Efficacy of xenon anesthesia in preventing postoperative cognitive dysfunction after cardiac and major non-cardiac surgeries in elderly patients: a topical review

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Abstract
Elderly patients undergoing major cardiac and non-cardiac surgeries have a high propensity (up to 40–60%) of developing postoperative cognitive dysfunction, which are caused by patient's factors, type of surgery, intraoperative and postoperative factors. All these pose a challenge to the clinicians. The noble gas xenon does not undergo metabolism or any kind of biotransformation in the body owing to its inert nature. Xenon confers excellent hemodynamic stability and provides excellent recovery at the end of surgery. This topical review discusses advantages of xenon anesthesia in elderly patients undergoing major cardiac and non-cardiac surgeries and whether it is worth using a costly anesthetic in elderly patients for preventing postoperative cognitive dysfunction.

Key words: cardiac surgery; cardiopulmonary bypass; cognitive dysfunction; delirium; elderly; non-cardiac surgery; open heart surgery; postoperative complications; xenon

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Introduction
Delirium is characterized by an acute cognitive decline, a fluctuating mental status, disturbance of consciousness, inattention, or disorganized thinking. The current criteria for the diagnosis of delirium are based on Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), Text Revision from the American Psychiatric Association.[1] Postoperative cognitive dysfunction (POCD) after cardiovascular surgeries and major non-cardiac surgeries is a well-known entity but even after so many years, the exact pathophysiology is poorly understood owing to multifactorial etiologies involved. Although medical research has come out with several explanations and suggestions to reduce POCD, the incidence remains the same over years (16–73% in cardiac patients and 10–54% after non-cardiac surgeries).[2,3]

POCD could start manifesting from the first week to 3 months postoperatively. POCD manifests as memory disturbances along with delirium (hyperactive, hypoactive, or mixed), an extended period of hospitalization, delayed rehabilitation, increased mortality, diminished quality of life, dependency on family members. This leads to a significantly high cost of treatment which includes diagnostic tests, medications and hospital stay.[4] There are several factors responsible for this which include patients' factors, preoperative, intraoperative, and postoperative factors. All the factors in various permutations and combinations can be implicated for POCD. This can be further categorized as modifiable factors and non-modifiable factors. Modifiable factors are addiction (nicotine, alcohol), blood pressure control, duration of surgery and cardiopulmonary bypass (CPB), glycemic control, temperature management, duration of ventilation, anesthetic agents and drugs used, early detection, and management. The non-modifiable factors are age, gender, pre-existing cerebrovascular, preexisting neurological conditions, renal and hepatic impairment, emergency surgeries, and environmental changes.[5,6]

An on-pump cardiac surgery theoretically carries a severalfold more risk of POCD due to cardioplegia, microembolic phenomenon due to CPB although this is not found to be statistically significant.[7,8] Although theoretically use of propofol-based total intravenous anesthesia sounds a better alternative to volatile anesthetics in preventing POCD after cardiac surgeries, the systematic review and meta-analysis by Chen et al.[9] compared cerebroprotective effects of volatile anesthetics to total intravenous anesthesia. Chen et al.[9] analyzed 13 studies and concluded that volatile anesthetics appear to provide better cerebral protection than total intravenous anesthesia for patients undergoing cardiac surgery with CPB.

There are several preoperative, validated tools available for screening and identifying elderly patients who are at high risk for POCD like Mini-Cog test, Clock-in-the-box test, Confusion Assessment Method intensive care unit worksheet, or Mini-Mental State Examination.[10,11]

The purpose of this review is to investigate how effective and feasible it is to use xenon anesthesia in elderly patients undergoing major cardiac and non-cardiac surgeries to avoid or reduce the incidence of POCD. We used keywords "cardiac surgery; cognitive dysfunction; delirium; non-cardiac surgery; xenon, cardiopulmonary bypass, open-heart surgery, postoperative complications, elderly" to search Medline, Scopus, Google Scholar, and Cochrane database to gather relevant articles published and retrieved articles starting from year 2007 till date.

Xenon as an Inhalational Anesthetic Agent

Xenon is a mono-atomic inhalational agent which does not undergo metabolism or any kind of biotransformation in the body. This means that xenon is practically an inert gas. Therefore, there is no reaction with carbon-dioxide absorbents nor dose it cause cobalamine depletion in the body unlike other inhalational agents. The blood-gas (0.115) and brain-blood (0.23) coefficients of xenon are the lowest among all inhaled agents due to which there is rapid onset and rapid recovery from general anesthesia.[12] However, monitoring the depth of anesthesia with xenon is a challenge. The use of bispectral index in the recommended range does not correlate well with adequate depth of anesthesia with the use of xenon. The inspired and expired fraction of xenon, when used as an inhalational agent, is essentially the same. There is no propensity for malignant hyperthermia, deleterious effects on renal or hepatic functions.[13] By activation of plasmalemmal adenosine triphosphate-sensitive potassium channels, xenon reduces neuronal excitability and hence protects against ischaemic injury. Owing to these properties, xenon is considered suitable in patients who are at a greater risk of postoperative neurological and cognitive dysfunctions.[14] Xenon provides stable hemodynamics and can be used in patients who are morbidly obese, elderly, and in deranged metabolism. Xenon possesses N-methyl-D-aspartate receptor inhibitory properties owing to competitive inhibition of the glycine co-activation site which is the mechanism of action of xenon as a general anesthetic agent.[15] Irrespective of the duration of use of xenon, the systemic vascular resistance is preserved which thereby maintains stable hemodynamics intraoperatively. A possible explanation for stable hemodynamics and maintaining systemic vascular resistance could be a small increase in circulating noradrenaline due to inhibition of synaptic noradrenaline re-uptake. The major limitation of the use of xenon is the high costs involved and the higher incidence of nausea/vomiting with its use.[16]

Xenon and Postoperative Cognitive Dysfunction in Cardiac Surgeries

Postoperative delirium and cognitive dysfunction are major adverse events after prolonged surgeries especially in elderly patients and in patients undergoing major cardiovascular surgeries. The incidence of POCD after cardiac surgeries hovers between 16% and 73% of patients.[17] Many case series have mentioned the efficacy of xenon in preventing the incidence of POCD in geriatric patients undergoing cardiac surgeries. POCD is a major concern in this age group as it increases overall intensive care unit and hospital stay thereby increasing the cost of treatment. Low ejection fraction, diabetes mellitus, renal impairment/failure, arrhythmia, extracardiac arteriopathies (cerebral, peripheral vascular diseases), pre-existing neurological and psychiatric diseases, substance abuse are the risk factors which could predispose elderly patients to POCD.[18]

Intraoperative factors that predispose to POCD after cardiac surgeries are valve surgeries, prolonged CPB time, complex surgical procedures leading to systemic inflammatory response syndrome mediated by cytokines and chemokines, perfusion management on CPB (mean arterial pressure, flow rates, temperature, hematocrit).[19] Several postoperative factors contributing to POCD after cardiac surgeries are prolonged mechanical ventilation and intensive care unit stay, sleep deprivation, low cardiac output state requiring stiff vasopressors or inotropes, medications like opioids, benzodiazepines, substance withdrawal.[20-24]

Al Tmimi et al.[25] performed a randomized controlled pilot trial by recruiting 42 patients undergoing elective off pump coronary artery bypass surgery. Xenon group patients fared well in terms of having stable hemodynamics and less incidence of postoperative delirium. However, the study involved a small sample size therefore generalization of these findings will not be appropriate unless backed by adequately powered randomized studies. Later Al Tmimi et al.[26] conducted a randomized, observer-blind, controlled trial in which 190 patients involving 65 years or older patients underwent on-pump cardiac surgery. Patients were randomized to receive xenon or sevoflurane as anesthetic. Patients received propofol on CPB. On analysis authors concluded that xenon anesthesia did not result in a significant reduction in POCD and therefore did not recommend xenon for preventing POCD.[26] Stoppe et al.[27] randomized 30 patients undergoing coronary artery bypass grafting under CPB to receive either xenon anesthesia or sevoflurane anaesthesia. They compared systemic and pulmonary dynamics in both groups and also parameters like blood loss, inotropic support, regional cerebral tissue oxygenation, and postoperative delirium in both groups using CAM-ICU. They concluded that there were comparable incidences of delirium between the xenon and sevoflurane groups[27] (**Table 1**).

Xenon and Postoperative Cognitive Dysfunction in Non-Cardiac Surgeries

Xenon has been used by several researchers as an anesthetic for complex brain surgeries. Due to the hemodynamic stability conferred by xenon, it was noticed that brain perfusion was adequately maintained without overzealous intravenous hydration using crystalloids and vasopressors. This stability was noted in patients with serious co-morbidities also.[32,33]

In 2007, Coburn et al.[28] randomized 38 patients undergoing non-cardiac surgeries ($n = 20$ in desflurane group and $n = 18$ in xenon group) and concluded that there was no difference in the postoperative cognitive testing at 6–12 and 66–72 hours. Later in 2018, Coburn et al.[31] conducted a multicenter, randomized clinical trial involving 256 patients posted for hip fracture surgeries (124 patients received xenon and 132 patients received sevoflurane). They found that the use of xenon did not significantly reduce the incidence of postoperative delirium after hip fracture surgery.

Table 1: Studies on the use of xenon in preventing POCD after cardiac and non-cardiac surgeries

Authors/year	Type of study	Number of patients included	Type of surgery	Outcomes/conclusion
Coburn et al.[28]/2007	Randomized, double-blinded, controlled study	38 (20-desflurane, 18-xenon)	Non-cardiac	Although xenon was associated with a faster emergence from general anaesthesia than desflurane there was no difference in the postoperative cognitive testing at 6–12 and 66–72 h.
Bronco et al.[29]/2010	RCT	60 (30 in each group, sevoflurane and xenon)	Non-cardiac	Xenon anaesthesia was associated with faster emergence and with better early postoperative cognitive recovery than sevoflurane anaesthesia.
Cremer et al.[30]/2011	Double-blinded randomized controlled trial	40 (20-sevoflurane, 20-xenon)	Non-cardiac	No difference in the incidence of POCD after xenon or sevoflurane anaesthesia although emergence from general anaesthesia was faster in the xenon group.
Stoppe et al.[27]/2013	Randomized, single-blind controlled trial	30 (15-xenon, 15-sevoflurane)	Cardiac (CPB)	The assessment of POCD by the CAM-ICU score revealed comparable incidences of delirium between the xenon and sevoflurane groups
Al Tmimi et al.[25]/2015	Randomized, observer-blind, controlled clinical trial	45	Cardiac (OPCAB)	Xenon anesthesia was associated with a lower risk for POD
Coburn et al.[31]/2018	Multicentre, randomized clinical trial	256 (124-xenon, 132-sevoflurane)	Hip surgeries	Xenon anaesthesia did not significantly reduce the incidence of postoperative delirium after hip fracture surgery
Al Tmimi et al.[26]/2020	Randomized, observer-blind, controlled trial	190	Cardiac (CPB)	Xenon anaesthesia did not result in a significant reduction in POD

Note: CAM-ICU: Confusion assessment method for intensive care unit; CPB: cardiopulmonary bypass; OPCAB: off pump coronary artery bypass; POCD: postoperative cognitive dysfunction; POD: postoperative delirium; RCT: randomized controlled trial.

In an RCT involving two groups (n = 20), Cremer et al.[30] compared xenon with sevoflurane in elderly patients undergoing a different set of surgeries which were comparable statistically. All emergence times and modified Aldrete score after xenon anesthesia were significantly higher during the 1st hour in the xenon group.

In a randomized study involving 60 patients (n = 30 in the sevoflurane group and n = 30 in the xenon group) undergoing non-cardiac surgeries, xenon anesthesia was confirmed to be associated with faster emergence and with better early postoperative cognitive recovery than sevoflurane anesthesia.[29] Stuttman et al.[34] randomized 61 patients undergoing non-cardiac surgeries (n = 31 in xenon group, n = 30 in isoflurane group) and concluded that recovery profile and the early return of post-operative cognitive functions are significantly better after xenon anesthesia when compared to isoflurane (**Table 1**).

Conclusion

Theoretically, xenon appears to be a better inhalational anesthetic agent in elderly patients undergoing cardiac and non-cardiac surgeries. Along with reduced POCD, hemodynamic stability, and cytoprotection are other desirable properties of xenon. Xenon could be considered in patients who are at risk of POCD based on preoperative scoring systems. Availability at all centers and cost are the factors that limit use of xenon as an anesthetic agent of choice as a result of which data is insufficient. Once xenon anesthesia is available and affordable, well-designed adequately-powered studies could explore the feasibility of xenon anesthesia over conventional volatile anesthetics in elderly patients.

Author contributions
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