Review Article

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The Effects of Inhaled Anesthetic Agents on Long-Term Cognitive Decline

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A B S T R A C T

Background: Anesthesia is generally considered safe, but studies have shown the potential relationship between anesthetic agents and dementia after surgery. Several studies have pointed out how the commonly used anesthetic drugs induce cytotoxicity, ultimately leading to neurodegeneration and even Alzheimer's Disease (AD). Specifically, inhaled anesthetics such as isoflurane, sevoflurane, and desflurane have been shown to impact the neurophysiology of the brain. However, there is no established relationship between anesthetics and long-term postoperative cognitive decline.

Objective: The objective of this study is to explore the available research on anesthetic agents and the potential role that they have played in postoperative cognitive decline.

Methods: Following PRISMA guidelines, a comprehensive electronic search was conducted to identify articles discussing long-term cognitive decline with anesthesia using PubMed, Medline, and CINAHL Complete. We restricted the search to (1) articles published between 2010 and 2023, (2) full texts in English, (3) articles discussing long-term cognitive decline with anesthesia, (4) humans 19+ years of age, and (5) clinically relevant data. The initial search yielded 108 articles, 7 of which were filtered out for duplicates. The remaining papers underwent a quality assessment procedure following the screening process. A total of six final studies were identified that focused on the long-term cognitive effects of anesthesia.

Results: Of the six studies, three recognized inhaled halogenated anesthesia to cause increased cognitive decline as opposed to a control group with intravenous anesthesia or without general anesthesia. Of particular note, none of the studies associated a correlation with an increased risk of Alzheimer\'s disease. Nitrous oxide used in adjunct to general anesthesia showed no difference in long-term cognitive decline compared to general anesthesia without nitrous oxide. Anesthesia without surgery in healthy participants showed no long-term change in cognitive status from baseline. Also, regional anesthesia was not associated with an increased risk of dementia.

Conclusion: Although half of the studies showed that exposure to inhaled halogenated anesthetics under surgery was associated with an increased risk of long-term cognitive decline, the results were inconclusive regarding whether anesthesia alone influenced this outcome. A study that had healthy volunteers undergo anesthesia without surgery showed that anesthesia had no long-term cognitive impacts. This study shows that surgery with or without chronic health conditions may play a role in this long-term cognitive decline. Limitations of the included studies included: limited studies done in this specific field, different screening tests to determine cognitive decline, and variable health conditions among participants. Overall, results showed contradictory evidence regarding the relationship between anesthesia and postoperative cognitive outcomes. These results demonstrate the need for further research to elucidate a stronger link between anesthesia and long-term postoperative cognitive outcomes.

Keywords: Anesthesia; Alzheimers disease; Dementia

Introduction

Anesthetic drugs are a mainstay in medical care, used for minor and major medical procedures to prevent pain and produce loss of feeling and awareness[1]. While anesthesia is generally considered safe, studies have shown the potential relationship between anesthetic drugs and dementia after surgery.

Several studies have pointed out the commonly used anesthetic drugs in inducing cytotoxicity, ultimately leading to neurodegeneration. Specifically, inhaled anesthetics such as isoflurane, sevoflurane, and desflurane, have been shown to impact the neurophysiology of the brain, leading to increased expression of β-amyloid (Aβ) and tau proteins along with other cytokines that are often found in Alzheimer's patients[2]. Alzheime's disease (AD) is caused by multiple factors. Human apolipoprotein E4 allele (ApoE4) is the strongest genetic risk factor that decreases age of onset and increases the risk of AD[3]. Neuroinflammation is a common precursor to cognitive decline as well. Additionally, research has shown that the human neuro-inflammatory response to surgery and anesthesia resembles Alzheimer's disease[4]. The acute neuroinflammatory impact of surgery on the brain is triggered by microglia. The microglia and peripheral immune cells have a role in this inflammatory reaction in the brain as a response to tissue trauma during surgery[5]. In cases such as in elderly patients, this protective response can impact cognition negatively if there is excessive response to inflammation from surgery.

Other proposed mechanisms involve calcium dysregulation leading to anesthetic-induced neurotoxicity[6]. The brain is vulnerable to anesthetic-mediated neurodegeneration[7]. Disruption of intracellular calcium homeostasis, particularly due to a persistent and excessive increase in the calcium concentration, can induce cell death by apoptosis. Volatile anesthetics, such as isoflurane, can induce apoptosis by significantly increasing both the cytosolic and mitochondrial calcium concentrations and decreasing the endoplasmic reticulum calcium concentration[7]. Isoflurane has been shown to be more potent than sevoflurane or desflurane at causing calcium release from the endoplasmic reticulum and in promoting aggregation of pathological proteins and apoptosis. These molecular pathways involved in intracellular calcium dysregulation can ultimately lead to anesthetic-mediated neurotoxicity and neuroapoptosis.

Post-operative cognitive decline (POCD) is a known phenomenon explaining the short-term effects of anesthesia on memory. It has been associated with prolonged hospital stays and increased healthcare costs[8]. However, much remains unknown on the definitive link between intravenous and inhaled anesthetics towards dementia and long-term complications[9]. While many proposed mechanisms exist, the lack of a defined relationship between anesthetics and post-operative dementia has posed a risk to many individuals undergoing anesthesia prior to operative procedures. In addition, there is a lack of a universal diagnostic criteria due to the varying symptom presentation of POCD. POCD is multifactorial, accounting for biological and pre-operative cognitive function. However, it is a perioperative priority, and the choice of anesthetic agent remains a plausible factor[10]. To address this, it is essential to acknowledge the current research regarding anesthetic agents and explore their significance and potential in inducing cognitive impairment. This scoping review explores the available research on anesthetic agents and their possible role that they play in post-procedural cognitive decline.

Materials & Methods

A comprehensive electronic search was conducted using PRISMA guidelines to identify articles discussing long-term cognitive decline with anesthesia. The studies used in this scoping review were found through searches in PubMed, Medline, and CINAHL Complete. According to the criteria described below, studies published from 2010 to 2023 were included. Based on the inclusion and exclusion criteria, two independent and blind reviewers conducted the selection process.

Search Strategy

A computer-assisted literature search was conducted using the databases mentioned earlier to identify studies that met the following inclusion criteria: (1) articles published between 2010 and 2023, (2) full texts in English, (3) articles discussing long-term cognitive decline with anesthesia (4) humans 19+ years of age, (5) clinically relevant data. Articles that were excluded involved those that focused on pathophysiology, only measured cognitive decline immediately post-operatively, or were published before 2010. The search was conducted in February 2023 and yielded 109 results.

Identification of Studies

((inhaled anesthetics) OR (inhaled anesthesia)) AND ((dementia) OR (Alzheimer) OR (cognitive impairment) OR (cognitive decline) OR (memory loss))

Data Extraction

All researchers assembled pertinent information on a data log that included the author and year, study type, sample size, and significant findings after screening and applying the inclusion criteria to the articles they got from the databases. A Google Docs spreadsheet contained the results. The information was then organized, and each article was thoroughly discussed to see if it met the criteria for inclusion and the standards for quality. Discussions were used to settle disagreements.

Based on the provided search criteria, the initial search yielded 108 articles. A further 95 were filtered out after seven duplicates were eliminated because they contained variables that did not meet the inclusion criteria or were not accessible. The remaining papers underwent a quality assessment procedure following the screening process. The final chosen articles focused on the long-term cognitive effects of anesthesia (**Figure 1**).

Results

A total of six studies were identified, labeled 1-6 in (**Table 1**), using the research selection pathway described in (**Figure 1**). (**Table 1**) reports the characteristics of the studies included in this scoping review, which included studies that utilized methods such as multiethnic cohort studies, surveys, and database extractions.

Of the six studies, three recognized inhaled halogenated anesthesia to cause increased cognitive decline as opposed to a control group without general anesthesia. No study could associate a correlation with an increased risk of Alzheimer's disease. Regional anesthesia was not associated with an increased risk of dementia.

Several additional variables were involved in many of these studies, which provided additional data concerning the overall relationship between anesthesia and potential cognitive decline.

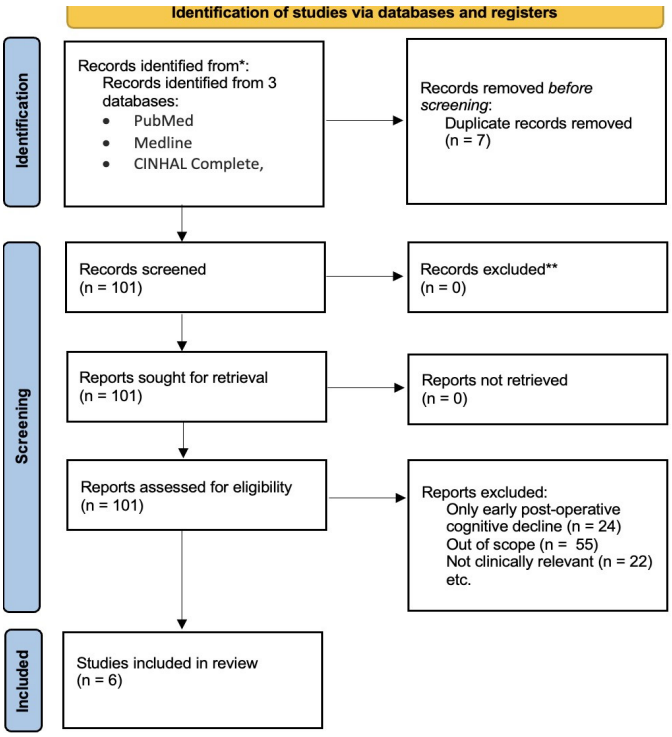

Figure 1. PRISMA flow diagram depicting the study selection process.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

N_2O and Dementia

One of the studies had a longitudinal approach to determine whether N2O was related to cognitive decline. Although the study was able to associate surgery with general anesthesia with a small but statistically significant decline in cognitive z scores, it could not establish a trend with N2O. This study focused on the elderly population and deemed appendectomies with N_2O use to not cause cognitive decline[2].

Anesthesia Without Surgery

Another study deemed no correlation between anesthesia and long-term cognitive decline in healthy adults who have not undergone surgical procedures. On day one, 91% of participants recovered, with only two not fully recovering at the 30-day mark. The two participants were followed-up at six months and fully recovered[4].

Inhaled General Anesthesia Versus Intravenous Anesthesia

Two studies showed that inhaled general anesthetics were statistically significantly associated with dementia and cognitive decline, whereas regional anesthesia was not significantly associated with an increased risk of dementia[1,9]. Another study showed there to be no statistically significant relationship[4].

Alzheimer's Disease and Anesthesia

Three studies suggest no independent correlation between inhaled or intravenous anesthesia with Alzheimer's disease[6,9,11]. Of these studies, two associated increasing age with the increased onset of Alzheimer's disease[5,11].

Table 1: The Summary of findings in selected studies.

Author	Number of participants	Study type	How they measured	Key results
1. Strand et al.	N = 457 (dementia) N = 420 (dementia-free)	Retrospective case-control study.	Exposure to anesthesia, with different methods (RA, GA without gas and GA with gas), within 20 years prior to diagnosis was compared against no such exposure.	Exposure to inhalational anesthetics with halogenated anesthetics was associated with an increased risk of dementia, compared to no exposure to anesthesia. However, regional anesthesia was not significantly associated with an increased risk of dementia.
2. Sprung et al.	N = 280 (HA w/o N2O) N = 256 (GA w/ N2O)	Longitudinal study using Mayo Clinic and Olmsted Medical Center database.	Patients who have undergone GA with and without N2O were cognitively assessed every 15 months. Most patients had a 4 to 8-year follow-up.	Exposure to surgery/GA is associated with a small, but statistically significant decline in cognitive z scores. Cognitive decline did not differ between anesthetics with and without N_2O.
3. Baxter et al.	N = 69 (healthy participants who have not undergone surgery)	Single-center cohort study of healthy adult volunteers 40 to 80 years old.	Cognitive function was accessed at 15 min, 60 min, 1, 3, 7, and 30 days. Additional assessments were done at 6 and 12 months.	52% recovered within 60 minutes and 91% within day 1. There was no association between age group and recovery to baseline on the Postoperative Quality of Recovery Scale (PQRS) which correlates to recovery to baseline on secondary cognitive measures.
4. Silber et al.	N = 60 (sevoflurane) N = 60 (propofol) N = 60 (lidocaine epidural) N = 60 (control)	Retrospective study using Medicare data.	Follow-up ranged from 5-15 years.	Exposure to appendectomy surgery and anesthesia did not increase the subsequent rate of Alzheimer disease and related dementia (ADRD).
5. Liu et al.	N = 10,161 (spine surgery patients) N = 25 (new onset Alzheimer) N = 10,135 (control)	Prospective, randomized parallel-group study	Patients had an L3 to L4 or an L4 to L5 spinal surgery. Patients with a history of GA or neurologic diseases were excluded. Patients' cognitive function was then measured two years after surgery.	Results: Two years after anesthesia, the number of AD cases that emerged did not differ significantly between the groups. However, the number of cases of progressive mild cognitive impairment (MCI) was greater in the sevoflurane group than in the control group. Age correlated linearly with amnestic mild cognitive impairment (aMCI progression), whereas sex did not.

6. Zuo et al.	N = 10,161 (spine surgery patients) N = 25 (new onset Alzheimer) N = 10,135 (control)	Univariate and multivariate logistic regression analyses	Searched the Clinical Data Repository for spinal surgery recipients. The patients would then be followed up at a 5-year minimum to assess if there is new-onset Alzheimer disease.	These results suggest that increasing age is a risk factor for AD in patients after spine surgery. Anesthesia and surgery are not independent factors for AD development.

Discussion

This scoping review aimed to examine the current literature on the role of anesthetic agents in post-operative cognitive decline. After thoroughly analyzing the articles chosen using a screening process following PRISMA guidelines, we determined that there are multiple different outcomes in patients who have received anesthetic agents towards their post-operative cognitive functions, along with numerous associated contributory factors.

Three of the six analyzed studies recognized inhaled halogenated anesthetics to cause increased cognitive decline[1,2,9]. Strand et al. showed that any exposure to surgery with anesthesia resulted in an increased risk of cognitive decline, especially with multiple exposures. They also showed how exposure to inhaled anesthetics with halogenated gasses increased the risk of dementia[1]. The other studies showed how other variables, such as age, gender, and anesthesia type, could influence the potential risk for dementia and cognitive decline. Data by Liu et al. also showed how the inhaled anesthetic class, with sevoflurane in particular, may promote the progression of cognitive impairment[9]. Finally, the study by Sprung et al. also showed the influence of anesthesia on cognitive decline, as those participants exposed to surgery and general anesthesia had accelerated cognitive decline[2].

These findings illustrate the significant contributory role of halogenated inhaled anesthetics, specifically in cognitive decline. Conversely, nitrous oxide, a non-halogenated anesthetic, did not contribute to long-term cognitive decline and thus may be a potentially safer alternative to employ in anesthesia. Additionally, with all three studies, multiple confounding factors such as age, type of surgery, and other comorbidities make it challenging to correlate the potential cognitive decline directly to the specific anesthetic employed, making these results inconclusive.

On the contrary, studies from 3, 4, and 6 as shown in (**Table 1**) demonstrated no association with anesthesia as an independent contributory factor resulting in post-operative cognitive decline[4,6,11]. Baxter et al. concluded that anesthesia alone may not be associated with cognitive recovery in patients without surgery, which aligns with most studies due to the many confounding factors involved[4]. Even when surgery involves anesthesia, in the form of appendectomy, as Silver et al. showed, there was no increase in the rate of Alzheimer's disease and related dementia[6]. Tis is also in line with Zuo and Zuo's findings which state that anesthesia and surgery are not independent factors leading to increased risk for AD development[11].

These findings from studies 3, 4, and 6 as shown in (**Table 1**) display the noncontributory impact of anesthesia and surgery as independent factors affecting cognitive decline and definitively state that many other factors may be involved, such as other prior chronic health conditions[4,6,11].

Furthermore, the cognitive decline observed in patients who underwent general anesthesia may be attributed to the event that led to the need for surgery. For example, following cardiac surgery, cognitive decline was observed in 50-70% of patients, with long lasting cognitive decline greater than one year impacting 13-40% of patients[12]. However, the contributing factor could be microemboli from cardiopulmonary bypass or a chronic contributor such as cerebrovascular disease[12].

Monitored Anesthesia Care (MAC) is a type of anesthesia service for procedures performed under local anesthesia in addition to sedation and analgesia. MAC preserves spontaneous breathing and airway reflexes, has fewer physiologic disturbances, and results in a more rapid recovery than general anesthesia[13]. Through the use of various nerve blocks prior to surgery and analgesic medications, MAC can be used as an alternative sedating procedure that can be used to reduce post-operative recovery time and risks associated with general anesthesia[14]. MAC does not use fluorinated anesthetics, so the patient is not at risk of the proposed cognitive decline associated with these volatile anesthetics. However, MAC is inadequate in some surgical procedures where general anesthesia is indicated.

Limitations of the Included Studies

An important limitation of this scoping review is the use of studies with no specific selection criteria for the age of adult participants. Age is a significant contributor to cognitive decline, as it is widely believed that increased age contributes to greater cognitive decline. The selection of studies in which there were no criteria in our review for the age of participants could potentially be a confounding variable affecting post-operative cognitive decline, as age is a significant contributor to cognitive decline. Future research may benefit from the inclusion of a strict age range of participants in the selected studies. Some of the studies also used healthy participants with normal cognition at baseline. This limits the application of these studies to clinical populations, in which individuals often have multiple comorbidities alongside poor baseline cognition levels. Another limitation is the design of the studies analyzed, in which cognition was measured one-day post-anesthetic administration, whereas this may not reflect long-term clinical outcomes years down the line, for dementia and cognitive decline. A large limiting factor in most of the studies analyzed focuses on the aspect of whether the surgery itself is a contributory factor towards neurocognitive decline rather than the anesthesia administered, as surgery has been shown to cause neuroinflammation, leading to post-operative cognitive decline[11].

Limitations of the Review Process

Articles prior to 2010 were excluded from our search criteria; thus earlier studies relevant to this topic were not included. The application of strict inclusion and exclusion criteria may have further excluded many relevant articles, particularly with the strict exclusion of animal studies. Also, all articles selected and reviewed were in the English language only.

Implications for future research and clinical practice

The findings of this review point to an inconclusive relationship between anesthesia and post-procedural cognitive decline. While some of the studies investigated in this review[1,2,9]point to a possible relationship between inhaled anesthetics and

cognitive decline, the other studies[4,6,11] point to the many other confounding factors in refuting the direct relationship between anesthesia and cognitive decline. These other factors include the age of participants, existing chronic medical conditions, and even the type of anesthetics administered.

Overall, limited research exists within the field of anesthetic agents and cognitive decline, so more research is needed to develop stronger conclusions regarding the direct impact of anesthesia on cognitive decline, and that can better differentiate between the different confounding variables that may also serve as contributory factors.

Conclusion

This study used scoping review methodology to examine the literature regarding anesthetic agents and post-operative cognitive decline. We found evidence to suggest that inhaled halogenated anesthetic agents can cause increased cognitive decline compared to a control group without anesthesia. A few of the studies examined also suggested no correlation between anesthesia and long-term cognitive decline in healthy adults. None of the studies examined found a correlation with an increased risk of Alzheimer's disease. This suggests that overall, there is significant contradictory evidence in the literature regarding the relationship between anesthesia and post-operative dementia. These results demonstrate the necessity for further research into this topic to elucidate the true link between anesthesia and post-operative cognitive outcomes, and improve overall postoperative patient outcomes.

Conflicts of Interest

This study does not have any conflict of interest.

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