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Neuroprotective Effects of Intravenous Anesthetics: A New Critical Perspective

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Abstract

Perioperative cerebral damage can result in various clinical sequela ranging from minor neurocognitive deficits to catastrophic neurological morbidity with permanent impairment and death. The goal of neuroprotective treatments is to reduce the clinical effects of cerebral damage through two major mechanisms: increased tolerance of neurological tissue to ischemia and changes in intra-cellular responses to energy supply deprivation. In this review, we present the clinical evidence of intravenous anesthetics on perioperative neuroprotection, and we also provide a critical perspective for future studies. The neuroprotective efficacy of the intravenous anesthetics thiopental, propofol and etomidate is unproven. Lidocaine may be neuroprotective in non-diabetic patients who have undergoing cardiac surgery with cardiopulmonary bypass (CBP) or with a 48-hour infusion, but conclusive data are lacking. There are several limitations of clinical studies that evaluate postoperative cognitive dysfunction (POCD), including difficulties in identifying patients at high-risk and a lack of consensus for defining the "gold-standard" neuropsychological testing. Although a battery of neurocognitive tests remains the primary method for diagnosing POCD, recent evidence suggests a role for novel biomarkers and neuroimaging to preemptively identify patients more susceptible to cognitive decline in the perioperative period. Current evidence, while inconclusive, suggest that intravenous anesthetics may be both neuroprotective and neurotoxic in the perioperative period. A critical analysis on data recorded from randomized control trials (RCTs) is essential in identifying patients who may benefit or be harmed by a particular anesthetic. RCTs will also contribute to defining methodologies for future studies on the neuroprotective effects of intravenous anesthetics.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

Keywords

Neuroprotection; intravenous anesthetic; neurotoxicity; neuropsychological testing

INTRODUCTION

Perioperative cerebral damage can occur in a variety of contexts, and can lead to wide array of clinical pictures ranging from subclinical or clinically minor neurocognitive deficits to catastrophic neurological morbidity with permanent impairment and death [1–6]. The goal of neuroprotective treatments (pharmacological or non-pharmacologic) is to reduce the clinical effects of cerebral damage via two primary mechanisms: by increasing the tolerance of neurological tissue to ischemia and by changing the intra-cellular response to energy supply deprivation [7].

Several pharmacological therapies have been evaluated for their neuroprotective effects, including intravenous and inhalational anesthetics, free radical scavengers, excitatory amino acid receptor antagonists and scavengers, calcium channel blockers, ionic pump modulators, anti neutrophil and anti-platelet factors, growth factors, estrogen and progesterone, and steroids [8–12]. Although some of these agents showed neuroprotective effects in preclinical studies (cell culture systems or animal models of focal or global cerebral ischemia), the evidence in human studies has been inconsistent and controversial [13–16].

In order to design clinical studies that evaluate the potential neuroprotective effects of pharmacological therapies, the pre-clinical evidence to support the rationale for human studies should be critically evaluated. Furthermore, specific methodological issues need to be addressed, including the timing and dosing of drug administration (which may differ from standard therapeutic use), the presence of co-morbidities, and the type and timing of neurocognitive testing [8, 17–23].

The aim of this review is to present the clinical evidence of intravenous anesthetics on perioperative neuroprotection. We also provide a critical perspective for future studies, including the requisite evidence from preclinical research, methodological issues in clinical research, and neurotoxicity of intravenous anesthetics.

PERIOPERATIVE NEUROPROTECTION WITH INTRAVENOUS ANESTHETICS

Thiopental

In preclinical models, barbiturates have several pharmacological effects that make for an ideal neuroprotective agent, including a reduction of cerebral metabolic rate of oxygen (CMRO2), suppression of neurotransmission, and an increase in brain tolerance to ischemic insults [24]. Thiopental, the intravenous barbiturate formulation used for anesthesia induction, was the first intravenous anesthetic agent tested in clinical trials for perioperative neuroprotection [24–27]. In cardiac surgery patients, thiopental infusion titrated to electroencephalographic (EEG) suppression induces hemodynamic changes favorable for

brain neuroprotection with a significant reduction of cerebrovascular resistance, cerebral blood flow (CBF) and cerebral oxygen delivery during cardiopulmonary bypass (CPB) [28, 29].

The ability of thiopental to mitigate the consequences of focal cerebral ischemia during cardiac surgery was evaluated in 172 patients who underwent elective cardiac surgery requiring the opening of a cardiac chamber (valve replacement or repair, ventricular aneurysm resection, or closure of a septal defect) [26]. These patients were subjected to a full neuropsychiatric evaluation performed one day prior to surgery, and repeated on the first and the fifth postoperative day. The test evaluated for strength of all upper and lower extremity motor groups, sharp-dull perception in all spinal nerve distributions, motor and sensory function of cranial nerves II-XII, activity of spinal and plantar reflexes, cerebellar function by finger-to-nose and heel-to-knee movements, gait and station, assessment of orientation, the presence of clearly inappropriate affect or atypical behavior such as hostility or withdrawal, glossy abnormal ideation including hallucinations or delusions, and short and long-term memory. Patients randomly assigned to the treatment group received thiopental in 50–100 mg increments until an isoelectric EEG was achieved, followed by a continuous infusion beginning a rate of 500 μg/Kg. Patients assigned to the control group received additional fentanyl 20–40 μg/Kg immediately after initiation of CPB. Neuropsychiatric dysfunction was evaluated within 24 h of emergence from anesthesia in 13 patients: five (5.6%) in the thiopental group and eight (8.6%) in the control group. By the tenth postoperative day, there were no neuropsychiatric abnormalities observed in the thiopental group, whereas in seven of the eight patients in the control group the abnormalities persisted (0% vs 7.5%, $p<0.05$) [26]. This study demonstrated that perioperative administration of thiopental significantly reduced the incidence of postoperative persistent neuropsychiatric complications. In the study, thiopental did not appear to decrease the frequency of embolization, but rather appeared to reduce its clinical expression presumably by decreasing the size of the resulting infarction.

The most appropriate infusion scheme for thiopental-induced neuroprotection was studied in 100 patients undergoing cardiac surgery with CPB [30]. The authors compared the neuroprotective effects of a single dose versus continuous infusion of sodium thiopental after CPB. Postoperative neuropsychiatric dysfunction occurred in 3 (6%) patients in the infusion group and 2 (4%) patients in the bolus group. The neuropsychiatric dysfunction persisted in the tenth postoperative day in only one patient, who was in the infusion group, and inotropic support requirements on separation from CPB did not differ between the two groups. Thus, sodium thiopental administered as a single bolus immediately before unclamping the aorta, without the need for EEG monitoring, achieved the same degree of brain protection as larger doses administered by infusion and titrated to burst suppression. However, administration via a single bolus did not reduce the need for inotropic support during separation from CPB [30].

Subsequently, the efficacy of thiopental in reducing the incidence of stroke was evaluated in a randomized clinical trial (RCT) in which 300 patients underwent elective cardiac surgery for coronary artery disease [27]. In this study, 149 patients were randomly assigned to receive thiopental and 151 patients received saline. The thiopental infusion was initially

rapidly administered to achieve an isoelectric EEG, was adjusted to sustain burst suppression, and was then terminated just after aortic decannulation. The primary outcome measure was pre and postoperative neurologic status on the second and fifth days. Neurologic sequelae were categorized as stroke, lethargy and psychological dysfunction, disorientations, combativeness and confusion. 5 patients in the thiopental group and 2 patients in the control group developed a postoperative stroke, with symptoms that persisted on the 10th postoperative day. The lack of differences in neurological outcomes observed between the two groups suggested that thiopental did not reduce major neurological sequelae.

In summary, there is conflicting evidence in humans for the neuroprotective effects of thiopental. The literature suggests that the neuroprotective effects of thiopental are unproven, and any potential benefit may be short term (10 days) [8].

Propofol

The effects of propofol on cerebral metabolism and cerebral blood flow (CBF) are similar to thiopental. However, compared with thiopental, propofol infusions result in a better flow-metabolism coupling with preserved CBF reactivity to changes in PaCO2 [31, 32].

The effect of propofol on the incidence and severity of perioperative cerebral injury was tested in a multicenter RCT in 225 patients who underwent elective cardiac valve surgery. Patients were randomly assigned to receive either propofol and sufentanyl infusion to maintain EEG suppression from aortic cannulation through the chest closure, or only sufentanyl infusion [33]. Patients underwent a battery of neurologic and neuropsychological tests preoperatively and on postoperative days 1–2, 5–7, and 50–70. Neurologic testing was based on the National Institute of Health Stroke Scale (NIHSS) and on the Western Perioperative Neurologic Scale (WPNS), while neuropsychological tests included the Digit Symbol subtest of the Wechsler Adult Intelligence Scale Revised, the Paired Associated Learning Subset of the Wechsler Memory Scale, The Trails A and B test, the Grooved Pegboard test, and the Letter Cancellation test. No differences were observed in the incidence and severity of adverse neurologic and neuropsychological function between the treatment and control group up to 2 months after surgery.

In a second RCT, 10 patients were randomly assigned to receive a propofol infusion at a rate of 6 mg/Kg/h until CBP, and 3 mg/Kg/h during CBP, and 10 control patients received isoflurane. In both groups, the tested hypnotic was titrated to maintain a bispectral index between 40 and 50 [34]. A neurologist performed a neurocognitive evaluation in all patients one day prior to surgery and on the third and sixth postoperative days. Trained anesthesiologists performed neuropsychological testing on the third and sixth postoperative days, including the mini mental state examination (MMSET) and the visual aural digit span test (VADST). Furthermore, in all patients, blood samples were collected for analysis of S-100β protein before anesthesia, after heparinization, 15 min after initiation of CPB, after protamine was administered after CPB, and 24 hours postoperatively. Despite an increase in S-100β protein levels, no overt neurological injury was detected in any of the patients and no differences in neuropsychological testing was observed between the treatment and control groups.

In conclusion, the two RCTs failed to demonstrate a neuroprotective effect of propofol [33, 34]. It is important to note that these two studies used study designs that greatly differed, which may have introduced a possible bias related to the methodological approach.

Ketamine

Ketamine is a non competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist that may reduce post-ischemic neuronal cell loss by preventing the excitotoxic injury caused by glutamate, by regulating apoptosis proteins and by interfering with inflammatory response [35–38].

The potential neuroprotective properties of ketamine, compared with that of remifentanil, were evaluated in a RCT in 106 patients undergoing elective open-heart cardiac surgery [39]. Patients were randomly assigned to receive a target controlled infusion (TCI) of propofol at 1–4 μg/ml in addition to a bolus of ketamine 2.5 mg/kg on anesthesia induction, followed by a maintenance infusion of ketamine at 125 μg/kg/min throughout the procedure. The control group received a TCI of propofol and remifentanil targeted at 1–4 μg/ml and 6–14 ng/ml, respectively. Neuropsychological testing was assessed the day before surgery, and at 1 week and 10 weeks after surgery. A wide range of cognitive domains were tested, including trailmaking A, trailmaking B, letter cancellation, groover pegboard, new adult reading test, symbol digit modalities test, Spielberg state anxiety, Spielberg trait anxiety, Beck depression inventory, Rey auditory verbal learning test, nonverbal memory, binary choice reaction time and visual reaction time. At 10 weeks postoperatively, there were no differences in neuropsychological test performance between the 2 groups. 10 (20%) patients in the ketamine group and 14 (25%) in the control group had deficits on two or more tests (P=NS). A limited benefit was observed in patients treated with ketamine, with a better performance on the trail-making B test. The results of this RCT suggested that ketamine did not reduce neuropsychological deficits, as there were no differences between neuropsychological outcomes in patients treated with ketamine compared with patients treated with remifentanil.

In a subsequent RCT, the efficacy of ketamine in attenuating postoperative cognitive decline (POCD) was evaluated in 52 patients scheduled for elective coronary artery bypass graft surgery and/or valve replacement/repair surgery with CPB [40]. Patients were randomly assigned to receive either an intravenous bolus of ketamine (0.5 mg/kg) or an equal volume of placebo (0.9% saline) during anesthesia induction. Neurological status and neurocognitive function was assessed preoperatively and 1 week after surgery. Neurological examination focused on detecting significant visual and auditory impairments, level of consciousness, cranial nerve function, motor strength, cerebellar ataxia, intention tremor, sensation, frontal lobe release signs, deep tendon and plantar reflexes, and gait ataxia. An additional total score was calculated using the Hachinski Ischemia Scale. A score of 44 was diagnostic of vascular dementia. The tests were comprised of standard clinical measures that were appropriate for use with subjects in the age group studied, which required minimal sensory or motor demands. The tests utilized three cognitive modalities: verbal recent memory, nonverbal recent memory, and executive function. To test verbal recent memory, Story Memory and Word List Memory subtests from the Repeatable Battery for the

Assessment of Neuropsychological Status were used. To test nonverbal recent memory, the Brief Visual Memory Test Revised was utilized. To test executive functions, Backward Digit Span, Semantic Fluency (i.e. 'name all the fruits and vegetables' [form A], 'all the animals in the zoo' [form B] that you can think of in 1min), and Phonemic Fluency (i.e. name all the words that you can think of that start with the letter 'S' (form A), and 'P' (form B) in 1min) were used. Depression was assessed with the Geriatric Depression Scale (15-item version). In this study, patients who received ketamine had a lower POCD; cognitive performance after surgery decreased by at least 2 standard deviations in 21 patients in the placebo group and only in 7 patients in the ketamine group ($p<0.001$).

The current literature suggests that a single dose of ketamine, when administered during induction of general anesthesia, effectively attenuates POCD when measured1 week after cardiac surgery.

Lidocaine

Lidocaine is a local anesthetic and class IB antiarrhythmic drug that crosses the blood brain barrier. Lidocaine may confer cerebral protection by causing a deceleration of the ischemic transmembrane ion shift, reduction of the cerebral metabolic rate, reduction of the ischemic excitotoxin release, modulation of the inflammatory response, and by preservation of cerebral blood flow [41–45]. The clinical effects of lidocaine on perioperative neuroprotection were tested in 4 RCTs in in 571 cardiac surgery patients, with conflicting results [46–49].

The effects of lidocaine on POCD after CPB was evaluated in 55 patients who underwent left heart valve surgery, and were randomized to receive either lidocaine or placebo [46]. In this study, lidocaine infusion was initiated on induction of general anesthesia and was continued for 48 hours. The infusion protocol was designed to deliver a 1 mg/kg "bolus" of lidocaine over 5 minutes, followed by 240 mg over the first hour and 120 mg over the second hour, and then 60 mg/h thereafter. Cognitive function was measured with six performance tests by 11 subscales (Rey figure, inspection time, Rey auditory verbal learning task, symbol digit modality test, trails A, trails B) and memory function with a self-rating inventory with two subscales. Two "control" inventories, one for depression and one for anxiety (two subscales) were also used. All patients were subjected to preoperative neuropsychological (NP) testing on the day prior to surgery, and again at 10 days, 10 weeks, and 6 months after surgery (with the exception of the memory inventory, which was only repeated at 10 weeks and 6 months). In this RCT, a significantly greater proportion of patients assigned to the placebo group showed "discrete" (as defined by the authors) decrements in NP test performance at the 10-day and 10-week postoperative time point, with a significant reduction as compared with preoperative results. In patients assigned to receive lidocaine, the results of NP testing demonstrated a better postoperative performance compared with patients who received a placebo (with the exception of the "Rey figure copy" test, in which a ceiling effect prevented significant change). In contrast, the improvements observed in the placebo group were significantly less in some tests and absent in others. According to this study, the use of lidocaine was associated with a better cognitive

performance in the postoperative period. Unfortunately, subsequent studies failed to definitively reproduce those findings.

In a subsequent RCT, the effects of lidocaine on cognitive dysfunction were evaluated only in the early postoperative period in 88 patients who underwent elective cardiac surgery for coronary artery disease [47]. Patients were randomly assigned to receive lidocaine as a bolus of 1.5 mg/kg over 5 min upon opening the pericardium, followed by a continuous infusion of 4mg/min until the end of the surgery. An additional dose of lidocaine (4 mg/kg) was administered to the priming solution of CPB. In the placebo group, normal saline was administered in the same volume and rate as that of 2% lidocaine. Neuropsychological tests were administered the day before surgery and 9 days after surgery. The tests included nine sub-scales: the Mental Control and Digit Span (forward and backward) subtests of the Wechsler Memory Scale (Chinese edition, Hunan Medical University, Hunan, China), measures of attention and concentration, the Visual Retention and Paired Associate Verbal Learning subtests of the Wechsler Memory Scale (Chinese edition, Hunan Medical University), measures of figural memory and verbal learning/memory, the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (Chinese edition, Hunan Medical University), a measure of psychomotor speed, the Halstead-Reitan Trail Making Test (Part A), a measure of hand-eye coordination, attention, and concentration, and the Grooved Pegboard Test (favored and unfavored hand), a measure of manual dexterity. Postoperative cognitive dysfunction (patients with deficits in 2 or more tests) occurred in 18 patients (40.0%) in the placebo group and in 8 patients (18.6%) in the lidocaine group ($p<0.05$). Thus, intraoperative administration of lidocaine significantly decreased the occurrence of early POCD.

More recently, 2 RCTs that tested the neuroprotective effects of lidocaine failed to confirm a reduction in POCD [48, 49]. In one of these trials, lidocaine was evaluated in 158 patients who underwent elective cardiac surgery for coronary artery disease and/or cardiac valve surgery. Patients randomly assigned to the treatment group received, on induction of general anesthesia, lidocaine as a bolus of 1 mg/Kg over 5 minutes, followed by 2 mg/min for 2 hours, and 1 mg/min thereafter for a total of 12 hours [48]. The neurocognitive tests were performed on the day before surgery, and were repeated at 10 and 25 weeks postoperatively. There were seven test scales utilized: Auditory-Verbal Learning for short-term verbal memory, Digit Span Forward and Backward (a subtest of the Wechsler Adult Intelligence Scale-Revised) for attention with overlay from short-term numerical memory and for short-term numerical memory and associated integration and manipulation functions, Digit Symbol and Digit Symbol A for psychomotor performance and the inherent requirement for integration of multiple cognitive processes, and Thurstone Word Fluency (two lists) for integrated cognition requiring organized thought and generation of associations to achieve a good score.

In the most recent RCT, lidocaine was evaluated in 182 randomized patients who underwent elective cardiac surgery for coronary artery disease or valve surgery [49]. The treatment group received lidocaine as a bolus of 1 mg/kg after induction of general anesthesia, followed by a continuous infusion at 4 mg/min for the first hour, 2 mg/min for the second hour, and 1 mg/min for the next 46 hours. The placebo group received normal saline

administered as a bolus and an infusion for 48 hours with an identical volume and rate as in the treatment group. Neuropsychological evaluation was conducted with a battery of 5 cognitive tests on the day before surgery and again at 6 weeks and 1 year after surgery, including the Short Story module of the Randt Memory Test (requires that subjects recall the details of a short story immediately after it was read to them and after a 30-minute delay, The Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test (requires subjects to repeat a series of digits that were orally presented to them both forward and, in an independent test, in the reverse order), Modified Visual Reproduction Test from the Wechsler Memory Scale (measures short and long-term figural memory and requires subjects to reproduce from memory several geometric shapes both immediately and after a 30-minute delay), The Digit Symbol subtest of the WAIS-R (a paper and pencil task that requires subjects to reproduce within 90 seconds as many coded symbols as possible in blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with symbols), and The Trail Making Test (part B) (requires subjects to connect, by drawing a line, a series of numbers and letters in sequence as quickly as possible). The study failed to demonstrate a neuroprotective effect of lidocaine. Additionally, diabetic patients assigned to receive lidocaine were more likely to suffer from cognitive decline at 6 weeks follow up. Furthermore, the multivariable linear regression analysis demonstrated that higher total doses of lidocaine were associated with increased neurocognitive decline in treated patients. A total dose of 35 mg/kg was approximated to be the threshold for the dose-dependent cognitive decline. In contrast to the overall findings of the study, exploratory multivariable analysis demonstrated that when the study sample was restricted to nondiabetic patients who received a lidocaine dose (<42.6 mg/kg), a protective effect of lidocaine on cognition was demonstrated. A marginally significant improvement in cognition was also detected at 1 year after surgery in those patients assigned to receive lidocaine, although this finding was limited by a substantial loss to follow up.

The study design used in these RCTs was extremely heterogeneous, with differences in 3 key variables: the timing and cognitive tests used to evaluate POCD, timing and dose of lidocaine administered, and patient selection. With regards to differences in timing and testing for cognitive evaluation, one study examined the POCD only in short-term follow up (9 days) [47], one in both short term and long-term follow up (10 days, 10 weeks, and 6 months) [46], and two in long-term postoperative follow-up (25 weeks, 6 months and 1 year) [48, 49]. With regards to differences in timing and dosing of lidocaine infusion, in two studies lidocaine was administered as a 48-hour continuous infusion [46, 49], in one study as a 12-hour continuous infusion [48], while in another study the lidocaine infusion was discontinued at the end of surgery [47]. With regards to possible biases related to patient selection, the enrollment criteria enrolled patients who underwent open and closed heart surgery (i.e. valve and CABG surgery) although the mechanisms of brain damage underlying these procedures may be different. The most recent evidence suggests that diabetic patients should possibly be studied separately from non-diabetic because of the unique pharmacodynamic effects of lidocaine in those patients. The authors, when explaining why their study failed to demonstrate any neuroprotective effects, also acknowledged some of these methodological differences. They pointed out that their infusion period was possibly too short, that they used an excessively high dose of lidocaine,

or that diabetic patients, in whom the paradoxical effects were observed, may be at increased risk for an adverse outcome. Lidocaine may possibly be neuroprotective in non-diabetic patients undergoing cardiac surgery with CBP, when a 48-hour infusion is administered with a total dose that does not exceed 35 mg. Conclusive data, however, are lacking.

Etomidate

Etomidate, a carboxylated imidazole derivative, is a non-barbiturate anesthetic. Etomidate pharmacologically acts through its similarity to [gamma]-aminobutyric acid (GABA) and stimulation of GABA receptors. Some preclinical studies have demonstrated a neuroprotective effect of etomidate through a depression of cerebral metabolism, the inhibition of postischemic hyperemia, and attenuation of vascular-mediated inflammation [50–54]. However, others have indicated that etomidate may exacerbate ischemic injury by inhibiting nitric oxide synthetase thereby intensifying the ischemic insult [55]. Finally, the use of etomidate for neuroprotection has fallen out of favor in clinical settings and there have been no RCTs to evaluate its neuroprotective efficacy.

CRITICAL PERSPECTIVE FOR FUTURE STUDIES

Requisites from Preclinical and Clinical Research

In order to fully understand and appreciate the biological complexity of cognitive decline, bidirectional translational studies are needed at both the preclinical and clinical level. Several limitations intrinsically affect clinical studies. For POCD research, there are issues related to “power” when identifying at-risk patients, as well as the lack of a firm diagnostic criteria and consensus over the neuropsychological evaluations [56]. Although neurocognitive test remain the primary method for diagnosing POCD, recent evidence suggests a role for novel biomarkers and neuroimaging to preemptively identify patients more susceptible to cognitive decline in the perioperative period [57].

In addition to well-designed and performed clinical studies, there is great importance in further developing relevant preclinical models to enable better translation of the molecular processes and drug development for cognitive decline. Animal models have been useful when investigating the cellular and molecular mechanisms underlying several human pathologies. Cognitive decline represents a major burden to our health care system, and the use of rodent models is currently offering insights into mechanisms as well as novel and safer therapeutics. These novel therapies may subsequently be translated in the clinic, and safer neuroprotective strategies may ensue. Over the past several years, animal models have significantly advanced our understanding in postoperative cognitive decline, neurotoxicity and neuroprotective strategies. For example, animal models have aided significantly to the characterization of the cellular and molecular response to surgical trauma [58], the contribution of surgery to neuroinflammatory [59, 60] and neurodegenerative processes [61,62], and the impact of anesthetics on the developing brain [63]. Indeed, animal models do not fully recapitulate the complexity of these conditions in humans. Recent work suggests that mice and humans respond differently in gene patterns when exposed to similar challenges like sepsis, trauma, burns and endotoxemia. This highlights the point that mouse models are in many ways limited when compared to human pathological conditions [59].

Research on POCD faces similar challenges, and the cognitive decline present in mice is often limited (more closely related to a human-type delirium response than prolonged neurocognitive impairments). As rodents are more resilient to injury, there are clear differences between that observed in rodent models and the recovery and persistent cognitive decline observed in some postoperative patients [64].

Memory processes are complex, and the cognitive reserve largely reflects the ability of some individuals to recover faster after surgery without being subjected to the negative effects of anesthesia and/or surgery. Such higher cognitive functions are difficult to be dissected and reproduced in rodent models, yet exacerbating factors due to co-morbidities like Alzheimer's disease and metabolic syndrome significantly delay recovery in animal models similar to that reported in humans [65, 66].

Laboratories worldwide are currently pursuing studies designed to better characterize the temporal resolution of soluble mediators that affect CNS functions after surgery, such as example pro-inflammatory cytokines. The elucidation of these pathways is also being replicated in clinical studies. For example, markers of neuroinflammation and neurodegeneration have been found to be increased after surgery and may be effectively modulated by anesthetic agents [67, 68]. Overall, transformational efforts directed to combine preclinical, clinical, and epidemiological studies will be required to further understand the pathogenesis of cognitive decline, how anesthetics may contribute to these processes, and which therapies can be translated to patient care.

In humans, cognition is the result of activities in multiple complex, distributed, and interacting neuronal circuits that underlie specific information-processing functions. Therefore, comprehensive neuropsychological assessment requires a battery of tests that assess a variety of cognitive domains. No consensus exists as to which are the best neuropsychometric tests for detecting and quantifying neurological damage and POCD. Similarly, there is no agreement on the optimal timing of postoperative testing with regards to research or for day-to-day clinical use [69–71].

INTRAVENOUS ANESTHETICS NEUROTOXICITY: THE VERY YOUNG AND THE ELDERLY

In pediatric and elderly patients, intravenous anesthetics may elicit neurotoxic effects by interfering with brain development or by triggering chronic neurodegenerative disease, respectively [17]. The goals of anesthesia are to induce a "transient" and "fully reversible" loss of consciousness and neurocognitive functions. Nevertheless, depending on the anesthetic regimen adopted and the accessory drugs utilized, early postoperative cognitive recovery is often delayed. Anesthetic drugs with longer a half-life, as well as issues related to the patient or surgery, can result in a delay in the early postoperative neurocognitive recovery and increase the risk of postoperative delirium [11, 72]. Cognitive changes are usually transient, and return to normal within hours to days. The cognitive impairments may persist for weeks (for one week after anesthesia in up to 25% of patients, and for up to 3 months after anesthesia in almost 10% of patients), and in some cases may be a precursor for further decline [11, 72–77]. Currently the term POCD is defined in the literature to include

acute (< 1 week), intermediate (< 3 months), and long-term (1–2 years) cognitive decline after surgery [78]. The pathogenesis of early and long-term postoperative cognitive dysfunction is unclear. However, age, alcohol abuse, low baseline cognition, hypoxia, hypotension and type of surgery have been alleged to contribute to this problem. The choice of anesthetic drugs can also affect postoperative cognitive behavior, because residual levels of anesthetics can produce change in central nervous system activity [11, 72]. The use of anesthetics that are rapidly eliminated, and with minimal metabolic breakdown, may reduce postoperative cognitive dysfunction in elderly surgical patients by facilitating a faster recovery from general anesthesia. Thus, the use of shorter-acting anesthetic and analgesic drugs may contribute to a reduced postoperative cognitive impairment and confusion in elderly patients [79].

Pediatric anesthetic neurotoxicity is related to many variables in addition to the potentially toxic effects of anesthesia, including maternal health, use of antecedent medications and other exposures during pregnancy, labor, and delivery, as well as confounding factors due to indications for surgery, preexisting medical conditions in the child, and environmental or ecological characteristics [80]. In one study, DiMaggio and colleagues demonstrated an association between pediatric anesthetic agents during surgery and subsequent learning or behavioral problems in children [80]. Although there has been an increasing acceptance of the basic laboratory evidence, and a movement toward investigations of potential interventions to mitigate these effects, there remain distinct challenges in translating the bench science to bedside practice. Although infant rats have a relatively short vulnerable synaptogenic period, in contrast to humans, and relatively high doses of anesthetic agents and long duration of anesthetic exposure have been used to trigger apoptosis in published reports, any extrapolation to humans may require frequent, repeated, or lengthy exposures [81–83]. The difficulty in monitoring neonatal rodents compared with human infants also raises the possibility that the effects in rodents might be due to hypoxia or other physiological or metabolic disturbances rather than due to anesthetic agents. Notably, most studies were not performed in animals undergoing surgery. In one study, however, in which animals received anesthesia in the presence of painful stimulation, ketamine attenuated pain-induced cell death and impaired neurocognitive behaviors induced by neonatal exposure to inflammatory pain [81–83].

Given this complexity, observational studies are hard put to demonstrate unequivocal associations or risk.

CONCLUSION

Several clinical studies have evaluated the potential neuroprotective effects of various intravenous anesthetics, including thiopental, propofol, ketamine, lidocaine, etomidate and NA-1. Currently available results, despite strong preclinical evidence, have yielded conflicting results and inconclusive evidence. Because perioperative brain damage lead to substantial morbidity with new neurological deficits and/or POCD, it is absolutely necessary to have effective therapies to minimize the clinical impact of this complication [8].

There are many lessons to be learned from available preclinical and clinical research on intravenous anesthetics used for perioperative neuroprotection, which now provides the critical perspective necessary to design future studies. Recent trends in research are also evaluated the potential neuroprotectant effects of inhalational anesthetics including halogenated vapors (isoflurane, sevoflurane and desflurane) and noble gasses (xenon and argon) with inconclusive results [84–89]. In addition to the need for consistent preclinical evidence necessary to support the rationale to design a clinical trial, it is important to assess "*in vivo*" pharmacokinetic properties in order to define the most appropriate dosing and timing of infusion. It is also necessary to define the most appropriate approach for detecting the clinical impact on cognitive function by using appropriate evaluation testing (at the most appropriate timing) or diagnostic tools (intraoperative EEG or transcranial Doppler) [90, 91]. Furthermore, currently available studies have enrolled relatively small sample sizes. As the incidence of POCD is estimated to be between 5 and 25%, these small sample sizes may be inadequate to demonstrate a clinically relevant effect.

The current literature, although inconclusive, suggests that intravenous anesthetics may induce both perioperative neuroprotection and potentially neurotoxic effects. A critical perspective analysis on data extracted from RCTs can contribute to identifying those patients in whom a specific anesthetic approach may be beneficial or harmful, and may also contribute to defining the methodological infrastructure by which future studies on perioperative pharmacologic neuroprotection should be designed.

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