How to Study the Brain While Anesthetizing It?! A Scoping Review on Running Neuroanesthesiologic Studies and Trials That Include Neurosurgical Patients

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This scoping review addresses the challenges of neuroanesthesiologic research: the population, the methods/treatment/exposure, and the outcome/results. These challenges are put into the context of a future research agenda for peri-/intraoperative anesthetic management, neurocritical care, and applied neurosciences. Finally, the opportunities of adaptive trial design in neuroanesthesiologic research are discussed.

INTRODUCTION

Discussing topics and methods for future trials in neuroanesthesiology should begin with a careful analysis of the current knowledge and the most relevant problems. Just after identification of these theoretical and practical challenges and limitations to future trials, it makes sense to define a path to follow for the next years. Of course, this paper entails our vision, but we try to provide arguments why we think this path should be followed.

Challenges Due to the Population

The "typical neurosurgical patient" does not exist. The disease treated by the neurosurgeon might be oncologic, traumatic, vascular, or spinal. The location of the disease might be supra- or infratentorial, intra- or extramedullary, on the dominant side or not. The disease itself might be an isolated neurosurgical problem or associated with or the result of a more or less serious problem in general health. And the treatment might be an open craniotomy, just a burr hole, or even an endovascular transfemoral neuroradiological intervention. These 5 sentences address one of the biggest problems in neuroanesthesiologic studies: Defining a homogenous patient population that will be helpful in understanding which results are applicable for the "real-world-situation"! Even in highly productive neurosurgical centers the numbers of patients treated are still much too low, to build up a homogenous patient database will take years, and in this period the general progression of the field is so fast that the treatment of the first and the last patients of the database might become completely different. Thus, international collaboration, standardized treatment protocols, and attention for the progression of the field during the inclusion period are the other cornerstones of a homogenous patient population.

Challenges Due to the Methods/Treatment/Exposure

A common problem of all studies in neuroanesthesiology is the fact that the anesthesia itself interferes with the brain. A homogenous anesthesia regimen should be applied, but this is a challenge on its own! What does homogenous mean? Is it administration of the same dose of anesthetic drugs per kg body weight, is it the administration of anesthetic drugs to reach the same target organ concentration, or is it administration of anesthetic drugs to reach the same anesthesia depth level measured by 1 of the available monitors with all their technical/algorithmic limitations? It is evident that giving the same dose does not mean reaching the same organ concentration nor reaching the same effect. Nevertheless, this question must be clearly addressed when setting up a study protocol and similarly executed in all arms of a trial. A common problem of all neurosurgical patients is the "triple hit" on the brain—the disease, the surgery, and the anesthesia—each with their own risks and impact.

Key words
- Applied neurosciences
- Adaptive trial design
- Neuroanesthesia
- Neurocritical care

Abbreviations and Acronyms
CNS: Central nervous system
ECMO: Extracorporeal membrane oxygenation
EEG: Electroencephalography
ERAS: Enhanced recovery after surgery
ICP: Intracranial pressure
NAN: Nociception-antinociception
NIRS: Near infrared spectroscopy
TIVA: Total intravenous anesthesia

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*Citation: World Neurosurg. (2022) 161:376-381.
https://doi.org/10.1016/j.wneu.2021.08.069*

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

Challenges Due to the Results/Outcomes

In times of patient-centered outcomes and value-based health care a statistically significant change in protein S100B, GFAP, or neuron-specific enolase can no longer be accepted as the only result of a trial.[1] The outcomes of future studies must be of clinical relevance and practical applicability. Considering the vulnerability of neuronal tissue, minimizing adverse outcomes and the quality-adjusted life years gained are extremely important for our patients. On the other hand, more studies addressing the optimization of processes (think about: faster, safer, more efficient), educational/training issues (e.g., when are you qualified to perform a safe awake craniotomy), and psychosocial dimensions of (the care for) neurosurgical patients (e.g., how much information and support should be provided to whom in which form?) are also absolutely needed.

THE FUTURE RESEARCH AGENDA: THE TOPICS

Twenty-two years after the end of the "decade of the brain" (https://www.loc.gov/loc/brain/) and all the expectations applied to clinical neuroanesthesia, few advancements have had a real impact on patient outcomes, and basic and clinical researchers still search for different magic bullets to prevent or limit cerebral damage. Unfortunately, despite herculean efforts, translational research from in vitro and in vivo studies to human models failed to show effective pharmacologic and nonpharmacologic strategies of brain and spinal cord protection after a traumatic or ischemic insult.[2]

Very recently, the Canadian Anesthesia Research Priority Setting Partnership identified the top 10 priorities for anesthesia and perioperative research:[3]

1) Which factors before, during, and after receiving anesthesia for surgery are most important to improve patient outcomes and satisfaction?
2) What are the impacts of involving patients in shared decision-making about anesthesia and care options before, during, and after surgery?
3) What data should be collected from patients about anesthesia care before, during, and after surgery to better understand their outcomes and experiences?
4) How can errors and patient injuries in anesthesia care be prevented?
5) How can outcomes in frail and/or elderly patients be improved after receiving anesthesia for surgery?
6) What is the impact of reducing opioids during anesthesia on patient outcomes and opioid dependence after surgery?
7) What preparation, treatment, or assessment before receiving anesthesia for surgery improves patient outcomes?
8) How can patient feedback about their experiences before, during, and after surgery be used to improve anesthesia care?
9) How can anesthesiologists improve pain control after surgery?
10) What are the common long-term side effects of anesthesia after surgery?

This list reflects priorities shared by patients and physicians and, as the authors declare, "they should serve as starting points for researchers, funders, and decision-makers. They also identify questions around anesthesia care, where the answers can have immediate translatable impacts on our patient' daily lives." Indeed, all these questions and starting points for research could be applied to the neurosurgical patients eliciting the construction of myriad of databases and audits worldwide.

Specifically, the role of anesthesia in neurosurgical enhanced recovery after surgery (ERAS) programs allied to personalized care has been highlighted and opens a wide road to multidisciplinary commitments towards an optimized perioperative management of the neurosurgical patients.[4,5] Researchers would have dozens of possible pathways to investigate how daily clinical practice may be improved.

In the light of the balance between rational funding and practical benefits, in the following paragraphs we will highlight the 3 main fields deserving extensive research: anesthesia for neurosurgical procedures, neurocritical care, and applied neurosciences to general anesthesia. Briefly, in each of these main groups we may elaborate on specific topics:

Perioperative Anesthetic Management

The peri-operative anesthetic management of the neurosurgical patient deserves special attention to provide hemodynamic stability throughout the entire procedure, an optimal surgical field, reliable intraoperative neurophysiologic monitoring, a fast and smooth emergence from general anesthesia or a comfortable and cooperative patient during awake interventions, and preventing or minimizing postoperative complications.

An appropriate (if not ideal) choice of drugs, optimizing their pharmacokinetic and pharmacodynamics and delivery, with close monitoring strategies, would allow for a successful outcome. The ideal anesthetic drug or combination of drugs for neurosurgical procedures have well-known properties: favorable pharmacokinetics with fast onset and fast offset, insensitive decrement times even after hours of administration for long-lasting neurosurgical procedures, providing hemodynamic stability, have a favorable effect on the physiology of the central nervous system (CNS), not affecting cerebrospinal fluid physiology, allowing neurophysiological monitoring with minimal interference, be anticonvulsant or at least not induce seizure activity, decrease edema, and should protect the CNS from ischemia. Unfortunately, such a drug does not exist and, in clinical practice, there is still some uncertainty whether there are differences between the common anesthetic approaches (e.g., balanced anesthesia including anesthesia vapors vs. total intravenous anesthesia [TIVA]) in short- and long-term outcomes.

A significant number of neuroanesthesiologists have been electing TIVA over inhalational anesthesia,[6] but many questions remain to be investigated after seminal studies (with the references given just as examples for the relevance of the question and the still existing doubts about the true answer):

1) Which drugs should be combined in TIVA to achieve the paradigm of multimodal general anesthesia?[7]
2) Is ketamine acceptable to use in neurosurgical patients, at least as a major player in the intraoperative nociception-antinociception (NAN) balance?[8]

3) What is the role of dexmedetomidine in long-term cognitive outcomes?[9,10]

4) How do intravenous anesthetic drugs affect the immune response after surgery and how may they affect cancer recurrence?[11,12]

5) Is the scalp block a potential influencer of outcome after brain tumor surgery?[13]

6) How to monitor the brain during anesthesia to guide dosing, avoiding under- and overdosing, and optimizing the NAN-balance and to detect and prevent complications?[14]

7) Which is the best anesthetic approach for awake neurosurgery (epilepsy surgery, tumor resection, and functional neurosurgery)?[15-17]

Neurocritical Care

Neurocritical care has become an essential player in the management of patients with critical neurological and neurosurgical illness. Recently, the future of this valuable subspeciality was reviewed and projected by Busl et al., emphasizing the poor improvement in functional outcomes.[18]

Pharmacologic strategies to prevent neuronal damage and to protect the brain have been unsuccessful. Areas that still need definitive evidence are the effects of hypertonic solutions compared with mannitol to decrease the intracranial pressure (ICP), the role of induced electroencephalographic burst suppression, and the effectiveness of hypothermia.[19-21]

Research addressing postoperative delirium will stay within focus. In neurosurgical patients, we are facing the consequences of a "triple hit": the disease causing the procedure, the neurosurgical procedure itself, and the anesthesia provided. All these factors can contribute to the emergence of a postoperative delirium and/or any other postoperative cognitive decline, and research on preventive and therapeutic measures must be continued.[22]

Another major topic permanently under the radar is how to evaluate and to preserve the perfusion and the physiologic cerebral autoregulation in neurocritical patients. In addition, the search for noninvasive monitoring tools has been a growing field of experimental and clinical research.[23,24]

One of the major clinical dilemmas in neurointensive care and deserving extensive research is how to identify the optimal cerebral perfusion pressure as target for autoregulation-oriented therapy and to continuously monitor the cerebrovascular reactivity and autoregulation.

Although invasive intracranial methods are the gold standard for ICP measurement and continuous monitoring, ultrasonography of the optic nerve sheath diameter has been suggested as a potential noninvasive ICP estimator.[25] The role of transcranial Doppler, brain oximetry using near infrared spectroscopy (NIRS), or functional NIRS with electroencephalography (EEG) is also pending to be effectively adopted as routine monitors.[26]

Applied Neurosciences to General Anesthesia

For decades, brain monitoring during anesthesia and surgery was widely seen as an exclusive option of neuroanesthesiologists despite the paradoxical conflicts of space existing between surgical requirements and the location of sensors.

Certainly, following the efforts of neuroanesthesiologists and the cooperative work with neurosurgeons, in recent years brain monitoring during anesthesia with EEG and NIRS oximetry was embraced by general clinical anesthesiologists and important evidence started to shed some light into the previously gray areas of anesthetic unconsciousness.[27,28]

Perioperative brain monitoring with EEG has been a crucial but incipient tool to understand, for example, the mechanisms of neural inertia behind loss and recovery of consciousness,[29,30] or how to detect, pre- and intraoperatively, patients at higher risk to develop postoperative cognitive complications.[31-33] An important contribution, for example, has come from patients undergoing deep brain stimulation and resection of brain tumors with intraoperative awakening.[34]

On the other hand, preoperative low saturation of cerebral oxygen has been associated with postoperative cognitive complications and poor outcomes.[35]

Despite mounting evidence supporting the use of these monitoring tools in every patient submitted to general anesthesia, there is still a long roadmap to follow until generalized acceptance. The role of neuroanesthesiologists and neurosurgeons will be pivotal to trigger more research in these fields yielding to a wide application in other surgical patients.

A final "basic neuroscience" aspect of future research is the possible impact of anesthesia on the structural integrity of the brain, especially the developing and the aging one: The jury is not yet out on the neurotoxicity of anesthetics, and we must answer the question whether the lack of sensory input completely explains the increased apoptosis after anesthesia, or whether genuine neurotoxicity of the anesthetic drugs also plays a role?! And even if the latter seems to be true, this again must be balanced against the impact of surgery performed without anesthesia or the impact of not performing surgery.

THE FUTURE RESEARCH AGENDA: THE METHODOLOGY

Based on the challenges elaborated above and the possible research topics, the future research methodology in neuroanesthesiology also deserves some thoughts. Of course, a classical prospective, randomized, double- or triple-blinded study design still has several merits, but it is not always feasible, and might not be the best design to address the burning questions. Therefore, new methodologic paths should be considered.

Adaptive Trial Design in Neuroanesthesia

Traditionally, clinical trials are designed, conducted, and analyzed, in that order. However, in an adaptive clinical trial, the trial design is intermittently updated during the conduction phase.[36] Advantages of this flexibility are that these trials reduce the use of resources and time, and/or improve the likelihood of success.[37] However, the actual benefit of adaptive trial designs is mostly determined by what part of the trial design is actually adapted. Most adaptive trials update treatment allocation ratio, sample size, or eligibility criteria. As a result, statistical power is increased, or arms with inferior treatment strategies are dropped.[38]

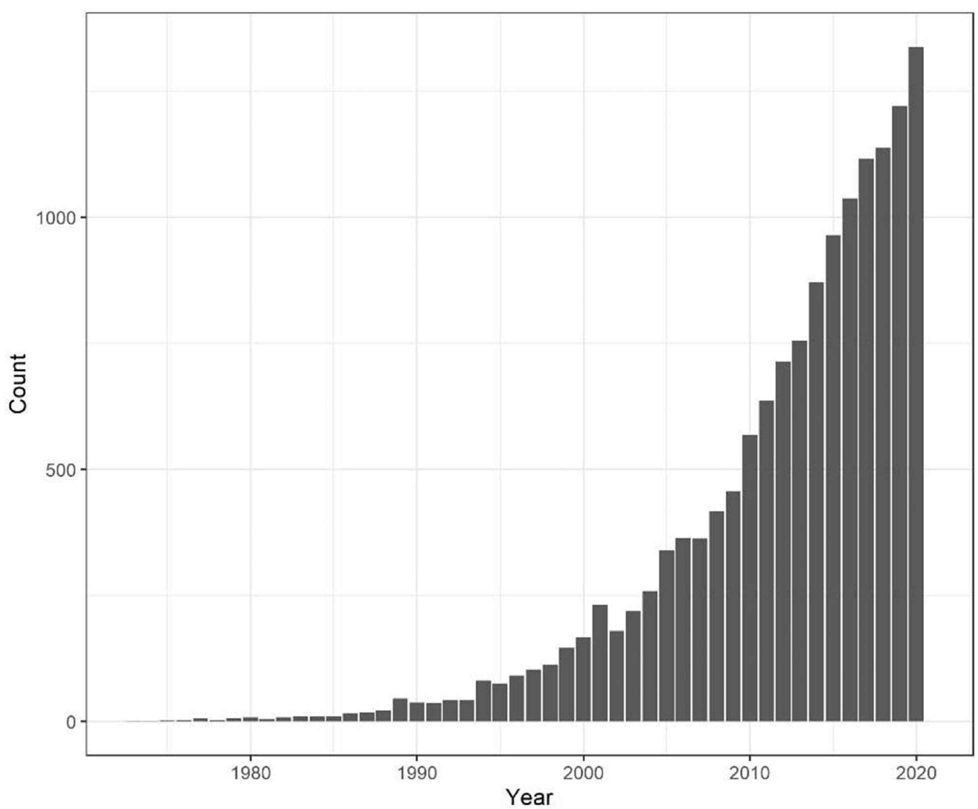

Figure 1. Number of PubMed hits when searching with the string "Adaptive trial design", up to the year 2020.

Their scientific popularity is rapidly increasing (**Figure 1**). Their popularity is expected to increase even further, due to recent success stories such as the REMAP-CAP study.[39] The scientific team of this adaptive randomized clinical trial, initially designed for community acquired pneumonia, was able to flexibly adapt the study to study treatments for COVID-19. For example, the study established the beneficial effect of interleukin-6 antagonists.[40]

The main obstacle, however, for implementing adaptive trial designs is the extensive work-up in designing the trial.[41] This workup involves complex multidisciplinary statistical trial simulation. In these rounds of statistical simulation, researchers define rules to inform trial design which are applied in the interim analyses. These predefined rules are essential: The alternative (post hoc analysis or post hoc adaption of trial design) increases the probability of false-positive research findings.[42]

We performed a search for published and ongoing adaptive clinical trials in neuroanesthesia (for search strings, see **Table 1**). We found interest in using an adaptive trial design for spinal cord injury, because this would provide solutions for challenges such as low incidence, high heterogeneity, lack of consensus on how to show a treatment effect, resistance to control group randomization, high per participant study costs, wrongly assumed trial designs in for example dose, timing, and duration of treatment.[41,43] However, we have not yet found reports of adaptive trial designs for spinal cord injury treatment.

There is one adaptive clinical trial currently ongoing in our field: The TICrH study aims to adaptively randomize time intervals to restart direct oral anticoagulants after traumatic intracranial hemorrhage.[44] They adapt their design during interim analyses using the following rules:

Table 1. Searches Performed to Identify Adaptive Trial Designs in Neuroanesthesia (26 April 2021)

Database	String	Number of Hits
PubMed	Adaptive clinical trial AND (anesthesia OR neurosurgery OR craniotomy OR spinal OR traumatic brain injury)	11
Clinicaltrials.gov	Adaptive clinical trial AND (anesthesia OR neurosurgery OR craniotomy OR spinal OR traumatic brain injury)	5

1) If in some treatment arms the event rate of thrombosis or bleeding is higher than expected, the odds of being randomized to that group is lower.

2) If the total event rate of thrombosis or bleeding is lower than expected, the inclusion criterium for the trial based on the CHA_2DS_2-VASc score (>2) increases so that more thrombotic events are ensured (because patients at higher risk of thrombotic events are included).

Both rules aim to ensure high enough power to detect a difference in event rates between groups. Therefore, the likelihood of a positive study result improves if there is an actual difference. Moreover, fewer patients are randomized to an inferior treatment arm, thereby reducing resources and time.

As illustrated by the TICrH-study, adaptive trial designs can be applied in the field of neuro-anesthesiology to flexibly adapt the study to improve success rate and reduce resources and time. The principles can be applied to almost all topics mentioned above as well.

Already a long-standing application of adaptive trial designs in the field of critical care is play-the-winner randomization.[45] For life-saving interventions without scientific foundation, this adaptive design might enable ethical randomization, which might be relevant for neuroanesthesiology, too. For example in 1985, Bartlett et al. reported a randomized study in which neonates with respiratory failure were randomized to either conventional therapy or extracorporeal membrane oxygenation (ECMO).[46] A successful outcome (survival) increased the odds of being randomized to that treatment arm. After just 12 inclusions (1 control patient died, all in the treatment arm survived) the authors were able to conclude the life-saving effect of ECMO. Although the design does not allow for the calculation of a relative risk, it does enable the systematic evaluation of a potentially life-saving intervention (sometimes ethically feasible without complete clinical equipoise).

CONCLUSIONS

In this scoping review, we elaborated on the challenges of neuroanesthesiologic studies, point to possible future research topics, and discuss the technique of adaptive trial design. A final aspect that should be taken into consideration is the fact that a huge number of neurosurgical patients is included in neurosurgical studies, which make it challenging to identify pure neuroanesthesiologic interventions and outcomes without any interfering biases. We hope that the ideas presented here will enable and inspire our colleagues—neurosurgeons and neuroanesthesiologists—to future common efforts to answer the still unanswered questions in the field.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Markus Klimek coordinated the process and wrote the initial draft of the introduction and the challenges, Benjamin Gravesteijn wrote the initial draft of adaptive trial design, Andreia Costa and Francisco Lobo wrote the initial draft of the future research agenda. All authors contributed to reviewing and editing the final version of the manuscript and agreed with the version submitted.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 31 May 2021; accepted 13 August 2021

Citation: World Neurosurg. (2022) 161:376-381.
https://doi.org/10.1016/j.wneu.2021.08.069

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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