co-administration of GM1. Co-administration of anti-BDNF attenuated the effect of GM1 at decreasing visual special learning deficits and apoptosis associated with ketamine exposure. GM1 may, at least in part, attenuate ketamine-associated neuroapoptosis and visual special learning deficits by upregulating expression of BDNF in the brain.

Tesic et al[191] report on the effect of 2 steroid-based anesthetic drugs on apoptosis and GABA-A currents in rats. The 2 drugs used in this study were (3α,5α)-3-hydroxy-13,24-cyclo-18,21-dinorchol-22-en-24-ol (CDNC24) and 5α-pregnan-3α-ol-11,20-dione (alphaxalone). The intraperitoneal effective dose-50 were determined based on loss of righting reflex and were found to be 0.68 ± 0.04, 1.58 ± 0.05, and 2.36 ± 0.13 mg/kg for CDNC24, alphaxalone, and propofol, respectively. Equipotent doses of propofol, CDNC24, or alphaxalone were administered hourly for 6 hours to rat pups on postnatal day 7. Physiological variables did not differ among groups. Propofol was associated with increased apoptosis evident by increased expression of cleaved caspase-3 in the subiculum and regions of medial prefrontal cortex by 1.8- to 4.7-fold compared with unexposed animals. Both CDNC24 and alphaxalone were not associated with increased cleaved caspase-3 expression in these brain regions compared with respective vehicle controls. Using subicular brain slices, the authors demonstrated that, unlike propofol that only has a postsynaptic effect to increase GABA-ergic signaling, both CDNC24 and alphaxalone work presynaptically and postsynaptically at GABA-ergic synapses to induce hypnosis.

Delirium

Delirium is a common disorder occurring in patients in the perioperative period and in hospitalized patients, especially those in the ICU.[192] The American Society for Enhanced Recovery and Perioperative Quality Initiative issued a joint consensus statement that provides evidence based recommendations to potentially reduce the risk for perioperative delirium and delirium associated with critical illness.[193] These recommendations are summarized in Table 2.

Frailty is an age-associated physiologic decline that renders the individual more vulnerable to adverse outcomes. Frailty is associated with perioperative cognitive disorders following cardiovascular surgery.[194] Mahanna-Gabrielli et al[195] prospectively classified a cohort of 167 patients 65 years old and above undergoing non-cardiovascular and nonintracranial elective surgery into 3 categories: robust (n = 64, 38%), prefrail (n = 72, 43%), and frail (n = 31, 19%) based on the FRAIL scale.[196] Delirium was diagnosed with the Confusion Assessment Methods for the ICU (CAM-ICU) performed twice daily starting in the recovery room. Patients also underwent a battery of neuropsychometric tests preoperatively and at 3 months after surgery. Rates of postoperative delirium were 13%, 30%, and 39% among those who were robust, prefrail, and frail, respectively ($P = 0.016$). Compared with robust patients, those who were frail or prefrail had a 2.7-fold (CI = 1.0-7.3) increased odds for developing delirium during their hospitalization. Rates of postoperative cognitive dysfunction, defined as a > 1 SD in Z-scores in

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TABLE 2. Summary of the American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention

Statement	Strength of Evidence	Quality of Evidence
We recommend that hospitals and health systems develop processes to reduce the incidence and consequences of postoperative delirium through an iterative multidisciplinary quality improvement process	Strong	D
We recommend that health care workers identify surgical patients at high risk for postoperative delirium	Strong	C
We recommend that surgical patients identified as high risk for postoperative delirium be informed of their risk	Weak	D
We recommend hospitals and health care systems develop a process to assess for postoperative delirium in older high-risk patients	Strong	C
We recommend the use of multicomponent nonpharmacologic interventions for the prevention of postoperative delirium in older high-risk patients	Strong	B
We recommend minimization of medications known to be associated with an increased risk for postoperative delirium in older high-risk patients	Strong	C
There is insufficient evidence to recommend using processed EEG monitoring in older high-risk surgical patients undergoing general anesthesia to reduce the risk of postoperative delirium	NA	NA
There is insufficient evidence to recommend specific anesthetic agents or doses to reduce the risk of postoperative delirium	NA	NA
There is insufficient evidence to recommend regional or neuraxial blockade as the primary anesthetic technique to reduce the risk of postoperative delirium	NA	NA
We recommend optimization of postoperative pain control to reduce the risk of postoperative delirium	Weak	C
There is insufficient evidence to recommend administration of prophylactic medications to reduce the risk of postoperative delirium	NA	NA
We recommend using intensive care unit protocols that include sedation with dexmedetomidine to reduce the risk of postoperative delirium in patients requiring postoperative mechanical ventilation	Strong	B

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria and consensus were used to quantify the strength of evidence and level of evidence. Level of evidence was stratified into the following categories:

A. High quality: further research is not likely to change this recommendation.

B. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

C. Low quality: further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

D. Very low quality: any estimate of effect is uncertain.

EEG indicates electroencephalography; NA, not applicable.

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neurocognitive tests at 3 months after surgery, were 11%, 13%, and 21% in robust, prefrail, and frail, respectively and were not significantly different among groups ($P = 0.42$). This finding is in contrast to that of Evered et al[197] who found that frailty was associated with increased odds of postoperative cognitive dysfunction at 3 and 12 months following total hip arthroplasty in a cohort of patients 60-year old and above. Similar to the findings of Mahanna-Gabrielli et al,[195] Sanchez et al[198] found that frailty was associated with increased risk for delirium in patients admitted to an ICU.

Susano et al[199] prospectively assessed whether preoperative frailty or cognitive screening can predict risk for postoperative delirium in patients above 70 years old having spine surgery. Pre-operatively, 219 patients underwent screening for frailty with the use of the FRAIL scale[196] and screening for cognitive dysfunction with both the Mini-Cog and Animal Verbal Fluency tests. Of this cohort, 54% and 24% were categorized as prefrail and frail, respectively. Twenty-three percent and 37% were identified as having preoperative cognitive impairment based on performance on the Mini-Cog and Animal Verbal Fluency tests, respectively. Overall, 24% of patients developed delirium postoperatively assessed by the CAM-ICU test. Factors found to be independently associated with increased risk for postoperative delirium were preoperative frailty (but not prefrailty), increased body mass index, impaired performance on the Animal Verbal Fluency test (but not the Mini-Cog test), and increased complexity and invasiveness of the surgical procedure.

Kim et al[200] developed a risk scoring system that could be used to predict increased risk for postoperative delirium in patients undergoing treatment for hip fracture. The investigators used data from 8871 patients contained in the American College of Surgeons National Surgical Quality Improvement Project Hip Fracture Procedure Targeted Participant Use Data File. This group was divided into a derivation cohort (n = 6210) and a validation cohort (n = 2661) to derive and validate the model. In the derivation cohort, 1816 (29%) patients developed delirium during their hospitalization and 9 factors were identified to be independently associated with increased risk for delirium. The authors used the β-coefficients from the analysis to develop a scoring system, based on these 9 factors, to predict risk for delirium. The points assigned per factor are illustrated in Table 3, allowing for a minimum score of 0 (associated with 4.5% odds for developing delirium) to a maximum score of 20 (associated with 92% odds for developing delirium). The area under the curve for the model to predict delirium was similar between the derivation and validation cohorts. Further study will be required to determine how each strata of scores will predict odds for delirium as the investigators only reported the odds of delirium in those with the lowest and highest scores.

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TABLE 3. Score System for Predicting Risk of Delirium Following Hip Fracture Surgery

Variable	Points Assigned
Preoperative delirium	8
Preoperative dementia	3
Age (y)	
60-69	0
70-79	2
≥80	3
Medical comanagement	1
ASA Physical Status Class III-V	1
Functional dependence	1
Smoking	1
SIRS, sepsis, or septic shock	1
Preoperative use of mobility aid	1

Risk of delirium is estimated by adding points for each factor present. Risk of delirium increases with increasing total number of points present.

ASA indicates American Society of Anesthesiologists; SIRS, systemic inflammatory response syndrome.

From Kim et al[200] with permission.

Neurosurgical patients may have additional risk factors for delirium.[24,201] Wang et al[202] prospectively identified 800 adult patients who underwent intracranial surgery and were admitted to the ICU following surgery. The CAM-ICU was administered daily on postoperative days 1, 2, and 3. Delirium was stratified into hyperactive if simultaneous Richmond Agitation and Sedation Scale score (RASS) was +1 to +4, hypoactive if simultaneous RASS was −3 to 0, or mixed if patients had episodes of both hyperactive and hypoactive delirium. In this cohort, 157 (20%) developed delirium during the first 3 days following surgery with 97 (62%), 33 (21%), and 27 (17%) having hypoactive, hyperactive, and mixed delirium, respectively. Factors found to be independently associated with increased odds of developing delirium were: increased age, surgery for malignant lesions or vascular disorders, frontal craniotomy, increased duration of surgery, episodes of SaO_2 <90% in the ICU, presence of emergence delirium, increased postoperative pain, and need for immobilization while in the ICU. Immobilization was due to presence of an endotracheal tube, central venous catheter, CSF drainage catheter, or need for physical or pharmacological restraints. Unfortunately, the sample size was not large enough to determine if risk factors for delirium in this cohort differed by the type of delirium exhibited (ie, hypoactive, hyperactive, mixed). Also, at the authors' institution, ICU admission following intracranial surgery depends on patient comorbidities, case complexity, and intraoperative factors, thus the cohort of patients included in this study may not represent all patients having intracranial surgery.

Durotomy during spine surgery can result in CSF hypotension and increased risk for infection. Following surgery, patients with durotomy are often managed with bedrest. If CSF pressure is low, patients may suffer from photophobia and headache. Immobilization, photophobia, and pain from headache may predispose to increased risk for delirium in those with durotomy. Kazarian et al[203] retrospectively identified 766 patients 65 years and above who underwent spine surgery at hospitals within a single network of whom 182 (24%) had durotomy during their surgery. Of the 766 patients, 142 (19%) had a diagnosis of delirium made during their hospitalization. Rates of delirium in those with and without durotomy were 26% and 16%, respectively ($P = 0.002$). Based on a propensity matched cohort of 325 patients, durotomy increased the odds of delirium by 1.9 (CI = 1.1-3.4; $P = 0.03$).

Elsamadicy et al[204] retrospectively identified 130 adult patients at a single institution who underwent spinal fusion to determine if intraoperative blood transfusion was associated with increased odds for developing delirium. Patients were stratified into those who received only allogenic blood (n = 15), only autologous blood (n = 23), both allogenic and autologous blood (n = 66), or no blood transfusion (n = 26). Average estimated blood loss was 1071 ± 578, 1397 ± 790, 2155 ± 1901, and 507 ± 427 mL for those who received allogenic, autologous, both allogenic and autologous, or no blood transfusion, respectively. The *P*-value reported for this analysis of variance was <0.0001 but the investigators did not state which point estimates accounted for this low *P*-value by performing post hoc *T* tests. Rates of in-hospital delirium were 47%, 17%, 8%, and 12% for those who received allogenic, autologous, both allogenic and autologous, or no blood transfusion, respectively ($P = 0.002$). However, when I performed post hoc χ^2 and Fisher exact tests with Bonferrroni correction, the only comparison that is significantly different are the rates of delirium between those who received allogenic only and both allogenic and autologous transfusions. Since patients in both of these groups received allogenic blood, it would be difficult to attribute the higher rate of delirium in the group that received only allogenic blood to transfusion of allogenic blood. Unfortunately, there are other perioperative variables, such as anesthetic drugs, blood pressure, preoperative cognitive status, that were not reported. Also, the authors did not specifically define how delirium was diagnosed. Thus, further studies would be required to determine if type of blood transfusion modulates risk for perioperative delirium.

When compared with other sedative drugs, dexmedetomidine is associated with a reduced risk for delirium likely due to α2-adrenergic receptor-mediated anti-inflammatory pathways.[205–207] Delirium has been reported to occur in approximately one-third of patients after ECT.[208,209] Qui et al[210] prospectively randomized 223 adult patients undergoing ECT to receive either dexmedetomidine (0.5 μg/kg iv) or an equivalent dose of saline after induction of anesthesia but before administration of ECT. Patients otherwise received standardized intra procedural and postprocedural management. The CAM-ICU was administered 10 minutes after emergence from anesthesia to assess for postprocedural delirium. Delirium occurred in 44% and 68% in those who did and did not receive dexmedetomidine, respectively ($P < 0.001$). There was no difference in seizure duration, recovery time, bradycardia, hypotension, or respiratory events between groups. Further research would be needed to determine if dexmedetomidine has any effect on the efficacy of ECT for the treatment of psychiatric disorders.

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Turan et al[211] randomized 798 patients undergoing cardiac surgery to receive either placebo or dexmedetomidine (0.1 to 0.2 μg/kg/h intraoperatively and increased and maintained at 0.4 μg/kg/h for the first 24 h after surgery). Delirium was diagnosed with the CAM-ICU that was assessed each morning for the first 5 days after surgery. Rates of delirium were similar in those who received dexmedetomidine and those who received placebo (17% and 12%, respectively; $P > 0.05$). The authors also evaluated rates of postoperative atrial fibrillation during hospitalization and found no difference between groups (30% vs. 34% in those who received dexmedetomidine and placebo, respectively; $P > 0.05$). The authors attributed the lack of an effect of dexmedetomidine on delirium risk to the hemodynamic changes associated with cardiac surgery and cardiopulmonary bypass and greater pain associated with cardiac surgery compared with other types of surgical procedures where dexmedetomidine has been found to decrease risk for delirium.

Lee-Archer et al[212] randomly assigned children aged 2 to 7 years undergoing same-day procedures to receive either intranasal dexmedetomidine (2 mg/kg before induction of anesthesia, n = 78), intravenous dexmedetomidine (1 mg/kg following induction of anesthesia, n = 78) or no dexmedetomidine (n = 78). All patients received a nasal spray and an injected liquid to allow for a double-blind study. The primary outcome was the incidence of negative behavior 3 days following their procedure assessed by the Post-Hospitalization Behavior Questionnaire for Ambulatory Surgery and the Strength and Difficulties Questionnaire. Rates of negative behaviors on postprocedure day 3 were similar among groups. Pain scores during recovery were significantly lower in both groups that received dexmedetomidine. However, duration of recovery room stay and duration in the hospital were both significantly longer in the groups that received dexmedetomidine.

Intraprocedural and postprocedural hypotension may increase risk for postprocedural delirium.[213] Xu et al[214] prospectively randomized 150 patients age 65 to 80 years old having total hip arthroplasty to have MAP maintained either 10% to 20% below (group L), 0 to 10% below (group M), or 0 to 10% above (group H) preoperative MAP. Patients with preexisting cognitive impairment, psychiatric disease, or other significant comorbidities were not included. Patients received a standardized general anesthetic without regional anesthesia and a standardized postprocedural analgesic management plan. The presence of delirium was assessed via the CAM-ICU. There were no differences among groups in demographics, comorbidities, types of surgical procedures performed, and surgical duration. Rates of emergence delirium were lower in group H (6%) compared with groups L and M (24% and 22%, respectively; $P < 0.025$ for both comparisons). On postoperative day 1, rates of delirium were 22%, 16%, and 4% in those in groups L, M, and H, respectively, with only statistically significant difference existing between groups L and H ($P = 0.014$). Rates of delirium were similar among groups on postoperative days 2 and 3. There was no difference among groups in postoperative pain score or rates of postoperative nausea and vomiting.

Angiotensin converting enzyme inhibitors and angiotensin receptor antagonists may attenuate cognitive decline.[215,216] Farag et al[217] retrospectively identified 4864 patients without preexisting cognitive dysfunction who underwent non-neurosurgical procedures and had at least one documented delirium assessment with the CAM-ICU postoperatively. Patients were stratified into those who did or did not take either angiotensin converting enzyme inhibitors or angiotensin receptor antagonists preoperatively. Rates of delirium were 39% in both groups ($P = 0.65$). Even when using propensity-matched cohorts of patients, preoperative use of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists were not significantly associated with postoperative risk for delirium. However, when evaluating rates of delirium stratified by use of angiotensin converting enzyme inhibitors and angiotensin receptor antagonists in the ICU, delirium occurred in 100 of 440 (23%) and 1795 of 4424 (41%) of patients who did and did not receive drugs from these classes in the ICU, respectively ($P < 0.001$). In propensity-matched cohorts, administration of angiotensin converting enzyme inhibitors or angiotensin receptor antagonists in the ICU was associated with a 0.55 (CI = 0.43-0.72; $P < 0.001$) decreased odds of developing delirium.

Pupillometry is a quantitative means to measure pupillary properties and function as impairment of pupillary function may be a marker for CNS dysfunction.[218] Favre et al[219] prospectively studied 100 patients without primary brain injury admitted to an ICU. Pupillometric measurement of the pupillary light reflex, quantifying maximum contraction and contraction rate, were performed twice per day on ICU days 3 to 5 with an Algiscan Pupillometer (ID-Med, Marseille, France). Normal maximal contraction and rate of contraction during exposure to light by the pupilometer were 30% to 40% and 1.5 to 2.2 mm/s, respectively. Delirium was assessed with the CAM-ICU twice daily during the ICU stay. Overall, 59% of patients were diagnosed with delirium with a median onset on ICU day 8 (IQR = 5 to 13 d). Mean maximum pupillary contraction and mean contraction rate were both significantly lower on ICU days 3, 4, and 5 in those who subsequently developed delirium, even when corrected for Sequential Organ Failure Assessment Score, total midazolam administered, and total fentanyl administered. Further study will be required to determine if a specific cut-off value of maximum pupillary contraction and contraction rate can optimally predict subsequent development of delirium in ICU patients.

In patients with delirium, a decrease in high frequency power and an increase in low frequency EEG power have been described.[220] Some have proposed that a decrease in frontal alpha band power may be a phenotype for the "vulnerable brain."[221] Using data from 70 patients enrolled in 2 ongoing prospective cohort studies, Tanabe et al[222] characterized EEG changes in those with and without postoperative delirium. Delirium was diagnosed in 22 (31%) patients via the CAM-ICU at the time of postoperative EEG assessment a median of 1 day following surgery. and delirium severity was quantified using the

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Delirium Rating of Severity-98.[223] Although decreases in alpha and beta power and increases in theta and delta power were noted in frontal regions in those with and without delirium, a common finding among patients with delirium was to note these same EEG characteristics in parietal and occipital regions of the brain. The degree of increase in power in the frequency range of <6 Hz in parietal and occipital regions of the brain was correlated with increased delirium severity. Based on EEG findings, delirium was also associated with impairment of functional connectivity between frontal and posterior regions of cerebral cortex. Thus, quantification of EEG changes in frontal regional of the brain may be inadequate to detect EEG changes that may be associated with delirium.

Increased duration of intraoperative EEG suppression may be associated with increased odds for postoperative delirium. EEG suppression may be minimized with closed-loop anesthesia delivery systems.[224,225] Completing a prespecified secondary analysis of data from patients enrolled in the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) Trial,[226] Fritz et al[227] assessed if an EEG-guided general anesthetic decreased risk of postoperative delirium. The ENGAGES Trial included patients 60 years old and above having surgery with general anesthesia where patients were randomized to either have or not have anesthesia guided by EEG. Specifically, in the EEG-guided group, anesthesiologists were told to use EEG to adjust anesthetic depth to minimize time in burst suppression. Of 1113 patients, 430 (39%) had preoperative cognitive abnormalities. The presence of postoperative delirium was assessed daily for 5 days following surgery with the CAM-ICU. Rates of postoperative delirium were 26% and 23% in those managed with and without EEG guidance, respectively ($P = 0.17$), despite the median duration of burst suppression being shorter in the EEG-guided group (8 min, IQR = 1 to 22 min vs. 12 min, IQR = 1 to 57 min in those without EEG guidance; $P < 0.001$). However, those with preoperative cognitive abnormalities had a higher rate of delirium compared with those without preoperative cognitive abnormalities (35% vs. 18%, respectively; $P < 0.001$). Therefore, preoperative cognitive deficits are a much stronger predictor for postoperative delirium than degree of EEG burst suppression. These findings are supported by the Anesthetic Depth and Post-operative Delirium-2 Trial[228] and a recent meta-analysis[229] that also did not find an association between the use of an EEG-guided anesthetic and a decreased risk for developing postoperative delirium.

Hayhurst et al[230] performed a post hoc analysis of prospectively collected data from a multicenter cohort of 582 survivors of respiratory failure or shock requiring ICU care. Sixty-six percent of patients were in the medical ICU. During their ICU stay, delirium was diagnosed with the CAM-ICU administered twice daily and the nature of delirium was classified as either hyperactive (in those with a RASS > 0) or hypoactive (in those with a RASS of ≤ 0). Patients underwent a neurocognitive battery at 3 and 12 months following discharge from the ICU. Overall, 411 (71%) had hypoactive delirium, 100 (17%) had hyperactive delirium, and 49 (8%) had mixed hypoactive and hyperactive delirium. The median duration of hypoactive delirium was longer (3 d, IQR = 1 to 7 d) than the median duration of hyperactive delirium (1d, IQR = 1 to 2 d). Longer duration hypoactive delirium was associated with worse global cognition at 3 months but not 12 months, and impairment of executive functions at both 3 and 12 months. Hyperactive delirium was not associated with the presence of global cognitive impairment or executive functional impairment at either 3 or 12 months. This finding supports data by Brown et al[231] and a meta-analysis by Goldberg et al[232] that found delirium, either in the perioperative period or while in the ICU, was a significant predictor of subsequent cognitive decline.

Postoperative Cognitive Dysfunction

Older individuals are at risk for short and long-term disorders of cognitive function following surgery and anesthesia.[233–235] Some hypothesize that surgery and anesthesia may increase deposition of β-amyloid protein in the brain, similar to what is found in individuals with Alzheimer dementia.[236] Recently, β-amyloid deposition can be measured *in vivo* via positron emission tomography using a carbon-11 derivative of thioflavin T that preferentially binds to β-amyloid where carbon-11 decays to boron-11 emitting a positron in the process that can be detected.[237] Using patients 70 to 97 years old included in the Mayo Clinic Study of Aging,[238] Sprung et al[239] identified 585 participants who had appropriate positron emission tomography scans and stratified subjects into those with did and did not have an anesthetic exposure. Participants in this cohort also had MRI scans to assess cortical thickness and positron emission tomography scans with 18-fluorodeoxyglucose to estimate regional cerebral metabolic rate for glucose. Anesthetic exposure was defined by one of 2 criteria: (1) at least 1 general anesthetic after the age of 40 years old, or (2) at least 1 general anesthetic within 20 years of positron emission tomography scan. Although those who had at least 1 general anesthetic exposure, by either criteria, were found to have cerebral cortical thinning, neither the distribution of glucose metabolism nor the amount and distribution of β-amyloid deposition differed between those with or without prior exposure to general anesthesia. Walker et al[240] also found no difference in β-amyloid deposition, measured with florbetapir positron emission tomography in patients who either did nor did not have a hospitalization to facilitate a surgical procedure within 24 years of imaging, even if only considering patients who underwent higher-risk surgical procedures. Florbetapir is a compound that, similar to thioflavin T, binds to β-amyloid but is radiolabeled with fluorine-18 that undergoes decay to oxygen-18, emitting a positron in the process.

Preexisting cognitive dysfunction is common in older individuals and is a significant risk factor for the development of postoperative worsening of cognitive abilities.[241,242] Preoperative cognitive training may be an opportunity for a form of cognitive "prehabilitation" before surgery and anesthesia but may be difficult to implement.[243,244] O'Gara et al[245] randomized 40 patients 60 to 90 years old undergoing

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cardiovascular surgery to either complete regular preoperative and postoperative cognitive training, the latter both during and following their postoperative hospitalization, or to not undergo cognitive training. Cognitive training was encouraged to be done at least twice per day for at least 15 minutes each starting at least 10 days before surgery and continuing for 4 weeks following surgery via the mobile device application Lumosity (Lumos Labs Inc.). Compliance rates were 39%, 6%, and 19% preoperatively, postoperatively during hospitalization, and following discharge, respectively. Those who were and were not randomized to complete cognitive training underwent daily in-hospital screening for delirium with the CAM-ICU and assessment for postoperative cognitive dysfunction at 1, 3, and 6 months following surgery with the Montreal Cognitive Assessment. Rates of delirium (25% vs. 15% in the cognitive training and control groups, respectively; $P = 0.69$) and any postoperative cognitive dysfunction (53% vs. 37% in the cognitive training and control groups, respectively; $P = 0.33$) were not different. Despite this, more patients randomized to complete training felt that there was an improvement in their memory and thinking ability than those randomized to the control group.

Nitrous oxide leads to the inhibition of methionine synthase that causes an increase in serum homocysteine concentration that may contribute to memory impairment in aged rats.[246,247] Using the Mayo Clinic Study of Aging,[238] Sprung et al[248] compared global and domain-specific cognitive function among 1819 adults without dementia stratified into 3 groups: (1) general anesthesia exposure but without nitrous oxide (n = 280), (2) general anesthesia exposure with nitrous oxide (n = 256), and (3) no exposure to general anesthesia (n = 1283). Patients were 70 to 91 years old at enrollment in the Mayo Clinic Study of Aging and had at least 2 formal cognitive assessments since enrollment. General anesthesia exposure was defined to occur within 20 years before enrollment through the time of final cognitive assessment. Those who had general anesthesia, either with or without nitrous oxide, had significant cognitive decline in global cognitive function, attributed to declines in memory and attention/executive functions as measured by the slope of Z scores over time. However, there was no difference in the rate of cognitive decline between those who had general anesthesia that included nitrous oxide and those who had general anesthesia without nitrous oxide, suggesting that nitrous oxide does not exacerbate long-term cognitive decline in older patients.

The combination of surgery and anesthesia is associated with an increase in inflammatory biomarkers in serum.[249] Deiner et al[250] measured 6 serum biomarkers in 59 healthy patients ages 40 to 80 years old before and following general anesthesia to facilitate MRI in an effort to study only the effect of anesthesia. All patients received general anesthesia maintained only with sevoflurane, titrated to a BIS of 40 to 60, before the start of imaging. Blood was sampled before induction of anesthesia and 2 hours following emergence from anesthesia. Biomarkers assessed were interleukin-6, tumor necrosis factor-α, neurofilament light protein, glial fibrillary acidic protein, tau protein, and C-reactive protein. Preprocedurally, only neurofilament light protein and glial fibrillary acidic protein increased with increasing patient age; the remainder did not differ with age. With anesthesia exposure, interleukin-6 increased and neurofilament light protein, glial fibrillary acidic protein, and tau protein decreased, with no significant change in the remainder. One should be aware that cerebral injury, microglial activation, and other local inflammatory processes in the brain may not result in an increase in serum inflammatory biomarkers.[251–253]

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