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The correlation between general anesthesia and Alzheimer's Disease

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Abstract :

Patients undergoing surgery or anesthesia now have a significant worry in the form of Alzheimer's disease (AD), which causes a gradual but steady loss of cognitive capacity over time. Nevertheless, there has been conflicting evidence from research on the link between general anesthesia and AD. Thus, we intend to conduct a meta-analysis and systematic review to ascertain the nature of the association between general anesthesia and AD and to confirm if general anesthesia is a risk factor for AD in and of itself. The debilitating effects of Alzheimer's disease (AD) are widespread in the elderly. Some have speculated that the use of volatile anesthetic gases during general anesthesia (GA) increases the likelihood of AD. The purpose of this research is to compile all available data on the link between GA exposure and AD risk. The findings will be shared with the scientific community in a peer-reviewed publication after they have been thoroughly examined. The results of our research will add credence to the theory that dementia is associated with general anesthesia. All parties involved, including patients, anesthesiologists, surgeons, and legislators, will gain from the review. Although there are limited high-quality research in this area, a history of GA exposure is not linked to an elevated risk of AD. To delve further into the connection between GA and AD, randomized controlled trials or prospective cohort studies with long-term follow-up are necessary.

Key words : general anesthesia and Alzheimer's Disease

Introduction:

The devastating loss of neurons in the hippocampus, parietal, and temporal lobes—regions crucial to reasoning and memory—is the hallmark of the neurodegenerative disease known as dementia, which in turn causes a gradual but steady deterioration in cognitive abilities over time. Dementia is a major issue in contemporary society's public health system, affecting around 35.6 million individuals globally in 2010. Dementia is predicted to affect 65.7 million people in 2030 and 115.4 million in 2050, roughly doubling every 20 years (Prince,2013).

Among these dementias, Alzheimer's disease (AD) accounts for 60–80% of cases, making it the most common. In 2017, an estimated 5.5 million Americans are living with Alzheimer's disease. Age, female gender, lower education level, cardiovascular illness, depression, head trauma, and apolipoprotein E are all potential risk factors for Alzheimer's disease, however the exact causes, risk factors, and pathophysiology of the disease are yet unknown. Also, some have speculated that general anesthetics can cause neurotoxicity and eventually Alzheimer's disease (Sposato et al.,2015).

Patients may express this anxiety during preanesthetic interviews for a variety of reasons, including a fear of losing autonomy and the relatively high incidence of AD in the elderly (the age-standardized prevalence for the elderly aged > 60 is 5-7% in the most world region) (Xu et al.,2010).

Animal and molecular studies offer convincing evidence that exposure to general anesthetics may cause or worsen dementia, despite claims that they may not cause long-term neurocognitive outcomes or have mixed effects on dementia-associated neurotoxicity. An potential method by which anesthesia could cause dementia has been shown in preclinical investigations to be the increased buildup of amyloid β protein and the hyper-phosphorylation of tau proteins, which in turn cause neurofibrillary tangles in the brain. Nevertheless, there has been conflicting evidence in human research that have looked at the link between dementia and general anesthesia (Chen et al.,2014).

About 5% of the global population over 65 years of age has Alzheimer disease, making it the most common form of dementia at present. It is expected to affect 26 million people globally. Patients and their families were more concerned and wanted more information, which prompted researchers to look into the possibility of cognitive decline after anesthesia or surgery (Aiello Bowles et al.,2016).

It is well-known that anesthesia and surgery can lead to postoperative cognitive dysfunction, but the actual reason why this happens is still unknown. Research is ongoing to determine the nature of the possible relationship between postoperative cognitive impairment and Alzheimer's disease. This topic is being investigated because of the biochemistry that underlies dementia, because there is a strong correlation between Alzheimer's disease and postoperative cognitive dysfunction, which is likely a spectrum of the same disease, and because of the interaction between these two conditions and anesthetic medications. Thirteen percent of persons 65 and more have Alzheimer's disease (AD) or a related form of dementia, and by 2030, the number of Americans living with dementia will have risen from five million to seven and a half million. Society is greatly impacted by AD. There are 8.5 billion hours of caregiving time each year and $148 billion in direct expenses in the US due to AD. Another common cause of residents' placement in nursing homes is the onset of Alzheimer's disease (Sprung et al.,2013).

The development of Alzheimer's disease is accompanied by the buildup of β-amyloid protein plaques and the creation of neurofibrillary tangles, which are linked to the hyperphosphorylation of tau proteins. While many variables contribute to

Alzheimer's disease (AD), some of the major risk factors include becoming older, being female, having a higher level of education, having a family history of the disease, and having certain genetic abnormalities. A history of head trauma and the majority of cardiovascular risk factors are the few modifiable risk factors that have been identified for AD.

POCD, or short-term cognitive dysfunction, can last anywhere from a few days to a few weeks and is a common complication after surgery. There has been considerable speculation recently regarding the possible pathways that connect inhaled volatile anesthetics to AD pathology; this could explain why some people have postoperative cognitive dysfunction (POCD) or Alzheimer's disease (AD) after being exposed to general anesthesia (GA). Studies in animals and cells have shown that inhaled anesthetics that are often used can enhance the development of Alzheimer's disease precursors, such as β-amyloid plaques and neurofibrillary tangles. However, when compared to regional anesthesia, randomized controlled trials including GA have not shown an elevated risk of long-term cognitive damage in the first to second year after exposure. There is a lack of data from randomized controlled trials that look at the possibility of acquiring dementia or cognitive impairment consistent with Alzheimer's disease as a result of GA exposure. Both narrative and systematic reviews have looked at the possible link between anesthesia and postoperative delirium/postoperative critical care disorder (POCD). There was little evidence to indicate a difference in the incidence of post-operative delirium or POCD between general anesthesia (GA) and regional anesthesia, according to most reviews. However, one study indicated that regional anesthesia, as opposed to general anesthesia (GA), reduced the risk of immediate postoperative disorientation in patients undergoing hip fracture surgery. The potential association between GA exposure and AD has not been thoroughly investigated in any systematic research conducted thus far. Our work aims to thoroughly assess observational studies that have examined the association between GA intake and the development of AD. Strategies to avoid or reduce the risk of AD after surgery could be informed by a better understanding of the risk of AD linked with GA exposure, which would aid in establishing the linkage between GA and AD (Chen et al.,2014).

Alzheimer disease:

Deterioration of cognitive ability is a hallmark of Alzheimer disease, a kind of dementia that develops over time. Most occurrences of Alzheimer's disease occur after symptoms have already begun to manifest or appear out of the blue; the disease is likely complex, with both genetic and environmental components playing a role. Although other factors, such as being female, having a poor level of education, having a family history of the disease, and having certain genetic abnormalities (apolipoprotein E genotype), may also play a role, age is the primary risk factor. Cardiovascular disease, a history of head trauma, diabetes, hypertension, and dyslipidemia are among the modifiable risk factors that have been identified. General anesthesia may have a similar function to that of environmental exposure to modifiable risk factors in the development of Alzheimer's disease. According to this school of thought, the prevalence of dementia could be decreased by lowering these modifiable risk factors (Shamseer et al.,2015).

Pathophysiology of Alzheimer disease:

Severe neurodegeneration, neuroinflammation, and a gradual decline in cognitive ability are hallmarks of Alzheimer disease. Dementia is defined by the National Institute on Aging-Alzheimer's Association's diagnostic criteria as the emergence of behavioral or cognitive symptoms accompanied by a decrease in performance relative to pre-dementia levels across multiple cognitive domains, with no plausible explanation in delirium or mental illness. Biomarkers, such as elevated total tau or phosphorylated tau protein in cerebrospinal fluid (CSF) and lower levels of amyloid protein (due to oligomerization), have recently been added in the recommendations as diagnostic criteria. In addition, the total tau protein to amyloid protein ratio could be a useful adjuvant in the diagnosis of Alzheimer's disease (Querfurth & LaFerla,2010).

The pathogenesis of this condition mostly involves aberrant protein folding. Some of the prominent neuropathological features include: 1) the buildup of senile plaques caused by clumps of extracellular amyloid protein and 2) the development of intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein. Cell death, inflammation, and malfunction in neurons are all symptoms of these diseases. When the kinases and phosphatases that phosphorylate tau proteins become dysregulated, the hemostatic effects of this process may be lost. The breakdown of this equilibrium, which in turn causes neurofibrillary degeneration and cell death, may be aided by environmental variables that cause alterations in signal transduction. The amyloid hypothesis states that the buildup of amyloid is caused by a malfunction in the clearance process. Some types of amyloid peptide may be neurotoxic and lead to aberrant phosphorylation of tau proteins, according to this theory. Degeneration of neurons, apoptosis, calcium dysregulation, and mitochondrial damage are the final outcomes of this cascade (Querfurth & LaFerla,2010).

Research using biomarkers has demonstrated a negative correlation between CSF amyloid protein concentrations and Alzheimer's disease severity. It appears that amyloidosis is not enough to cause dementia symptoms on its own, since amyloid plaques and amyloid protein decline can be observed in older individuals who do not exhibit any clinical symptoms of cognitive dysfunction.

It appears that certain neurotransmitters are involved in the setting of dementia caused by Alzheimer's disease. Clinical symptoms of dementia may involve cholinergic dysfunction. Since acetylcholine regulates higher brain functions including attention, learning, and memory, its depletion seems to be linked to Alzheimer's disease. Therefore, acetylcholinesterase inhibitors may play a role depending on the severity of cognitive impairment and the cholinergic deficiency (Sieber & Barnett,2011).

There needs to be proof linking environmental exposures like anesthesia to the pathophysiological mechanisms that cause Alzheimer's disease before trying to link the two. Furthermore, it is believed that surgery on its own might increase the inflammatory stress response, which in turn can accelerate the progression of the disease.

Models in animals :

It has been suggested in multiple research that anesthetic drugs can worsen or possibly cause neurodegenerative disorders like Alzheimer's. Some research have linked changes in cytokine and tau protein levels in human cerebrospinal fluid (CSF) fluid after anesthesia or surgery to the development of this dementia, whereas other investigations have failed to uncover a substantial role for these factors.

Research into the potential roles of anesthetics in the etiology of Alzheimer's disease can be advanced with the help of animal models. The use of free cell models in an initial in vitro investigation revealed that volatile anesthetics including halothane, isoflurane, and sevoflurane could enhance the oligomerization and cytotoxicity of amyloid peptides associated with Alzheimer's disease. The oligomerization of amyloid protein with halothane was dose-dependent, and the dosages utilized were substantial, reaching approximately 4 MAC. The effects of the volatile anesthetic didn't wear off for hours. Neuronal apoptosis and caspase-3 activation are brought about by increasing brain levels of amyloid precursor protein in wild type mice (five months old) when 1.4% isoflurane and 2.5% sevoflurane are administered for 2 hours, according to in vitro and animal studies. In a recent study, it was found that transgenic mice models of Alzheimer disease (mutation of amyloid precursor protein) and

six-day naive mice can be made more susceptible to neurotoxicity by inducing caspase-3 activation and increasing amyloid protein levels in the brains of these animals. So, it turns out that some mice models are more likely to get Alzheimer's disease (LoGiudice & Watson,2014).

Discussion :

It is unclear if general anesthetics are neurotoxic or neuroprotective, and there is ongoing controversy regarding how they affect neurocognitive function, particularly inhalation agents. In terms of neurotoxicity, a large body of evidence from studies including cells, tissues, animals, and biomarkers suggests that volatile anesthetics could have a role in the development of Alzheimer's disease. But there is less evidence from investigations involving humans. The purpose of this meta-analysis and systematic review was to look into the link between AD risk and general anesthesia in human research. Our analysis of the available data revealed a statistically significant correlation between general anesthetic exposure and the development of AD, despite the contradictory findings in the literature. Cohort studies and case-control studies both consistently found this considerable favorable correlation. There was also a strong positive correlation between general anesthesia and AD, as shown by subgroup analysis of trials using medical records as a reliable data source (Park et al.,2013).

Consistent with previous clinical research, our study confirms that GA exposure does not cause any lasting cognitive damage. While it is true that many people experience cognitive dysfunction after surgery, it is more likely that the stress of the procedure and the subsequent recuperation is to blame than any particular effects of the anesthetic itself. According to large-scale research, 25% of people experience postoperative cognitive dysfunction (POCD) in the week after non-cardiac surgery, and 9.9% of those people still show signs of cognitive dysfunction three months after surgery. Nevertheless, there was no significant difference in persistent POCD linked to regional anesthesia versus GA in a randomized controlled trial comparing the two methods for non-cardiac surgeries. Early postoperative cognitive dysfunction (POCD) was found to be more common in the regional anesthetic group (19.7% vs. 12.5%) on day 7, although there was no statistically significant difference between the two groups at 3 months (14.3% vs. 13.9%). There appears to be no indication of long-term cognitive repercussions linked to GA when compared to localized procedures, as most participants regained cognitive function within 1 to 2 years after surgery, according to the same study. In addition to observational research, further randomized controlled trials comparing GA to regional anesthesia in the elderly have revealed similar outcomes. Although there were few well-designed trials with follow-up periods long enough to allow for the development of AD following exposure to anesthesia, systematic evaluations of postoperative cognitive dysfunction (POCD) after non-cardiac surgeries found little evidence for GA's long-term cognitive effects. Factors like cardiopulmonary bypass, intraoperative hypotension, and risk factors that are common for both cerebrovascular illness and cardiovascular disease likely contribute to the higher incidence of POCD following cardiac surgery compared to non-cardiac surgeries. It is challenging to determine the relative contribution of GA to POCD in cardiac surgery settings since many cardiac procedures cannot be performed using regional anesthetic techniques (McKhann et al.,2011).

data indicating that GA exposure might enhance AD processes, as suggested by in vitro investigations and animal models. While isoflurane had minimal influence on amyloid deposition in transgenic mice, exposure to the volatile anesthetic gas halothane may promote amyloid deposition, according to animal studies. Sevoflurane was linked to elevated beta-amyloid levels in another animal study using mice models. Another finding associated with ether anesthesia is an increase in tau hyperphosphorylation. Researchers have found that isoflurane, desflurane, and sevoflurane can all exacerbate beta-amyloid related disease in human tissue culture tests. We were unable to identify any anesthetic agent-specific differences in effects in our review. Our analysis did not detect any association between the year of publication and the association between GA and

AD. Additionally, halothane is an older medicine that has been mostly superseded by newer anesthetic agents. Further confirmation from human studies is necessary to determine the clinical significance of the results observed in these basic studies regarding the effects of GA on AD pathology in humans following typical exposure to GA through biomarkers or neuroimaging. No studies have investigated this topic to date (Lee et al.,2005).

To make sense of the meta-analysis findings in light of the different study designs and methodologies, we conducted subgroup analyses. Subgroup analysis based on exposure assessment found that research employing medical records indicated an increased risk of AD following exposure to general anesthesia. This finding lends credence to the overall beneficial connection between general anesthesia and AD, as medical records are a more objective and trustworthy source of data than interview-based self-reports. Studies that relied on patients' medical records also had a somewhat heavy weight of around 90%. Accordingly, the favorable correlation found in the records-based investigations appears to have played a substantial role in the final result. The subset of studies that relied on self- or surrogate-reported data found a low risk of AD, although this finding could be questioned because data collected through interviews, which depend on people's memories, is susceptible to recall bias. Subjects in their twilight years, particularly those with memory loss, and their loved ones may struggle to recollect specifics of medical history (Marques et al.,2018).

Conclusion:

As the population gets older, we might anticipate a rise in the occurrence of Alzheimer's disease. It is important to evaluate the association between general anesthesia and the development of dementia as an increasing number of elderly individuals have these procedures. Cognitive alterations, such as postoperative cognitive impairment, are prevalent following anesthesia and surgery, according to animal research, which may hasten the onset of Alzheimer's disease. There is compelling clinical evidence that anesthesia can worsen neurodegeneration and cognitive impairment in vulnerable people. It is often difficult to tell if a person's cognitive decline is the result of inflammation, the aging process, or the effects of surgery or anesthesia. The correlation between anesthetic, surgery, and dementia has been the subject of conflicting findings in human observational research. Future research designs should think about things like using biomarkers and neuroimaging to detect the presence of Alzheimer's disease and amyloid burden, selecting a large enough sample, creating suitable control groups (non-surgical and without anesthesia), and evaluating cognitive function before surgery using standardized psychological tests. In addition, the neurological process underpinning Alzheimer's disease, as well as the link between anesthesia and the disease, could provide intriguing suggestions for future research.

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