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REVIEW ARTICLE/BRIEF REVIEW

Outcomes in neuroanesthesia: What matters most?

Critères d'évaluation en neuroanesthésie: qu'est-ce qui est le plus important?

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Abstract

Purpose *The goal of this narrative review is to consider and categorize the clinically relevant outcomes that have been previously investigated in neuroanesthesia and to propose the essential outcomes and directions that deserve priority in clinical care and future outcome-oriented research.*

Principal findings *The current body of neuroanesthesia research has created an important and comprehensive fundamental knowledge base by defining the effect of anesthetic care on various outcomes. The translation of animal data to patients has been limited, however, and must be done cautiously. The literature to date has focused on short-term perioperative outcomes but should now shift towards understanding the role of the neuroanesthesiologist in long-term and disease-specific outcomes that are of great concern to patients. In addition, the term "neurologic outcome" is nonspecific and deserves a better definition, possibly through the integration of multiple scales and measurements.*

Conclusions *Future endeavours in neuroanesthesia research should advocate prospective randomized trials that focus on long-term neurologic outcomes. These initiatives will require coordination of multiple centres through a clinical trials network.*

Author contributions *Alana Flexman*, *Lingzhong Meng* and *Adrian Gelb* contributed substantially to all aspects of this manuscript, including conception and design; drafting of the manuscript and contributed to all revisions.

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Résumé

Objectif *L'objectif de ce compte rendu narratif était d'évaluer et de catégoriser les résultats pertinents d'un point de vue clinique ayant précédemment fait l'objet de recherches en neuroanesthésie et de proposer les critères d'évaluation et les pistes à prioriser à l'avenir en matière de soins cliniques et de recherches portant sur les pronostics.*

Constatations principales *Le corpus actuel de recherche en neuroanesthésie constitue une base de connaissances fondamentales à la fois importante et exhaustive qui permet de mieux saisir l'effet des soins anesthésiques sur divers résultats cliniques. La traduction de données tirées d'études animales vers l'humain est toutefois limitée, et il convient de faire preuve de prudence. À ce jour, la littérature a porté une attention particulière aux résultats périopératoires à court terme, mais elle devrait désormais se tourner vers une élucidation du rôle du neuro-anesthésiologiste en matière de résultats à long terme et spécifiques à la maladie, deux éléments qui préoccupent beaucoup les patients. De plus, le terme « résultat neurologique » n'est pas assez spécifique et mérite une meilleure définition, dans laquelle on pourrait peut-être intégrer plusieurs échelles et mesures.*

Conclusion *À l'avenir, la recherche en neuroanesthésie devrait préconiser des études randomisées prospectives qui s'intéresseront principalement aux résultats neurologiques à long terme. De telles initiatives nécessiteront la*

coordination de plusieurs centres via un réseau d'études cliniques.

Most anesthesiologists who care for neurologically at-risk or overtly compromised patients would agree that their primary goal is for their patient to have a "good outcome" or, more specifically, a "good neurologic outcome". Yet, the concept of a "good outcome", neurological or not, is poorly defined and often in the eye of the beholder. Much of the neuroanesthesia literature to date has focused on short-term perioperative outcomes such as intracranial pressure (ICP), brain relaxation, cerebral perfusion, and neurophysiological monitoring. Long-term outcomes, such as neurologic function, disability, quality of life, and survival, have remained relatively neglected, although they are clearly more important to patients.[1-3] Although short-term outcomes are still viable research targets, they should not necessarily be assumed to be suitable surrogates for long-term outcomes.

The study of the outcomes that matter the most in neuroanesthesia is complex. Some outcomes are disease-specific and the contribution of anesthesia to the outcome can be difficult to define. In addition, and while not specifically covered in this review, neurosurgical patients are at risk of adverse outcomes common to all surgical patients (e.g., myocardial infarction, acute kidney injury) that themselves are associated with poor long-term outcomes.[4,5] Going forward, the outcomes that matter most to our patients need to be better defined, standardized, and incorporated into clinical trials. In this review, we discuss the importance of a spectrum of outcomes in neuroanesthesia and propose both short- and long-term outcomes on which to focus future research.

The challenges of translating animal data to patients

The pioneers of research in the field of neuroanesthesiology focused much of their inquiry on the effects of various anesthetic agents on neurophysiological outcomes such as ICP, cerebral perfusion pressure, cerebral blood flow, and cerebral metabolic rate of oxygen ($CMRO_2$). Defining the effect of anesthetic agents on cerebral metabolic and hemodynamic physiology provides an essential framework on which to base the anesthetic care of neurologically compromised patients. Most of these early studies were done in animal laboratories that allowed for careful documentation of the effects of anesthesia on the brain in a controlled setting. Although preclinical animal studies are fundamental for understanding these questions and developing clinical hypotheses, one must be cautious when extrapolating these results to humans. The limitations of animal studies include small sample size, overly controlled conditions, and minimal chronic comorbidities. As a result, they frequently do not reflect the complexity that is usually seen in the setting of clinical care.

Studies on the neuroprotective effect of anesthetic agents provide a useful example of the limitations of extrapolating animal data to humans. Although numerous anesthetic agents have consistently been shown to attenuate short-term ischemic injury in animal models, there are few data to support their use in humans for this purpose.[6] A *post hoc* subgroup analysis of the International Hypothermia for Aneurysm Surgery Trial (IHAST) found that the outcomes in patients who received purported neuroprotective agents (e.g., thiopental) were similar to those without these agents, either with or without hypothermia, during cerebral aneurysm clipping. This analysis was limited, however, by the lack of randomization of the neuroprotective agent and standardization of techniques.[7] Likewise, despite promising preclinical data,[8] randomized clinical trials of magnesium sulfate did not result in better neurologic outcomes in clinical trials in acute stroke or traumatic brain injury.[9,10] To date, we are lacking in large prospective randomized trials of neuroprotection in humans.[11]

Short-term outcomes: perioperative effects of anesthetics

There are several short-term clinical outcome measures of importance to neuroanesthesia (Table 1). Using short-term outcomes to answer research questions has several advantages. These outcomes are easier to collect, more economical, and do not require lengthy follow-up periods. Many studies attempt to replicate the results of preclinical animal studies in humans using these measures. Although short-term outcomes are viable research targets, we must be careful when assuming a relationship exists between these measures and the clinically meaningful outcomes. The assumption that short-term outcome predicts meaningful long-term outcomes may not always hold true.

An illustration of this concept is the debate on the superiority of total intravenous anesthesia over volatile anesthesia for intracranial neurosurgery. Earlier trials showed that volatile anesthesia was associated with excess cerebral vasodilation, impaired autoregulation, and increased ICP (i.e., increases on the order of 2-5 mmHg).[12-15] As a result, intravenous anesthesia is often seen as advantageous for neurologically at-risk patients. Recently, however, Citerio *et al.* conducted a multicentre randomized equivalence trial comparing three different anesthetic regimens, including both volatile and propofol-based anesthesia, and found equivalent outcomes in

Table 1 Proposed short- to medium-term outcomes in neuroanesthesia

Measurement	Importance	Comments/Examples
Cerebral blood flow	Determinant of metabolic substrate supply; Cerebral ischemia ensues if inadequate for metabolic demand.	Currently no direct and continuous measurement method; e.g., TCD measures flow velocity in a specific major intracranial artery.
Cerebral metabolic rate of oxygen	One aspect of metabolic demand; Cerebral hypoxia ensues if consumption cannot be met by supply.	Direct and continuous measurement difficult; Ideally needs simultaneous measurement of metabolic substrate supply (CBF) to diagnose cerebral ischemia or hypoxia.
Intracranial pressure	Determines CPP along with MAP; Used as surrogate for intracranial volume.	Often invasive and requires simultaneous systemic arterial blood pressure measurement to determine CPP.
Systemic arterial blood pressure	Determines CPP along with ICP.	Require simultaneous ICP measurement to determine CPP.
Brain relaxation during craniotomy	Determinant of surgical operating condition.	Related but different from ICP.
Neurophysiological monitoring	Designed for timely detection of adverse but reversible intraoperative events that affect the functional integrity of the neurological system.	e.g., EEG, SSEP, MEP, EMG
Quality of recovery from anesthesia	Allows early neurological assessment; may influence time to discharge from PACU/ICU.	e.g., Time to eyes opening; time to extubation; Aldrete score[16]
Early cognitive function	Useful to detect subtle changes in cognition, such as memory, attention, language, and executive function in the hours to days following a procedure or intervention.	e.g., MMSE,[43] Trail Making test[42]
Postoperative complications during initial hospital stay	Determinant of the quality of hospitalization course. Influences resource consumption and cost.	Short-term measurement reflecting adverse events during hospital stay.
Hospital length of stay	Influences resource consumption and cost; May influence patient's postoperative quality of life	Non-specific outcome measurement.

CBF = cerebral blood flow; CPP = cerebral perfusion pressure; EEG = electroencephalography; EMG = electromyography; EPs = evoked potentials; ICP = intracranial pressure; MAP = mean arterial pressure; MEP = motor evoked potentials; MMSE = Mini Mental State examination; PACU = postanesthesia care unit; SSEP = somatosensory evoked potentials; TCD = transcranial Doppler; ICU = intensive care unit

intraoperative hemodynamics, quality of surgical field, and time to meet discharge criteria from the recovery room (i.e., Aldrete score[16] of 9).[17] Their results are supported by other similar randomized clinical trials.[18-20] Although not all aspects of these randomized trials may be generalizable to all centres, the balance of evidence does not support one technique over another in terms of more meaningful clinical outcomes such as time to awakening, early cognitive performance, and readiness for discharge from the recovery room.[21]

Another example is the use of ketamine in neurologically compromised patients. As a result of early studies showing elevations in ICP and $CMRO_2$ with high doses of ketamine, it was once common to avoid ketamine in neurologically impaired patients. Nevertheless, many of these studies were conducted over forty years ago[22,23] and contrast with more recent work, including a systematic review that did not show differences in neurologic outcomes, intensive care unit length of stay, or mortality in neurologically injured patients given ketamine *vs* other anesthetic agents.[24]

In both examples, however, these trials measured short-term outcomes and the long-term consequences of the interventions were not investigated. Nonetheless, both examples suggest that any effect of an anesthetic regimen on the short-term clinical outcome of the patient is frequently outweighed by surgical and patient factors in the clinical context.

Long-term outcomes in neuroanesthesia: defining the contribution of the neuroanesthesiologist

Few studies have investigated the effect of anesthetic variables on long-term disease-specific outcomes, although these outcomes are of great interest to patients. In contrast to the short-term outcomes described above, long-term outcomes extend beyond the immediate perioperative period and are characterized by neurological integrity, quality of life, and both disability- and disease-free survival (Table 2).[1,25] The reason for the paucity of studies on long-

Table 2 Proposed long-term outcomes in neuroanesthesia

Outcome	Importance	Examples
Basic neurologic outcome	Easily applied, simple scoring systems to grade gross neurologic function.	e.g., mRS[38], GOS[37]
Global neurologic outcome	Integration of multiple neurological assessments and scales into a global measure.[44,45]	e.g., composite outcome measure
Disability-free survival	May be more important than overall survival and influences quality of life.	e.g., Barthel's Index,[39] WHODAS 2.0[40]
Disease-free survival	May be more important than overall survival and influences quality of life.	e.g., Time to tumour recurrence
Quality of life	Patient-centred outcome measurement.	e.g., Stroke Impact Scale,[33] Quality of Life in Epilepsy Inventory;[34] Oswestry Disability Index[35]
Disease-specific outcomes	Different diagnoses and procedures have different treatment goals.	e.g., Long-term need for anti-epileptic drugs; tumour recurrence; cranial nerve dysfunction after skull base surgery
Mortality	Non-specific outcome measurement.	

GOS = Glasgow Outcome Scale; mRS = modified Rankin scale; WHODAS = World Health Organization Disability Assessment Schedule

term outcomes in neuroanesthesia is likely multifactorial. First, well-conducted clinical trials are costly, time-consuming, and require a large number of patients to provide sufficient power for an outcome study. For example, cardiorespiratory complications occur in approximately 5% of neurosurgical patients.[26] In order to conduct a randomized clinical trial of an intervention, an estimated 2,000 patients would be required to detect a 50% reduction (which itself is likely an overestimate of any biologically plausible effect) in the frequency of the outcome. Studies such as these would clearly need to involve multiple centres and require substantial funding. Second, the role of anesthesia in long-term outcomes is not obvious when compared with the role of patient and surgical factors and therefore may have been underemphasized. For example, a potential role for local anesthesia in preventing chronic post-craniotomy pain was reported only recently and deserves further attention.[27] Despite these challenges, there are several specific areas in neuroanesthesia that require prospective high-quality trials to elucidate the effect of anesthetic interventions on outcome even further.

An illustration of the difficulty in defining the contribution of anesthesia to long-term outcome is seen when comparing awake craniotomy *vs* surgery under general anesthesia for brain tumour resection. Many experts consider awake brain tumour resection the standard of care for tumours in close proximity of eloquent brain, although controversy continues to exist about the optimal technique, particularly in the context of recent advances in functional neuroimaging.[28-30] Improved neurologic outcomes can be attributed to the surgeon's ability to resect the tumour precisely and extensively while concurrently preserving language and sensorimotor function using intraoperative stimulation mapping.[29] In a previous review, we discussed the benefits of awake craniotomy, including a greater extent of tumour resection, longer survival, fewer late neurological deficits, less postoperative pain, less opioid use, and shorter hospital stays.[31] These benefits may be due to avoidance of general anesthesia-associated lung injury as well as physiological disturbances such as blood pressure perturbations.[31] Finally, a recent study reported reduced immune cell populations during craniotomy performed under general anesthesia.[32] It is currently unknown whether local anesthesia avoids these immunological consequences and thereby reduces tumour recurrence and improves disease-free survival. From an anesthesiologist's perspective, this speculation needs to be investigated, first by a pilot trial and then followed by a large-scale randomized-controlled trial specifically comparing awake craniotomy *vs* surgery under general anesthesia. There is sufficient uncertainty and variation in clinical practice that such a trial could be justified given the potential patient benefit. This example shows the complexity of determining the aspects of clinical care that contribute to long-term outcome and the need for rigorous evidence based on randomized-controlled trials to validate or refute these speculations.

Although many common outcomes across a variety of procedures are considered important (e.g., mortality), the long-term outcomes of relevance will vary depending on the type of neurosurgical procedure. For example, in a patient undergoing resection of an intracranial tumour, the outcomes of primary importance will be the risk of tumour recurrence, and long-term survival. For a patient presenting for elective clipping of an intracranial aneurysm, the prevention of postoperative neurologic deficits would be paramount. Similarly, an outcome of relevance to cortical resection for epilepsy is the adequacy of postoperative seizure control, with or without antiepileptic medications. In contrast, specific persistent cranial nerve dysfunction may be more relevant after skull base neurosurgery. In addition to the disease-specific neurological outcome, there is a need to evaluate them in the context of overall functionality. Several tools that may be of use for anesthesia studies have been developed to assess patients' quality of life after specific neurologic surgeries or conditions. The Stroke Impact Scale, Quality of Life in Epilepsy Inventory, and the Oswestry Disability Index for spine disorders are examples of outcome scales developed from the perspective of patients to measure quality of life in specific diseases and should be used during outcome-oriented care.[33-35] How anesthesia care affects these disease-specific outcomes is of importance not only for the patient and surgeon but also for the specialty of neurosurgical anesthesia.

Towards a standardized definition of neurologic outcome

The term "neurologic outcome" is often used in neuroanesthesia research. Although this outcome is clearly relevant, it is nonspecific and lacking standardized measurement. A single measurement tool can neither encompass all dimensions of neurologic function nor be suitable for every diagnosis of neurological diseases.

The choice of measurement tool has depended on the research question at hand.[36] For example, several validated outcome measures have been used to measure recovery after neurologic injury, including the modified Rankin Scale and the Glasgow Outcome Scale.[37,38] These scales provide a global assessment of function ranging from good recovery through to vegetative state and death. They have the advantages of ease of administration and good inter-rater reliability. While differences in each level of these scales are clearly important and relevant to patient outcomes, these scales have limitations. They lack resolution and granularity, particularly amongst those with "good recovery" or no disability. In addition, they are also somewhat ambiguous because they lack clear definitions for each category.[36] It would be inappropriate to use these scales if we wanted to study changes in cognitive or social function, which may occur in the absence of a significant "traditional" functional disability. Although other validated global scales of functioning and disability were not developed specifically for patients with neurologic disease, they can be applied to neuroanesthesia and capture a broad range of multidimensional disability and dependency. Examples of such scales include the World Health Organization Disability Assessment Schedule and Barthel's Index.[39,40] In addition, there are multiple neuropsychological tests available that can be applied to the postoperative period, typically in combination to capture a detailed cognitive assessment (e.g., Mini Mental State Examination, the Trail Making Test).[41-43] Although it may be more cumbersome to use complex and time-consuming outcome measures, some authors have advocated integrating multiple scales to generate a global outcome statistic. This could increase both the statistical power and the impact of the results because the outcome would reflect a spectrum of relevant outcomes.[36,44,45]

Clinical trials in neuroanesthesia: future directions

Large-scale randomized-controlled trials (RCTs) are essential for guiding how we practice and are critical to our understanding of the role of the anesthesiologist in improving outcome. Clinical outcome trials also play an important role in confirming or refuting the results of preclinical studies; there are notable examples in the neuroanesthesia literature. For example, the IHAST investigators showed that gross neurological outcome (as assessed by the Glasgow Outcome Scale) and long-term neuropsychological outcomes were not improved when mild intraoperative hypothermia (to 33°C) was employed during aneurysm surgery.[41,46] These results were contradictory to conventional practice and animal experiments and changed clinical practice in many centres.[47] The General Anesthesia versus Local Anesthesia for Carotid Surgery trial showed similar outcomes (a composite of 30-day stroke, myocardial infarction, and death) between regional *vs* general anesthesia for carotid endarterectomy.[48] These results refuted the hypothesis that avoiding general anesthesia and allowing an intraoperative neurologic exam would reduce perioperative risk in this particular patient population.

Despite the vitally important implications of randomized clinical trials with clinical outcomes relevant to our practice, relatively few rigorous RCTs, such as the ones above, have been conducted in the field of neuroanesthesia. In our opinion, there are several areas that require prospective high-quality investigations going forward to address outstanding questions in neuroanesthesia and neurosurgery. First, as proposed earlier in the review, there is a need for larger multicentre RCTs that examine the potential benefits of awake craniotomy as compared with general anesthesia for brain tumour surgery. The outcomes of interest to examine would include neurologic deficits, long-term neurologic function and survival, and the effects of local and general anesthesia on immune function and recurrence of brain tumours. Similarly, the effect of general anesthesia on outcomes after acute ischemic stroke is another issue that has remained controversial and debated in the literature as we await high-quality prospective data.[49] Although recent studies have shown poorer outcomes associated with general anesthesia, few details about the anesthetic, including blood pressure management and airway support, have been recorded or analyzed.[50] It would be equally important for both studies to ensure that depth of sedation is well controlled and documented to substantiate clear separation of the anesthetic states. Finally, we lack RCTs that address the effect that incorporating neurologic monitoring technologies (e.g., evoked potentials, cerebral oximetry) has on postoperative neurologic function, despite expanding adoption into practice. Such trials should be mandatory before these noninvasive monitoring techniques become *de facto* standards of practice. Although many neurologic monitors are associated with postoperative neurologic outcomes, we continue to be in need of prospective data that signifies whether altering management based on these monitors changes outcome.[51] Finally, in order to achieve the above, there is an urgent need for a clinical trials network that focuses on anesthesia for neurosurgery and patient-relevant important outcomes. As seen in other subspecialty areas, such a group would enhance collaborative discussions about project planning, facilitate funding applications, and mentor young investigators.[52]

Conclusion

In summary, the current body of neuroanesthesia research has created a comprehensive and fundamentally important knowledge base by defining the effect of anesthetic care on various outcomes. We have identified the short- and long-term outcomes that are clinically important to the subspecialty of neuroanesthesia. The literature to date has focused on short-term perioperative outcomes but should now shift towards understanding the role of the neuroanesthesiologist in long-term and disease-specific outcomes that are of greatest concern to patients. In addition, the term "neurologic outcome" is nonspecific and deserves a better definition, possibly through the integration of multiple scales and measurements. We have proposed several directions for future research, including clearly defining the contribution of general anesthesia to longer term outcomes in patients with brain tumours and acute stroke as well as the effect of neurological monitoring techniques on neurologic outcome. Future neuroanesthesia research endeavours should advocate prospective RCTs that focus on long-term neurologic outcomes. These initiatives will require coordination of multiple centres through a clinical trials network.

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