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REVIEW ARTICLE

Protecting the Brain With Xenon Anesthesia for Neurosurgical Procedures

Anna Rylova, MD, PhD and Mervyn Maze, MB, ChB†*

Abstract: Xenon possesses some, but not all, of the clinical features of an ideal anesthetic agent. Besides well-known advantages of rapid awakening, stable hemodynamics and lack of biotransformation, preclinical data lead to the expectation of xenon's advantageous use for settings of acute ongoing brain injury; a single randomized clinical trial using an imaging biomarker for assessing brain injury corroborated xenon's preclinical efficacy in protecting the brain from further injury. In this review, we discuss the mechanisms and hence the putative applications of xenon for brain protection in neurosurgery. Although the expense of this rare monoatomic gas will likely prevent its widespread penetration into routine clinical neurosurgical practice, we draw attention to the theoretical benefits of xenon anesthesia over other anesthetic regimens for awake craniotomy and for neurosurgery in older, high-risk, and sicker patients.

Key Words: xenon, neuroanesthesia, neurovascular surgery, awake craniotomy, cerebral ischemia, neuroprotection

(*J Neurosurg Anesthesiol* 2018;00:000–000)

Xenon was predicted to be an anesthetic at atmospheric pressure, based on its relative solubility in fat compared with argon, krypton, and nitrogen. The behavioral effects after xenon administration were first shown in animals by Lawrence and colleagues in 1946. Sedation, ataxia, and among other actions were reported in mice exposed to xenon between 0.40 and 0.78 atmospheres.[1] Xenon was first used as a general anesthetic in the 1950s by Cullen and Gross[2] in the United States; they reported successful anesthesia in 2 patients using 80% xenon and 20% oxygen. Over the years, the ability of xenon to provide stable hemodynamic conditions, rapid emergence with no transformation into potentially toxic metabolites, led some proclaim it to be the "ideal anesthetic"; however, xenon satisfies only some, but not all, of the criteria of an ideal anesthetic falling short on its high cost, incidence of postoperative nausea and vomiting, as well as its low potency.[3] Xenon's market penetration for routine surgery has not matched its hyperbolic predictions. Reasons for this lack of widespread uptake include the concern that xenon is an expensive and price-inelastic anesthetic,[4] and that is difficult to administer because of the need to deliver the gas through a closed, recirculating system. A possible salvation for xenon anesthesia will be a clear-cut demonstration that it can address concerns for surgical indications in which other agents fall short. A recently published phase II randomized clinical trial (RCT) reported that xenon-receiving comatose patients following cardiac arrest had less brain damage, as assessed by a neuroimaging biomarker, than those treated with usual standard of care; the trial was not powered to detect, nor did it find, a difference in clinical outcomes.[5] In this review we will address xenon's potential to be the anesthetic of choice for neurosurgical procedures in which protection against acute ongoing neurological injury is required.

As reviews are meant to synthesize high-quality evidence from the peer-reviewed literature, the authors set out with that objective in a PubMed Search using the keywords "xenon," and "neurosurgery" and filtered by clinical trial. Apart from trials in which a xenon isotope was used to measure cerebral blood flow, there is a lack of high-quality clinical evidence, as well as limited overall clinical experience with xenon anesthesia to discuss its effectiveness for neurosurgical procedures. Therefore, the authors have also referred to case reports, conference presentations, and abstracts.

Among the 12 European countries that have market authorization for xenon anesthesia, the most active users are in Germany, France, and Russia. Therefore, the authors have also searched publications in French, German, and Russian medical literature. Several studies were initially presented at European Society of Anaesthesiologists meetings after which they were only published in the Russian literature; because of the relevance to the topic of the review, references to these data from Russian manuscripts are included. In accordance with the Journal's

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M.M. is a cofounder and Board Member of NeuroproteXeon, a spinout company formed by Imperial College, London on the basis of patents that were filed when he was employed at that institution. NeuroproteXeon's mission is to develop xenon for clinical use to prevent acute ongoing neurological injury. M.M. has an equity stake in NeuroproteXeon through (i) founder status, (ii) exercised stock options, and (iii) personal investment. M.M is neither an employee of NeuroproteXeon nor does he have an executive role in the company. A.R. declares no funding or conflict of interest to disclose.

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policy we have also included studies that are only present in abstract form. In some cases, we have referred to secondary endpoints of studies in order to further elaborate on xenon's actions. Case reports were only used in situations where the underlying disease or condition is rare and therefore the generation of randomized trials would be very difficult.

In the event that high-level clinical evidence for the use of xenon for neurosurgical procedures is lacking, the authors provide a theoretical basis for xenon's utility by extrapolating from the known features of xenon in non-neurosurgical settings. The authors offer thoughts on future research efforts that are required to bridge the information gap with evidence from well-conducted clinical trials performed under Good Clinical Practice guidelines.

PROTECTING THE BRAIN DURING NEUROSURGICAL PROCEDURES

Pharmacological agents have failed to provide clinically meaningful protection during neurosurgery[6]; therefore, physiological manipulations,[7] together with surgical reversal following early detection of perioperative complications, are the foundations for preventing neurological injury.[8] In this review, we address the actual as well as putative roles of xenon to facilitate physiological manipulations and to enable early detection of intraoperative and postoperative complications. We also consider the mechanisms for the putative use of xenon to provide pharmacological neuroprotection.

Physiological Neuroprotection

Optimizing cerebral perfusion[9] and oxygenation while avoiding increases in cerebral metabolism and paroxysmal electrical activity are the foundational principles for physiological neuroprotection.[7] This section addresses xenon's effects upon systemic hemodynamics, intracranial pressure (ICP), cerebral perfusion, cerebral metabolism, and electrical activity.

Hemodynamic Effects: Maintenance of Stable Systemic Blood Pressure

In the absence of intracranial hypertension (ICH), cerebral perfusion is a function of systemic arterial blood pressure. Multiple trials, mostly in non-neurosurgical settings, have shown that xenon has a clear advantage over conventional general anesthetics (both inhaled and intravenous) in providing hemodynamic stability.[10–13] In the recent systematic review by Law et al[14] of 31 studies comparing xenon to inhaled anesthetics and 12 studies comparing xenon to propofol, patients receiving xenon consistently had higher systemic blood pressure (Figs. 1, 2). Neukirchen and colleagues reported that xenon anesthesia does not alter sympathetic activity and baroreflex gain, despite increased mean arterial pressure. In vitro studies reveal that xenon blocks the reuptake of norepinephrine at the synaptic cleft, a possible reason for the hemodynamic stability that is provided by xenon anesthesia during surgery.[15] Off-pump coronary artery bypass graft surgical patients randomized to receive xenon required significantly less norepinephrine intraoperatively to achieve the predefined hemodynamic goals than sevoflurane-anesthetized patients.[16] Interestingly, there was also a lower incidence of postoperative cognitive dysfunction in the xenon group.[16]

In the realm of neurosurgery, older carotid endarterectomy patients who were randomized to receive xenon experienced about 50% reduction in hypotensive episodes

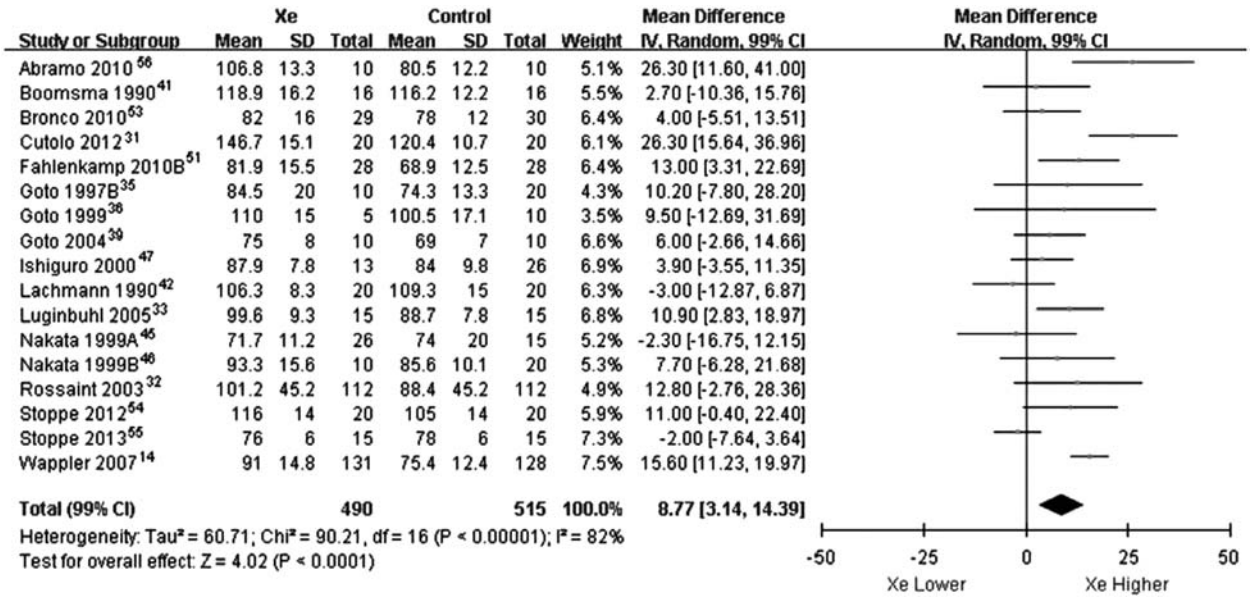


FIGURE 1. Mean arterial pressure (mm Hg), xenon versus other inhaled agents. IV indicates inverse variance; random, random effect; 99% CI, 99% confidence interval. Reprinted with permission from Law et al[14] (http://journals.lww.com/anesthesia-analgesia/Fulltext/2016/03000/Xenon_AnesthesiaA_Systematic_Review_and.16.aspx).

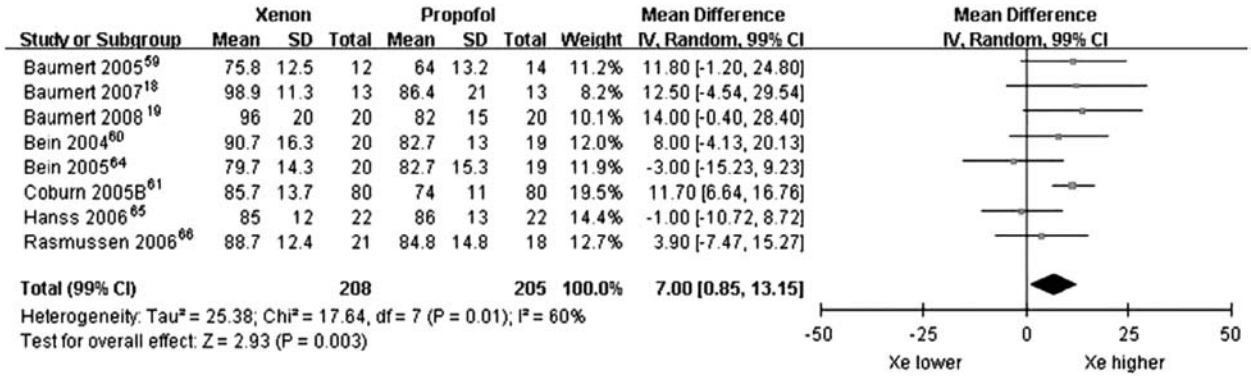


FIGURE 2. Mean arterial pressure (mm Hg), xenon versus propofol. IV indicates inverse variance; random, random effect; 99% CI, 99% confidence interval. Reprinted with permission from Law et al[14] (http://journals.lww.com/anesthesia-analgesia/Fulltext/2016/03000/Xenon_AnesthesiaA_Systematic_Review_and.16.aspx).

and required less vasopressors compared with those anesthetized with sevoflurane.[17] Furthermore, sevoflurane demonstrated a significant reduction in the blood pressure gradient between radial arterial blood pressure and the occluded carotid artery pressure in patients having carotid endarterectomy, presaging worse cerebral perfusion during cross-clamping.[18] In a nonrandomized observational study of carotid endarterectomy patients, blood pressure targets were achieved with less volume expansion and lower ephedrine supplementation in xenon-anesthetized versus propofol-anesthetized patients[19]; furthermore, cerebral oxygen saturation during cross-clamping was higher in the xenon-exposed patients.[19]

Baumert et al[20] reported faster homeostatic response to an acute hemorrhage in pigs anesthetized with xenon than in those receiving isoflurane anesthesia. A patient with Eisenmenger syndrome undergoing cholecyctecomy[21] and a patient with dilated cardiomyopathy undergoing intramedullary tumor removal[22] were successfully anesthetized with xenon with minimal, or no requirement for inotropic/vasopressor support; postoperative recovery of both patients was rapid and uncomplicated.

The prospect of decreasing volume loading may be especially appealing in patients with hypocoagulation as well as in patients with cardiac compromise. The decreased or avoided use for vasopressor support may be particularly advantageous for enhanced recovery,[23] especially in the elderly and/or ASA III patients who have increased length of hospital stay after craniotomy for brain tumors.[24] Further RCTs are needed to demonstrate that the expected benefits accrue from less fluid and vasopressor administration in neurosurgical patients.

Effects on Intracranial and Cerebral Perfusion Pressures (CPP)

When ICH is present or when the risk of its development is high, care should be exercised to avoid further rise in ICP because of its potential to compromise cerebral perfusion. Even though the relevance of ICP changes during general anesthesia for craniotomy remains controversial, it is important to consider what effect xenon has on ICP.

All inhalational anesthetics, including xenon, are expected to increase ICP because of pial vasodilation[25]; the increased ICP may be counteracted by anesthetic-induced suppression of cerebral metabolism.[26] There may be greater interindividual variability regarding xenon's effect on ICP. For example, Plougmann et al[27] studied 30% xenon inhalation in 13 comatose brain trauma patients and noticed that ICP increased during the first 5 to 6 minutes, then declined to a plateau in 4 patients, remained at a plateau in 6 patients, or continued to increase in 3 patients. In contrast, Marion and Crosby[28] observed no increase in ICP in a similar patient population. Giller et al[29] noted that 85% of patients responded to xenon inhalation with an increase in ICP with the remainder exhibiting a decrease. The inconsistency in the reports addressing the effects of xenon anesthesia on ICP may be attributed to the relatively low number of patients that have been rigorously studied, the heterogeneity of the pathologic conditions under which ICP was assessed, and the duration of xenon exposure. Notwithstanding this controversy, there is consensus that hyperventilation effectively mitigates xenon-induced increase in ICP.[30–34]

Rylova et al[35] measured ICP with different concentrations of xenon when delivered by closed-circuit xenon anesthesia in neurosurgical patients.[33] Closed circuit xenon anesthesia requires 3 phases, namely, a denitrogenation phase under intravenous anesthesia (usually propofol), a phase of initial xenon administration with accumulation in the circuit during decreasing administration of propofol; and steady-state phase of xenon monoanesthesia. Closed circuit xenon administration permits a direct intrapatient comparison of the ICP under anesthesia with propofol versus xenon. Initially, Rylova and Lubnin[33] focused on patients without ICH who had low-volume intracranial tumors amenable to trans-sphenoidal endoscopic surgery, in which lumbar CSF drainage is part of the standard of care. Compared with propofol alone, statistically significant (paired *t* test) but clinically irrelevant elevations in ICP were noted during xenon anesthesia alone.[33] In a follow-up study, Rylova et al[35] included 20 patients with and without existing ICH; in these patients the complexity

of surgery, the expected postoperative complications or the underlying pathologic condition prompted insertion of a subdural ICP sensor for ICP measurement. Again, taking advantage of the closed circuit xenon administration, these patients were studied sequentially at equivalent anesthetic states achieved with propofol alone, a combination of 30% xenon (MAC-awake or sedative dose) with propofol supplementation, and 65% xenon anesthesia alone. At baseline (propofol anesthesia) 7/20 patients had ICH (mild [range: >16 to ≤ 19 mm Hg]: 6 and moderate [range: >19 to ≤ 24 mm Hg]: 1). At 30% xenon (with propofol supplementation) 8/20 patients had ICH (mild: 1 and moderate: 7). With xenon anesthesia alone, 10/20 patients had ICH (mild: 2, moderate: 2, and severe [>24 mm Hg]: 6). According to the protocol when severe ICH occurred, it was required to revert to propofol anesthesia; therefore, no information is available regarding the durability of severe ICH in the presence of xenon monoanesthesia. The mean ($\pm$SD) ICP values progressively and significantly increased from 14 ± 5 mm Hg in the propofol alone phase to 19 ± 7 mm Hg in the xenon anesthesia alone phase. Interestingly, interindividual variability was again present but there were no identified factors that contributed to variability. Despite the fact that the study population included patients with high-volume intracranial mass lesions, perifocal edema, and fundoscopic signs of preoperative ICH that required control with the use of steroids and/or diuretics, xenon anesthesia alone did not result in clinical complications.

Studies designed to investigate xenon's effects on cerebral blood flow have also yielded conflicting results depending on the techniques used (intracranial Doppler vs. positron emission tomography), the mode of ventilation (spontaneously breathing volunteers vs. mechanically ventilated patients), the duration of the exposure, and type of neurosurgical condition.[33] In the aforementioned study of patients with ICH, the highest CPP was observed when a sedative concentration of xenon was combined with a subanesthetic dose of propofol.[34]

Similar to other inhaled anesthetic agents, xenon has the potential to increase ICP that becomes clinically significant in patients with preexisting ICH; in these patients hyperventilation remains a viable option for short-term, episodic control of ICP. Long-term protection can be achieved with intravenous anesthetics such as propofol. As rises in ICP are of greatest concern before the opening of the dura mater, it would be reasonable to use intravenous anesthesia in patients with known ICH before dura mater opening and convert to xenon anesthesia thereafter, to realize the putative benefits of neuroprotection, hemodynamic stability and rapid emergence.

Effect Upon Cerebral Metabolism

All general anesthetics are known to decrease cerebral metabolism to some degree, with inhalational anesthesia being equivalent to anesthesia with propofol alone.[36] In volunteers, xenon has been shown to induce changes in cerebral metabolism and blood flow that resemble those induced by volatile anesthetics.[25] Rylova and Lubnin[37] compared oxygen content and glucose concentration in the left radial artery and right internal jugular vein in 10 patients undergoing aneurysm clipping or supratentorial tumor removal. Using the same protocol as for the ICP studies, including anesthesia depth monitoring, Rylova and Lubnin[37] reported a decrease in the arteriovenous difference in oxygen and glucose with increasing concentrations of xenon reaching a nadir during monoanesthesia with xenon; no changes in lactate levels were observed. From these data the authors concluded that xenon decreased cerebral metabolism to greater extent than propofol. These findings corroborate those of Godet et al[19] who showed improved cerebral oxygenation (higher rSO_2) with xenon compared with propofol during cross-clamping.

Effect on Cerebral Electrical Activity

Paroxysmal electrical activity is known to increase cerebral metabolism, cerebral blood flow and ICP. Rylova et al[38] showed that electrical activity under xenon closely resembled electrical activity under propofol anesthesia; xenon neither amplified nor masked preexisting abnormal electrical activity. Laitio et al[39] in the study of bispectral index, entropy, and qualitative electroencephalogram during xenon anesthesia came to the same conclusion that xenon-induced changes in the electroencephalogram closely resembled those induced by propofol. Of note, the anesthesia depth monitors, including bispectral index, were adjudged accurate and correlated with electroencephalographic data. Interestingly, during the Total Body hypothermia plus Xenon (TOBY-Xe) study in neonates with hypoxic ischemic encephalopathy, 8/14 patients exhibited seizures before xenon administration while only 1/14 had epileptiform activity during xenon inhalation.[40] Larger studies are required to confirm xenon's anticonvulsant effect in other populations. If confirmed, this effect may be exploited to the benefit of neurosurgical patients.

Prevention and Early Detection of Intraoperative/Postoperative Complications With Neurophysiological and Neurological Testing

For effective brain protection, it is crucial to detect deteriorating neuronal vitality as early as possible by neurophysiological monitoring as changes in somatosensory evoked potentials (SSEP) can be highly predictive of perioperative injury.[41] Inhaled anesthetics interfere with neurophysiological monitoring, leading to unreliable data requiring a departure from inhalation anesthesia for the period of monitoring. Halogenated anesthetics decrease amplitude and increase latency of evoked potentials. Propofol, "the gold-standard" anesthetic agent for neurosurgical procedures, preserves SSEP amplitude. Neukirchen et al[42] compared SSEP amplitude and latency under propofol versus xenon anesthesia; xenon decreased SSEP amplitude to 43% of baseline while SSEP latencies remained unaltered. Therefore, the value of SSEP monitoring as a tool for guiding intraoperative management

will be less effective with xenon than with propofol anesthesia.

Awake craniotomy is the preferred technique to facilitate clinical monitoring during the surgical management of tumors in the eloquent brain.[9,43] If general anesthesia is required, it must be provided with agents that facilitate rapid intraoperative awakening to assure high-quality functional testing. Xenon has a theoretical advantage of combining both safe ventilation and rapid awakening. In their systematic review, Law et al[14] reported that non-neurosurgical patients receiving xenon anesthesia had significantly faster emergence from anesthesia (> 50% reduction of time to eye opening, tracheal extubation, orientation and countdown) than those receiving volatile anesthetics (Fig. 3). Rasmussen et al[44] confirmed faster emergence time from xenon anesthesia (260 s) than from propofol anesthesia (590 s) in patients, aged 60 and over, undergoing knee replacement surgery after relatively short anesthetic exposures. In a study by Dingley et al[45] involving postoperative patients following cardiac bypass surgery who were randomized to receive either propofol or xenon for postoperative sedation, the mean recovery time from propofol sedation was 25 ± 29 versus 3 ± 5 minutes following xenon sedation, a statistically and clinically significant finding. However, in short duration non-neurosurgical procedures there was no difference in the emergence time from xenon versus propofol anesthesia.[11] Xenon's unique combination of low blood-gas partition coefficient, no biotransformation, and no accumulation explains the rapid and full awakening. Kulikov et al[46] described a successful case of awake craniotomy under xenon anesthesia with a laryngeal mask airway in a patient with preoperative speech deterioration and severe ICH. It has yet to be rigorously studied whether the physiochemical properties of xenon can facilitate successful intraoperative or postoperative testing in a neurosurgical patient population.

Apart from the rapid awakening that may be required in special circumstances intraoperatively, rapid and complete emergence is required for the early detection of postoperative complications for all neurosurgical patients. In a study comparing propofol, dexmedetomidine and

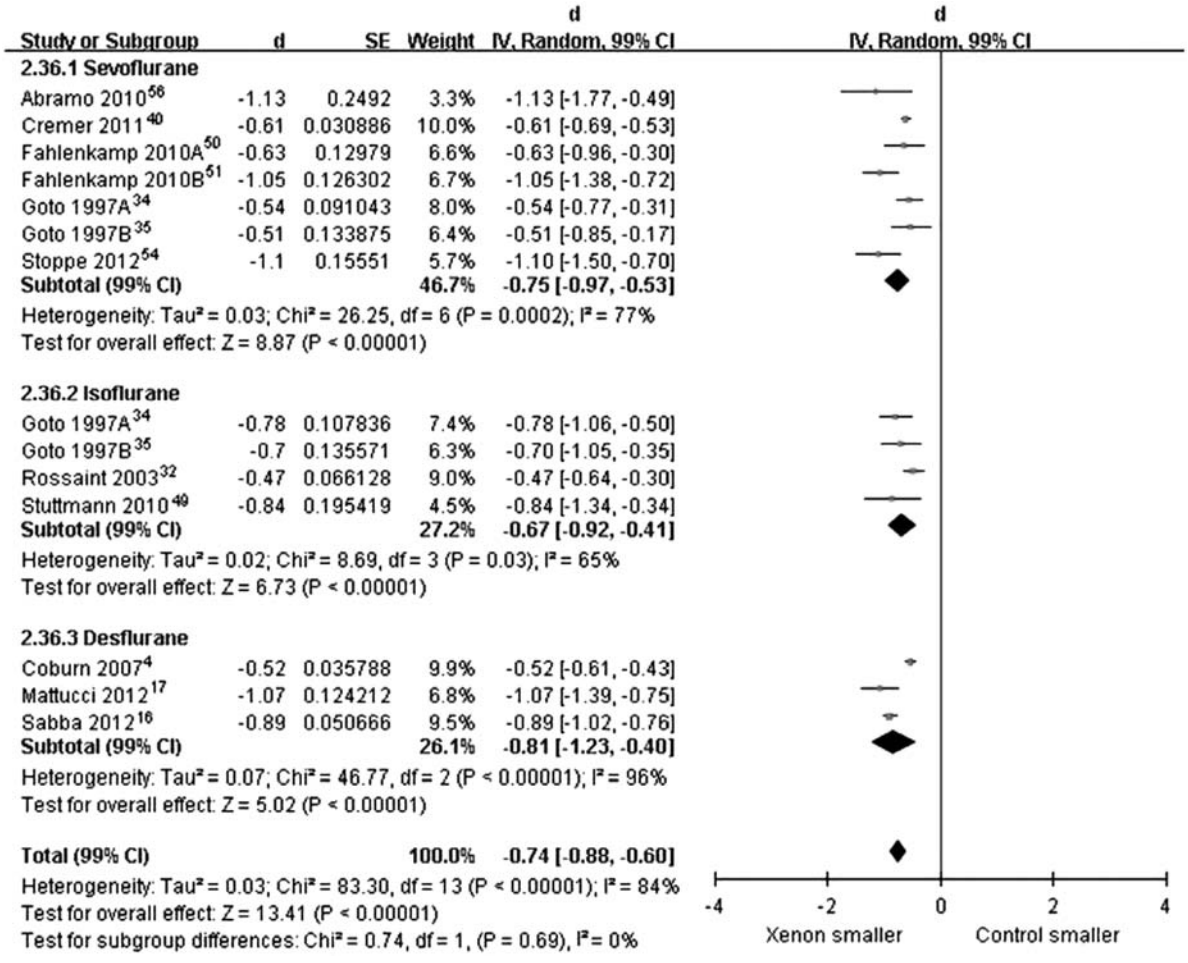


FIGURE 3. Time to open eyes, xenon versus volatile agents (subgroup: sevoflurane, isoflurane and desflurane). d indicates mean difference in the natural-log-transformed scale; IV, inverse variance; random, random effect; 99% CI, 99% confidence interval. Reprinted with permission from Law et al[14] (http://journals.lww.com/anesthesia-analgesia/Fulltext/2016/03000/Xenon_AnesthesiaA_Systematic_Review_and.16.aspx).

xenon, Kulikov et al[47] reported that time to neurologic testing was shorter in the xenon group than in patients receiving either dexmedetomidine or propofol with/without airway protection. However, there is a justified concern that there could be extensive loss of xenon from the circuit in which an LMA rather than an endotracheal tube is used, thereby increasing the cost of the anesthetic. Kulikov et al[47] pragmatically suggested use of xenon for anesthesia before testing, and continue with propofol after testing to limit the loss of xenon. Rylova and colleagues reported a case in which rapid emergence from a xenon anesthesia facilitated the early postoperative detection of a life-threatening posterior fossa epidural hematoma following removal of a recurrent tumor from temporal bone pyramid prompting surgical evacuation without neurological sequelae.[48] If these encouraging findings are to be corroborated in RCTs, then xenon has the potential to be the anesthetic of choice for craniotomy patients that require rapid awakening and testing.

The intensive care unit (ICU) is another setting in which rapid recovery from sedation is needed to perform reliable neurological testing. As noted above, Dingley et al[45] showed that the mean recovery time from prolonged xenon sedation was significantly shorter than a similar duration of propofol exposure (both in the presence of a remifentanil infusion). As xenon also has an analgesic component, hemodynamic and consciousness altering analgesics can be avoided when used for postoperative sedation.[49] Bedi et al[50] showed that xenon-exposed patients required a minimal amount of hypoventilation-inducing opioid supplementation. A nonsignificant trend toward faster ICU discharge and shorter hospital stay was noted in 120 craniotomy patients that received anesthesia with propofol infusion.[51]

Pharmacological Neuroprotection

Both new, and deterioration of existing, neurological injuries can occur in neurosurgical settings. Theoretically, these may be mitigated by the use of an anesthetic with neuroprotective properties. In a recent meta-analysis exploring the neuroprotective efficacy of general anesthetics in preclinical model of middle cerebral artery occlusion, it was noted that almost all anesthetics that have been studied have shown some improvement based on infarct size and neurobehavioral function as outcomes.[52] However, translation of these neuroprotective general anesthetics into clinical utility has not transpired.[53] Only thiopental[54] and lidocaine,[55,56] were reported to significantly improve clinical outcome through a putative neuroprotective effect; however, these findings have not been corroborated by the same or other investigators.[55]

Why is it likely that xenon will be effective when other anesthetic and non-anesthetic preclinical neuroprotectants have failed? First, xenon acts on several steps in the acute neurological injury pathway. Perhaps, the most important one is the antiexcitotoxic effect,[57] due to competitive antagonism of the glycine coactivation site on the *N*-methyl-D-Aspartate (NMDA) subtype of the glutamate receptor.[58,59] Xenon's actions at the NMDA receptor should be distinguished from the open-channel blockers of NMDA receptors, such as ketamine, memantine and MK-801. Open-channel blockers of NMDA receptors invariably show changed kinetics following the application of the agonist, in the presence of the inhibitor. For example, when NMDA is applied, the rate of closure of the NMDA receptor ion channel is always much faster when an open-channel blocker such as ketamine, memantine or MK-801 inhibitor is present.[60] With xenon, there is no increase in the rate of closure of the NMDA ion channel.[58,59] A characteristic feature of open-channel blockers is that they change the apparent affinity of the agonist. For example, memantine changes the apparent affinity of NMDA acting on the NMDA receptor,[60] whereas there is no change in the apparent affinity of NMDA in the presence of xenon.[58] Also, open-channel blockers such as memantine and ketamine invariably increase the decay of excitatory postsynaptic currents,[61] but this is not observed with xenon.[62] Thus, with both heterologous expression systems and in intact synapses, xenon does not behave as an open channel blocker.

A major deterrent to the use of NMDA antagonists as neuroprotective agents is the pyramidal neuronal damage in the region of the posterior cingulate and retrosplenial (PC/RS) cortices first reported by the Olney group, commonly referred as "Olney lesions."[63] These lesions can be identified histologically as vacuolization, or by expression of proteins that are indicative of neural stress/injury such as heat shock proteins or the immediate early genes.[64] These pathologic changes in the PC/RS cortices have been reported with another NMDA class of gaseous anesthetic/analgesic, nitrous oxide (N_2O), also by the Olney laboratory.[65] It is notable that NMDA antagonists that produce its receptor blockade by competing for the glycine coactivation site do not produce the type of neurotoxicity seen with the open channel-blockers.[66] Gavestinel, the competitive antagonist at the glycine binding site, was investigated in humans and has also been found to lack the neurotoxicity and psychotomimetic effects of the NMDA receptor open channel-blockers.[61]

To study whether xenon produces the typical NMDA receptor antagonist neurotoxicity in the PC/RS cortices, we undertook studies to determine whether protein expression of an immediate early gene (c-Fos) was induced by xenon[62]; this form of assessment of damage by NMDA antagonists has been previously reported.[67] In control animals, the number of c-Fos positive neurons was 109 ± 29 and this did not change significantly in the presence of xenon up to 75% of one atmosphere. Contrastingly, N_2O and ketamine significantly increased the number of c-Fos positive neurons in a dose-dependent manner. As a positive control, the effects of MK801 at the dose (0.5 mg/kg) produced a large and highly significant increase in the number of c-Fos positive neurons in the PC/RS cortices. A study from another laboratory also showed that xenon 70% of one atmosphere did not produce lesions in the PC/RS cortices while N_2O 70% was neurotoxic in the region of the PC/RS cortices; remarkably, the neurotoxicity induced by ketamine was enhanced by N_2O but inhibited by xenon.[68]

Because both morphologic lesions as well as the psychotomimetic behavioral responses of the NMDA antagonists can be prevented by blocking the dopamine D_2 receptor, we undertook further studies to explore whether dopamine release could explain the differences in neurotoxicity between the NMDA antagonist anesthetics.[69] Although both ketamine and N_2O increased release of dopamine into the nucleus accumbens over the same dose-range that induced lesions in the PC/RS cortices, xenon did not change dopamine release. Again, while N_2O increased ketamine-induced release of dopamine, xenon prevented this increase in dopamine release.[69]

Apart from its actions at the NMDA receptor, xenon has other action mechanisms that contribute to its neuroprotective properties. While excitotoxicity occurs relatively early in the pathophysiological acute neurological injury pathway,[70] the window of opportunity for neuroprotection is greatest for processes that take some days to develop; neuroapoptosis has such a time-course. Therefore, it was particularly noteworthy that the protection conferred by xenon also involves antiapoptotic effects.[62] Furthermore, the synergistic interaction noted above with hypothermia was promoted by the enhanced expression of antiapoptotic factor, such as B-cell lymphoma 2 and the downregulation of the proapoptotic BAX.[57]

A remarkable property of xenon is its ability to upregulate the expression of the transcription factor hypoxia-inducible factor 1α by enhancing its translational efficiency through activation of the mTOR pathway.[71] The action of hypoxia-inducible factor 1α on hypoxia responsive elements on genes, such as erythropoietin and vascular endothelial growth factor, results in a long-lived increase in the levels of these cytoprotective molecular species.

Cyclic-AMP response-element binding protein is a pivotal transcription factor that binds to DNA sequences known as cAMP response elements for genes that include brain-derived neurotrophic factor. Exposure to xenon increases the expression of the activated phosphorylated species of cyclic-AMP response-element binding protein and the neuroprotective downstream effector brain-derived neurotrophic factor.[71]

When activated, 2-pore potassium channels (K_{2P} channels) hyperpolarize the membrane potential, taking it farther from a depolarization threshold. Xenon was shown to activate TREK-1, a subspecies of these channels.[72] TREK-1 channels are the mechanism whereby intracellular acidification as well as polyunsaturated fat acids produce neuroprotection.[73]

Neuroinflammation propagates ongoing neuronal damage through several pathways, including through the elaboration of proinflammatory cytokines that further injure the penumbra around an infarcted core, and preventing neuroinflammation attenuates brain injury.[74] Xenon decreases neuroinflammation and the associated neuronal dysfunction.[75] Xenon pretreatment prevents glucose-deprived and oxygen-deprived neuronal cells from dying in primary cultures; a key mechanism involves xenon's activation of the K_{ATP} channels.[76,77]

A recent study on the efficacy of xenon in out-of-hospital cardiac arrest survivors[5] provides guarded optimism for its potential benefit in the setting of global ischemia reperfusion brain injury that complicates the postcardiac arrest syndrome (PCAS). Using global fractional anisotropy, a validated magnetic resonance imaging surrogate marker of white matter injury, Laitio and colleagues reported a statistically significant reduction in brain injury in PCAS patients randomized to receive xenon in addition to standard of care, compared with those who only received standard of care that included targeted temperature management (Fig. 4). This relatively small 2-center study involved 110 patients who experienced a witnessed cardiac arrest due to a "shockable" arrhythmia and were successfully resuscitated (sustained return of spontaneous circulation) within 45 minutes; the study was not statistically powered to address whether xenon exposure to PCAS patients results in a long-term improvement in clinical outcomes (mortality and functional outcome). A large (1436 patients) RCT (Xenon for Neuroprotection During Post-Cardiac Arrest Syndrome in Comatose Survivors of an Out of Hospital Cardiac Arrest [XePOHCAS]; ClinicalTrial.gov identifier NCT03176186) is planned to determine whether 90-day clinical outcome is improved by coadministration of xenon during targeted temperature management in PCAS patients.

Xenon's efficacy as a neuroprotectant has not been tested clinically in the setting of stroke but was demonstrated in preclinical stroke models by Sheng et al.[78] Xenon conferred brain protection in the widely investigated setting of oxygen deprivation from flow obstruction.[78] Moreover, xenon was also effective as a neuroprotectant in preclinical models of intracerebral hemorrhage.[78] Xenon-exposed rats had both lower neurologic score and total infarct size 7 days after awake middle artery occlusion. To address xenon's putative long-term benefit, no statistically significant difference was shown between the 30% xenon and control groups; however, a clear difference was observed when xenon was combined with modest hypothermia (Fig. 5). To describe histologic outcome 24 hours after collagenase-induced intracranial hemorrhage, hematoma volume, brain water content, and microglial activation were assessed. All were shown to be significantly lower in the 30% xenon group. Finally, investigators have assessed rotarod latency to fall, in order to evaluate neurological (functional) outcome 24 hours after hemorrhage. This was better maintained in mice treated with 30% xenon. The comprehensive studies by Sheng et al[78] reveal xenon's efficacy in both ischemia and hemorrhage, 2 scenarios converging on several pathologies in neurosurgery.

DRAWBACKS AND LIMITATIONS OF XENON USE IN NEUROSURGERY

Postoperative Nausea and Vomiting (PONV)

According to a study by Latz et al[79] incidence of PONV after neurosurgery can be as high as 50%. This is increased to 55% to 70% with infratentorial surgery or without prophylactic antiemetics. Multiple factors contribute to this very high incidence including surgical manipulations

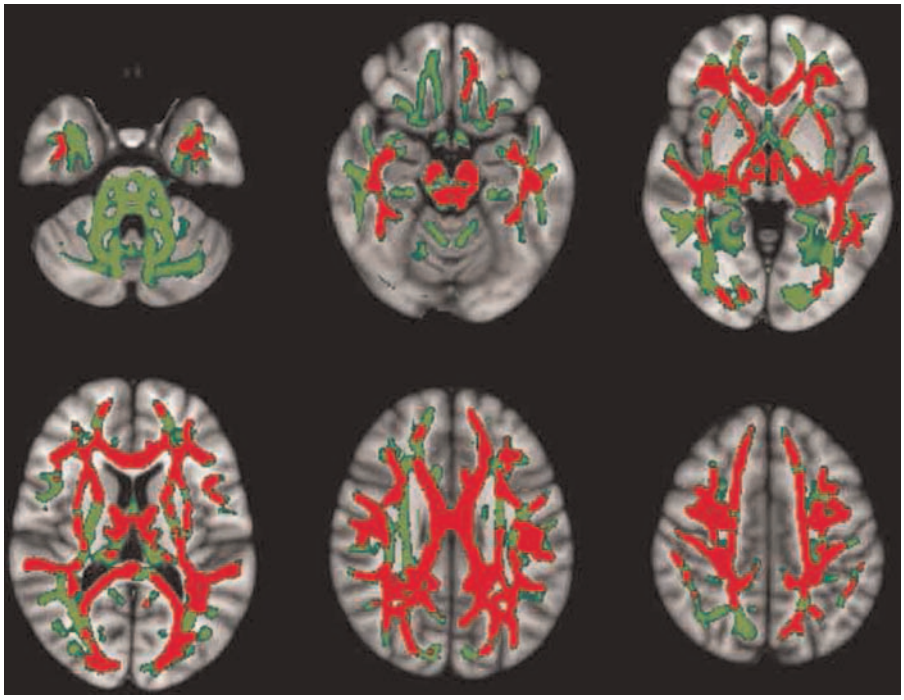


FIGURE 4. Whole brain visualization of the results of cerebral white matter damage. Voxel-wise tract-based spatial statistics analysis of fractional anisotropy values between the xenon group and the control group were performed. Voxels with significantly ($P < 0.05$, family-wise error corrected for multiple comparisons) lower fractional anisotropy values in the control group were identified and are shown in red in the statistical visualization (ie, 41.7% of all 119,013 analyzed voxels), whereas the areas in which there was no significant difference in fractional anisotropy values between the groups are shown in green (ie, 58.3% of all analyzed voxels). Reproduced with permission from Laitio et al.[5] American Medical Association, 2016. All rights reserved. Copyright [American Medical Association], [location of copyright holder]. All permission requests for this image should be made to the copyright holder.

close to emetic centers, as well as cerebellar structures integral to maintenance of equilibrium.[80] As such neurosurgery can be considered as high-risk surgery for the development of PONV. Xenon is associated with higher incidence of PONV than propofol. In their recent meta-analysis, Law et al[14] aggregated results from 9 RCTs with a high number of participants (459 in xenon group vs. 473 in control group) and invariably showed higher incidence of PONV in patients receiving xenon than in patients who received propofol (incidence 34 vs. 20%; risk ratio [99% confidence intervals] of 1.72 [1.10-2.69]). However, the same authors subsequently moderated their comment in the light of the study on 488 non-neurosurgical patients in which the incidence of PONV was significantly lower than predicted by the Apfel score (28% observed; 42% expected).[81] It is noteworthy that in the abovementioned studies, no patient received antiemetic prophylaxis. While important to obviate a confounding variable in a clinical trial, antiemetic prophylaxis is standard practice in moderate and high-risk PONV surgical patients. It remains unknown whether PONV can be preempted by antiemetics in xenon-exposed neurosurgical patients.

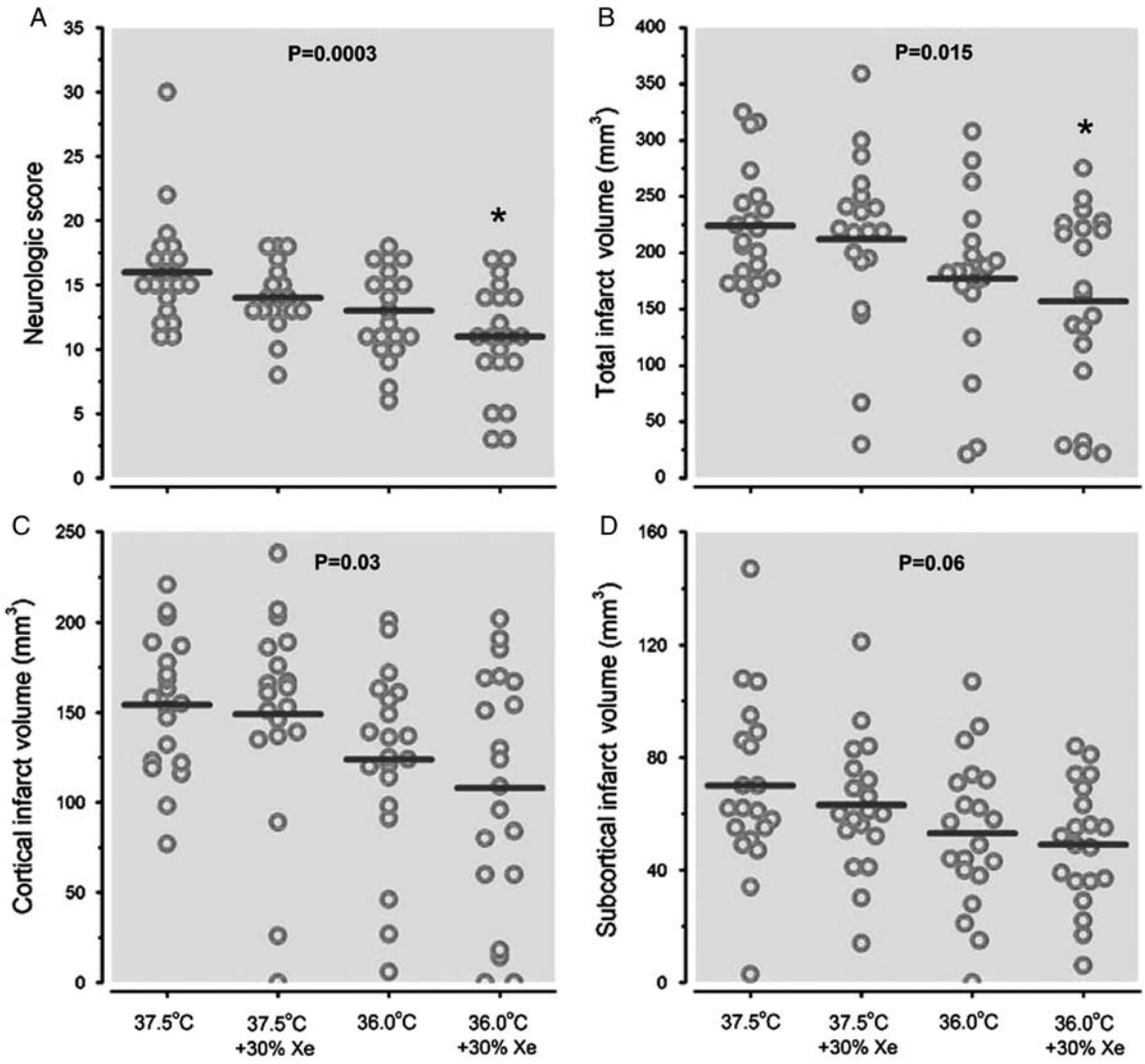
ICH

While there seem to be no untoward clinical effect of xenon anesthesia in patients without ICH, its use in patients with preexisting ICH does pose concerns (vide supra). Xenon administration in high doses, may result in an increase in ICP among susceptible patients with known ICH.[26,28,35] It is notable that other inhalational anesthetics (isoflurane, sevoflurane and desflurane) that are successfully used for many neurosurgical procedures also produce an increase in ICP although its effects in the setting of patients with established ICH have not been thoroughly investigated. As with other volatile anesthetics, inhalation of xenon should be used with caution in patients with clinically relevant ICH. Should a critical rise in ICP occur during xenon anesthesia this may be mitigated by concomitant administration of low-dose propofol or hyperosmolar solutions, as well as short-term hyperventilation.

Even in situations where the ICP does not exceed 20 mm Hg, a slight increase in brain volume can lead to an increase in brain tension such that the operating conditions deteriorate for the surgeon. We are not aware of any study focusing on the effect of xenon anesthesia upon brain tension as assessed by surgeons.

High MAC and Limited Range of Inspired Oxygen Fraction

MAC for xenon varies with age and sex.[82–84] Even though in some settings, the MAC has been noted to be considerably <65% (eg, elderly Japanese women),[83] the use of xenon as the only anesthetic is not advocated when



AQ10 **FIGURE 5.** Xenon as an adjunct to subtherapeutic hypothermia (outcome). Rats were subjected to 70 minutes awake normothermic (37.5°C) middle cerebral artery occlusion and 90 minutes reperfusion. They were then randomly allocated to control of pericranial temperature at 37.5 or 36.0°C with or without exposure to 30% Xe for 20 hours. Neurological score and cerebral infarct size were measured 4 weeks postischemia. Open circles indicate individual animal values. Horizontal lines indicate mean values for (A) neurological score and (B) total, (C) cortical, and (D) subcortical infarct sizes. For neurological scores, 0 = no neurological deficit (potential range: 0 to 48). *P*-values indicate main effect. *$P < 0.05$ versus 37.5°C/0% Xe. Xe indicates xenon. Reprinted with permission from Sheng et al[78] (http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1934368).

surgical patients require an inspired oxygen concentration (f_iO_2) of >35%. Interestingly, a combination of xenon (at sub-MAC doses) with propofol supplementation provided appropriate CPP.[35]

Special Technology and the Need for Closed-circuit Ventilators

While automated, and user-friendly closed-circuit anesthesia machines are now available (PhysioFlex, Drager, Lubeck, Germany; Zeus, Drager; TAEMA Felix Dual, Air Liquide Medical Systems, France; Akzent X Color, Stephan GMBH, Germany), ventilators suitable for use with closed-loop circuits for ICU sedation with xenon are not commercially available. Enterprising investigators were able to successfully sedate patients with the use of stationary ventilators and custom-designed closed circuits. In the study by Bedi et al[50] a bellows-in-bottle breathing interface was added to a commercially available ventilator (Bennett Puritan 7200A) without altering the performance of ventilator. As noted by these investigators, it was feasible to use xenon for intensive care sedation and propose that it may have theoretical advantages over standard drugs in the sedation of hemodynamically unstable patients.[50] In the study by Dingley et al[45] in which significantly faster recovery from ICU sedation was demonstrated in the xenon group than in the propofol group, the bellows-in-bottle system was placed between the patient and the Drager Evita IV ventilator (Drager).

Sedative doses of xenon are quite low (MAC awake is 33%) and therefore can be used for ICU sedation in patients that require f_iO_2 of $>60\%$.[85] In the feasibility and cardiac safety study of xenon for out-of-hospital cardiac arrest survivors,[86] xenon (~48%) was delivered through closed system PhysioFlex ventilator (Drager). In the study of xenon (~30%) and hypothermia for hypoxic ischemic encephalopathy[87] a closed-circuit device specially designed for the study (SLE, Croydon, UK) was used. Whether short-term xenon administration delivered via a conventional, nonclosed circuit is cost-effective has not been tested.

High Cost of Xenon

The relatively high cost of xenon anesthesia continues to be a serious limitation for its widespread utility. As long as the only reliable source of xenon is the atmosphere the cost of retrofitting air separation units to obtain this dense gas, that is present at only 88 parts per billion, will result in high manufacturing costs. Therefore, xenon use will be confined to situations in which its incremental cost effectiveness is established. Apart from the usual health-related quality of life measures, pharmacoeconomic studies are required on the "cost" side to determine whether savings can be reliably achieved by reduction in the use of other expensive resources including length of stays in the ICU and hospital. Without the benefit of these types of studies we can only speculate whether cost effectiveness can be achieved in high-risk and older neurosurgical patients, especially for procedures in which rapid and full recovery is desired. Use of xenon for ICU sedation in settings in which acute neurological injury is imminent may be a future area of expanded use as there are no therapeutic alternatives apart from targeted temperature management in a limited number of clinical settings.

CONCLUSIONS

The demonstrated value of xenon for non-neurosurgical patients needs to be further explored in neurosurgical settings. Theoretically, xenon helps to achieve most, if not all, of the anesthetic goals required for the successful management of the neurosurgical patient, providing appropriate brain perfusion without the need for volume replacement and vasopressor support even in patients with significant comorbidity. Xenon confers pharmacological neuroprotection both under normal surgical conditions when brain tissue is traumatized and during ischemia and hemorrhage. Xenon assures rapid awakening, irrespective of the duration of inhalation, thereby facilitating both intraoperative neurological testing as well as postoperative neurological monitoring. Xenon also contributes to intraoperative and postoperative analgesia as an opioid-sparing drug. While the above-mentioned positive attributes of xenon should theoretically benefit neurosurgical patients, experience with xenon in neurosurgery is scarce (mostly confined to Germany, Russia, and France) and larger clinical trials are needed. In particular we look forward to studies that address whether benefits observed in non-neurosurgical patients (hemodynamic stability, avoidance of vasopressors, and fluid supplementation) also obtain in neurosurgical patients. Furthermore, comparative studies are needed to assess the incremental cost effectiveness ratio of the use of xenon versus other general anesthetics. These studies need to carefully investigate the putative benefits that may accrue from the potential neuroprotective effects of xenon. Only when RCTs performed under Good Clinical Practice confirm xenon's clinical superiority over conventional regimens will its added expense be justified for neurosurgical patients.

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