Spine Surgery under General Anesthesia May Not Increase the Risk of Alzheimer's Disease

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Key Words

Alzheimer's disease · Anesthesia · Anesthetics · Spine surgery

Abstract

Background: Volatile anesthetics cause Alzheimer's disease (AD)-like neuropathology in animals. We determined whether spine surgery under general anesthesia and anesthetic choice contributed to AD development. **Methods:** We searched the Clinical Data Repository of the University of Virginia for patients receiving spine surgery from January 1, 1992 to March 1, 2004. Patients with newly-diagnosed AD after the surgery but before March 1, 2009 (a minimal 5-year follow-up time after the surgery) were identified. **Results:** Among 10,161 spine surgery patients, 26 patients had new-onset AD. Univariate and multivariate logistic regression analyses of the data from these 26 patients and from 161 randomly selected spine surgery patients without new-onset AD suggest that increasing age is a risk factor for new-onset AD. Gender, anesthesia/surgery time, use of volatile anesthetics versus propofol (an intravenous anesthetic) and length of hospital stay were not different between patients with and without new-onset AD. Similar results were found with the case-control study. The frequency of new-onset AD in spine surgery patients was similar to that of patients who had never had a surgery. **Conclusion:** These results suggest

that increasing age is a risk factor for AD in patients after spine surgery. Anesthesia/surgery may not be independent factors for AD development.

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Introduction

Alzheimer's disease (AD) is the most common cause of dementia in humans [1, 2]. Its prevalence in people aged 60–65 years is approximately 1%. This prevalence doubles with every 5-year increase in age [3]. In 2000, AD affected over 4 million people in the USA and 10 million more in the world [2, 4]. These figures increase at an annual rate of 2–3% due to an aging population and improvements in diagnosis. It is estimated that by 2050, AD will affect 13.2 million Americans [5].

Millions of patients have surgery under general anesthesia each year in the world. The majority of these patients will receive volatile anesthetics because these anesthetics are easy to use and render patients unconscious, unaware, insensate, amnesic and muscle-relaxed – effects often required for general anesthesia. However, there is a growing concern in recent years that these drugs may impair cognitive functions for a long time, especially in patients at an advanced age [6–10]. Although the mechanisms for these effects are largely unknown, recent stud-

ies have shown that volatile anesthetics can increase amyloid β peptide (A β) production and A β -induced neurotoxicity [11, 12], pathological changes considered to be involved in AD [13]. Thus, anesthesia and surgery have been hypothesized as a risk factor to speed up the onset of AD. This issue can be clinically significant because the elderly (≥ 65 years) have higher surgery rates than younger people [14].

Although there are ample experimental results that suggest a role of anesthesia/anesthetics in the development of AD-like pathology in animal brains, there is as yet no human data to indicate this role. Prospective human data on the relationship between anesthesia and AD development are very unlikely to be obtained, even in the future, for some obvious reasons. The available retrospective population-based human data on the contribution of anesthesia and surgery to AD are very controversial, with most studies showing that anesthesia and surgery are not associated with the development of AD [15–18] and only one study showing that patients who had surgery before 50 years of age had an earlier onset of AD than patients who had surgery after the age of 50 years [19].

To provide additional data on the possible contribution of general anesthesia and surgery to AD development and to identify risk factors for AD during the perioperative period, we performed a retrospective study by using patients who had spine surgery, a commonly performed surgery in patients across a wide range of ages. Spine surgery is very often performed under general anesthesia and possibly has a lower risk of intravascular emboli and brain ischemia than many cardiovascular surgeries. Thus, the interference from brain ischemia that is a risk factor for acute brain injury and the subsequent development of dementia in our determination of the contribution of general anesthesia and surgery to AD development may be less in patients receiving spine surgery. In addition, spine surgery can have a wide range of surgery durations (from 1 to >10 h) and can therefore provide more heterogeneous intensities of anesthetic and surgical trauma exposure in patients. Such heterogeneity may be helpful in detecting a dose-response relationship between general anesthesia/surgery and the development of AD.

Patients and Methods

The Clinical Data Repository (CDR) was established in 1992 and contains de-identified information of inpatients and outpatients in the University of Virginia Health System from the beginning of 1992 to the present day. Various pieces of information –

including demographics, diagnosis, medications including major anesthetics used in the surgery, laboratory results, procedures, and length of surgery and hospital stay – are included. The CDR is developed and managed by the Department of Health Evaluation Sciences and Health System Computing Services of the University of Virginia, and is updated with new data monthly from multiple transaction systems.

The CDR was first searched for all patients with spine surgery (from minimally invasive discectomy to complex spine fusion) from January 1, 1992 to March 1, 2004. The end date was chosen to allow a minimal 5-year period after the surgery for the development of AD. This choice was because previous studies often followed patients for a minimal 5-year period to study the contribution of surgery and anesthesia to the development of dementia or AD [18, 20] and a follow-up time longer than 5 years after surgery would decrease the number of patients that could be analyzed in our study. The patients with spine surgery (10,161 patients) were then split into 2 groups: one group of patients whose diagnosis of AD was after the surgery (new-onset cases, 26 patients) but before March 1, 2009, the date that the CDR was last updated when the search was performed; the other group of patients (10,135 patients) were not diagnosed with new-onset AD. Those with previous diagnoses of AD or diagnoses during hospital stay for the procedure were not considered new-onset AD. The CDR uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to list diagnosis. Patients with the ICD-9-CM codes 331.0 (AD), 290.0 (uncomplicated senile dementia) and 290.10 (uncomplicated presenile dementia) were considered to have AD in this study.

The age, gender, length of operating room time, length of hospital stay, and type of anesthetic used during surgery of the patients with new-onset AD were recorded. Due to the large number of patients who had spine surgery but did not have new onset AD, we randomly selected 161 patients (~ 6 times of the number of patients with new-onset AD) from the group and the data of these 161 patients were also recorded. The process of choosing these 161 patients is as follows. Each CDR page lists multiple patients. To simplify the random selection of patients from a large population of patients (10,135 patients), we randomly picked up 9 CDR pages from total 542 pages containing all 10,135 patients. These 9 CDR pages listed 161 patients. We selected a relatively large number of control patients ($\sim 1:6$ ratio of patients with new onset AD vs. control patients) to increase the possibility of detecting a difference between these 2 groups of patients.

A second small group of patients (52 patients) from the patients with spine surgery but without new-onset AD were identified and their data were recorded. These patients did not have a diagnosis of AD or any forms of dementia prior to the spine surgery, were matched for age and date of surgery (within 1 year) with the new-onset AD patients, had at least 1 follow-up visit after the surgery, were randomly selected from the corresponding patient populations and were in a 2:1 ratio to each of the patients with new-onset AD. These 52 patients are case-control patients for the new-onset AD patients after spine surgery. Due to the strict selection criteria, we could not find more case-control patients to have a ratio higher than 2:1.

A third control group of patients was identified by searching the CDR for people who had undergone a medical examination/office visit in the University of Virginia Health System. Similar to the patients with spine surgery, the indexed visit must occur be-

Table 1. Comparison of new-onset AD in patients with or without prior spine surgery

Age group (years)	Spine surgery			No surgery			p value
	total, n	AD, n	frequency, %	total, n	AD, n	frequency, %	
0–9	178	0	0	1,670	0	0	
10–19	658	0	0	2,422	0	0	
20–29	657	0	0	3,764	0	0	
30–39	1,646	0	0	3,805	1	0.03	0.666
40–49	2,210	1	0.05	4,178	1	0.02	0.775
50–59	1,931	0	0	3,630	1	0.03	0.748
60–69	1,442	5	0.35	3,237	14	0.43	0.860
70–79	1,129	13	1.15	2,115	34	1.61	0.378
80–89	310	7	2.26	805	31	3.85	0.259
Total	10,161	26	0.26	25,626	82	3.20	0.373

Table 2. Comparisons of patients with and without new-onset AD after spine surgery

	AD	No AD	p value
Number of patients	26	161	
Age, years	76 (72–81)	44 (31–58)	<0.001
Males (%)	13 (50)	74 (46)	0.864
Length of hospital stay, days	3.5 (1–7)	2.0 (1–5)	0.507
Length of operating room time, min	229 (178–253)	225 (155–338)	0.620
Volatile anesthetic (%)	18 (69)	103 (64)	0.765

fore March 1, 2004 to allow a minimal 5-year period after the indexed visit. Because the CDR cannot handle the searching of the enormous number of cases during the entire date range (1992–2004), 5 years were randomly selected from the 13-year span: 1994, 1995, 1999, 2000 and 2002. For any patients with multiple visits during these years, the first visit was considered as the indexed visit. Any patients with a history of surgery requiring anesthesia were excluded. The remaining patients (25,626 patients) were split into a group that was diagnosed with AD after the indexed visit (82 patients) and a group that was not diagnosed (25,544 patients). The frequency rate of new onset AD in each age group was calculated.

Results are presented as the number of patients with percentage or median and 25–75% confidence interval as appropriate. Statistical analysis was performed by χ^2 or Mann-Whitney rank-sum test. Multivariate logistic regression was used to identify risk factors for new-onset AD. First, the age, gender, length of operating room time, length of hospital stay, and type of anesthetic used during surgery were all considered. Both forward and backward stepwise approaches were used to identify the risk factor(s) for new-onset AD. Only the identified risk factor(s) were put into the final model to calculate the effect size of each factor. All analyses were performed with using SigmaStat 3.5 (Systat Software, Inc., Point Richmond, Calif., USA). Values of $p < 0.05$ were considered significant.

Results

There were 10,161 patients with spine surgery in the CDR. Among them, 26 patients had new-onset AD. As shown in table 1, 25 patients with new-onset AD were 60 years of age or older. The frequency rates of new-onset AD doubled for every 10-year increase in age. A similar trend was found with new-onset AD in patients who had office visits, but no surgery. There was no statistically significant difference in the frequency rates in any age group and the pooled data from all age groups between the patients who had or did not have a spine surgery under general anesthesia (table 1).

The results of the 26 patients who had new-onset AD after spine surgery and the randomly selected 161 patients who did not have new-onset AD after spine surgery are listed in table 2. There was a very significant difference in age between these 2 groups of patients. However, there was no difference in gender composition, length of operating room time, length of hospital stay, and type of anesthetic (volatile anesthetics vs. propofol as the major anesthetics) (table 2). Consistent with these results, multivariate logistic regression with the data from the 26 pa-

Table 3. Risk factors for new-onset AD by multiple logistic regression

	Odds ratio	95% CI		p value
		lower	upper	
Age	1.172	1.103	1.244	<0.001
Males	1.176	0.513	2.693	0.702
Length of hospital stay	0.990	0.931	1.053	0.742
Length of operating room time	1.000	0.991	1.010	0.960
Volatile anesthetic	1.267	0.519	3.094	0.603

Table 4. Comparisons of patients with new-onset AD and their case-control patients after spine surgery

	AD	Case-control	p value
Number of patients	26	52	
Age, years	76 (72–81)	76 (72–81)	0.953
Males (%)	13 (50)	27 (52)	0.936
Length of hospital stay, days	3.5 (1–7)	3.0 (2.0–6.0)	0.949
Length of operating room time, min	229 (178–253)	217 (172–289)	0.923
Volatile anesthetic (%)	18 (69)	38 (73)	0.929

tients with new-onset AD and the 161 control patients identified that age is the only risk factor for new-onset AD among the factors analyzed in patients after spine surgery (table 3).

The comparison of results from the 26 patients with new-onset AD and the 52 case-control patients is presented in table 4. There was no difference between these 2 groups of patients in gender composition, length of operating room time, length of hospital stay, and types of anesthetics.

Discussion

The most well-known and most definite risk factor for AD is increasing age [1, 3]. Consistent with this knowledge, our study showed that patients with new-onset AD were significantly older than randomly selected patients without new-onset AD after spine surgery under general anesthesia, and age was identified as a risk factor for new onset AD after the surgery. Our study also showed that the frequency of new-onset AD increased with increasing age.

Recently, postoperative cognitive decline (POCD) has attracted significant attention. Studies have shown short-term and long-term POCD after cardiac and non-cardiac surgeries [8, 10, 21]. POCD can be associated with increased mortality [10, 22]. Increasing age has been con-

sistently identified as a risk factor for POCD [8, 10]. Although duration of anesthesia is identified as a risk factor for short-term POCD [8], there is no study suggesting that duration of anesthesia is a risk factor for long-term POCD. In fact, whether general anesthesia per se contributes to the development of POCD is controversial. Patients who had general anesthesia showed worse cognitive functioning than patients who had regional anesthesia at 1 week after surgery in one study [23], but this difference was not revealed in another study [24]. In addition, there was no difference in cognitive functions assessed at 3 or 6 months after surgery between patients who received general or regional anesthesia [23–25]. A recent study showed that anesthesia and noncardiac surgery were not contributing factors for long-term cognitive decline in the elderly [26]. In contrast, animal studies and basic science research have indicated the possibility of general anesthesia/anesthetic-induced neurotoxicity and cognitive impairment. A 2-hour exposure to general anesthetics impaired the learning and memory functions of middle-aged rats and old rats [27]. General anesthetics have been shown to increase activated caspase 3 expression and β -A β production in the mouse brain [12]. General anesthetics at clinical relevant concentrations can also induce A β oligomerization in vitro [11]. In addition, anesthesia-induced hypothermia has been shown to induce tau protein phosphorylation and tau pathology in the mouse brain [28, 29]. A β overproduction, oligomer-

ization and accumulation, and hyperphosphorylated tau protein accumulation in the brain are considered as underlying neuropathology for AD. The two pathological hallmarks in the brains of patients with AD are extracellular amyloid plaques formed by accumulated A β and intracellular neurofibrillary tangles consisting of hyperphosphorylated tau protein [13]. Thus, it is possible that general anesthesia/anesthetics may contribute to the development of AD. This is an extremely important issue with profound clinical implications as millions of patients have surgery under general anesthesia each year, and the elderly – who have less cognitive reserves and a high propensity to develop AD – have a greater chance to have a surgery [14, 30].

Since it is not ethical and practical to anesthetize a large number of volunteers and monitor them for a long time, it is very unlikely that a prospective randomized study to determine the contribution of general anesthesia/anesthetics alone to AD development will ever be performed. A prospective randomized study to determine the role of anesthesia and surgery in AD development is very difficult and costly to perform because a large number of patients and a long follow-up time are needed. In addition, use of anesthesia and surgery on patients in either the control group or the anesthesia/surgery group during the follow-up period will decrease the number of patients for final analysis. Thus, up till now, there are only retrospective studies regarding the relationship of anesthesia/surgery and the development of AD in humans.

Two studies suggest that anesthesia and surgery may play a role in AD development [19, 20]. The first study looked at 252 AD patients and found that patients receiving anesthesia and surgery before the age of 50 years had an earlier onset of AD than patients receiving anesthesia and surgery after age 50 years [19]. These results suggest that anesthesia and surgery speed up the development of AD. However, this suggestion was questioned due to the findings in another study from the same investigators [15]. They used the same 252 AD patients and performed a population-based case-control study. They showed that there was no statistically significant link between AD and the exposure to general anesthesia and surgery.

The second study suggesting a contribution of anesthesia and surgery to the development of AD retrospectively analyzed data from 9,170 patients who had coronary arterial bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the Veterans Affairs Registry [20]. Patients who had CABG had a higher chance (hazard ratio: 1.71; $p = 0.04$) of being diagnosed with AD than patients receiving PTCA in the 5–6 years

after the surgery/procedure. Since CABG is performed under general anesthesia and PTCA is not, these results suggest that general anesthesia and CABG are risk factors for AD. However, this suggestion was not supported by a population-based case-control study [18]. The investigators identified 557 dementia patients and 557 controls. There was no difference in the number of patients who had CABG between the dementia patient group and control group. A similar conclusion was drawn if only AD patients (481 cases) from the dementia group were included in the analysis. The perioperative courses of CABG for dementia patients and controls were comparable in that study.

A few other population-based case-control studies also showed no link between general anesthesia and surgery and the development of AD [15–18]. Our study implied that there was no difference in anesthesia/surgery time between patients with new-onset AD and the randomly selected 161 patients who did not have new-onset AD. Multivariate logistic regression analysis also did not identify anesthesia/surgery time as an independent factor for AD. These results suggest that anesthesia and surgery may not be a predictor for the development of AD. To substantiate this suggestion, the frequency rates of newly diagnosed AD in each age group were similar in patients who had never had any surgeries and patients who received general anesthesia and surgery. In addition, patients with new-onset AD had a similar length of anesthesia/surgery time to patients without new-onset AD after spine surgery in our case-control study.

Spine surgery is always performed under general anesthesia with a large portion of patients receiving total intravenous anesthesia, such as the propofol-based anesthetic technique. Unlike volatile anesthetics, propofol has been shown to have minimal effects on A β oligomerization in vitro [11] and may be less potent than volatile anesthetics to induce AD-like pathology. Our results showed that the rate of using volatile anesthetics and propofol-based total intravenous anesthetics was very similar in patients with and without new-onset AD after spine surgery, suggesting that neither volatile anesthetics nor propofol are associated with the development of AD.

An important question is then why animal studies provide evidence for the relationship between anesthesia and AD-like brain changes, but human studies have not yet shown this relationship. Obviously, species differences may be an important factor causing this discrepancy. Also, it is questionable whether the experimental conditions in animal studies simulate clinical situations. For example, patients are always monitored closely and their

hemodynamics and temperatures during surgery and anesthesia are maintained. These situations may be different in animal studies. Finally, large and well-designed prospective human studies are needed to determine the contribution of anesthesia and surgery to AD development.

Our study has the inherent limitations of a retrospective study. One particularly significant issue is that many patients may not be closely followed after surgery in our health system and that making a diagnosis of AD may not be the focus during the subsequent office visits and hospitalizations. These problems may be the reasons for the lower frequency rates of new-onset AD than reported in each age group [3]. Another significant issue is that the follow-up time/period is different among the patients. This issue includes two factors. One factor is that the earliest patients that are in our study had surgery in January, 1992 and a theoretical follow-up time of 17 years and the latest patients had surgery in March, 2004 and a theoretical follow-up time of 5 years. The other factor is that patients who had the same theoretical follow-up time may have different actual follow-up times. These significant issues can question the usefulness of our data. To alleviate this concern, we studied the frequency rates of new-onset AD in patients of office visit. These patients will have the same follow-up issues as described above. In addition, we matched surgical date in the case-control

study. Results from these two additional analyses support our initial findings that anesthesia, surgery, and choice of anesthetics during the surgery may not be significant independent factors for AD development. Finally, the majority of our patients did not have a formal cognitive assessment before spine surgery to exclude pre-existing cognitive decline or dementia. This practice would increase the number of patients with new-onset AD after the surgery. This may not be a significant issue because we did not find an increased incidence of new-onset AD in patients after spine surgery compared with patients without a surgery.

In summary, our results suggest that increasing age is a risk factor for new-onset AD in patients after spine surgery under general anesthesia. Anesthesia, surgery, choice of anesthetics, length of hospital stay, and gender may not be independent risk factors for AD in this surgical population.

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