Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by accumulation and aggregation of amyloid-β (Aβ) peptides and hyperphosphorylated tau, neuronal death, and consequent progressive impairment of cognitive functions. AD is the main cause of dementia today in the geriatric population, and the World Health Organization estimates over 18 million people worldwide presently suffer from the disease [1]. In addition, anywhere between 0.5% to 32% of the aged population is likely to be suffering from amnestic mild cognitive impairment (aMCI), the clinical prodrome to AD [2]. Individuals with aMCI are at high risk for developing AD, with a progression rate of 10% to 15% per year [2].

With such a substantial percentage of the aging population being affected by AD, it is likely that in the coming years anesthetists will encounter an ever increasing number of patients with AD and aMCI. Anesthesia can be broadly categorized into local, regional, and general anesthesia. These anesthesia techniques can be induced by different types of anesthetic agents, e.g., intravenous (iv) such as propofol, and inhaled such as sevoflurane. General anesthesia often involves the usage of combination of these anesthetic agents. The type of the anesthetic protocol to be applied is determined on the basis of several factors, including surgical procedures, clinical condition of the patient, and comorbidities.

An increasing number of preclinical as well as clinical studies have indicated that exposure to anesthetics may lead to persistent cognitive deficits, meeting clinical criteria of aMCI or AD. Thus far, there have been few retrospective human clinical studies that have assessed the risk of AD after surgery and anesthesia. While some of these retrospective studies have discounted the notion that general surgery and anesthesia can induce or exacerbate AD [3–6], others have demonstrated a correlative link between anesthesia exposure and AD [7, 8]. A retrospective study found that early-life exposure to anesthesia is associated with an earlier onset of AD [7]. Further, in an aged population of 80 years of age or greater, general anesthesia has been associated with a greater risk of developing AD [8]. Studies have also shown that anesthetics can exacerbate AD pathogenic pathways, with documented changes in cerebrospinal fluid (CSF) Aβ and tau levels after surgery [9, 10]. A prospective clinical study demonstrated that patients who underwent coronary artery bypass surgery showed long-term pathological changes in the CSF, with significant decrease in CSF Aβ and concurrent increase in CSF tau levels [10]. Given that these alterations in CSF are characteristic...
of AD pathology and have been indeed used as biomarkers for incipient AD [11, 12], it is conceivable that anesthetics may indeed promote AD pathogenesis. However, all of the above retrospective studies suffer from the inherent limitation that they cannot distinguish the relative roles of surgery, types of anesthesia protocol, neuroinflammation, stress factors, or other pre-existing co-morbidities; as such, while being suggestive of an association between anesthesia and AD, these studies remain inconclusive.

To date, there have been no prospective randomized controlled clinical outcome studies that have longitudinally assessed the effect of different anesthetics on AD progression in subjects undergoing surgery. A recent prospective randomized clinical study [13] has demonstrated that sevoflurane, an inhaled anesthetic that is commonly used for anesthesia during surgical procedures, may accelerate the clinical progression of aMCI in aged patients. The clinical study assessed the long-term effects of different anesthetics on the clinical progression of 180 elderly (≥65) patients with aMCI that were scheduled for spinal surgery [13]. The patients were randomly assigned to three different anesthesia protocols: general inhaled anesthesia with sevoflurane, general intravenous anesthesia with propofol, and regional epidural anesthesia with lidocaine [13]. Additionally, 60 aMCI patients who did not undergo anesthesia were taken as controls. Prior to surgery, these patients were quantitatively assayed for CSF biomarkers for AD, namely Amyloid-β, total tau, and phosphorylated tau. These levels were found to be similar between the four groups. Two years post-surgery, the patients underwent neuropsychological assessments to establish their clinical status. The study demonstrated that a significantly higher percentage of aMCI patients treated with sevoflurane met the progressive aMCI criteria, i.e., had significant reduction in follow-up Montreal Cognitive Assessment and Mini-Mental State Examination scores, compared to controls (p < 0.01). On the other hand, propofol and lidocaine exposure did not affect aMCI progression [13]. In summary, sevoflurane exposure significantly accelerated the progression of aMCI to pathologically progressive MCI, as assessed by their clinical evaluation [13].

Furthermore, subjects who developed progressive MCI were also found to have significantly decreased Amyloid-β levels and elevated phosphorylated tau levels in the CSF post-anesthesia [13]; these changes have been shown to be strong predictors of progression of aMCI to dementia [11, 12], further evidencing an adverse effect of sevoflurane on the clinical outcome of aMCI patients. The potential clinical implication of these findings is significant; certain anesthetic agents might influence the long-term cognitive outcome of aMCI patients, with increased risk of clinical escalation [13].

Prospective randomized clinical studies, while being effective clinical research tools for obtaining definitive conclusions, are complicated, largely due to the difficulties in applying standardized anesthesia protocols to persons with multiple co-morbidities, controlling for the multiple confounders that are associated with both disease risk and reasons for the surgery itself, and maintaining long-term follow up. This clinical study also has several limitations. The small sample size and low retention rate of this study limit the interpretability of the study’s findings. Further, the study did not find any correlation between gender or education and aMCI progression, while both have previously been shown to be risk factors for AD [14–16]. It is feasible that this disparity is due to the small sample size of this study and that such differences would have emerged in a study with a larger cohort. Additionally, possible confounders such as medication use and co-morbidities may influence the results. Despite these limitations, this prospective clinical study indicates that choice of anesthetic drug might have significant long-term effects on the cognitive outcome of aMCI patients.

A large body of in vitro and in vivo studies lend support to the notion that anesthetics, especially inhaled anesthetics, may modulate various stages of the AD pathogenic pathway to exacerbate AD-related pathology. Nuclear magnetic resonance spectroscopy studies have indicated that smaller sized inhaled anesthetics can induce AD oligomerization [17]. Preclinical studies with anesthetics such as sevoflurane and isoflurane have also shown that these anesthetics can induce changes consistent with AD neuropathogenesis, i.e., caspase-mediated apoptosis, increased Aβ levels and tau phosphorylation [18–20]. Intriguingly, transgenic AD mice have been shown to be more susceptible to sevoflurane-induced neurotoxicity as compared to naïve mice [21], suggesting that brains with pre-existing AD neuropathology may be more sensitive to the adverse effects of sevoflurane. While findings from these in vitro and in vivo animal studies suggest that inhaled anesthetics could contribute to the AD pathology and clinical progression, at this point their clinical relevance remains unknown.
In summary, while the current clinical link between anesthesia and AD is by no means conclusive in nature, together the preclinical and clinical studies provide enough evidence to warrant aggressive research on the incidence and progression of long-term cognitive impairment and dementia after exposure to anesthesia. Further comprehensive research is required to review the anesthesia protocols [22] to combat the impact of anesthesia on patients with, or at risk of AD. Research needs to prioritize adequately powered multi-centric prospective randomized controlled clinical trials aimed at comparing the effects of different anesthesia protocols, particularly volatile anesthetics, on the risk of AD. Large scale prospective studies that correlate cognitive function with CSF as well as imaging biomarkers of anesthesia. Furthermore, powered multi-centric prospective randomized controlled clinical trials aimed at comparing the effects of different anesthesia protocols, particularly volatile anesthetics, on the risk of AD. The next step is our sincere hope that future clinical studies will guide research efforts toward devising more specific and safer anesthetic interventions.

DISCLOSURE STATEMENT


REFERENCES