

## Effect of xenon anesthesia on the incidence of postoperative delirium and postoperative cognitive dysfunction: a systematic review

J. GIJS (\*), S. REX (\*\*,\*\*\*), G. DEWINTER (\*\*), S. DEVROE (\*\*), M. VAN DE VELDE (\*\*,\*\*\*), D. HOOGMA (\*\*), L. AL TMIMI (\*\*,\*\*\*)

**Abstract :** *Summary:* Postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are frequent complications after major surgery, especially in elderly patients. These complications cause long-term sequelae such as loss of independence, persistent cognitive deficits, and increased mortality for up to 2 years. There are a few perioperative strategies to reduce the incidence of POD and POCD. The noble gas xenon has been shown to offer neuroprotection in different animal models. This review aims to evaluate the effects of xenon anesthesia compared with conventional anesthesia on the incidence of POD and POCD of the available literature. In addition to this, we review safety, feasibility and emergence data. *Methods:* We performed a literature search on PubMed and Embase using the terms “xenon” AND “anesthesia”, “xenon” AND “cognitive function”, and “xenon” AND “delirium”. We only included randomized controlled clinical trials comparing xenon anesthesia to routinely used anesthetics such as sevoflurane, desflurane, isoflurane or propofol. No restriction on the year of publication was applied.

*Results:* Out of 396 articles, 10 articles were found eligible for a detailed analysis of full text. Eight trials had a sample size between 30 and 101 patients, while two multicenter trials had respectively enrolled 492 and 256 patients. Six trials reported POD and/or POCD as primary outcome. In other studies, neurocognitive function was a secondary outcome parameter. Two studies showed a significantly lower incidence of POD or POCD after xenon anesthesia. In 6 trials, emergence time after xenon anesthesia was significantly shorter compared to conventional anesthesia. No trial found a significant higher incidence of adverse events in xenon group compared to conventional anesthetic group.

*Conclusion:* Evidence for the effectiveness of xenon to reduce the incidence of POCD and/or POD is inconclusive. Future adequately powered randomized controlled clinical trials should be targeted on POD and POCD as a primary outcome, specifically including high-risk patients for POD and POCD. Compared to routinely used anesthetics, xenon has been demonstrated to be safe and feasible but more expensive.

**Key Words:** Xenon anesthesia, postoperative delirium, postoperative cognitive dysfunction.

### INTRODUCTION

Postoperative delirium (POD) is a frequent complication after major surgery in elderly patients occurring with an incidence ranging from 7% to 53% (1, 2). POD is an acute state of confusion that can be diagnosed using validated and simple-to-use standardized screening tools (3, 4). Postoperative cognitive dysfunction (POCD) is only recognized by a comprehensive neuropsychological assessment and is defined as a deterioration in cognitive function without a change in mental status or awareness (5). POCD is even more frequent than POD with an incidence up to 70% (6).

Besides being a short-term and temporary complication after surgery, POD causes long-term sequelae. A recent systematic review demonstrated that POD is an independent predictor of postoperative mortality up to 10 years, readmission to the hospital and neurocognitive decline (7). Similarly, POCD also appears to be associated with long-term sequelae and a higher postoperative mortality (8, 9).

According to the National Institute for Health and Clinical Excellence guidelines, prevention of POD is mostly limited to non-pharmacological means. These include recognizing and treating patients' risk factors and providing adequate multi-disciplinary care (10). However, a previous systematic review with meta-analysis demonstrated

J. GIJS, S. REX MD, PhD, G. DEWINTER MD, PhD, S. DEVROE, MD, M. VAN DE VELDE MD, PhD; D. HOOGMA, MD, L. AL TMIMI MD

(\*) Student, 3rd master medicine, KU Leuven - University of Leuven, 3000 Leuven, Belgium

(\*\*) Department of Anesthesiology, University Hospitals Leuven, 3000 Leuven, Belgium.

(\*\*\*) Department of Cardiovascular Sciences, University Hospitals Leuven, 3000 Leuven, Belgium.

**Corresponding author:** Layth Al tmimi, MD, Department of Anesthesiology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.

E-mail: layth.altmimi@uzleuven.be

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that several pharmacological agents such as dexamethasone, rivastigmine, risperidone, ketamine, dexmedetomidine, propofol, and clonidine might prevent POD in some cases (11). Nevertheless, the quality of evidence for the prevention and treatment of POD was respectively rated as moderate and inconclusive (11).

The noble gas xenon has been known to possess anesthetic properties in humans since 1951 (12). Although its mechanism of action is complex, N-methyl-D-aspartate receptor antagonism is probably the primary mechanism of action of xenon for anesthesia. It distinguishes it from other conventionally used anesthetics such as propofol, sevoflurane, isoflurane or desflurane (13,14) that primarily stimulate the  $\gamma$ -aminobutyric acid type A receptor (GABA-AR). The GABA-AR is the most abundant inhibitory neurotransmitter receptor in the central nervous system (15). Xenon has been demonstrated to offer protection against neuronal ischemic injury and to protect from postoperative neurocognitive dysfunction in rats (16,17). Moreover, xenon anesthesia is associated with superior hemodynamic stability and has been shown to mediate cardioprotection (18-20).

The primary aim of this review is to evaluate the effects of xenon anesthesia compared with conventional anesthesia (i.e., non-xenon) on the incidence of POD and POCD. The secondary goal is to extract safety, feasibility and emergence data from the included literature.

## METHODS

### *Search strategy*

The present review was performed according to the PRISMA guidelines (21). The search was conducted in PubMed and Embase database On March 13, 2018. No restriction on the year of publication was applied. The following search terms were used: “xenon” AND “anesthesia”, “xenon” AND “cognitive function”, and “xenon” AND “delirium”.

### *Study selection*

The inclusion criteria were :

- 1) Randomized controlled trials in humans,
- 2) An intervention group receiving xenon anesthesia,
- 3) Conventional anesthetic agent in the control group,
- 4) POCD and the incidence of POD as a primary or secondary endpoint.

Trials that reported results only for emergence time and postoperative early recovery (time to open eyes, time to react on demand and time to tracheal extubation) with no other cognitive function endpoints were excluded. Additionally, studies without full text, letters to the editors, review articles, in vitro studies, observational studies and publications with a language other than English were excluded. Trials comparing routinely used anesthetic agents with other noble gases than xenon were also not included.

To identify studies with inclusion criteria, titles and abstracts of articles were screened. After this first check, duplicates were removed. To select the finally included studies, the methods and results were then screened.

### *Data extraction*

The following trial characteristics were analyzed: patients' characteristics and demographic data, i.e. number of patients, age, American Society of Anesthesiologists (ASA) physical status and EuroSCORE, intraoperative data namely type of surgery, type of anesthetic agent administered in the control group, mean end-tidal concentration of xenon, need for rescue anesthetics and bispectral index (BIS) monitoring and data concerning the primary or secondary endpoints (i.e. incidence of POD and or POCD). Finally, other data such as the type and the time of assessment of cognitive function, the patient's exclusion criteria, the incidence of awareness, the time to tracheal extubation, the early postoperative recovery, the incidence of adverse and serious adverse events were also analyzed.

### *Quality assessment*

The quality of the included studies was assessed using the Jadad scale (22). The Jadad scale evaluates study characteristics as randomization, blinding, methods, and whether or not all patients were included in the analysis.

## RESULTS

The search resulted in 396 citations including 323 articles from PubMed and 73 articles from Embase (Fig. 1). Forty-three articles (out of 323) and 34 articles (out of 73) were found eligible for a detailed analysis of the full texts.

Out of 77 articles that were randomized controlled clinical trials comparing xenon anesthesia to another routinely used anesthetic agent, 26 records

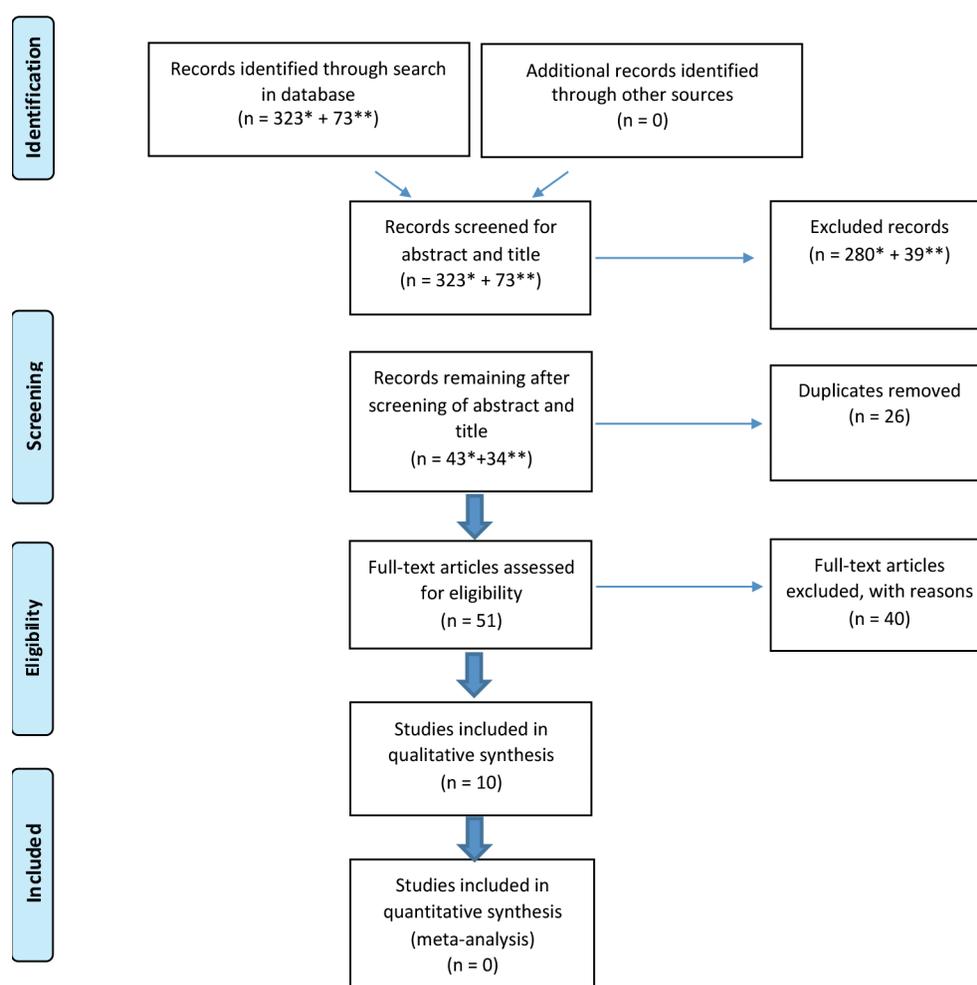


Fig. 1. — Flow diagram of literature review process. Adapted from the PRISMA flow diagram (21). \* refers to the PubMed search, the second number followed by \*\* refers to the Embase search.

were rejected as duplicates or unrelated to our search. Among the fifty-one remaining randomized controlled clinical trials, only 11 studies mentioned postoperative cognitive function or the incidence of postoperative delirium as a primary or secondary endpoint and met our inclusion criteria (20, 23-32) (Fig. 1). Nevertheless, one of these studies reported the incidence of POCD immediately after patient's tracheal extubation (within 30 and 60 min) and was therefore excluded from the present review (27). Ten trials were reviewed entirely and were included in the current qualitative analysis (Fig. 1).

#### Quality assessment

Of the ten included trials, 4 studies were performed in a double-blind manner (23, 24, 29, 32). Three studies gained a 5/5 score on the Jadad scale (24, 29, 32), and 7 received a score of 4/5 (20, 23, 25, 26, 28, 30, 31) (Table 1).

#### Trial characteristics

Five trials compared xenon to sevoflurane (28-32). Only one trial compared xenon with desflurane (24), another one with isoflurane (26), and 2 with propofol (23, 25). In the last study, patients in the intervention group received 30%-xenon as an adjuvant to a target-controlled infusion of propofol (25). Finally, one study compared xenon to propofol and sevoflurane (20).

#### Population characteristics

The number of included patients varied between 30 and 101 for 8 trials (23-26, 28-31). A first multicentric trial included 492 patients (20) and a second one included 256 patients (32). Patients' age ranged from 18 to above 65 years in all the reviewed trials, except in one study in which patients' age was less than 4 years (31). The age of

Table 1

Quality assessment of articles included in the systematic review (Jadad score) (22).

| First author        | Year of publication | Randomized | Double blind | Sample size calculation | Drop out | Control (routinely used agents) | Jadad Score |
|---------------------|---------------------|------------|--------------|-------------------------|----------|---------------------------------|-------------|
| L.S. Rasmussen (23) | 2006                | 1          | 1            | 1                       | 0        | 1                               | 4           |
| M. Coburn (24)      | 2007                | 1          | 1            | 1                       | 1        | 1                               | 5           |
| L. AL Tmimi (25)    | 2017                | 1          | 0            | 1                       | 1        | 1                               | 4           |
| R. Stuttman (26)    | 2010                | 1          | 0            | 1                       | 1        | 1                               | 4           |
| C. Stoppe (28)      | 2013                | 1          | 0            | 1                       | 1        | 1                               | 4           |
| J. Cremer (29)      | 2011                | 1          | 1            | 1                       | 1        | 1                               | 5           |
| L. Al Tmimi (30)    | 2015                | 1          | 0            | 1                       | 1        | 1                               | 4           |
| S. Devroe (31)      | 2017                | 1          | 0            | 1                       | 1        | 1                               | 4           |
| J. Hofland (20)     | 2017                | 1          | 0            | 1                       | 1        | 1                               | 4           |
| M. Coburn (32)      | 2018                | 1          | 1            | 1                       | 1        | 1                               | 5           |

(1= yes, 0= no)

patient at the inclusion was not specified in only one trial (20). Seven studies included patients with an ASA score I or II and 3 trials enrolled patients with an ASA score of III or IV (25, 28, 30). Seven of 10 trials excluded patients with neurological illnesses including history of cerebrovascular disease, head injury, epilepsy, and dementia (23-25, 28-30, 32). Six studies also excluded patients with psychiatric disorders i.e. delirium, schizophrenia or depression (24, 25, 28-30, 32). Moreover, 6 trials also excluded patients with other comorbidities such as a history of myocardial infarction, severe auditory or visual loss and chronic obstructive pulmonary disease (20, 24, 25, 28-30) (Table 2).

#### *Surgery-related data*

Six of the 10 reviewed studies were performed in non-cardiac surgery i.e. knee replacement surgery, elective abdominal or urological surgery, thyroidectomy, breast augmentation or reduction, liposuction in obese patients, knee arthroscopy or hip fracture surgery (23, 24, 26, 29, 32). Four studies were conducted in elective off-pump or on-pump coronary artery bypass graft surgery (20, 25, 28, 30). Only one trial was performed in pediatric patients who were scheduled for diagnostic or interventional heart catheterization (31) (Table 3).

#### *Postoperative cognitive dysfunction and post-operative delirium*

Five studies reported POD/POCD as a primary endpoint (23, 24, 26, 29, 32), and the five remaining trials analyzed POD/POCD as a secondary outcome (Table 3). In most of the studies, different

neuropsychiatric tests, such as the test for attentional performance (TAP test), the syndrome short test, the confusion assessment method (CAM), the shortened CAM (consisting of the first four criteria of the full CAM), the confusion assessment method for intensive care unit (CAM-ICU test), the pediatric anesthesia emergence delirium scale (PAED scale), the four point agitation scale for emergence delirium and the mini-mental state examination (MMSE), were used to measure cognitive function.

Baseline cognitive function was always measured before surgery. Postoperative measurements were performed at different time points, starting within one hour to six hours after surgery (24, 26, 29, 32). Two studies followed up patients between 28 days and 3 months after surgery (23, 32). Patients were examined for cognitive function and daily POD until hospital discharge or until the ninth day in the ward in two studies (28,30). One trial measured postoperative cognitive function only on the post-anesthesia care unit (26). Finally, one trial measured cognitive function 3h after surgery followed by twice-a-day measurements for a maximum of 28 days (32), one study daily screened patients for POD during the first five postoperative days (25) and the last five trials measured cognitive function at two moments postoperatively at variable intervals (20, 23, 24, 26, 29) (Table 3).

The incidence of POCD was investigated and was similar for xenon and control group in four trials (23, 24, 26, 29) (Table 3).

Six studies investigated the effects of xenon anesthesia on the incidence of POD in human patients (20, 25, 28, 30-32). Among these, 4 studies did not demonstrate any benefit of xenon compared to the control group regarding the incidence of

Table 2  
Characteristics of the patient population

| First author        | Year of publication | Age (yrs.) | EuroSCORE, Xenon/Control | ASA score    | Exclusion criteria  |
|---------------------|---------------------|------------|--------------------------|--------------|---|
| L.S. Rasmussen (23) | 2006                | >60        | N.A.                     | ASA I to III | 1. Laryngeal mask contraindicated<br>2. High operative risk (plasma creatinine >200µmol/litter)<br>3. ASA > III<br>4. CNS disease   |
| M. Coburn (24)      | 2007                | 65-75      | N.A.                     | ASA I to III | 1. Chronic alcohol or drug abuse<br>2. Disturbed renal or liver function<br>3. Diabetes mellitus<br>4. Neuropsychiatric disorders<br>5. History of stroke<br>6. CPR and brain trauma < 12 months<br>7. History of myocardial infarction, congestive heart failure<br>8. Emergency, hypersensitivity to anesthetics, increased ICP   |
| L. Al Tmimi (25)    | 2017                | >18        | 1.2 [1.0]                | ASA II to IV | 1. Hypersensitivity to study medication<br>2. Chronic obstructive pulmonary disease with a global initiative for chronic obstructive lung disease status >II<br>3. Risk for malignant hyperthermia;<br>4. Single-vessel grafting<br>5. Preoperative renal dysfunction with serum creatinine >1.5 mg/dL<br>6. Critical preoperative state<br>7. Disabling neuropsychiatric illness: schizophrenia, epilepsy, history of stroke with residuals, mental retardation, dementia, and severe depression<br>8. MMSE <25 or preoperative delirium |
| R. Stuttman (26)    | 2010                | >18        | N.A.                     | ASA I to II  | 1. Predefined, not mentioned  |
| C. Stoppe (28)      | 2013                | >50        | 3.3 ± 4.4                | ASA II to IV | 1. Cardiac, respiratory liver or renal failure<br>2. LVEF <50%<br>3. EuroSCORE >8<br>4. Acute coronary syndrome < 24h<br>5. Hemodynamic instability<br>6. Emergency operations<br>7. Severe neurological dysfunction<br>8. MMSE <24<br>9. Depression, geriatric depression score >5   |
| J. Cremer (29)      | 2011                | 65-75      | N.A.                     | ASA I to III | 1. Diabetes mellitus<br>2. Congestive heart failure<br>3. Adrenal insufficiency<br>4. Reduced renal and/or hepatic function<br>5. Chronic alcohol or drug abuse<br>6. Disabling neuropsychiatric disorders<br>7. Increased intracranial pressure<br>8. History of stroke<br>9. Cardiopulmonary resuscitation or brain trauma <12 months<br>10. Anaphylactic reactions to anesthetics<br>11. Legal incapacity, lack of cooperation, emergency  |
| L. Al tmimi (30)    | 2015                | >18        | 1 [0.95]                 | ASA II to IV | 1. Lack of informed consent<br>2. COPD GOLD stage >II<br>3. Renal dysfunction, creatinine >1.5mg/dl<br>4. Acute coronary syndrome < 24h<br>5. Left ventricular ejection fraction <30%<br>6. Hemodynamic instability with preoperative requirement of inotropic support<br>7. Single vessel grafting<br>8. MMSE < 25<br>9. Delirium assessed with confusion assessment method<br>10. Depression<br>11. History of stroke<br>12. Others including hypersensitivity, risk for malignant hyperthermia, uncooperativeness                      |
| S. Devroe (31)      | 2017                | <4         | N.A.                     | N.A.         | 1. Intra-procedural oxygen requirement above 40%<br>2. Procedures defined as high-risk and complex by the pediatric cardiologist<br>3. Lack of parental informed consent  |
| J. Hofland (20)     | 2017                | Mean 65    | 1 [1.9]                  | N.A.         | 1. Recent or ongoing myocardial damage/infarction.<br>2. Severe renal dysfunction<br>3. Severe hepatic dysfunction<br>4. Positive pregnancy test in female patients of childbearing potential<br>5. Severely depressed left ventricular function, corresponding to an ejection fraction below 35%,<br>6. Late discovery of any condition not in compliance with selection/non-selection criteria, including consent withdrawal  |
| M. Coburn (32)      | 2018                | >75        | N.A.                     | ASA I to III | 1. Severe dementia or Alzheimer's disease, MMSE <24<br>2. Schizophrenia<br>3. Recent Brain trauma or history of stroke<br>4. Moderate to severe depression<br>5. Delirium determined by shortened confusion assessment method   |

ASA : American Society of Anesthesiologists classification ; CNS : Central nervous system ; COPD : chronic obstructive pulmonary disease ; CPR : cardiopulmonary resuscitation ; GOLD stage : Global Initiative for Chronic Obstructive Lung Disease stage ; ICP : intracranial pressure ; LVEF : left ventricular ejection fraction ; MMSE : mini-mental state examination ; N.A : not available.

Table 3  
Early recovery, postoperative cognitive decline and postoperative delirium

| First author        | Year of publication | No. of patients | Anesthetic comparison    | Time of measurement   | POD/POCD as 1° or 2° outcome | Effect of xenon on early recovery | Incidence of POCD/POD xenon vs. non-xenon (±)                                       | Limitations   |
|---------------------|---------------------|-----------------|--------------------------|---|------------------------------|-----------------------------------|---|---|
| L.S. Rasmussen (23) | 2006                | 39              | Propofol                 | - Before surgery<br>- At discharge<br>- 3 months after surgery                            | POCD, 1°                     | Enhanced (p<0.001)                | Similar (p=0.77)  | 1. Not powered to show a difference in POCD<br>2. Neuro-protective properties of xenon have been primarily demonstrated in connection with hypoxic and ischemic events. It is not known whether POCD is caused by such events.  |
| M. Coburn (24)      | 2007                | 38              | Desflurane               | - 12h - 24h before surgery<br>- 6h - 12h after surgery<br>- 66h - 72h after surgery       | POCD, 1°                     | Enhanced (p=0.001-0.007)          | Similar (p=0.22-1.0)  | 1. Lower rate of neuro-cognitive decline compared to high-risk surgery<br>2. Limited findings due to high dropout   |
| L. AL. Tmimi (25)   | 2017                | 50              | Propofol                 | - 1 day before surgery<br>- Every day until 5 days after surgery                          | POD, 2°                      | N.A.                              | Similar (p=0.138)   | 1. Not powered to show a difference in POD  |
| R. Stüttman (26)    | 2010                | 61              | Isoflurane               | - 1 day before surgery<br>- 1h after surgery<br>- 3h after surgery                        | POCD, 1°                     | Enhanced (p<0.05- p<0.001)        | Similar (p=0.05)  | 1. Higher early state of attentiveness and faster emergence time might not influence later cognitive function   |
| C. Stoppe (28)      | 2013                | 30              | Sevoflurane              | - 1 day before surgery<br>- Daily until discharge   | POD, 2°                      | N.A.                              | Similar (p=0.666)   | 1. Small sample size<br>2. Fast recovery after xenon anesthesia was prevented by prolonged postoperative sedation with propofol and sufentanil  |
| J. Cremer (29)      | 2011                | 40              | Sevoflurane              | - 12h - 24h before surgery<br>- 6h - 12h after surgery<br>- 66h - 72h after surgery       | POCD, 1°                     | Enhanced (p=0.014-0.001)          | Similar (p=1-0.438), except TMT A test (p=0.027)                                    | 1. High drop-out rate<br>2. Cut off of 20% decrease in test performance is too high   |
| L. Al Tmimi (30)    | 2015                | 42              | Sevoflurane              | - Daily until day 9 on the ward   | POD, 2°                      | N.A.                              | ↓ in xenon (p=0.044)  | 1. Probably not a causal relationship between xenon anesthesia and POD<br>2. Results should be interpreted with caution due to the small sample size  |
| S. Devroe (31)      | 2017                | 40              | Sevoflurane              | - Until transfer to ward  | POD, 2°                      | Enhanced (p<0.001)                | ↓ in xenon with four-point agitation scale (p=0.02). Similar with PAED test (p=0.1) | 1. PAED test very difficult to assess in neonates<br>2. Four-point agitation scale has higher overall sensitivity and specificity<br>3. Given the small sample size, an adequately powered clinical trial with Emergence delirium as primary outcome is warranted to confirm our results. |
| J. Hofland (20)     | 2017                | 492             | Sevoflurane and propofol | - At inclusion<br>- 24h after surgery<br>- 48h after surgery                              | POD, 2°                      | N.A.                              | Similar (p=N.A)   | 1. Very low rate of POD (3%) possibly due to relatively healthy study population.   |
| M. Coburn (32)      | 2018                | 256             | Sevoflurane              | - 3h after surgery<br>- Twice daily (10 am/6 pm) until discharge or for a max. of 28 days | POD, 1°                      | Enhanced (p<0.001)                | Similar (p=0.33-0.46)   | 1. Strict inclusion criteria lowering the POD rate<br>2. Strict inclusion criteria lowering the patient population<br>3. Strict inclusion criteria not representing real patient population<br>4. Points 1 and 2 rendered the power of the study insufficient                             |

↓ : decrease ; N.A : not available ; p : p-value, range was given if several p-values were available ; PAED : pediatric anesthesia emergence delirium scale ; POCD : postoperative cognitive decline ; POD : postoperative delirium ; TMT A : trail making test A.

Table 4  
Safety and feasibility of xenon anesthesia

| First author and reference | Year | Xenon (vol%), mean or range | Rescue medication in the xenon group                                    | BIS values comparison between groups | AE and SAE comparison between groups   | Intraoperative awareness |
|----------------------------|------|-----------------------------|---|--------------------------------------|--|--------------------------|
| L.S. Rasmussen (23)        | 2006 | 50-70                       | Propofol in 6 patients (29%)  | N.A.                                 | No significant differences   | N.A.                     |
| M. Coburn (24)             | 2007 | 53-60                       | Remifentanyl, no significant differences                                | No significant differences           | N.A.   | N.A.                     |
| L. AL Tmimi (25)           | 2017 | 30                          | Xenon 30% adjuvant to propofol  | No significant differences           | No significant differences   | No                       |
| R. Stuttman (26)           | 2010 | 63                          | Fentanyl, no significant differences                                    | No significant differences           | No significant differences   | No                       |
| C. Stoppe (28)             | 2013 | 45-50                       | When lowering xenon (%), infusion of propofol                           | BIS values lower in xenon group      | No significant differences except for AKI: higher in sevoflurane group                   | No                       |
| J. Cremer (29)             | 2011 | 53-60                       | Remifentanyl, No significant differences                                | No significant differences           | N.A.   | N.A.                     |
| L. Al Tmimi (30)           | 2015 | 52                          | No rescue medication  | No significant differences           | No significant differences   | No                       |
| S. Devroe (31)             | 2017 | 57                          | Sevoflurane, to target BIS value 40-60, necessary in all but one child  | No significant differences           | No significant differences   | No                       |
| J. Hofland (20)            | 2017 | 52-56                       | Propofol, need for more rescue anesthesia compared to sevoflurane group | No significant differences           | No significant differences   | N.A.                     |
| M. Coburn (32)             | 2018 | 55-65                       | N.A.  | No significant differences           | No significant differences for AE. SAE twice as common in the sevoflurane group (p=0.05) | N.A.                     |

AE : adverse events ; AKI : acute kidney injury ; BIS : bispectral index ; N.A : Not available ; SAE : serious adverse events.

POD (Table 3). In contrast, Al tmimi et al. showed a lower incidence of POD in patients receiving xenon for off-pump CABG when compared to patients receiving sevoflurane (30). Moreover, Devroe et al. showed that children undergoing interventional cardiac catheterization and younger than 4 years old performed significantly better on the four-point agitation scale after xenon-sevoflurane anesthesia than children receiving sevoflurane alone (31) (Table 3).

#### *Safety and feasibility of xenon anesthesia*

Safety of xenon anesthesia was evaluated in most trials by the incidence of intra and postoperative adverse events (AEs) or serious adverse events (SAEs). The incidence of these events was similar between xenon and routinely used anesthetics (20, 23, 25, 28, 30, 31). Interestingly, Coburn et al. revealed in a multicentric study on elderly patients undergoing hip fracture surgery that the rate of AEs and SAEs was twice as high in the sevoflurane group as in the xenon group, respectively 15.9 % and 8% ( $P = 0.05$ ) in each group (32) (Table 4).

The main feasibility criterion was the ability of xenon to induce an equal depth of anesthesia

compared to the control agent, as demonstrated by the lack of need to administer rescue anesthetics and/or by similar BIS values. Depth of anesthesia was continuously monitored with the BIS monitor in nine studies (20, 24-26, 28-32) and was evaluated on clinical observation without using any neuromonitoring in one trial (23).

Adequate depth of anesthesia could be maintained with solely-xenon anesthesia without extra-anesthetic supplementation in four studies. In these trials, mean inspiratory xenon concentrations were included between 52% and 60% and end-tidal xenon concentrations between 53% and 63% (24, 26, 29, 30) (Table 4).

Devroe et al. used in young children, except one, sevoflurane as a standard supplement to xenon anesthesia with a minimum alveolar concentration (MAC) value of xenon around 92% (31, 33) to achieve target BIS-values between 40 and 60 (31). A significantly higher need for rescue medication in the xenon group to obtain BIS values between 40 and 60 was reported in 2 trials (20, 28). Five trials reported no episode of intraoperative awareness neither in the xenon group nor the control group (25, 26, 28, 30, 31) (Table 4).

### *Emergence and early recovery from xenon anesthesia*

Six trials assessed early recovery parameters including time to open eyes, time to react on demand, time to extubation and time to spatial orientation (23, 24, 26, 29, 31, 32). In all of these 6 trials, early recovery was significantly faster in the xenon group than in the comparison group (Table 3). These 6 trials included control groups of patients anesthetized with propofol, sevoflurane, isoflurane or desflurane.

### DISCUSSION

To the best of our knowledge, this review is the first that systematically describes the effects of xenon anesthesia on the incidence of POCD and POD in humans.

#### *Effects of xenon on POD/POCD*

In the current review, 8 trials (80%) failed to show any benefit for Xenon on the incidence of POD/POCD, when 2 trials (20%) showed a statistically significant reduction in the incidence of POD or POCD after xenon anesthesia (30, 31). Al tmimi *et al.* showed a lower incidence of POD in patients receiving xenon for elective off-pump CABG when compared to patients receiving sevoflurane (30). Nevertheless, this study was not explicitly designed to evaluate this neurological outcome. Moreover, neither type of delirium, nor its duration and severity were evaluated. In another study, Devroe *et al.* demonstrated that children younger than 4 years old undergoing cardiac catheterization with xenon-sevoflurane anesthesia had a decreased incidence of emergence delirium, on the four-point Agitation Scale, but not on the PAED scale than children receiving only sevoflurane (31). Again, given the secondary nature of this endpoint and the limited sample size of the study, such finding does not prove any causal relationship. In this case, the lower incidence of emergence delirium could also be attributed to the lower concentration of sevoflurane that was administered in the xenon-sevoflurane group compared to the sevoflurane group. Bronco *et al.* demonstrated in 60 non-cardiac surgical patients that patients receiving xenon had a significantly better early postoperative cognitive recovery at 30 and 60 minutes after tracheal extubation than patients in the sevoflurane group (27). However, it was unclear whether this finding had an important clinical implication.

The statistically non-significant results in the other trials could be attributed to several issues. First, most of the trials were not powered to assess POD or POCD. This lack of statistical power was acknowledged as a limitation in 3 trials with similar findings between xenon and control anesthetic agent (23, 25, 32). Six trials with similar findings were actually due to relatively small sample size with a maximum of 61 patients (23-26, 28, 29). In contrast, we identified 2 multicentric trials including respectively 492 and 256 patients (20, 32). However, even these large-scale multicentric trials showed no reduction for the incidence of POD when using xenon. Nevertheless, the observed POD rate was much lower than assumed in one of these trials (32). In the other one, POD was “only” a secondary outcome parameter (20). As a result, both trials were underpowered to provide conclusive results. Moreover, two trials with negative findings suffered from a high dropout rate (24, 29).

Second, in most of the studies, the patient population might not have been adequately selected to assess the effects of xenon on neurocognitive function. Several systematic reviews with meta-analyses identified various risk factors for delirium including patient’s age, dementia or cognitive deficits, ASA physical status > III, heart failure, multiple comorbidities and alcohol abuse (34-37). Notably, the majority of trials that were included in our review (70%) excluded patients with neurological illnesses (23-25, 28-30, 32). Moreover, 6 trials excluded patients with a history of psychiatric illness or patients with delirium at baseline (24, 25, 28-30, 32). Five trials (50%) also excluded patients with several comorbidities such as those with renal, liver or heart failure, chronic obstructive pulmonary disease and severe visual, auditory or motor handicap (20, 23, 26, 30, 31). Thirty percent of the reviewed trials included patients with an ASA physical status > III (25, 28, 30). Therefore, to correctly assess the impact of xenon anesthesia on POD and POCD, future trials should actively include patients at high risk of POD and/or POCD.

Third, POCD was assessed in 4 trials (23, 24, 26, 29), but only 2 trials used the same cognitive test battery (the TAP test). Although all the tests assessed memory and attention, they significantly differ in their sensitivity, specificity and the technique to assess memory, attention and other cognitive functions. For example, the TAP test consists of low complexity tasks to control for factors such as sensory or motor failures while the test battery of one trial included scores for executive functions and

motor skills. Moreover, tests differed with respect to the definition of POCD, the threshold below which POCD was diagnosed and the number of cognitive functions that needed to be affected to diagnose POCD. Screening tests for POD did differ far less. Five of 6 trials screened for POD with the CAM or CAM-ICU (20, 25, 28, 30, 32). In the last one, PAED scale and four-point agitation scale were used as screening tools for diagnosing emergence delirium in children (31).

#### *Safety and feasibility*

In this review, we demonstrated that general anesthesia (GA) with xenon was associated with a similar incidence of adverse or serious adverse events compared to GA with other routinely used anesthetic agents. These results are consistent with the findings of a previous systematic review by Law et al. (38). Hitherto, xenon is not routinely used as an anesthetic agent. Among other reasons, this is due in particular to the considerable costs of xenon gas. As a consequence, anesthesia with xenon is only justified if the use of xenon is associated with a clearly proven benefit.

In all included studies that intraoperatively used a BIS-monitor to assess depth of anesthesia, investigators aimed to achieve BIS-values lower than 60 (20, 24-32). In 4 trials (40%), there were no significant differences in anesthetic supplementation between groups (24, 26, 29, 30). However, in 2 trials (20%), more patients in the xenon group than in the control group significantly needed rescue medication to maintain an adequate depth of anesthesia (20,28). This need for rescue could be attributed to the relatively younger age of patients included in the studies (respectively 65 and 66 years) and the moderate low mean end-tidal value of xenon that was administered (<56%) (20, 28). Notably, the MAC of an inhalation agent is known to be negatively correlated with the patient's age (33). Different authors reported that the MAC of xenon in adults is around 63-71% (39-41).

Xenon has a blood gas partition coefficient of 0.14 or even lower (40, 42), allowing to accelerate the onset of and the emergence from anesthesia as it could be demonstrated in the majority of included trials. These results are consistent with recent reports (43).

However, in 2 trials, recovery from xenon was not faster than for the control anesthetic agent. This lack of difference was most probably due to the fact that patients receiving xenon were postoperatively sedated with propofol for several hours, masking any potential benefit from xenon (28, 30).

#### *Limitations*

Our systematic review suffers from several limitations.

*First*, we included only articles written in English. Data from publications written in other languages than English were not considered.

*Second*, despite a broad search strategy with different terms and search engines, essential articles might have been missed.

*Third*, the effects of xenon on the incidence of POD or POCD in the included trials in cardiac surgery were studied as a secondary outcome. Therefore, the results from these studies should be interpreted with caution.

*Last*, due to the several shortcomings and obvious heterogeneity of the included studies i.e. lack of uniform endpoints, wide variety of tests used to investigate POCD/POD, different kind of surgeries, different kind of control medications, different duration of postoperative neurological screening, lack of power in the majority of trials, and POD/POCD as primary study endpoint in only 6 trials, the performance of a meta-analysis is inappropriate or inconceivable.

#### CONCLUSIONS

The evidence for the effectiveness of Xenon to reduce the incidence of POCD and POD is inconclusive. Future randomized controlled clinical trials should be adequately powered and targeted for POD and POCD as a primary outcome, especially for high-risk patients to POD and POCD.

Xenon was demonstrated to be safe and feasible compared to routinely used anesthetics. However, its high cost makes this noble gas unlikely to gain widespread use as long as strong evidence for beneficial effects on clinical outcome is lacking. Therefore, further studies are essential to investigate the cost-effectiveness of using xenon in high-risk patients.

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