Neurologic and cognitive outcomes associated with the clinical use of xenon: a systematic review and meta-analysis of randomized-controlled trials

Effets neurologiques et cognitifs associés à l'utilisation clinique du xénon : revue systématique et méta-analyse des essais randomisés contrôlés

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Abstract

Background Xenon has been shown to have positive neurologic effects in various pre-clinical models. This study systematically reviewed the randomized-controlled trials (RCTs) investigating neurologic and cognitive outcomes associated with the clinical use of xenon.

Methods We searched PubMed, CENTRAL, EMBASE, CINAHL, elibrary.ru (for Russian studies), Google Scholar (for Russian studies), and Wanfang (for Chinese studies) for appropriate RCTs comparing neurologic or cognitive outcomes after clinical use of xenon with control treatment or with other anesthetic agents.

Results Seventeen RCTs met the inclusion criteria. Two studies investigated the effects of xenon plus therapeutic hypothermia to treat neonatal asphyxia or out-of-hospital cardiac arrest. Compared with therapeutic hypothermia alone, xenon and therapeutic hypothermia reduced cerebral

white matter abnormalities after cardiac arrest but had no effect on neurocognitive outcome and mortality. Xenon had no added value when used to treat neonatal asphyxia. Thirteen RCTs compared neurocognitive effects of xenon with other anesthetic agents in surgical patients. While xenon may be associated with improved short-term (< three hours) cognitive outcome, no medium-term (six hours to three months) advantage was observed, and longer-term data are lacking. No differences in biochemical (S-100 β , neuron-specific enolase) and neuropsychologic (attentional performance) outcomes were found with xenon compared with other anesthetic drugs. Finally, two studies suggest that brief, intermittent administration of sub-anesthetic doses of xenon to patients during the acute phase of substance withdrawal may improve neurocognitive outcomes.

Conclusions Despite promising pre-clinical results, the evidence for positive clinical neurologic and cognitive outcomes associated with xenon administration is modest. Nevertheless, there is some evidence to suggest that xenon may be associated with better neurologic outcomes compared with the standard of care therapy in certain specific clinical situations. More clinical trials are needed to determine any potential benefit linked to xenon administration.

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Résumé

Contexte Différents modèles précliniques ont montré que le xénon a des effets neurologiques positifs. Cette étude a systématiquement passé en revue les essais cliniques randomisés (ECR) étudiant les effets neurologiques et cognitifs associés à l'utilisation clinique du xénon.

Méthodes Nous avons recherché les ECR appropriés comparant les effets neurologiques ou cognitifs de

l'utilisation clinique du xénon à ceux d'un traitement témoin ou d'autres agents anesthésiques dans les bases de données PubMed, CENTRAL, EMBASE, MEDLINE, elibrary.ru et Google Scholar (pour les études russes) et Wanfang (pour les études chinoises).

Résultats Dix-sept ECR ont correspondu aux critères d'inclusion. Deux études ont recherché les effets du xénon et de l'hypothermie thérapeutique dans le traitement de l'asphyxie néonatale ou de l'arrêt cardiaque hors de l'hôpital. Comparativement à l'hypothermie thérapeutique seule, le xénon associé à l'hypothermie thérapeutique a réduit les anomalies de la substance blanche cérébrale après un arrêt cardiaque, mais n'a eu aucun effet sur l'évolution neurocognitive et la mortalité. Le xénon n'a apporté aucune valeur ajoutée au traitement de l'asphyxie néonatale. Treize ECR ont comparé les effets neurocognitifs du xénon à ceux d'autres agents anesthésiques chez des patients chirurgicaux. Bien que le xénon puisse être associé à une amélioration à court terme (< trois heures) des fonctions cognitives, aucun avantage à moyen terme (six heures à trois mois) n'a été observé et il n'existe pas de données à plus long terme. Aucune différence sur des critères biochimiques (énolase spécifique des neurones, S-100 β) et neuropsychologiques (performance de l'attention) n'a été constatée avec le xénon par rapport aux autres agents anesthésiques. Enfin, deux études suggèrent qu'une administration brève et intermittente de doses infra-anesthésiques de xénon à des patients en phase aiguë de sevrage de substance peut améliorer l'évolution neurocognitive.

Conclusions Malgré des résultats précliniques prometteurs, les données probantes d'effets cliniques neurologiques et cognitifs positifs associés à l'administration de xénon restent modestes. Néanmoins, il existe quelques données indiquant que le xénon pourrait être associé à une meilleure évolution neurologique par rapport aux traitements de référence dans certaines situations cliniques particulières. D'autres essais cliniques sont nécessaires pour déterminer un éventuel avantage lié à l'administration de xénon.

Xenon is a noble gas with potential benefits when used for general anesthesia.^{1,2} Neurologic and cognitive outcomes associated with xenon administration have been tested in various pre-clinical *in vitro* and *in vivo* models^{3,4} (Table 1) concerned with neurotoxicity,³⁻⁹ neonatal asphyxia,¹⁰⁻¹⁴ cardiac arrest,¹⁵⁻¹⁷ and ischemic¹⁸⁻²³ and traumatic²⁴⁻²⁶ brain injury. Most of the pre-clinical investigations showed positive central nervous system (CNS)-related outcomes. For instance, xenon has been shown to prevent isoflurane-induced neurotoxicity and neuroapoptosis in rats.^{4,5,9} Xenon has also been shown to improve outcomes following

neonatal asphyxia¹⁰⁻¹⁴ and cardiac arrest¹⁷ when combined with conventional therapeutic hypothermia in rodent and porcine models.

The positive CNS-related effects of xenon are thought to be conferred mainly through antagonizing N-methyl-D-aspartate (NMDA) receptors at the glycine site, thus reducing the neuronal injury caused by excessive glutamate-induced stimulation in the early phase of reperfusion injury.^{22,25,27} It may also reduce apoptosis by activating anti-apoptotic factors in the later phase of reperfusion injury.⁴ Other postulated mechanisms include the modulation of neuroinflammation,^{28,29} potassium channels,^{30,31} and hypoxia-inducible factor 1 α .³² When used as an anesthetic, xenon has been associated with a more stable intraoperative blood pressure than other inhaled agents or total intravenous anesthesia using propofol.¹ As such, xenon's hemodynamic stability may be an underlying mechanism for its protection of neural, cardiac, and renal function.³³

Despite these encouraging results, clinical data are needed to confirm the neurologic and cognitive benefits of xenon. Two randomized-controlled trials^{34,35} (RCTs) investigated the neuroprotective effects of xenon when used as therapeutic treatment following neonatal asphyxia or cardiac arrest. Several RCTs have assessed the effects of xenon in other clinical settings, for instance, general anesthesia or the acute phase of substance abuse.³⁶⁻³⁹ Nevertheless, there is no systematic review or meta-analysis of these clinical studies. This article is the first systematic review of RCTs investigating the potential neurologic and cognitive benefits associated with xenon administered to human patients.

Methods

Search strategy

This study conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.⁴⁰ We searched for RCTs that compared xenon with any type of control treatment for influence on neurologic or cognitive outcomes of clinical relevance including radiologic or biochemical effects. We used the search term “xenon AND (neuroprotect* OR neurocognit* OR cognit*)” in PubMed, CENTRAL, EMBASE, and CINAHL. We searched for Russian language publications with the search term “ксенон” in elibrary.ru and “ксенон [xenon] AND (нейропротекции [neuroprotection] OR неврологический [neurologic] OR познавательный [cognitive])” in Google Scholar, as we expected a considerable number of Russian studies.⁴¹ We searched for Chinese language publications with the search term “氙 [xenon] and (神經 [neuro] or 認知 [cognitive])” in Wanfang [萬方數據]. We did not impose restrictions on the year of publication or

Table 1 Pre-clinical trials: xenon (Xe) plus therapeutic hypothermia (TH) compared with therapeutic hypothermia

Author	Model	Neurologic Injury	Delay of Treatment	Xenon Treatment	Duration of Xenon Inhalation	Therapeutic Hypothermia (TH)	Duration of TH	Outcomes	Important Result
Ma (2015) ¹⁰	Rats	Right carotid artery ligation with hypoxic gas exposure	4 hr	70%	1.5-6 hr	33°C	1.5-6 hr	Neurologic function: performance on balance beam and rotarod Histopathology: weight, apoptosis and necrosis	Synergistic effect Xe+TH
Martin (2007) ¹¹	7-day-old rats	Right carotid artery ligation with hypoxic gas exposure	1 or 5 hr	20%	90 min	35°C	2 hr	Histology: Infarct size	Xe+TH were neuroprotective but had no effect individually
Hobbs (2008) ¹²	Neonatal rats	Right carotid artery ligation with hypoxic gas exposure	0 hr	50%	3 hr	32°C	3 hr	Early behavioural test (negative geotaxis test); long-term behavioural test (staircase test) Histopathology: grading on the severity of damage on cortex, basal ganglia, thalamus, and hippocampus	Xe and TH had effect alone and were additive
Thoresen (2009) ¹³	Rats	Right carotid artery ligation with hypoxic gas exposure	0 or 2 hr	50%	1 or 3 hr	32°C	3 hr	Long-term 'staircase' testing Histopathology: grading on the severity of damage on cortex, basal ganglia, thalamus, and hippocampus	Xe+TH better than TH 2 hr delay of Xe was still effective 3 hr Xe exposure better than 1 hr
Chakkarapani (2010) ⁶²	Pigs	Hypoxic gas exposure	30 min	50%	18 hr	33.5°C	12 or 24 hr	Neurology assessment: score based on consciousness, respiration, walking, ability to control limbs, tone, and pathologic movements Neuropathology assessment: global and regional neuropathology score corresponding to the proportion of damaged brain areas	Xe and TH had effect alone and were additive
Faulkner (2011) ⁶¹	Piglets	Right carotid artery ligation with hypoxic gas exposure	2 hr	50%	24 hr	33.5°C	24 hr	Brain lactate to N-acetyl/aspartate ratio in magnetic resonance spectroscopy Histology: cell death and glial activation	Both Xe+TH and TH were effective but Xe+TH had no added value to TH alone
Fries (2012) ¹⁷	Pigs	Induced cardiac arrhythmia with cardiopulmonary resuscitation	1 hr	70%	1 hr	33°C	16 hr	Neurohistopathology: score based on neuron death and glial /leukocyte activation	Only Xe+TH showed protective effect
Sabir (2014) ¹⁴	Rats	Right carotid artery ligation with hypoxic gas exposure	0 or 4 hr	20 or 50%	5 hr	32°C or 35°C	5 hr	Histopathology: infarct size, tissue loss, and a neuropathology score	50% Xe+TH better than TH 20% Xe: no effect 4 hr delay TH+ Xe: no effect
Sabir (2016) ²³	Rats	Right carotid artery ligation with hypoxic gas exposure	0 hr	50%	5 hr	32°C	5 hr	Hemispheric brain area loss in 1 week	TH vs TH+50%Xe: no difference

language. We only included human studies and excluded all non-RCTs. The latest search was done in February 2018. The two co-first authors (L.L. and E.L.) independently searched and assessed the English and Chinese literature for eligibility. The first and third authors (L.L. and C.C.) independently searched for the papers written in Russian. Conference abstracts published prior to 2016 were excluded.

Data extraction

Included studies were categorized according to clinical scenario, namely, neonatal asphyxia, cardiac arrest, general anesthesia, and substance addiction. Meta-analysis was conducted for the following outcomes: plasma levels of S-100 β (ng·L⁻¹; biomarker for glial injuries and the integrity of blood-brain barrier) and neuron-specific enolase (NSE, g·L⁻¹; biomarker for neuronal injuries) and tests for cognitive performance associated with xenon anesthesia versus other anesthetic agents. The number of studies involving neonatal asphyxia, cardiac arrest, and substance addiction was limited so the results from these studies were systematically reviewed and descriptively summarized.

Quality assessment

We assessed the methodologic quality of included RCTs with the Jadad score⁴² and bias risk using the Cochrane tool for risk of bias.⁴³ Results of meta-analyses were graded for quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Working Group system.⁴⁴

Statistical analyses

Meta-analysis was conducted with Review Manager 5.3 (Cochrane Collaboration, Copenhagen). Standard deviation (SD) was estimated by the following formulae: $SD = SEM\sqrt{N}$; $SEM = \frac{95\%CI}{1.96}$ (SEM, standard error of mean; 95% confidence interval [CI]). If SD could not be determined, we substituted the missing SD with the pooled SD of other studies by: $\sqrt{\frac{\sum NSD^2}{\sum N}}$. For continuous variables, standardized mean differences⁴⁵ were compared with the inverse variance method. Because of the limited number of studies, we used a random effect model with adjustments according to the Satterthwaite approach⁴⁶ for all comparisons regardless of the heterogeneity. For all comparisons, statistical significance was set at $P < 0.05$ (two sided) and 95% CIs were reported. Due to the limited number of studies, sensitivity and subgroup analyses were not conducted.

Results

Study selection

Of the 1,064 studies initially identified, 17 RCTs^{34-39,47-56} met the inclusion criteria (Fig. 1). Ten^{34,35,38,39,51-55,57,58} were published in English and seven^{36,37,47-50,56} in Russian or Ukrainian. No study published in Chinese met the inclusion criteria. Characteristics are presented in Table 2.

One RCT³⁴ examined the effect of xenon plus therapeutic hypothermia in out-of-hospital cardiac arrest patients. One RCT³⁵ investigated the effect of xenon plus therapeutic hypothermia in birth-related neonatal asphyxia. Thirteen RCTs^{38,39,47-50,52-58} compared xenon anesthesia with other inhaled agents or total intravenous anesthesia (propofol). Two studies^{36,37} investigated the effect of xenon as an adjuvant therapy during the withdrawal phase of addictive substances. Reasons for exclusion of the other identified studies are summarized in Fig. 1. Table 2 summarizes the major results of included studies.

Xenon plus therapeutic hypothermia treatment for out-of-hospital cardiac arrest

Laitio *et al.*³⁴ randomized 110 out-of-hospital cardiac arrest patients presenting initially with ventricular fibrillation or pulseless ventricular tachycardia into either therapeutic hypothermia treatment (33.5°C for 24 hr) or inhaled 40% xenon plus therapeutic hypothermia treatment. The investigators performed diffusion tensor magnetic resonance imaging at 36-52 hr after cardiac arrest to evaluate fractional anisotropy as the primary outcome. Fractional anisotropy was used to estimate the cerebral white matter abnormality and a greater value is believed to be predictive of a better neurocognitive outcome after cardiac arrest.⁵⁹ The raw and adjusted mean global fractional anisotropy values were greater in the xenon group than in the control group.

Secondary endpoints including mortality rate and neurocognitive outcome were not significantly different between the xenon and control groups at six months. Nevertheless, the absolute reduction in mortality rate in the xenon group compared with the control group may have been clinically (though not statistically) significant (27.3% vs 34.5%, $P = 0.053$).

Xenon plus therapeutic hypothermia for neonatal asphyxia

Azzopardi *et al.*³⁵ compared the effect of inhaled xenon (30% for 24 hr) plus hypothermia (33.5°C for 72 hr) with hypothermia alone in 92 full-term birth-asphyxiated neonates. The investigators used magnetic resonance spectroscopy (to measure lactate to N-acetyl aspartate ratio in the thalamus)

Fig. 1 Flow chart for included studies

and diffusion tensor magnetic resonance imaging (to evaluate the fractional anisotropy in the posterior limb of the internal capsule) at approximately six days after birth. No differences were observed between the two treatment groups. Similarly, all secondary outcome variables including the maximum Thompson Hypoxic Ischemic Encephalopathy Score in the first week of life, neurologic assessment at discharge, mortality rate, incidence of seizures, intracranial hemorrhage, and length of hospital stay were also unaffected.

Cognitive outcomes after general anesthesia

The included studies comprised a wide range of surgical procedures including coronary artery bypass, knee

replacement, and brain surgery, as summarized in Table 2. Two studies^{39,54} assessed attentional performance at 6–12 and 66–72 hr after surgery. Meta-analysis showed no difference in patients anesthetized with xenon compared with other volatile agents (sevoflurane or desflurane; see Electronic Supplementary Material (ESM) - Supplementary Figs. 1 and 2). The quality of evidence was high according to GRADE. Five studies^{38,52–55} compared other short-term postoperative cognitive outcomes between xenon (50–70%) and other anesthetic drugs (1.1–1.4% sevoflurane,^{38,54,55} 0.6% isoflurane,⁵² or 3–5 mg kg⁻¹ h⁻¹ propofol).⁵³ Various cognitive assessments were made using the “Short Orientation Memory Concentration Test”, “Syndrome Short Test”, “Recall of Digit Span”, “Digit Symbol Substitution

Table 2 Characteristics and important outcomes of the included randomized-controlled trials

Author	Inclusion criteria for participants	Experimental Group	<i>n</i>	Control Group	<i>n</i>	Important Outcomes
Cardiac arrest						
Laitio (2016) ³⁴	Out-of-hospital cardiac arrest, 24-76 yr old	≥ 40% xenon (mean 48.2% ± 3.8%) with TH (33°C) for 24 hr	55	TH alone	55	<ol style="list-style-type: none"> 1. Xenon plus TH resulted in less white matter damage (fractional anisotropy of diffusion tensor MRI) 2. There was a trend that the mortality rate of the xenon group (27.3%) was lower than that of the control group (34.5%) at 6 months (adjusted hazard ratio 0.49 [95% CI, 0.23 to 1.01], <i>P</i> = 0.053) 3. No difference in neurocognitive outcomes at 6 months
Neonatal asphyxia						
Azzopardi (2016) ³⁵	Infants <ol style="list-style-type: none"> 1. Born in 36-43 weeks of gestational age 2. Moderate to severe encephalopathy with abnormal clinical signs and EEG background activity ≥ 30 min 3. Apgar score ≤ 5 at 10 min, continued need for resuscitation at 10 min, or acidosis within 1 hr 	30% inhaled xenon for 24 hr with cooling to rectal temperature of 33.5°C for 72 hr	46	Cooling to rectal temperature of 33.5°C for 72 hr	46	No difference in (1) lactate to N-acetyl aspartate ratio in thalamus, (2) fractional anisotropy in the posterior limb of the internal capsule, (3) maximum Thompson hypoxic ischemic encephalopathy score in the 1st week of life, and (4) neurologic assessment upon discharge
General anesthesia (English)						
Al Tmimi (2015) ³⁸	CABG patients	50-60% xenon anesthesia	21	1.1-1.4% sevoflurane anesthesia	21	<ol style="list-style-type: none"> 1. Patients receiving xenon anesthesia had a lower risk for postoperative delirium 2. No difference in MMSE on POD 3 and upon discharge 3. No difference in serum S-100β and inflammatory markers
Bronco (2010) ⁵⁵	Adults undergoing elective non-cardiac surgery	60% xenon anesthesia	29	1.4% sevoflurane anesthesia	30	Better early (30-60 min) postoperative cognitive recovery after xenon anesthesia (Short Orientation Memory Concentration Test)
Cremer (2011) ⁵⁴	Adults 65-75 yr old, undergoing elective surgery (trauma, orthopedics, ENT, gynecology, neurosurgery, abdominal surgery)	60% xenon anesthesia	19	1.1-1.4% sevoflurane anesthesia	20	No difference in postoperative cognitive function at 6-12 and 66-72 hr (Test of Attentional Performance and several Paper-Pencil-Tests)

Table 2 continued

Author	Inclusion criteria for participants	Experimental Group	<i>n</i>	Control Group	<i>n</i>	Important Outcomes
Coburn (2007) ³⁹	Adults 65-75 yr old, undergoing elective general surgery (trauma, head/neck/ear, gynecology, urology)	60% xenon anesthesia	18	5.2-5.5% desflurane anesthesia	20	No difference in postoperative cognitive function at 6-12 and 66-72 hr (Attentional Performance Test)
Coburn (2018) ⁵⁷	Elderly ≥ 75 yr old undergoing hip fracture surgery	60% xenon anesthesia	124	1.1-1.4% sevoflurane anesthesia	132	No difference in postoperative delirium in both early (POD 0-4) and late ($\geq$ POD 5) postoperative periods
Devroe (2017) ⁵⁸	Children < 4 yr old undergoing interventional or diagnostic cardiac catheterization	50-65% xenon and titrating sevoflurane according to BIS target: 40-60	20	Sevoflurane only, titrating sevoflurane according to BIS target: 40-60	20	1. Xenon reduced emergence agitation but not delirium 2. Patient who received xenon had a shorter period of low cerebral saturation intraoperatively 3. No difference in S-100 β
Rasmussen (2006) ⁵³	Adults ≥ 60 yr old, undergoing elective knee replacement under spinal anesthesia	50-70% xenon anesthesia	21	Total intravenous anesthesia with propofol 3-5 mg·kg ⁻¹ ·hr ⁻¹	18	No difference in cognitive function at 3-5 days and 10-14 months (Visual Verbal Learning Test, Concept Shifting Test, Stroop Color Word Interference Test, Letter Digit Coding Test)
Stuttman (2010) ⁵²	Adults undergoing elective thyroidectomy, augmentation or reduction mammoplasty, liposuction for obesity, and knee arthroscopy	63% xenon anesthesia	31	0.6% isoflurane anesthesia	30	Xenon anesthesia had a better recovery of early postoperative cognitive function (Syndrome Short Test and Recovery Index) at 60 and 180 min post extubation
General anesthesia (Russian)						
Bagaev (2015) ⁴⁷	Children 5 to 17 yr	60-65% xenon anesthesia with Xe-O ₂	22	2.5% sevoflurane anesthesia	20	No difference in serum S-100 β and brain-derived neurotrophic factor
Mizikov (Мизиков) (2013) ⁴⁹	Neurosurgery	Group 1: xenon alone [0.8-1.0 MAC] Group 2: 50% xenon with isoflurane [0.2-0.3 MAC] Group 3: 50% xenon with sevoflurane [0.2-0.3 MAC]	Group 1: 12 Group 2: 20 Group 3: 20	Sevoflurane alone [0.8-1.0 MAC]	20	No difference in serum S-100 β and neuron-specific enolase
Grantovna (Петросян) (2014) ⁵⁰	Neurosurgery	50% xenon with sevoflurane [0.2-0.3 MAC]	36	Sevoflurane alone [0.8-1.0 MAC]	41	Xenon anesthesia was associated with lower serum neuron-specific enolase in patients with convexital tumours but higher serum S-100 β in patients with tumours located in base of brain

Table 2 continued

Author	Inclusion criteria for participants	Experimental Group	<i>n</i>	Control Group	<i>n</i>	Important Outcomes
Shishneva (Шишневa) (2009) ⁵⁶	CABG surgery patients, 53-67 yr old	Group 1: xenon anesthesia	20	Group 4: traditional operation. (group 2-3 not relevant)	38	Patients received xenon anesthesia had better cognitive function and psycho-emotive state
Shishneva (Шишневa) (2010) ⁴⁸	CABG surgery patients	Group 2 (<i>n</i> = 30): 60% xenon anesthesia	30	Group 1: traditional operation (group 3 not relevant)	29	Serum S-100β was lower in the xenon group before removing the aortic clamp but no difference on POD 1 and POD 2
Withdrawal from addictive substance						
Striepetova (2014) ³⁷ [Ukraine]	Alcohol addiction	Standard treatment + xenon inhalation therapy (25-30% for 10-15 min once a day)	67	Standard therapy: benzodiazepines, anesthetics (propofol), anxiolytics (hydroxyzine), neuroleptics, and symptomatic treatments	70	1. Patients in the xenon group had higher scores in MMSE and Wechsler Memory Test on 2 nd -6 th days of ICU stay 2. The duration of delirium was shorter in the xenon group
Tzigankov (Цыганков) (2013) ³⁶ [Russian]	Acute alcohol or opioid withdrawal	Standard treatment + xenon inhalation (Xe:O ₂ = 1:2); 3 inhalations in the first 2 days of ICU admission, then 1-2 inhalations per day for 3 days	60	Standard treatment: antipsychotics, tranquilizers, vasopressors, antiplatelet agents, vitamins, glucose, amino acids	60	1. More patients in the xenon group had an improvement in neuropsychologic assessments (memory, abstraction, etc.) in 5-6 days 2. Rheoencephalography (a non-invasive technique that evaluates cerebral blood flow): xenon group had a lower vascular tone and higher pulse wave amplitude, which were signs of cerebral hemodynamic normalization 3. EEG: the xenon group had less pathologic waves

BIS = bispectral index; CABG = coronary artery bypass graft; CI = confidence interval; EEG = electroencephalography; ENT = ear, nose, and throat; ICU = intensive care unit; MAC = minimal alveolar concentration; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; POD = postoperative day; TH = therapeutic hypothermia

Test”, “Trail Making Test”, and “Mini-Mental State Examination”. Nevertheless, these outcomes were too heterogeneous for meta-analysis. While xenon anesthesia was associated with improved cognitive function in the early postoperative period (30-180 min),^{52,55} such benefit was not maintained after six hours.

The results for postoperative delirium were mixed. The incidence of delirium was found to be lower after xenon anesthesia for coronary artery bypass surgery³⁸ but not hip fracture surgery⁵⁷ in adults. Xenon as an adjuvant to sevoflurane anesthesia reduced emergence agitation but not delirium in children (< four years old) undergoing interventional or diagnostic cardiac catheterization.⁵⁸

Biomarkers for glial and neuronal injuries

Six studies^{38,47-50,58} measured S-100β and two studies^{49,50} measured NSE plasma levels. Meta-analysis showed that xenon (either 60% xenon alone^{38,47,48} or a combination^{49,50} of xenon [50%] and sevoflurane (0.2-0.3 minimal alveolar concentration [MAC]) had no significant effect on the serum levels of either S-100β or NSE compared with sevoflurane (0.8-1.1 MAC) (Figs. 2 and 3). The quality of evidence was moderate according to GRADE. Devroe *et al.*⁵⁸ did not report the exact levels of S-100β (and therefore were not included in the meta-analysis), but they also found that xenon had no effect on S-100β levels.

Bagaev *et al.*⁴⁷ also reported that serum levels of brain-derived neurotrophic factor were not significantly different in children (5–17 yr old) anesthetized with either xenon (65%) or sevoflurane (2.5%).

Withdrawal from addictive substances

Striepetova *et al.*³⁷ assessed 137 patients admitted to the ICU for the acute phase of alcohol detoxification. Seventy patients underwent the standard therapy, which included sedation (with benzodiazepines [diazepam], anesthetics [propofol], anxiolytics [hydroxyzine]) or neuroleptics. Sixty-seven patients received 25–30% xenon for 10–15 min once a day in addition to the standard therapy. Patients in the xenon plus standard therapy group had higher scores on the Mini-Mental State Examination and Wechsler Memory Test from the second to sixth days of their ICU stay ($P < 0.001$). The duration of delirium was also shorter in the xenon plus standard therapy group.

Tzigankov *et al.*³⁶ recruited 120 ICU patients who experienced acute withdrawal syndrome associated with alcohol or opioid addiction. Half of the patients received the standard therapy, which included antipsychotics, tranquilizers, vasopressors, antiplatelet agents, vitamins, glucose, and amino acids. The other half received the standard therapy in addition to 33.3% xenon inhalation three times a day for two days and one to two times a day for another three days, 10–15 min each time. Compared with standard therapy, patients in the xenon plus standard therapy group showed improvement over five to six days in their neuropsychologic assessments (e.g., memory, abstraction) and electroencephalography (duration of pathologic waves) and rheoencephalography scans (a non-invasive technique that evaluates cerebral blood flow).⁶⁰

Assessment of biases

There was a wide variation of the risk of biases and Jadad scores of the included studies (see Appendix). Most studies were unable to blind the personnel to the group assignment. Some studies did not report the risk of biases.

The funnel plots of the meta-analysis on S-100 β and NSE are shown in the ESM - Supplementary Figs. 3–8. There are no asymmetric patterns suggesting publication bias.

Discussion

Despite promising pre-clinical reports, the current clinical evidence for positive neurologic and cognitive outcomes after xenon exposure is modest. Compared with therapeutic hypothermia, addition of xenon reduced cerebral white

matter abnormality after out-of-hospital cardiac arrest but failed to have an impact on neurocognitive outcomes and mortality.³⁴ In addition, in asphyxiated neonates, xenon did not provide additional benefit compared with therapeutic hypothermia.³⁵ Compared with commonly used volatile anesthetics, xenon may improve short-term neurologic or cognitive outcomes in the early postoperative period, but evidence for long-term outcome benefits is lacking.^{38,52–55} The biomarkers associated with neuronal injury were also not significantly different in patients exposed to xenon compared with other commonly used volatile anesthetics.^{38,47–50} To date, the only population that appears to benefit from xenon administration is patients going through substance withdrawal.^{36,37} Brief intermittent exposure to sub-anesthetic doses of xenon improves short-term neurocognitive outcome in the acute phase of substance withdrawal.

Xenon plus therapeutic hypothermia

It is quite surprising that in the RCTs xenon exposure conferred no added benefit to therapeutic hypothermia in asphyxiated neonates and cardiac arrest patients given the encouraging pre-clinical animal data.^{10–14,17,61,62} We postulate that the RCTs may not have been sufficiently powered. In the study by Azzopardi *et al.*,³⁵ only 92 of 138 intended subjects were recruited. Moreover, the sample size estimation was based on mortality, which has a higher incidence compared with abnormal neurologic outcome. Similarly, Laitio *et al.*³⁴ powered their study to detect a change in fractional anisotropy of 15% but not to detect a change in clinical outcome. More data are needed to determine whether the negative findings of these RCTs are real or simply reflect a false-negative type 2 error.

The failure of the RCTs to show added benefit of xenon exposure to therapeutic hypothermia may also reflect fundamental errors in study design. Table 1 summarizes key study characteristics and results of the nine pre-clinical trials. All pre-clinical trials showed either additive or synergistic effects of xenon with therapeutic hypothermia when it was administered at a concentration of 50–70% for a total duration of one to 24 hr. Moreover, xenon had a neuroprotective effect if administered within zero to two hours of the neurologic insult but the effect diminished if treatment was delayed for more than four hours.^{13,14} In point of fact, xenon's neuroprotective effect appeared to be dose dependent as a greater effect was observed with higher concentration¹⁴ (20% vs 50%) and longer duration¹³ (one vs three hours) of exposure. On the other hand, in the identified RCTs,^{34,35} xenon was started at an average of four hours after the out-of-hospital cardiac arrest and a median of ten hours following the birth-related neonatal asphyxia. Azzopardi *et al.* targeted an end-tidal

S-100 β : Preoperation **S-100 β : Immediate Postoperation** **S-100 β : Postoperative Day 1**

Fig. 2 Meta-analysis of S-100 β levels (xenon vs control). The confidence intervals (CI) shown in the figure are those calculated by Review Manager 5.3, which uses the Z-statistic. Adjustment according to the Satterthwaite approach; preoperation, standardized mean

difference (SMD) = -0.33 (95% CI, -1.15 to 0.49), $P = 0.36$; immediate postoperation, SMD = -0.43 (95% CI, -1.48 to 0.62), $P = 0.36$; postoperative day 1, SMD = -0.32 (95% CI, -0.91 to 0.27), $P = 0.22$

concentration of only 30% based on previous clinical studies in neonates,³⁵ while Laitio *et al.* did not rationalize their end-tidal concentration of approximately 48%.³⁴ Of note, in both these studies, a lower xenon end-tidal concentration was used compared with that in the pre-clinical studies (or, for that matter, what would normally be used during administration of general anesthesia). Although the total xenon MAC-hours administered in the two clinical studies may be theoretically adequate (xenon concentration at 30–48% for 24 hr), the effect of higher MAC at shorter duration may not be therapeutically equivalent to a lower MAC at a longer duration. We therefore conclude that either xenon contributes no added neurologic benefit to therapeutic hypothermia or that it may confer benefit but that it was administered too late following the neurologic insult, or at too low a dose. Future studies should take these

issues into consideration as well as the confounding variable of the severity of neurologic injury before administration of xenon and therapeutic hypothermia.

General anesthesia: postoperative delirium and cognitive dysfunction

The study by Al Tmimi *et al.*³⁸ suggests that xenon administration may be associated with a decreased incidence of postoperative delirium compared with sevoflurane in off-pump coronary artery bypass patients. Nevertheless, this study has some noteworthy shortcomings including a relatively small number of patients randomized to either of the anesthetics and an incomplete randomization process. With other types of surgical patients in whom volatile agents were compared, xenon anesthesia was associated

Neuron-specific enolase: Preoperation **Neuron-specific enolase: Immediate Postoperation** **Neuron-specific enolase: Postoperative Day 1**

Fig. 3 Meta-analysis of neuron-specific enolase levels (xenon versus control). The confidence intervals (CI) shown in the figure are those as calculated by Review Manager 5.3, which uses the Z-statistic. Adjustment according to the Satterthwaite approach; preoperation,

standardized mean difference (SMD) = 0.26 (95% CI, -0.60 to 1.12), $P = 0.41$; immediate postoperation, SMD = -0.03 (95% CI, -1.33 to 1.39), $P = 0.95$; postoperative day 1, SMD = -0.20 (95% CI, -1.42 to 1.02), $P = 0.64$

with a better recovery of cognitive functions soon (zero to three hours) after emergence from general anesthesia.^{52,55} Nevertheless, such benefit was not observed at later stages (six hours to three months).^{53,54}

Most of the included studies are limited by their small sample size (18–38 patients per group). Coburns³⁹ and Cremer⁵⁴ initially used a 20% reduction in the attentional performance for sample size calculation but later argued that 10–15% would have been more appropriate. Rasmussen *et al.*⁵³ acknowledged that their study was not powered for cognitive outcomes and some studies may have attrition biases (e.g., Coburn³⁹ and Cremer⁵⁴: 9/38 and 8/40 patients dropped out, respectively).

The recovery of cognitive function in the early postoperative period (< three hours) can be accounted for by the rapid emergence that presumably relates to xenon's extremely low blood-gas coefficient.¹ Moreover, xenon may reduce the incidence and duration of low cerebral

saturation intraoperatively,⁵⁸ which theoretically could be related to an improved postoperative cognitive function. Nevertheless, a more prolonged neurocognitive benefit would be required to stimulate further interest in using this drug as a general anesthetic. This assumes that anesthesia-associated postoperative cognitive dysfunction proves to be a real phenomenon.^{63,64}

Biomarkers for glial and neuronal injury after general anesthesia

S-100 β and NSE are considered surrogate markers for damage to neural tissues.^{65–70} Nevertheless, S-100 β may be a better neurologic outcome predictor than NSE because of its shorter half-life (12 vs 48 hr).⁷¹ Both biomarkers have been correlated with neurologic outcomes in previous studies^{72,73} and were proposed to predict neurologic outcomes after traumatic brain injury, to monitor on-going

brain injury, and to assess treatment response.⁷¹ Nevertheless, our meta-analysis showed that xenon had no effect on plasma levels of either S-100 β or NSE (Figs. 2 and 3).

The appropriateness and specificity of S-100 β and NSE as surrogate endpoints for neurologic outcomes are still in question. Both biomarkers have extracranial sources: S-100 β is found in melanocytes, adipocytes, cardiomyocytes, and Langerhan's cells and NSE is found in erythrocytes. As such, plasma levels of these biomarkers may not accurately reflect changes originating in the CNS. There are a few additional caveats to be considered. First, none of the trials detailed the sample size calculation, making it hard to rule out a type 2 error. Second, two studies^{49,50} recruited patients who underwent neurosurgery, which may confound the neurologic outcomes including biomarker levels. Third, two studies^{49,50} compared xenon plus sevoflurane (rather than xenon alone) with sevoflurane, potentially obscuring any beneficial neurologic effect of xenon.

Withdrawal from addictive substances

Withdrawal from alcohol or opioids is associated with negative neurologic and cognitive effects, including memory, attention, and visual processing deficits,⁷⁴⁻⁷⁷ and neurologic impairment may be worse in patients requiring ICU admission.^{78,79} Our review indicates that in addition to standard treatment, brief intermittent inhalation of sub-anesthetic doses of xenon may improve neurologic and cognitive outcomes.^{36,37} In addition, xenon-treated patients required fewer benzodiazepines and neuroleptics. The mechanism of the effect of xenon on patients undergoing withdrawal from addiction is unclear. Possibly, xenon decreases the requirement for other sedative agents that may themselves contribute to the delirium. Alternatively, its action as an NMDA receptor antagonist might attenuate the neural excitotoxicity associated with substance-abuse withdrawal.⁸⁰⁻⁸³ Limitations of the studies include bias secondary to experimental design inadequacies. For instance, Tzigankov³⁶ included patients undergoing withdrawal from opiates and alcohol in the study group, but there were only alcohol-withdrawal patients in the control group. Moreover, the processes of randomization, allocation concealment, and blinding were not explicitly reported.

Safety issues

The studies we reviewed were not specifically designed to assess safety outcome and were almost certainly underpowered to reveal relatively rare adverse effects. With these caveats in mind, the following observations can be made. In the studies concerning the addition of xenon to therapeutic hypothermia, the severe adverse event rates

were similar between the experimental and control groups (e.g., death, kidney injury, seizure, cardiac arrhythmia, pneumonia, sepsis).^{34,35,51,84} In the studies where xenon was compared with other general anesthetic drugs in surgical patients, six of 11 studies^{39,47,48,52,54,56} did not mention safety outcome assessments whereas three studies^{49,53,55} reported that xenon increased the risk of postoperative nausea and vomiting. With the investigations concerning patients undergoing substance-abuse withdrawal, one study³⁶ did not observe any adverse events (details not reported in the paper) and the other³⁷ did not report safety outcomes.

Future directions

Xenon's potential neurologic benefit has been studied in two types of patients: surgical patients (with presumably normal CNS function) and those with specific CNS-related pathophysiology (i.e., hypoxic brain injury, substance withdrawal). Xenon may confer potential benefit selectively to the latter type of patient. Future studies may reveal positive outcomes in appropriately targeted patients consistent with the promising results shown in the pre-clinical studies (Table 1). Importantly, consensus is required for the assessment of neurologic function using standardized neurocognitive assessment tools that will enable comparison of studies and the pooling of data for meta-analyses. While radiologic, electrophysiologic, and biochemical measurements provide interesting quantitative data ideally suited to such analyses, they cannot replace clinical assessment of neurologic and cognitive function. Rather, they may be considered important ancillary information that may also offer clues as to the mechanism(s) of action.

Conclusions

The current clinical evidence for the neurologic and cognitive benefits associated with the use of xenon is modest. Our review raises the possibility of a narrow therapeutic window in terms of dose, duration of therapy, delay of treatment, and type of neurologic injury. More adequately powered and appropriately designed clinical trials are needed to draw a reliable conclusion.

Conflicts of interest None declared.

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APPENDIX Risk of bias assessment of the included randomized-controlled trials

Author	Risk of Bias						Jadad Score			
	Adequate Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Total	Randomization	Blinding	Attrition
Al Tmimi (2015) ³⁸	Low	Low	High	Low	Low	Low	5	2	2	1
Azzopardi (2016) ³⁵	Low	Low	High	Low	Low	Low	3	2	0	1
Bagaev (2015) ⁴⁷	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0
Bronco (2010) ⁵⁵	Low	High	High	Low	Low	Low	5	2	2	1
Coburn (2007) ³⁹	Low	Unclear	High	Low	High	Low	5	2	2	1
Coburn (2018) ⁵⁷	Unclear	Unclear	Low	Low	High	High	4	1	2	1
Devroe (2017) ⁵⁸	Low	Low	Low	High	Low	Low	3	2	0	1
Cremer (2011) ⁵⁴	Low	Unclear	High	Low	High	High	5	2	2	1
Laitio (2016) ³⁴	Low	Low	High	Low	Low	Low	3	2	0	1
Rasmussen (2006) ⁵³	High	Unclear	High	Low	Low	Low	5	2	2	1
Shishneva (2009) ⁵⁶	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0
Striepetova (2014) ³⁷	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0
Stuttman (2010) ⁵²	Low	High	High	Low	Low	Low	5	2	2	1
Tzigankov (Цыганков) (2013) ³⁶	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0
Мизиков (2013) ⁴⁹	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0
Петросян (2014) ⁵⁰	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0
Шишнева (Shishneva) (2010) ⁴⁸	Unclear	Unclear	Unclear	Unclear	Low	Low	1	1	0	0

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