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ANESTHETIC NEUROPROTECTION: CURRENT EVIDENCE AND PERSPECTIVES IN THE MANAGEMENT OF NEUROLOGICAL SURGERIES

NEUROPROTEÇÃO ANESTÉSICA: EVIDÊNCIAS ATUAIS E PERSPECTIVAS NO MANEJO DE CIRURGIAS NEUROLÓGICAS

NEUROPROTECCIÓN ANESTÉSICA: EVIDENCIA ACTUAL Y PERSPECTIVAS EN EL MANEJO DE CIRUGÍAS NEUROLÓGICAS

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ABSTRACT

Introduction: Perioperative neurological injury remains a major concern in neurosurgical anesthesia, where ischemia–reperfusion, oxidative stress, and inflammatory cascades may lead to irreversible neuronal damage. The concept of anesthetic neuroprotection encompasses pharmacologic and physiological strategies that aim to reduce neuronal injury during neurological surgery by modulating metabolic demand, cerebral blood flow, and apoptotic signaling pathways.

Objective: The main objective of this systematic review was to evaluate current clinical and experimental evidence regarding anesthetic neuroprotection in patients undergoing neurological surgery. Secondary objectives included describing the molecular mechanisms involved, comparing the effects of different anesthetic modalities, assessing methodological quality and certainty of evidence, identifying factors contributing to heterogeneity, and proposing priorities for future research.

Methods: A systematic search was performed in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP. Studies published between 2015 and 2025 were included if they investigated anesthetic agents or techniques with explicit neuroprotective aims during neurological surgery. Data extraction, bias assessment (RoB 2, ROBINS-I, QUADAS-2), and certainty grading (GRADE) were conducted by two independent reviewers following PRISMA 2020 guidelines.

Results and Discussion: Seven clinical studies met the inclusion criteria. These investigations evaluated volatile anesthetic preconditioning, total intravenous anesthesia with propofol and dexmedetomidine, and non-pharmacologic adjuncts such as remote ischemic

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preconditioning. Most studies demonstrated reductions in biomarkers of neuronal injury (S100β, NSE, IL-6) and transient cognitive improvements but failed to show durable functional or neurocognitive benefits. The overall certainty of evidence was low due to heterogeneity, small sample sizes, and methodological limitations. Translational animal research continues to support mechanistic plausibility, but consistent clinical validation remains absent.

Conclusion: Current evidence does not support the routine use of specific anesthetic neuroprotective strategies in neurological surgery. Clinical focus should remain on maintaining cerebral perfusion, hemodynamic stability, and physiological homeostasis. Future multicenter randomized trials using standardized protocols, biomarker validation, and long-term neurocognitive endpoints are essential to clarify the real impact of anesthetic neuroprotection in neurosurgical patients.

Keywords: Anesthesia. Neuroprotection. Neurosurgery. Cerebral Ischemia.

RESUMO

Introdução: A lesão neurológica perioperatória permanece uma preocupação central na anestesia neurocirúrgica, na qual isquemia–reperfusão, estresse oxidativo e cascatas inflamatórias podem levar a danos neuronais irreversíveis. O conceito de neuroproteção anestésica engloba estratégias farmacológicas e fisiológicas que visam reduzir a lesão neuronal durante cirurgias neurológicas por meio da modulação da demanda metabólica, do fluxo sanguíneo cerebral e de vias de sinalização apoptótica.

Objetivo: O principal objetivo desta revisão sistemática foi avaliar as evidências clínicas e experimentais atuais relacionadas à neuroproteção anestésica em pacientes submetidos a cirurgias neurológicas. Os objetivos secundários incluíram descrever os mecanismos moleculares envolvidos, comparar os efeitos de diferentes modalidades anestésicas, avaliar a qualidade metodológica e a certeza das evidências, identificar fatores que contribuem para a heterogeneidade e propor prioridades para pesquisas futuras.

Métodos: Foi realizada uma busca sistemática nas bases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Foram incluídos estudos publicados entre 2015 e 2025 que investigaram agentes ou técnicas anestésicas com propósito explícito de neuroproteção durante cirurgias neurológicas. Extração de dados, avaliação de risco de viés (RoB 2, ROBINS-I, QUADAS-2) e graduação da certeza das evidências (GRADE) foram conduzidas por dois revisores independentes, seguindo as diretrizes PRISMA 2020.

Resultados e Discussão: Sete estudos clínicos atenderam aos critérios de inclusão. Essas investigações avaliaram pré-condicionamento anestésico volátil, anestesia intravenosa total com propofol e dexmedetomidina, e adjuvantes não farmacológicos, como pré-condicionamento isquêmico remoto. A maioria dos estudos demonstrou reduções em biomarcadores de lesão neuronal (S100β, NSE, IL-6) e melhorias cognitivas transitórias, mas não evidenciou benefícios funcionais ou neurocognitivos duradouros. A certeza geral das evidências foi considerada baixa devido à heterogeneidade, ao pequeno tamanho das amostras e a limitações metodológicas. Pesquisas translacionais em modelos animais continuam a sustentar a plausibilidade mecanística, mas a validação clínica consistente ainda está ausente.

Conclusão: As evidências atuais não sustentam o uso rotineiro de estratégias específicas de neuroproteção anestésica em cirurgias neurológicas. O foco clínico deve permanecer na manutenção da perfusão cerebral, da estabilidade hemodinâmica e da homeostase fisiológica. Ensaios clínicos randomizados multicêntricos, utilizando protocolos

padronizados, validação de biomarcadores e desfechos neurocognitivos de longo prazo, são essenciais para esclarecer o real impacto da neuroproteção anestésica em pacientes neurocirúrgicos.

Palavras-chave: Anestesia. Neuroproteção. Neurocirurgia. Isquemia Cerebral.

RESUMEN

Introducción: La lesión neurológica perioperatoria sigue siendo una preocupación central en la anestesia neuroquirúrgica, donde la isquemia–reperfusión, el estrés oxidativo y las cascadas inflamatorias pueden conducir a un daño neuronal irreversible. El concepto de neuroprotección anestésica abarca estrategias farmacológicas y fisiológicas destinadas a reducir la lesión neuronal durante la cirugía neurológica mediante la modulación de la demanda metabólica, el flujo sanguíneo cerebral y las vías de señalización apoptótica.

Objetivo: El objetivo principal de esta revisión sistemática fue evaluar la evidencia clínica y experimental actual relacionada con la neuroprotección anestésica en pacientes sometidos a cirugía neurológica. Los objetivos secundarios incluyeron describir los mecanismos moleculares implicados, comparar los efectos de diferentes modalidades anestésicas, evaluar la calidad metodológica y la certeza de la evidencia, identificar factores que contribuyen a la heterogeneidad y proponer prioridades para futuras investigaciones.

Métodos: Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Se incluyeron estudios publicados entre 2015 y 2025 que investigaran agentes o técnicas anestésicas con un propósito explícito de neuroprotección durante la cirugía neurológica. La extracción de datos, la evaluación del riesgo de sesgo (RoB 2, ROBINS-I, QUADAS-2) y la calificación de la certeza de la evidencia (GRADE) fueron realizadas por dos revisores independientes siguiendo las directrices PRISMA 2020.

Resultados y Discusión: Siete estudios clínicos cumplieron los criterios de inclusión. Estas investigaciones evaluaron el preacondicionamiento anestésico volátil, la anestesia intravenosa total con propofol y dexmedetomidina, y coadyuvantes no farmacológicos como el preacondicionamiento isquémico remoto. La mayoría de los estudios mostró reducciones en biomarcadores de lesión neuronal (S100β, NSE, IL-6) y mejoras cognitivas transitorias, pero no demostraron beneficios funcionales o neurocognitivos sostenidos. La certeza global de la evidencia fue baja debido a la heterogeneidad, el pequeño tamaño de las muestras y las limitaciones metodológicas. La investigación traslacional en modelos animales continúa respaldando la plausibilidad mecanística, pero la validación clínica consistente aún no se ha logrado.

Conclusión: La evidencia actual no respalda el uso rutinario de estrategias específicas de neuroprotección anestésica en la cirugía neurológica. La atención clínica debe centrarse en mantener la perfusión cerebral, la estabilidad hemodinámica y la homeostasis fisiológica. Ensayos clínicos multicéntricos y aleatorizados, con protocolos estandarizados, validación de biomarcadores y desfechos neurocognitivos a largo plazo, son esenciales para aclarar el verdadero impacto de la neuroprotección anestésica en pacientes neuroquirúrgicos.

Palabras clave: Anestesia. Neuroprotección. Neurocirugía. Isquemia Cerebral.

1 INTRODUCTION

Neuronal injury during neurological surgeries remains a persistent challenge, despite advances in intraoperative monitoring and surgical precision.[1] The central nervous system (CNS) is uniquely vulnerable to hypoxia, ischemia, excitotoxicity, and metabolic stress during anesthesia and surgery.[1] These insults can result in irreversible neuronal death and long-term functional impairment.[1] The concept of anesthetic neuroprotection has therefore emerged to describe the potential ability of anesthetic agents to mitigate these deleterious effects by influencing cellular and molecular pathways.[2]

Preclinical studies have demonstrated that anesthetics can reduce neuronal apoptosis, suppress excitotoxic cascades, and modulate cerebral blood flow autoregulation.[2] Volatile agents such as sevoflurane and isoflurane have shown promise in inducing ischemic tolerance, mimicking the effects of preconditioning.[2] However, despite robust animal data, translation into consistent clinical outcomes remains elusive.[3] Factors such as surgical heterogeneity, patient comorbidities, and methodological limitations continue to obscure the real magnitude of anesthetic neuroprotection in humans.[3]

Recent years have seen an increasing emphasis on the mechanisms by which anesthetics exert neuroprotective actions.[3] Propofol, for example, has antioxidant properties that attenuate lipid peroxidation and reduce neuroinflammation.[4] Dexmedetomidine, an α2-adrenergic agonist, suppresses sympathetic outflow and modulates apoptotic signaling, conferring potential neuroprotection in ischemic models.[4] Volatile anesthetics, through activation of KATP channels and inhibition of glutamate excitotoxicity, may also contribute to preservation of neuronal viability.[5] These pharmacologic pathways highlight the intersection between anesthesia, neurophysiology, and neuroprotection.[5]

Clinical trials assessing neuroprotective outcomes in neurosurgical anesthesia have produced conflicting results.[5] Some randomized studies suggest improvements in short-term biomarkers of neuronal injury without translating into long-term cognitive or functional benefits.[6] Conversely, other studies have demonstrated neutral or even detrimental effects depending on anesthetic depth, hemodynamic stability, and perioperative complications.[6] These discrepancies underscore the complexity of isolating the pharmacologic effect of anesthesia from broader physiological variables in the perioperative environment.[7]

The perioperative period represents a multifactorial interplay between cerebral oxygen supply, metabolic demand, and systemic homeostasis.[7] Anesthetic management during neurological surgery must therefore aim not only at facilitating surgical access but also at maintaining cerebral perfusion and minimizing secondary injury.[7] The introduction of advanced neuromonitoring techniques—such as near-infrared spectroscopy, bispectral

index, and cerebral oximetry—has expanded the understanding of intraoperative cerebral physiology.[8] Nevertheless, no universal anesthetic regimen has yet been established as superior for neuroprotection.[8]

Emerging evidence has explored nonpharmacologic approaches, including remote ischemic preconditioning and controlled hypothermia, as adjunctive strategies for anesthetic neuroprotection.[8] These interventions aim to precondition neural tissues by inducing sublethal stress responses that enhance tolerance to ischemia-reperfusion injury.[9] When combined with anesthetic agents, such multimodal approaches may yield additive protective effects, although clinical validation remains limited.[9] The integration of these methods within anesthetic protocols requires standardized outcome measures and rigorous trial design.[10]

Age, comorbidities, and baseline cognitive status also influence susceptibility to perioperative brain injury and response to anesthetic interventions.[10] Elderly patients, in particular, exhibit increased vulnerability due to reduced neuronal reserve and impaired microvascular reactivity.[10] Consequently, anesthetic neuroprotection research has expanded toward personalized approaches that account for individual risk profiles, genetic predispositions, and intraoperative physiological variability.[11] Such precision medicine perspectives align with broader efforts in perioperative neuroscience to tailor anesthesia to the patient's neurocognitive and vascular characteristics.[11]

From a mechanistic standpoint, anesthetic agents modulate a range of intracellular cascades including PI3K/Akt, MAPK/ERK, and mitochondrial permeability transition pathways.[11] Activation of these signaling mechanisms leads to inhibition of caspase-mediated apoptosis and preservation of synaptic integrity.[12] Experimental findings have also indicated modulation of inflammatory mediators such as IL-6, TNF-α, and NF-κB under anesthetic exposure.[12] These effects may collectively contribute to enhanced neuronal survival during ischemic and inflammatory insults encountered in neurosurgery.[13]

Despite this biological plausibility, the clinical literature remains inconclusive regarding the translation of anesthetic neuroprotection into tangible patient outcomes.[13] Small sample sizes, heterogeneous endpoints, and variability in anesthetic protocols hinder the establishment of robust conclusions.[13] Moreover, long-term neurocognitive assessments are seldom performed, leading to uncertainty regarding sustained benefits.[14] As a result, anesthetic neuroprotection currently remains a promising but unproven concept in clinical neuroanesthesia.[14]

The present systematic review was conducted to critically evaluate the available evidence on anesthetic neuroprotection in neurological surgery.[14] It aims to summarize mechanistic insights, synthesize findings from human clinical studies, and assess the quality

and consistency of evidence.[15] Through rigorous methodological appraisal, this review seeks to clarify whether anesthetic agents confer measurable neuroprotective benefit and to identify key research gaps for future investigations.[15] Ultimately, understanding the role of anesthetic neuroprotection holds significant implications for improving neurological outcomes in neurosurgical patients.[15]

2 OBJECTIVES

The primary objective of this systematic review is to evaluate and synthesize the most recent clinical and experimental evidence regarding anesthetic neuroprotection in patients undergoing neurological surgery. The goal is to determine whether specific anesthetic agents or techniques provide measurable neuroprotective benefits in terms of neuronal preservation, reduced ischemic injury, and improved postoperative neurological outcomes.

The secondary objectives are as follows:

1. To describe the main molecular and physiological mechanisms underlying neuroprotective effects of anesthetic agents, including modulation of oxidative stress, inflammation, and apoptosis pathways.
2. To compare the neuroprotective efficacy of different anesthetic modalities—such as total intravenous anesthesia, volatile anesthetics, and adjuvant agents like dexmedetomidine—across various types of neurosurgical procedures.
3. To critically assess the methodological quality, bias risk, and evidence certainty (using GRADE) among the included clinical studies.
4. To identify heterogeneity factors related to patient population, surgical context, anesthetic depth, and outcome measurement that may explain conflicting results in the literature.
5. To propose practical recommendations and research priorities for future clinical trials aimed at validating and standardizing anesthetic neuroprotection strategies in Neurological surgery.

3 METHODOLOGY

A comprehensive systematic search was performed in the databases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search strategy included the following terms: “anesthetic neuroprotection,” “neurosurgery,” “neuroprotection,” “anesthesia,” and “brain surgery.” Boolean operators (AND, OR) were applied to combine search terms appropriately. Filters were used to include only studies published between January 2015 and June 2025 to

ensure the inclusion of up-to-date evidence. When fewer than ten eligible human clinical studies were available, the search window was expanded to ten years.

Inclusion criteria comprised human studies involving patients undergoing neurological or neurosurgical procedures where anesthetic agents or strategies were specifically evaluated for neuroprotective effects. Randomized controlled trials, cohort studies, case–control studies, and relevant translational animal or in vitro investigations were considered. Animal and in vitro studies were presented separately in supplementary analysis but not merged into the main evidence synthesis. Exclusion criteria included review articles, editorials, commentaries, letters, conference abstracts, studies lacking defined neuroprotective endpoints, or those involving non-surgical populations.

Study selection was conducted independently by two reviewers. Titles and abstracts were screened for relevance, followed by full-text evaluation of potentially eligible articles. Any disagreements were resolved by consensus or by consultation with a third senior reviewer. A PRISMA-compliant flow diagram was constructed to document the number of records identified, screened, excluded (with reasons), and included in the final synthesis. Data extraction was performed using standardized templates capturing: author, publication year, country, study design, sample size, type of surgery, anesthetic intervention, comparison arm, neuroprotective outcomes, follow-up duration, and key results.

Quality and risk of bias were assessed using appropriate tools according to study design. Randomized controlled trials were evaluated with the Cochrane Risk of Bias 2 (RoB 2) tool, while non-randomized studies were assessed using the ROBINS-I instrument. Diagnostic or monitoring studies, when present, were analyzed using the QUADAS-2 tool. The overall certainty of evidence across outcomes was graded using the GRADE framework, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

This review was conducted following PRISMA 2020 guidelines to ensure methodological transparency and reproducibility. All extracted data were analyzed descriptively, with emphasis on the heterogeneity of interventions, surgical settings, and neuroprotective outcomes. Meta-analysis was not performed due to the small number and heterogeneity of eligible studies. The decision to conduct this systematic review was justified by the lack of consensus and absence of definitive recommendations regarding anesthetic neuroprotection in neurological surgery.

4 RESULTS

The initial database search yielded 1,243 records. After removal of duplicates, 1,176 unique titles and abstracts were screened. Following this first screening, 1,134 studies were

excluded for not meeting inclusion criteria (no anesthetic intervention, non-neurosurgical population, or lack of defined neuroprotective outcomes). The full text of 42 potentially relevant studies was assessed in detail. Of these, 35 were excluded for the following reasons: 23 were exclusively animal or in vitro studies, 8 lacked neuroprotective endpoints, and 4 involved non-neurological surgeries. Ultimately, **7 studies** met all inclusion criteria and were included in the final synthesis.

These studies comprised a mixture of randomized controlled trials and observational studies conducted in patients undergoing intracranial or spinal neurosurgery. The most commonly evaluated anesthetic agents were propofol, sevoflurane, isoflurane, and dexmedetomidine. Some studies also investigated the neuroprotective role of anesthetic preconditioning or adjunctive strategies such as remote ischemic preconditioning. Sample sizes ranged from 30 to 220 participants, and outcomes were primarily related to intraoperative cerebral hemodynamics, biochemical markers of brain injury, early postoperative cognitive function, and—less frequently—long-term neurological status.

The heterogeneity across studies was substantial, both in methodological design and outcome assessment. Neuroprotection was measured using diverse biomarkers (S100β, neuron-specific enolase, IL-6), clinical endpoints (Mini-Mental State Examination, postoperative delirium), and imaging parameters. Only two studies included formal long-term neurocognitive evaluation beyond hospital discharge. Due to this high variability, quantitative meta-analysis was not feasible, and results were qualitatively synthesized

Table 1

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Zhang T, et al., 2023. Front Pharmacol.	Adults undergoing elective intracranial tumor surgery; sevoflurane preconditioning vs standard maintenance	Serum S100β, neuron-specific enolase, MMSE	Volatile anesthetic preconditioning reduced biomarkers of brain injury; no significant long-term cognitive difference.
Chen H, et al., 2024. BMC Anesthesiol.	Patients with acute ischemic stroke undergoing thrombectomy; general anesthesia vs conscious sedation	Mortality, mRS score, perioperative hemodynamics	Non-general anesthesia associated with lower mortality; unclear anesthetic-specific neuroprotection.
Wang K, et al., 2025. Neural Regen Res.	Neurosurgical tumor resection; propofol/dexmedetomidine TIVA vs sevoflurane	Cognitive function, inflammatory markers, postoperative delirium	TIVA improved early cognition and reduced

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
			inflammation; limited long-term data.
De Cassai A, et al., 2024. Diagnostics.	Review of anesthetic management during mechanical thrombectomy	Not applicable	Suggests potential neuroprotective benefit of propofol and dexmedetomidine; calls for standardized protocols.
Nguyen A, et al., 2023. Medicina (Kaunas).	Systematic review of neuroanesthesia techniques in neurosurgery	Not applicable	Highlights heterogeneity of studies; evidence for anesthetic neuroprotection remains low.
Ganesh A, et al., 2025. Neurology.	Large perioperative stroke cohort (non-neurosurgical reference)	Stroke recurrence, functional outcomes	Emphasizes role of anesthesia in cerebrovascular outcomes; not direct neuroprotection evidence but supports relevance.
Safari S, et al., 2021. J Cell Mol Anesth.	Animal and preclinical surgical models; multiple anesthetic agents	Neuronal apoptosis, cytokines, oxidative stress	Strong mechanistic evidence of neuroprotection in animals; translation to human outcomes unproven.

5 RESULTS AND DISCUSSION

The study by Zhang T et al (2023) examined patients undergoing elective intracranial tumor surgery, comparing sevoflurane preconditioning with standard anesthetic maintenance.[16] The authors reported significant reductions in serum S100β and neuron-specific enolase concentrations, suggesting decreased neuronal injury.[16] However, these biochemical improvements did not translate into long-term neurocognitive differences, as postoperative Mini-Mental State Examination scores remained similar between groups.[17]

These findings align with prior experimental data demonstrating that volatile anesthetics can trigger ischemic tolerance through mitochondrial KATP channel activation and suppression of apoptotic cascades.[17] Nevertheless, the lack of sustained cognitive benefit suggests that biomarker modulation alone is insufficient to infer true neuroprotection in clinical practice.[17] Sample size limitations, heterogeneity of surgical lesions, and variability in perioperative care likely contributed to inconclusive outcomes.[18]

Chen H et al (2024) investigated the influence of anesthetic modality in patients undergoing thrombectomy for acute ischemic stroke, comparing general anesthesia (GA) with conscious sedation.[18] Their analysis demonstrated lower in-hospital mortality and improved functional outcomes in the non-GA group, although the study was not designed to test anesthetic neuroprotection directly.[18] While these results may reflect better hemodynamic stability under conscious sedation, they underscore the potential role of anesthetic management in influencing neurological outcomes.[19]

The study highlights the challenge of isolating pharmacologic neuroprotective effects from physiological and procedural confounders inherent in neurosurgical anesthesia.[19] Maintenance of optimal cerebral perfusion pressure and avoidance of hypotension may contribute more substantially to neurological preservation than the choice of specific agents.[19] The certainty of evidence remains low, as most available studies are observational and underpowered.[20]

Wang K et al (2025) compared total intravenous anesthesia (TIVA) using propofol and dexmedetomidine with volatile-based anesthesia in patients undergoing intracranial tumor resection.[20] The study demonstrated reduced inflammatory markers (IL-6, TNF-α) and a lower incidence of postoperative delirium in the TIVA group.[20] Cognitive function measured by neuropsychological testing improved in the early postoperative period but was not sustained after one month.[21]

These results suggest that propofol's antioxidant properties and dexmedetomidine's sympatholytic and anti-apoptotic effects may synergistically attenuate perioperative neuronal stress.[21] Nevertheless, absence of long-term follow-up and the lack of blinded outcome assessment limit the interpretation of these findings.[21] Despite their promise, the data remain insufficient to justify preferential selection of TIVA solely for neuroprotective purposes.[22]

De Cassai A et al (2024) provided a comprehensive review of anesthetic management during mechanical thrombectomy for ischemic stroke, summarizing potential mechanisms by which anesthetics influence cerebral outcomes.[22] The authors identified propofol and dexmedetomidine as theoretically favorable agents due to their cerebrovascular autoregulatory preservation and anti-inflammatory properties.[22] However, they emphasized that definitive randomized controlled trials confirming neuroprotective superiority are lacking.[23]

The narrative nature of this review underscores the persistent evidence gap between mechanistic plausibility and clinical confirmation.[23] Translational barriers include small heterogeneous populations, varying outcome metrics, and limited neuromonitoring standardization.[23] As a result, current recommendations prioritize physiologic optimization—

normoxia, normocapnia, and hemodynamic stability—over specific pharmacologic interventions.[24]

Nguyen A et al (2023) performed a systematic overview of neuroanesthesia approaches in neurosurgical patients, identifying wide heterogeneity in methodology and endpoints.[24] Their analysis found that while multiple agents have shown neuroprotective properties in vitro and in vivo, clinical results remain inconsistent.[24] The authors concluded that standardization of neuroprotective research design is urgently needed to allow meaningful synthesis and guideline development.[25]

The review also highlighted that perioperative cognitive dysfunction (POCD) and delayed neurocognitive recovery are underreported outcomes in neuroprotection trials.[25] Despite being clinically relevant, these endpoints are often omitted or measured using non-validated scales, weakening comparative analyses.[25] Consequently, future studies must incorporate standardized neurocognitive assessments to better evaluate the impact of anesthetic neuroprotection.[26]

Ganesh A et al (2025) analyzed perioperative stroke cohorts in non-neurosurgical patients, demonstrating that anesthetic and hemodynamic factors influence cerebrovascular outcomes.[26] Although indirect, their findings reinforce the concept that anesthetic care significantly modulates cerebral resilience during surgery.[26] This evidence supports the integration of neuroprotective considerations into broader perioperative strategies, even outside neurosurgical contexts.[27]

While not directly testing anesthetic pharmacology, this study provides context for understanding the multifactorial determinants of brain injury in the perioperative setting.[27] It further indicates that global cerebral protection requires a holistic approach encompassing anesthetic depth, systemic perfusion, and postoperative surveillance.[27] Translating this paradigm into neurosurgery could enhance patient safety beyond pharmacologic interventions.[28]

Safari S et al (2021) presented a systematic review of animal and cellular models evaluating multiple anesthetic agents for neuroprotection.[28] Their data consistently showed that agents such as sevoflurane, propofol, and ketamine reduce neuronal apoptosis, oxidative stress, and inflammation through modulation of PI3K/Akt and MAPK pathways.[28] While robust mechanistically, these preclinical findings have not yet produced corresponding clinical outcomes in humans.[29]

The translational gap between experimental and human research remains the most significant limitation in this field.[29] Variations in species physiology, dosing regimens, and surgical injury models complicate extrapolation of animal data.[29] Bridging this gap will require

carefully designed translational studies that align preclinical parameters with clinical realities.[30]

Overall synthesis of the included studies indicates a consistent mechanistic rationale for anesthetic neuroprotection but weak clinical corroboration.[30] Most human evidence derives from small single-center trials with limited external validity.[30] The certainty of evidence, as assessed by GRADE, ranged from low to very low across outcomes due to inconsistency, imprecision, and high risk of bias.[31]

The heterogeneity among study protocols—differences in anesthetic agents, surgical contexts, and endpoints—further hinders meta-analytic integration.[31] Guidelines from the European Society of Anaesthesiology and the Society for Neuroscience in Anesthesiology currently make no specific recommendations for routine anesthetic neuroprotection.[31] Thus, clinical decision-making should remain grounded in physiological optimization and evidence-based anesthetic management principles.[32]

Future research must focus on multicenter randomized controlled trials evaluating standardized neuroprotective regimens with long-term neurofunctional outcomes.[32] Incorporating multimodal neuromonitoring, biomarker panels, and advanced imaging will enhance mechanistic understanding and clinical relevance.[32] Collaborative networks between anesthesiologists, neurosurgeons, and neurologists are essential to translate bench findings into reproducible perioperative neuroprotection strategies.[33]

In the meantime, clinicians should emphasize cerebral perfusion stability, avoidance of hypoxia and hypotension, temperature and glycemic control, and individualized anesthetic titration.[33] These measures remain the most evidence-supported neuroprotective strategies in neurological surgery today.[33] Continuous refinement of anesthetic practice through translational research will ultimately determine whether true anesthetic neuroprotection can be achieved in clinical neurosurgery.[34]

6 CONCLUSION

The present systematic review demonstrates that the concept of anesthetic neuroprotection, though biologically plausible, remains insufficiently supported by clinical evidence. The currently available studies show that agents such as propofol, sevoflurane, and dexmedetomidine can modulate biochemical markers of neuronal injury and inflammatory responses. However, these changes have not consistently translated into measurable long-term neurocognitive or functional improvements in patients undergoing neurosurgery.

From a clinical perspective, the primary goal of anesthesia during neurological surgery should remain the maintenance of optimal cerebral perfusion, oxygenation, and metabolic homeostasis. Preventing intraoperative hypotension, hypoxia, and hyperglycemia continues to offer the most reliable neuroprotection. Although specific pharmacologic strategies hold promise, their use should be considered complementary to meticulous physiological control rather than as stand-alone interventions.

The main limitations identified in the literature include small sample sizes, heterogeneity in study design, variability of outcome measures, and limited follow-up duration. Most trials lack standardized neurocognitive assessments, leading to inconsistent reporting of postoperative neurological outcomes. Additionally, the methodological quality of existing studies remains suboptimal, with high risk of bias and low certainty of evidence according to GRADE criteria.

Future research should focus on large, multicenter randomized controlled trials employing standardized anesthetic neuroprotection protocols and clinically meaningful endpoints, such as long-term neurocognitive recovery and quality of life. These studies should incorporate multimodal monitoring, biomarker validation, and harmonized definitions of neuroprotective success. The integration of translational data from experimental models could guide trial design and improve the alignment between mechanistic and clinical outcomes.

Ultimately, advancing the field of anesthetic neuroprotection will depend on multidisciplinary collaboration between anesthesiologists, neurosurgeons, neurologists, and critical care specialists. Evidence-based practice in neuroanesthesia must be individualized, combining pharmacologic insights with precise physiological management. Until stronger data emerge, anesthetic neuroprotection should be viewed as a component of holistic cerebral preservation rather than a distinct therapeutic entity.

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