Practice Trends and Research Priorities of Neurosurgical Anesthesia
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ABSTRACT

Aim of review: One of the goals of neurosurgical anesthesia is to facilitate the execution of neurosurgical procedures including intraoperative neurological monitoring. However, it should also and always aim at benefiting the patients by improving the patient’s long-term and disease-specific outcomes.

Method: In this review, we highlighted some perspectives of today’s practice trends and research priorities of neurosurgical anesthesia for the purpose of exploring the best care based on evidence, and speculation where relevant evidence is lacking.

Recent findings: The advancement in general anesthesia and better understanding of neurological diseases have promoted the evolution of the sub-specialty of neurosurgical anesthesia. Facilitating modern neurosurgical procedures including intraoperative neurological monitoring is a priority of neurosurgical anesthesia. However, a focus on the patient outcomes can never be over-emphasized. The effect of any component of anesthesia care, such as drugs choice and dose, ventilation management, and intravascular volume and cardiac output care, on patient’s outcome should be appraised by quality research.

Summary: It is important to recognize that different patient populations have different and disease/surgery-specific outcomes that should also be taken into account during the customization of anesthesia techniques.

Neurosurgical anesthesia is defined as anesthesia care provided during neurosurgical procedures or in patients with neurological diseases but undergoing non-neurological surgeries. Neurosurgical anesthesia has evolved into a subspecialty that is geared to facilitate various neurosurgical procedures, including intraoperative neurological monitoring, while riding on the tide of the advancement of general anesthesia (GA) and better understanding of various neurological diseases. However, the evolution of neurosurgical anesthesia should not lose sight of improving overall patient outcomes. With this perspective in mind, we highlight some of the current practice trends and research priorities for neurosurgical anesthesia.

Drugs to Maintain Anesthesia: Which and Why

Today’s neurosurgery is featured by the gradually increasing application of intraoperative neurological monitoring (1). This includes, but not limited to, electroencephalogram (EEG), transcranial somatosensory evoked potential (SSEP) and motor evoked potential (MEP), cortical and subcortical language and sensorimotor stimulation mapping. Different anesthetic drugs exert different effects on these monitoring modalities (2-7). The choice of anesthetic drugs used during surgery needs to take into account the type of neurological monitoring.
with the goal of facilitating its execution. Muscle relaxant is normally only used during induction to facilitate endotracheal intubation and patient positioning, and rarely used afterward in order to preserve the motor response, if it is a component of monitoring. Anesthesia is rarely maintained using a single agent because both inhalational agents (2-4) and propofol (6, 7) when used alone and in large dose have been shown to suppress MEP. A popular regimen of anesthetic maintenance is a mixture of hypnotics (for example, propofol) and narcotics (for example, remifentanil or fentanyl) infusions, with or without <0.5 minimum alveolar concentration (MAC) volatile agent or nitrous oxide.

However, there is no consensus on which regimen benefits an individual patient or a patient population the best or which is most ideal for a specific neurological monitor. The anesthesiologists are often requested by the neurological monitoring team to lighten or reduce the depth of anesthesia by turning off the inhalational agent completely and/or decrease the propofol infusion rate. However, whether a good signal via the customization of anesthesia, especially the reduction of anesthesia depth, is beneficial to patient's long-term outcome is unknown. The concerns with lightening anesthesia while providing no pharmacological paralysis are intraoperative recall and movement. Whether an anesthesia depth monitoring can help with the recall prevention in this circumstance remains controversial (8-10). In regard to movement, fortunately, if the procedure is craniotomy, the brain parenchyma itself has no pain sensation, thus reducing the chance of pain-related movement (11), and the painful or sensitive phases of craniotomy including scalp incision and dura opening can be effectively managed with local anesthetics infiltration (12, 13).

However, the strategy used for craniotomy may not be suitable for major spine surgeries, especially in patients who have chronic pain conditions. In this patient population, some anesthesiologists prefer to use fentanyl instead of remifentanil infusion due to the concern for remifentanil-induced hyperalgesia. However, clinical evidence for this is lacking in craniotomy patients (14). Some anesthesiologists believe that the seemingly large dose requirement of longer acting narcotics after remifentanil anesthesia is simply due to the fact that the drug is quickly metabolized. In most tertiary hospitals in the United States, the anesthetic regimen for major spine surgery often includes ketamine and lidocaine infusions, in addition to propofol and narcotic infusions, for the purpose of maintaining adequate anesthesia while facilitating neurological monitoring primarily by decreasing the infusion rate of propofol and/or refraining from using inhalational anesthetic agents (15-17). Clinically, it appears that intraoperative ketamine and lidocaine infusion facilitates pain management after surgery. Excellent pain control in a patient with a chronic pain condition and undergoing a painful procedure without pharmacological paralysis is crucial in preventing patient movement. However, the anesthesia care accommodating these strategies during major spinal surgeries is more experience-based than evidence-based. Again, whether the practice that enables better intraoperative monitoring also benefits the patients by improving long-term outcomes needs to be validated or refuted by randomized controlled trials (RCTs).

Continuous remifentanil infusion is popularly used by neuroanesthesiologists. In addition to its analgesic property, its quick titratability makes early neurological examination possible (14). Importantly, it does not adversely affect neurological monitoring in the clinical doses used (18, 19). Clinically, it appears to possess sympatholytic property because it typically decreases heart rate and reduces the fluctuation of blood pressure. It also makes the emergence process smoother as evidenced by calmness, better ability to follow command and less chance of shivering and nausea. The concern with using remifentanil is postoperative hyperalgesia, especially in patients with chronic pain conditions and undergoing major spine surgeries (20, 21). However, whether this is a phenomenon of true hyperalgesia or merely means that longer-acting narcotic replacement is needed after remifentanil infusion stops needs to be defined by more rigorous research. The fundamental question to ask is if remifentanil is beneficial to the overall long-term outcome, not just the benefits observed during the perioperative period.

The better outcome associated with awake craniotomy for the resection of brain tumors
that encroach on or in close proximity to the eloquent brain including language and sensorimotor pathways compared with surgery under GA has been recently discussed (13). The anesthesia care during awake craniotomy is different to surgery under general endotracheal anesthesia. Whether the drug choice and dose have something to do with the beneficial outcome after awake brain tumor resection has been discussed (22). However, due to the heterogeneity of the anesthesia care for awake brain tumor resection and the lack of RCTs, the best anesthetic regimen for this type of surgery remains unknown and the contribution of the anesthesia care to the better overall outcome remains speculative.

In summary, the application of intraoperative neurological monitoring, the patient's baseline condition and the nature of surgery mandate thoughtful customization of the anesthetic regimen to not only facilitate the surgery and the monitoring, but also benefit the patient in the best way possible. However, most regimens defined by the drug choice/dose are experience-based, especially considering that these regimens are often influenced by institutional and individual preference. Importantly, outcome research is needed to better guide anesthesia practice, because the care that is beneficial in the perioperative period may not necessarily lead to long-term and fundamental benefits to the patients care.

Lung Protective Ventilation: Is the Beneficial Outcome Duplicable during Neurosurgery?

Mechanical ventilation is not benign. It has inherent lung-damaging potential (23). Previous studies show that small tidal volume ventilation, the so-called lung protective ventilation, not only benefits the patients with acute respiratory distress syndrome (24, 25) but also the patients with healthy lungs undergoing abdominal surgery (26). Patients undergoing craniotomy may require transient hyperventilation to facilitate intracranial pressure control or brain relaxation. Therefore, it is a valid question to ask what the ideal ventilation strategy in neurosurgical patients is and if the beneficial outcome associated with lung protective ventilation is duplicable during neurosurgical procedures. So far, there is only one registered and ongoing RCT tackling this [NCT02386683].

Optimizing Intravascular Volume and Monitoring Cardiac Output: Is It Necessary?

Previous studies show the beneficial outcome associated with goal-directed fluid therapy during abdominal surgery (27). It is likely that the optimized intravascular volume and cardiac output lead to better tissue perfusion, and thus reduce tissue hypoperfusion-related adverse consequences (28). During craniotomy, mannitol is frequently used to facilitate brain relaxation primarily via the reduction of brain tissue water (29, 30). However, mannitol is also an osmotic diuretic, its use leads to a large urine output and intravascular volume depletion as a consequence (31). Whether the depleted volume should be replaced is debated. Hypovolemia-related low cardiac output can lead to decreased tissue perfusion including in the brain (32-36). The counter argument is that the repleted volume may translocate from the intravascular space to the brain tissue and would negate the primary reason for administering mannitol. The choice of intravenous fluid may be important, in this regard. 0.9% normal saline is probably a better option than lactated Ringer's solution or plasmalyte because it has higher sodium concentration (154 mEq/l) and osmolality (308 mOsmol/l). Future studies should investigate if mannitol administration leads to decreased organ perfusion, if it does, to what extent, and if the volume repletion adversely restores the brain water.

A related issue is if cardiac output should be monitored during neurosurgery. This can be done nowadays by taking advantage of the rapidly developing non-invasive or minimally invasive cardiac output monitoring technologies (37, 38). It can be argued that, in the face of mannitol-induced intravascular volume depletion, cardiac output monitoring can better guide clinical care than blood pressure alone. It can also be argued that cerebral blood flow is a portion of cardiac output (39), and an optimized cardiac output can facilitate the optimization of cerebral blood flow. Nonetheless, whether cardiac output monitoring in neurosurgical patients, especially those who receive mannitol administra-
Outcome-Oriented Care: Defining the Role of Neuroanesthesiologists

Every medical or surgical intervention should aim at improving outcomes that are fundamental patient interests. The question is how to define these fundamental outcomes that patients care is most about. Some outcomes are common across different diagnoses and surgeries while some are disease-specific. In the field of neurosurgery, for example, the disease-specific outcomes for brain tumor patients are the extent of tumor resection, chance of malignant transformation, recurrence and metastases, and finally survival; while for aneurysm clipping, the chance of vasospasm, perioperative rupture, neurological deficit and survival are becoming more relevant. As neuroanesthesiologists, we should recognize the disease-specific nature of outcomes and provide the anesthesia care that is most beneficial to these outcomes.

This brings up another important issue, which is that outcome is normally determined by multiple factors including the patient's baseline condition, diagnosis, nature of surgery and anesthesia care, to name a few important ones. It is challenging to differentiate the contribution of anesthesia care to the outcomes because the outcome is usually multifactorial and is usually detected sometime after surgery. Nonetheless, efforts should be devoted to the understanding of how differences in anesthesia care affect the outcome for the purpose of quality improvement. This task requires large-scale clinical studies.

The most frequently seen neurosurgical procedure is probably the craniotomy for brain tumor resection. Glioma has the highest incidence and prevalence among all brain tumors (40, 41). The current consensus is that the greater the resection of any grade glioma, the better the oncological outcome and the longer the survival (42). Awake glioma resection is regarded as the standard of care for those lesions that reside in close proximity to the eloquent brain (13, 43, 44). Accumulating evidence shows the better outcomes, including extent of resection, late neurological deficits and survival, associated with awake brain tumor resection compared with surgery under GA (45-47). While the surgeon's ability to perform cortical and subcortical stimulation mapping for the purpose of maximizing tumor resection while preserving language and sensorimotor function in an awake patient is crucial, the anesthesiologist's role is also speculated to be substantial (22). Meng et al. (22) discussed the potential contribution of avoiding general endotracheal anesthesia to the better outcome associated with awake brain tumor resection. The three aspects that were discussed include the reduced physiological disturbance by avoiding GA, the decreased chance of mechanical ventilation-related lung injury, and the less adverse effect on anti-tumor immunity and tumor progression by avoiding GA. However, due to the heterogeneity of the anesthesia care and the lack of RCTs, these advantages associated with awake brain tumor resection remain speculative. Future research needs to define the role the neuroanesthesiologists play in the outcome in this patient population. Currently, there are two registered clinical trials tackling this query [NCT02228993, NCT02193568].

Recently, 4 RCTs, published in the New England Journal of Medicine (N Engl J Med), all found superior outcomes, including rate of successful treatment, mortality and long-term quality of life, associated with mechanical recanalization therapy of acute large vessel ischemic stroke compared with intravenous thrombolysis (48-51). For neuroanesthesiologists, the debate is on how to choose the anesthetic technique, GA versus monitored anesthesia care (MAC). Retrospective data consistently show the better outcome associated with MAC in acute ischemic stroke patients undergoing mechanical recanalization (52, 53). Therefore, it appears that MAC should be the preferred technique in this patient population. However, patients with acute ischemic stroke have complex clinical conditions, such as compromised airway, desaturation, uncooperativeness and/or movement, which may threaten the patient's safety and adversely affect the procedure if choosing MAC instead of GA. Therefore, this is an important outcome issue as well as a decision making dilemma that the anesthesiologist has to handle. Therefore, expert consensus on how to choose the anesthetic tech-
The advancement in GA and better understanding of neurological diseases have promoted the evolution of the sub-specialty of neurological anesthesia. Facilitating modern neurological procedures including intraoperative neurological monitoring is a priority of neurological anesthesia. However, a focus on the patient outcomes can never be over-emphasized. The effect of any component of anesthesia care, such as drugs choice and dose, ventilation management, and intravascular volume and cardiac output care, on patient's outcome should be appraised by quality research. It is important to recognize that different patient populations have different and disease/surgery- specific outcomes that should also be taken into account during the customization of anesthesia techniques.

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