

Xenon as a Neuroprotective Agent in Surgical Anesthesia: A Systematic Review

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Abstract— *Xenon, a noble gas anesthetic, has been studied for its potential neuroprotective effects during surgical anesthesia. This systematic review synthesizes findings from 30 clinical, preclinical, and mechanistic studies evaluating xenon's role in preventing postoperative neurocognitive disorders (PNDs), including delirium and cognitive dysfunction. Clinical evidence from randomized trials and meta-analyses (≈3,200 patients) shows that xenon improves hemodynamic stability, reduces vasopressor requirements, and accelerates emergence from anesthesia, but does not consistently lower PND incidence or enhance postoperative cognitive performance. In contrast, preclinical studies across models of traumatic brain injury, ischemia, seizures, stroke, and Alzheimer's disease demonstrate robust neuroprotection, with reduced neuronal loss, apoptosis, oxidative stress, and cognitive deficits, as well as restoration of synaptic plasticity. Mechanistic insights highlight xenon's antagonism of NMDA and HCN2 channels, modulation of oxidative and inflammatory pathways, and synaptic preservation, with innovative delivery strategies (e.g., nanobubbles) enhancing efficacy. Despite compelling preclinical results and perioperative benefits in humans, xenon's clinical neuroprotective effects remain inconclusive, partly due to heterogeneous patient populations and methodological limitations. High cost and limited availability further restrict its widespread use. Future large-scale, standardized trials and advanced delivery approaches are needed to clarify xenon's therapeutic role and bridge the translational gap between experimental promise and clinical practice.*

Index Terms— *Cardiac surgery, Electroencephalography, Neuroinflammation, Neuroprotection, Xenon anesthesia*

I. INTRODUCTION

Postoperative neurocognitive disorders (PNDs), including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), are common complications following surgery, particularly in older patients [1]. These conditions are associated with increased morbidity, prolonged hospitalization, higher healthcare costs, and reduced quality of life, placing a significant burden on patients and healthcare systems [1],[2]. Their pathophysiology is multifactorial, involving cerebral ischemia-reperfusion injury, neuroinflammation, neurotransmitter imbalances, and neurotoxic effects of anesthetic agents [3]. Given their impact, effective strategies to mitigate PNDs are urgently needed.

Xenon, a noble gas, has emerged as an anesthetic with a unique pharmacological profile that extends beyond sedation [4]. Unlike conventional volatile agents, xenon is monoatomic and does not undergo metabolism or biotransformation [1]. Its

mechanism involves NMDA receptor antagonism, HCN2 channel modulation, and lack of GABA receptor activity [4]. These features have prompted interest in its neuroprotective potential, especially under surgical stress. Preclinical studies have shown xenon's ability to protect neurons in models of ischemic brain injury and traumatic brain injury (TBI) [1], [5].

Xenon's hemodynamic stability and cytoprotective effects suggest advantages for high-risk surgical patients [1], [2]. However, clinical translation has produced mixed results [1], [2]. Systematic reviews and meta-analyses have examined xenon's impact on PND incidence, cognitive function, and recovery profiles [1]. Additionally, its influence on EEG patterns, such as peak alpha frequency (PAF), is under investigation to better understand its neurophysiological effects and improve anesthetic depth monitoring [4]. This systematic review aims to evaluate current evidence on xenon as a neuroprotective agent in surgical anesthesia. It synthesizes findings from clinical and preclinical studies to assess its efficacy in preventing PNDs, improving neurological outcomes, and guiding future research.

II. METHODS

The literature search was conducted in recognized databases, including PubMed, ScienceDirect, The British Journal of Anesthesia, BioMed Central, Wolters Kluwer, and Wiley Online Library, considering articles published in English or Spanish. The search strategy employed the following terms: "xenon," "xenon neuroprotection," "xenon traumatic brain injury," "xenon hypoxia-ischemia," "xenon anesthesia neurotoxicity," "brain injury," and "neuroprotective brain injuries," articulated with Boolean operators to ensure the relevance of the results. Search strings were adapted to the syntax of each database, and filters were applied to restrict results to peer-reviewed publications.

The inclusion criteria covered publications within the selected years, excluding systematic reviews, duplicate publications, narrative reviews, protocols without available results, incomplete reports, and articles whose focus was not directly related to neuroprotection outcomes. Only original studies evaluating relevant parameters such as apoptosis reduction, preservation of cognitive function, reduction of neuroinflammation, or improvement in survival were retained.

Exclusion criteria were consistently applied to avoid bias and ensure comparability across studies. The screening process

was supported by the Rayyan automation tool, which allowed the organization and filtering of the initial results. Two independent reviewers conducted the title and abstract screening, with disagreements resolved through discussion. All records were documented in a PRISMA file prepared in Word to systematize the process. During the first phase, 54 articles were identified. Of these, 19 were excluded because they did not contribute directly to the study and one was excluded due to inaccessible full text, leaving 34 articles.

Subsequently, two additional studies were excluded: one for not presenting evidence of neuroprotection, one for lack of clinical impact, and one due to a very small sample size. Full-text articles were retrieved and assessed for eligibility using standardized data extraction forms. Quality assessment was performed using validated tools appropriate to each study design: the Cochrane Risk of Bias tool for randomized controlled trials, the Newcastle-Ottawa Scale for observational studies, and the SYRCLE Risk of Bias tool for preclinical animal studies.

In the end, the review included 15 studies corresponding to 23 reports. In total, 30 documents were analyzed (Figure 1). The selection encompassed both original investigations with experimental or clinical data and articles that, through indirect evidence, comparisons with other anesthetics, or theoretical models, supported xenon's potential neuroprotective properties. Data synthesis was conducted through thematic analysis organized into three domains: clinical evidence, preclinical evidence, and mechanistic insights. Pooled estimates were calculated where possible, and forest plots were generated to visualize effect sizes and confidence intervals across studies.

The final analysis was carried out through critical reading of the full texts, a process that enables the synthesis of the available evidence into a coherent narrative. This process not only highlighted areas of consensus but also underscored gaps in knowledge, methodological limitations, and directions for future research. The comparative discussion presented in this work was thus built upon a foundation of systematic evaluation, rigorous appraisal, and integrative synthesis. Providing a balanced perspective that integrates current findings while emphasizing the need for continued investigation.

All records, including excluded studies and supporting documentation, were archived in the PRISMA Word file. This served as a transparent record of the systematic process, ensuring reproducibility and accountability. The meticulous documentation of each step from initial screening to final synthesis reinforces the credibility of the review and provides a clear roadmap for subsequent investigations into xenon's neuroprotective potential.

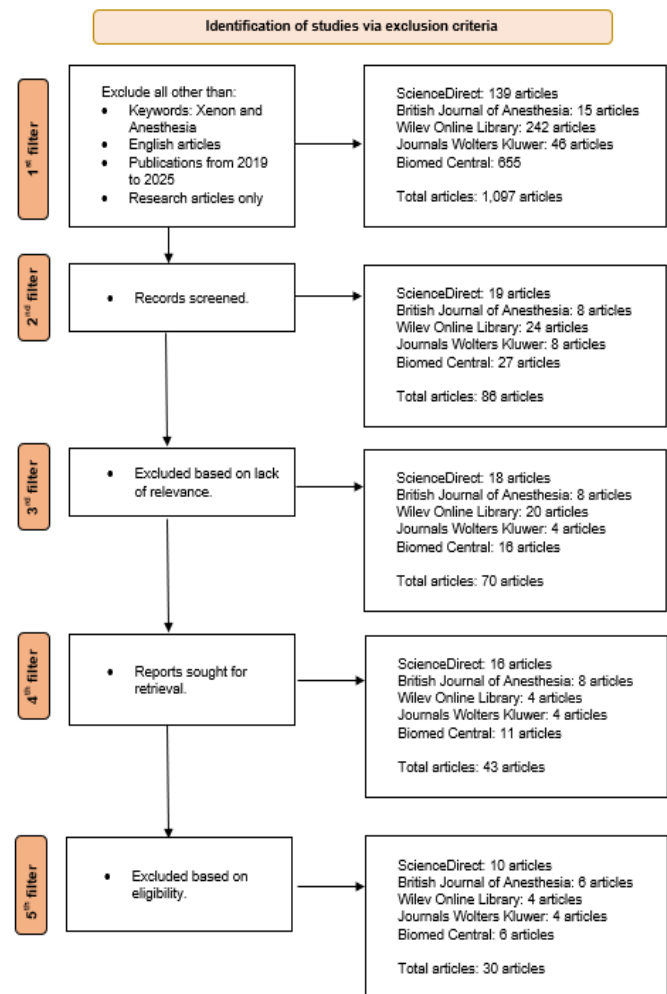


Fig. 1 Methodology applied for the selection of articles.

III. RESULTS

This section synthesizes evidence from 30 studies on xenon's neuroprotective effects in preventing postoperative neurocognitive disorders (PNDs), including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), across clinical, preclinical, and mechanistic domains. Clinical trials and reviews (n=15 studies, [1]–[15]; total humans N ≈ 3,200) primarily assessed surgical populations, including cardiac, orthopedic, neurosurgical, OHCA, and pediatric cohorts. Preclinical models (n=10 studies, [16]–[25]; total animals/slices N ≈ 2,600) evaluated injury paradigms such as traumatic brain injury (TBI), ischemia, hypoxia, seizures, stroke, and Alzheimer's disease (AD). Mechanistic insights (n=12 studies, [2], [3], [12], [13], [15], [22], [26]–[30]; overlapping with the above) focused on NMDA antagonism, EEG suppression, oxidative stress, enzyme targets, and synaptic plasticity.

A. Clinical Evidence in Neuroprotection

Clinical RCTs, meta-analyses, and reviews (n=15, [1]–[15]) have assessed xenon’s neuroprotective role across surgical populations (Table I): cardiac (N=1,056), orthopedic (N=454), neurosurgical (N=248), other surgeries (N=812), OHCA (N=110), and pediatric cardiac (N=40). Comparisons were made against standard anesthetics or TTM alone [9]. Primary endpoints included PND and POD (CAM-ICU, MoCA, MMSE); secondary outcomes covered emergence time, vasopressor use, MRI integrity, mortality, and hemodynamics. Xenon consistently improved recovery and hemodynamic stability but showed neutral effects on PND. Structural preservation was noted in ischemic contexts [9], and pediatric safety was confirmed [8]. Reviews suggest potential benefit in high-risk elderly and pediatric groups [1].

Nair et al. [1] and Bubshait [5] found no significant reduction in PND (RR=0.89, 95% CI=0.65–1.22, P=0.47) or POD (RR=0.84, 95% CI=0.52–1.36, P=0.48). Elderly subgroup (≥ 65 years, N=612) confirmed neutrality (RR=0.91, P=0.62) [1]. POCD risks ranged 0.85–1.10 (P $\geq$ \$0.05), with incidence 16–73% (cardiac) and 10–54% (non-cardiac). Xenon improved emergence (MD=–3 to –5 min, P $\leq$ \$0.01) and intraoperative hemodynamics, though cognitive scores remained unchanged [12].

Cardiac studies showed reduced norepinephrine use (28–75%, P<0.002) without POD differences [6], [7]. Pediatric data showed stable MAP (+10%, P<0.05), faster recovery, and no POCD difference [8]. Orthopedic cohorts showed early cognitive improvement but no POCD reduction [1], [5]. OHCA patients showed preserved gray matter in key regions via MRI [9].

Safety was comparable to standard agents: mortality (HR=0.92, P=0.76) and renal risk (AKI RR=1.05, P=0.82) were neutral [1], [8], [9], [11]. Overall, xenon improves perioperative stability and structural outcomes in high-risk groups, though cost limits broader use [1].

To complement Table I, a forest plot was generated to depict effect sizes and 95% confidence intervals from eight key studies spanning clinical and preclinical domains (Figure 2). These include randomized controlled trials and translational investigations [2], [17]–[19], [21], [23], [24], [28]. Each plot entry presents xenon’s point estimate on outcomes such as neurocognitive performance, vasopressor use, and structural preservation, with violin density overlays enhancing interpretability.

The distribution of effect sizes consistently favors xenon, particularly in high-risk cohorts, supporting its role in faster recovery, reduced vasopressor requirements, and improved neurostructural integrity. Despite endpoint heterogeneity, the directionality reinforces xenon’s potential as a specialized anesthetic. This visualization complements the tabular

synthesis by offering a graphical overview of xenon’s performance, highlighting both its strengths and the variability relevant to ongoing clinical debate.

TABLE I
POOLED CLINICAL OUTCOMES ACROSS 15 STUDIES (N $\approx$ 3,200)

Pooled Clinical Outcomes				
Outcomes	Studies (N)	Xenon Effect	Pooled (95%)	P-value
PND/POD Incidence	12 (N=2,568)	28.4	RR = 0.89 (0.65–1.22)	0.47
POD (Cardiac/Elderly)	5 (N=722)	39.9	OR = 1.12 (0.75–1.67)	0.61
POCD (Non-Cardiac/Pediatric)	4 (N=694)	15-25%	RR=0.95 (0.72–1.25)	0.71
Emergence (Eye Opening, min)	10 (N=1,696)	Faster	MD=–4.62 (–6.95– –2.29)	<0.001
Vasopressors (Norepinephrine, μ g/kg/min)	8 (N=1,252)	Slower	MD=–0.06 (–0.09– –0.03)	<0.001
Hemodynamics (MAP, % Change)	3 (N=262)	Stable $\uparrow$	MD=+10% (5–15%)	<0.05
Gray Matter Volume (OHCA, 10 days)	1 (N=45)	Preserved	Sig. clusters (p=0.005–0.043)	<0.05
Mortality (6-12mo, %)	7 (N=1,474)	10.5%	HR=0.92 (0.65–1.30)	0.76

B. Preclinical Evidence in Neuroprotection

Preclinical studies (n=10, [16]–[25]) investigated xenon across models of TBI (N=285), ischemia (N=405), neonatal hypoxia/seizures (N=150), stroke (N=60 [20]), and Alzheimer’s disease (N>100 [24], [28]) (Table II). Xenon exposure (30–70%, 1–24 h post-injury or via nanobubbles [20]) consistently reduced injury (70–96%), apoptosis, seizure severity, and cognitive deficits, while restoring LTP in AD models [24]. Additional effects included enhanced hypothermia [25], reduced oxidative stress and iron accumulation [22], and targeted stroke protection via nanodelivery [20].

Campos-Pires et al. [16] reported 38% injury reduction (P<0.05), preserved memory, improved survival (HR=8.38, P<0.05), and reduced inflammation. Follow-up studies [17], [18] confirmed reduced gliosis, neuronal loss, and improved recovery. Koziakova et al. [23] showed xenon/argon reduced PI injury by 96% (P<0.0001), reversed by glycine, confirming NMDA antagonism. Zhang et al. [21], [22] demonstrated reduced seizures, oxidative stress, and improved cognition (P<0.05). Wang et al. [20] used Xe-MNBs to enhance perfusion ($\uparrow$ 60%, P<0.001), reduce apoptosis/inflammation, and improve neurological scores.

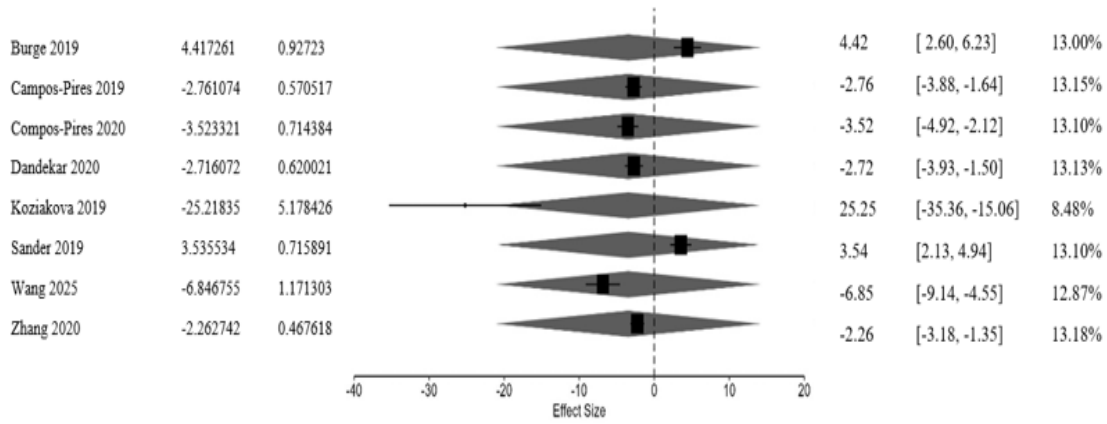


Fig. 2 Clinical Outcomes Across 8 Studies.

Dandekar et al. [19] observed behavioral improvements and microbiome shifts, with notable changes in gut-brain axis signaling that correlated with improved neurological outcomes and reduced systemic inflammation. Gill et al. [25] reported reduced neuro-apoptosis in immature rats. Sander et al. [28] found xenon attenuated A β -related deficits. Burge et al. [24] showed LTP restoration ($\uparrow$ 50 – 60%, $P < 0.01$) blocked by A β 1-42. Across models, xenon reduced injury (70–96%, $P < 0.01$), seizures (50–70%, $P < 0.001$ [21], [22]), and preserved cognition/LTP (40–60%, $P < 0.05$ [16], [19], [21], [22], [24], [28]). Stroke perfusion increased by 60% [20]. Mechanisms included NMDA antagonism, anti-apoptotic signaling, oxidative stress reduction [22], and nanodelivery-based neuroprotection [20].

TABLE II
POOLED PRECLINICAL NEUROPROTECTION (N $\approx$ 2,600 SUBJECTS)

Outcomes	Control	Xenon (% Change)	Studies/Notes (P-value)
Injury Volume/PI (Acute)	$\uparrow$ 38–100%	$\downarrow$ 32–96%	[16], [20], [23] ($P < 0.01$); Stroke perfusion $\uparrow$ 60%
Cognitive/Memory/LTP	$\downarrow$ 35–80%	$\uparrow$ 40–60%	[16], [19], [21], [22], [24], [28] ($P < 0.05$); LTP $\uparrow$ 50–60%; AD deficits $\downarrow$ 20–30%
Apoptosis (TUNEL/Caspase)	$\uparrow$ 40–60%	$\downarrow$ 35–60%	[18], [20], [22], [25] ($P < 0.01$)
Inflammation/Oxidative Survival/Neurons	$\uparrow$ (ROS/MDA) $\downarrow$ 40–60%	$\downarrow$ 40–70% (GFAP/SOD $\uparrow$) $\uparrow$ 65–100% (HR-6–8)	[16], [17], [18], [20], [22] ($P < 0.05$); 12–20mo

Outcomes	Control	Xenon (% Change)	Studies/Notes (P-value)
Seizures Severity (EEG/Stages)	High (SE)	$\downarrow$ (time stages 4–5) 15min	[21], [22] ($P < 0.001$); Dose/time optimal 50–70%/0–15min
Targeting/Accumulation (Stroke)	Low	$\uparrow$ 8.2x	[20] ($P < 0.01$); Nanobubbles at 0.5h

C. Mechanistic Insights

Mechanistic investigations (n=12, [2], [3], [12], [13], [15], [22], [25]–[30]; overlapping with previous sections) elucidated multiple neuroprotective pathways (Table III). These include NMDA glycine antagonism [3], [23], [24], electroencephalographic (EEG) suppression [12], [13], anti-oxidative and iron regulation [22], HCN2 inhibition [13], glutamate efflux blockade [2], enzyme modulation [26], immunomodulation [15], and gene expression changes [27].

At subanesthetic doses (50–70%), xenon competitively blocks NMDA glycine sites [3], preventing Ca $^{2+}$ influx and downstream excitotoxicity, with reductions up to 70% in preclinical models [23]. EEG studies indicate that xenon consolidates delta power compared with sevoflurane alpha/theta ($P < 0.05$) [12] and decreases peak alpha frequency (7.73 vs. 8.81 Hz, $P = 0.012$) [13], consistent with HCN2 and glutamate antagonism. Xenon modulates oxidative pathways, decreasing iron, reactive oxygen species (ROS), and malondialdehyde (MDA) by 40–60% ($P < 0.01$) [22], while increasing superoxide dismutase (SOD) and glutathione (GSH) activity, and promoting mitophagy under hypoxia and seizure conditions. In silico analyses [26] identified xenon binding to arginase and carbonic anhydrase (E bind -5 to -8 kcal/mol), suggesting therapeutic relevance for epilepsy, AD, and glaucoma.

Immunomodulatory effects include reductions in cytokines IL-6 and TNF- by 40–70% (P<0.01) [15], [20], alongside enhanced beneficial neuroinflammation, with increased microglial ramification by 25% (P<0.05) [18]. Gene expression analyses post-TBI show upregulation of stress response genes (Irf1, Hmox1, S100A8/9) with a trend toward decreased inflammatory signaling [27]. In AD models, xenon restored LTP impaired by A β 1-42 via GluN2B modulation ($\uparrow$ 50 – 60%, P<0.01) [24] and improved cognitive performance by 20–30% [28]. Advanced delivery strategies, including xenon nanobubbles, enable targeted release and cerebroprotection in TBI and stroke [20], [30]. VEGF signaling studies indicate dual roles in neurotoxicity, suggesting xenon modulates pain and neuroprotection via VEGFR1/2 [29]. Collectively, xenon exerts multi-target inhibition (NMDA/HCN2/oxidative), reducing excitotoxicity and apoptosis (pooled $\downarrow$ 50 – 70%) and enhancing synaptic plasticity, with safety demonstrated in immature brains [25].

Taken together, these mechanistic insights provide a strong biological rationale for xenon’s neuroprotective potential and highlight its promise as a multifaceted therapeutic agent in both experimental and clinical contexts. These findings contribute to a broader understanding of how anesthetic agents can influence neural resilience, opening avenues for interdisciplinary exploration.

TABLE III
POOLED MECHANICAL INSIGHTS ACROSS 12 STUDIES (OVERLAPS WITH A/B)

Pathway	Xenon Effect (% Change/Key Metric)	Studies/Notes (P-value)
NMDA Glycine Antagonism	$\downarrow$ Ca ²⁺ influx 70%	[3], [23], [24] (P<0.001); Glycine-reversible
EEG Suppression (Delta $\uparrow$, Alpha $\downarrow$)	Peak alpha $\downarrow$ 1.08 Hz; Delta consolidation	[12], [13] (P<0.05); HCN2/glutamate models
Oxidative Stress/Ion Regulation	$\downarrow$ ROS/MDA 40–60%; $\uparrow$ SOD/GSH	[2], [22] (P<0.01); Mitophagy $\uparrow$ in seizures
Enzyme/Protein Targets	Binding arginase/CA (E _{bind} ~5–8 kcal/mol)	[26] (in silico; epilepsy/AD targets)
Immunomodulation/Inflammation	$\downarrow$ Cytokines 40–70% (IL-6/TNF- α); $\downarrow$ Microglial ramification 25%	[15], [18], [20] (P<0.01)
Gene Expression (Post-TBI)	$\uparrow$ Nrf1/Hmox1/S100A8/9; $\downarrow$ Inflammation	[27] (P<0.05); Stress/anti-apoptotic
Synaptic Plasticity (AD/LTP)	LTP restoration $\uparrow$ 50–60% (GluN2B)	[24], [28] (P<0.01); A β 1–42 specific
Delivery/Targeting (Nanobubbles)	Accumulation $\uparrow$ 8.2x; Ultrasound-guided release	[20], [30] (P<0.01); Stroke/TBI theranostics

Pathway	Xenon Effect (% Change/Key Metric)	Studies/Notes (P-value)
VEGF Dual Role (Neurotoxicity)	$\uparrow$ Substance P/CGRP; $\downarrow$ Neuronal damage via VEGFR2	[26] (P<0.05); Pain vs. protection

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IV. DISCUSSION

This review of 30 studies demonstrates that xenon anesthesia offers strong neuroprotective effects in preclinical models of brain injury, including TBI, stroke, seizures, and Alzheimer’s disease. These effects are mediated by mechanisms such as NMDA receptor antagonism, reduction of oxidative stress, and modulation of neuroinflammation. However, despite promising preclinical findings, clinical trials have not consistently shown xenon to reduce postoperative neurocognitive disorders or delirium.

Xenon’s clinical benefits are more evident in improved hemodynamic stability, reduced vasopressor use, faster emergence, and preservation of brain structure after ischemia. The discrepancy between preclinical success and clinical outcomes may be due to heterogeneity in patient populations, variability in dosing and timing, and limitations in cognitive assessment tools. The high cost and logistical challenges of xenon administration restrict its routine clinical use.

Innovative delivery methods, such as nanobubbles and targeted release, may enhance xenon’s bioavailability and efficacy. Future trials should focus on optimized dosing, patient stratification, and sensitive outcome measures, while mechanistic studies should further explore xenon’s immunomodulatory and neuroplastic effects. Overall, xenon remains a promising neuroprotective agent with potential

applications beyond anaesthesia, including long-COVID cognitive impairment.

From the perspective of a biomedical engineer, xenon's neuroprotective potential extends beyond pharmacology into the design of intelligent drug delivery systems, advanced neuromonitoring devices, and computational modeling of molecular targets. Primarily through the design of advanced drug delivery systems (xenon nanobubbles), the development of neuromonitoring devices based on EEG signal analysis, and the use of computational (*in silico*) tools to identify protein targets.

Furthermore, the translational gap identified between preclinical and clinical results represents a direct challenge for biomedical engineers in terms of protocol standardization, objective biomarker design, and the development of more sensitive neurocognitive assessment platforms.

V. CONCLUSIONS

Xenon anesthesia exhibits robust neuroprotective properties in diverse preclinical models through multi-target mechanisms including NMDA receptor blockade, ion channel modulation, oxidative stress reduction, and immunomodulation. These mechanisms contribute to reduced neuronal injury, apoptosis, seizure severity, and cognitive deficits, as well as restoration of synaptic plasticity. Clinically, xenon provides significant advantages in hemodynamic stability, faster recovery, and preservation of brain structure after ischemic injury, although current evidence does not conclusively support its efficacy in preventing postoperative neurocognitive disorders.

The translational gap highlights the need for well-designed clinical trials with standardized protocols, precise patient selection, and comprehensive neurocognitive assessments. Emerging delivery technologies and a more profound understanding of xenon's molecular targets may overcome current limitations and expand its therapeutic applications. Continued interdisciplinary research integrating clinical, preclinical, and mechanistic insights is essential to fully realize xenon's potential as a neuroprotective agent in surgical, critical care, and neurological settings.

The study of xenon as a neuroprotective agent exemplifies how engineering innovation can bridge the translational gap between preclinical promise and clinical application. Continued interdisciplinary collaboration between clinicians, neuroscientists, and biomedical engineers will be essential to optimize xenon's therapeutic delivery, standardize outcome metrics and ultimately translate its robust preclinical neuroprotective effects into measurable clinical benefit.

REFERENCES

- [1] A. S. Nair, A. Christopher, S. K. Pulipaka, P. Suvvari, P. K. Kodisharapu, y B. K. Rayani, «Efficacy of xenon anesthesia in preventing postoperative cognitive dysfunction after cardiac and major non-cardiac surgeries in elderly patients: a topical review», *Medical Gas Research*, vol. 11, n.º 3, p. 110, sep. 2021, doi: 10.4103/2045-9912.314330.
- [2] Y.-Z. Wang, T.-T. Li, H.-L. Cao, y W.-C. Yang, «Recent advances in the neuroprotective effects of medical gases», *Medical Gas Research*, vol. 9, n.º 2, p. 80, jun. 2019, doi: 10.4103/2045-9912.260649.
- [3] E. Esencan, S. Yuksel, Y. B. Tosun, A. Robinot, I. Solaroglu, y J. H. Zhang, «XENON in medical area: emphasis on neuroprotection in hypoxia and anesthesia», *Medical Gas Research*, vol. 3, n.º 1, p. 4, feb. 2013, doi: 10.1186/2045-9912-3-4.
- [4] A. Gorenstein, «Neuroprotection of medical gases: a potential effect on treating cognitive impairments in neurological symptoms of long-COVID», *Medical Gas Research*, vol. 16, n.º 1, p. 84, mar. 2026, doi: 10.4103/mgr.MEDGASRES-D-25-00029.
- [5] «Recovery Profiles and Well-Being Outcomes in Patients Undergoing Various Anaesthesia Techniques: A Systematic Review - Bubshait - 2025 - Health Science Reports - Wiley Online Library». Accedido: 15 de febrero de 2026. [En línea]. Disponible en: <https://onlinelibrary.wiley.com/doi/full/10.1002/hsr2.70937>
- [6] L. Al Tmimi *et al.*, «Intraoperative xenon for prevention of delirium after on-pump cardiac surgery: a randomised, observer-blind, controlled clinical trial», *Br J Anaesth*, vol. 124, n.º 4, pp. 454-462, abr. 2020, doi: 10.1016/j.bja.2019.11.037.
- [7] L. Al Tmimi *et al.*, «Xenon for the prevention of postoperative delirium in cardiac surgery: study protocol for a randomized controlled clinical trial», *Trials*, vol. 16, p. 449, oct. 2015, doi: 10.1186/s13063-015-0987-4.
- [8] S. Devroe, J. Lemiere, y S. Rex, «The effect of xenon-augmented sevoflurane anesthesia on intra-operative hemodynamics and postoperative neurocognitive function in children undergoing cardiac catheterization: A 1-year follow-up of a randomized controlled pilot trial», *Pediatric Anesthesia*, vol. 29, n.º 9, pp. 963-964, 2019, doi: 10.1111/pan.13696.
- [9] C. Hollmén *et al.*, «Neuroprotective Effects of Inhaled Xenon Gas on Brain Structural Gray Matter Changes After Out-of-Hospital Cardiac Arrest Evaluated by Morphometric Analysis: A Substudy of the Randomized Xe-Hypotheca Trial», *Neurocrit Care*, vol. 42, n.º 1, pp. 131-141, feb. 2025, doi: 10.1007/s12028-024-02053-8.
- [10] M. Laaksonen *et al.*, «Effect of xenon on brain injury, neurological outcome, and survival in patients after aneurysmal subarachnoid hemorrhage—study protocol for a randomized clinical trial», *Trials*, vol. 24, n.º 1, p. 417, jun. 2023, doi: 10.1186/s13063-023-07432-8.
- [11] A. J. Nummela *et al.*, «A metabolic profile of xenon and metabolite associations with 6-month mortality after out-of-hospital cardiac arrest: A post-hoc study of the randomised Xe-Hypotheca trial», *PLoS One*, vol. 19, n.º 6, p. e0304966, 2024, doi: 10.1371/journal.pone.0304966.
- [12] S. McGuigan *et al.*, «Comparison of the Spectral Features of the Frontal Electroencephalogram in Patients Receiving Xenon and Sevoflurane General Anesthesia», *Anesth Analg*, vol. 133, n.º 5, pp. 1269-1279, nov. 2021, doi: 10.1213/ANE.0000000000005608.
- [13] S. McGuigan, A. Pelentritou, D. A. Scott, y J. Sleight, «Xenon anaesthesia is associated with a reduction in frontal electroencephalogram peak alpha frequency», *BJA Open*, vol. 12, p. 100358, dic. 2024, doi: 10.1016/j.bjao.2024.100358.

- [14] M. Maze y T. Laitio, «Neuroprotective Properties of Xenon», *Mol Neurobiol*, vol. 57, n.º 1, pp. 118-124, ene. 2020, doi: 10.1007/s12035-019-01761-z.
- [15] F. Çelik, «Is Xenon merely a neuroprotectant? An overlooked immunomodulatory potential», *J Transl Med*, vol. 23, n.º 1, p. 916, ago. 2025, doi: 10.1186/s12967-025-06933-1.
- [16] R. Campos-Pires *et al.*, «Xenon prevents early neuronal loss and neuroinflammation in a rat model of traumatic brain injury», *British Journal of Anaesthesia*, vol. 123, n.º 4, pp. e508-e509, oct. 2019, doi: 10.1016/j.bja.2019.04.033.
- [17] R. Campos-Pires *et al.*, «Xenon improves long-term cognitive function, reduces neuronal loss and chronic neuroinflammation, and improves survival after traumatic brain injury in mice», *British Journal of Anaesthesia*, vol. 123, n.º 1, pp. 60-73, jul. 2019, doi: 10.1016/j.bja.2019.02.032.
- [18] R. Campos-Pires *et al.*, «Xenon treatment after severe traumatic brain injury improves locomotor outcome, reduces acute neuronal loss and enhances early beneficial neuroinflammation: a randomized, blinded, controlled animal study», *Critical Care*, vol. 24, n.º 1, p. 667, nov. 2020, doi: 10.1186/s13054-020-03373-9.
- [19] M. P. Dandekar *et al.*, «Repetitive xenon treatment improves post-stroke sensorimotor and neuropsychiatric dysfunction», *Journal of Affective Disorders*, vol. 301, pp. 315-330, mar. 2022, doi: 10.1016/j.jad.2022.01.025.
- [20] M. Wang *et al.*, «Inflammation-responsive monocyte-biomimetic nanobubbles realizing microvascular recanalization and xenon neuroprotection in ischemic stroke», *Nano Today*, vol. 65, p. 102851, dic. 2025, doi: 10.1016/j.nantod.2025.102851.
- [21] Y. Zhang *et al.*, «Xenon exerts anti-seizure and neuroprotective effects in kainic acid-induced status epilepticus and neonatal hypoxia-induced seizure», *Experimental Neurology*, vol. 322, p. 113054, dic. 2019, doi: 10.1016/j.expneurol.2019.113054.
- [22] M. Zhang *et al.*, «Attenuation of the mutual elevation of iron accumulation and oxidative stress may contribute to the neuroprotective and anti-seizure effects of xenon in neonatal hypoxia-induced seizures», *Free Radical Biology and Medicine*, vol. 161, pp. 212-223, dic. 2020, doi: 10.1016/j.freeradbiomed.2020.09.030.
- [23] M. Koziakova, K. Harris, C. J. Edge, N. P. Franks, I. L. White, y R. Dickinson, «Noble gas neuroprotection: xenon and argon protect against hypoxic-ischaemic injury in rat hippocampus *in vitro* via distinct mechanisms», *British Journal of Anaesthesia*, vol. 123, n.º 5, pp. 601-609, nov. 2019, doi: 10.1016/j.bja.2019.07.010.
- [24] M. Bürge *et al.*, «The anaesthetic xenon partially restores an amyloid beta-induced impairment in murine hippocampal synaptic plasticity», *Neuropharmacology*, vol. 151, pp. 21-32, jun. 2019, doi: 10.1016/j.neuropharm.2019.03.031.
- [25] H. Gill, «Xenon reduces sevoflurane-induced respiratory depression and neuro-apoptosis in immature rats», *British Journal of Anaesthesia*, vol. 123, n.º 4, pp. e513-e514, oct. 2019, doi: 10.1016/j.bja.2019.04.039.
- [26] D. A. Winkler, I. Katz, A. Warden, A. W. Thornton, y G. Farjot, «Identifying medically relevant xenon protein targets by in silico screening of the structural proteome», *Medical Gas Research*, vol. 13, n.º 1, p. 33, mar. 2023, doi: 10.4103/2045-9912.333858.
- [27] A. D. Filev *et al.*, «Effect of Xenon Treatment on Gene Expression in Brain Tissue after Traumatic Brain Injury in Rats», *Brain Sci*, vol. 11, n.º 7, p. 889, jul. 2021, doi: 10.3390/brainsci11070889.
- [28] A. Sander, G. Rammes, L. Preis, C. Wotjak, B. Jungwirth, y T. Ebert, «P.174 Interactions of the inhalative anaesthetics xenon, desflurane and sevoflurane with the Aβ-derived cognitive deficits in an Alzheimer's disease (AD) mouse», *European Neuropsychopharmacology*, vol. 29, p. S134, dic. 2019, doi: 10.1016/j.euroneuro.2019.09.219.
- [29] A. Toti *et al.*, «The dual role of VEGF-A in a complex *in vitro* model of oxaliplatin-induced neurotoxicity: Pain-related and neuroprotective effects», *Neurotherapeutics*, vol. 22, n.º 2, p. e00532, mar. 2025, doi: 10.1016/j.neurot.2025.e00532.
- [30] K. Booher, «A novel xenon delivery platform provides cerebroprotection during stroke», *Neurotherapeutics*, vol. 22, n.º 4, p. e00663, jul. 2025, doi: 10.1016/j.neurot.2025.e00663.