Anesthesia and the risk of dementia in the elderly

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Summary

Cognitive complications are common after surgery in the elderly, and with an increased number of elderly patients undergoing surgery, a potential impact of anaesthesia and surgery on long term cognition, and especially dementia would be concerning. The question whether anaesthesia and surgery in itself induce structural changes in the brain and thereby cognitive deterioration, or reveal a preexisting cognitive impairment remains unresolved. Several studies show an increased risk of reversible cognitive impairment after surgery in the elderly, but the risk of inducing dementia remains speculative. Further studies are needed to elucidate this potential association. Meanwhile, elderly frail patients need to be closely followed including preoperative cognitive screening, since they are at increased risk of cognitive deterioration after surgery and discharge.

Glossary

CAM Confusion Assessment Method
DSM-V Diagnostic and Statistical Manual for Mental Disorders, fifth edition
HIV Human Immunodeficiency Virus
MMSE Mini Mental State Examination
POCD Postoperative Cognitive Dysfunction

Impact of anaesthesia and surgery on cognition

It is estimated that three out of four adults have been exposed to general anaesthesia at least once, and that 10% of the population is undergoing surgery every year in developed countries [1]. Cognitive impairment is a common complication after surgery in the elderly, as they are more vulnerable due to a decreased cognitive reserve [2]. Additionally the risk of dementia increases with an advanced age [3]. With an aging population, and an increased number of patients...
undergoing surgery, a potential impact of anaesthesia and surgery on long term cognition, and dementia in particular, would be alarming [4,5]. Already, dementia is an increasing burden to the healthcare system [6].

**Dementia**

Dementia is a common condition in the elderly population, with an estimated prevalence of 8% in persons above 65 years and up to 33% of persons above 85 years of age in parts of the western world [7-9]. The most important risk factor for developing dementia is increasing age [10]. Several types of dementia exist, and different etiological factors are linked to each one of them. The most common form of dementia is Alzheimer’s disease, and it is estimated that around 60% of cases are categorized to this type of dementia [7,11]. Other subtypes are vascular dementia, Parkinson’s dementia, or HIV-associated dementia [12]. Dementia is classified as a major neurocognitive disorder according to the fifth edition of Diagnostic and Statistical Manual for Mental Disorders (DSM-V) criteria being both a significant decline in cognition (one or more domains), not explained by delirium or another mental disorder, which impairs everyday activities of daily living (box 1) [13]. The cognitive deficit can be screened for using different tools, and a well-known and commonly used short screening tool is the Mini Mental State Examination (MMSE) that provides a score between 0-30 for an overall evaluation of cognitive impairment in both research and clinical settings [14]. A lower score indicates more severe cognitive impairment. A specific threshold does not exist for dementia, but a MMSE < 24 would often suggest some cognitive decline, and a MMSE < 18 indicates severe impairment.

The pathophysiology underlying Alzheimer’s disease and other types of dementia is multifactorial and complex. There are genetic risk factors such as polymorphisms in Apolipoprotein E encoding genes associated with the appearance of amyloid plaques and neurofibrillary tangles in the cerebral cortex, but also vascular risk factors including hypercholesterolaemia, diabetes mellitus, hypertension, and smoking [11]. Other risk factors such as gender, cerebral herpes infection, head injury, or educational level can play a role in the development of dementia [15].

There is a concerning association between the number of plaques in the brain and the severity of dementia [16]. Despite intense research on dementia, the condition remains irreversible and progressive in most cases.

Preexisting cognitive impairment and dementia: cognitive impairment can be detected preoperatively in a substantial proportion of elderly surgical patients but very few institutions have implemented procedures to preoperative screening — it is often overlooked. In a study of patients scheduled for hip replacement surgery, cognitive impairment was detected using neuropsychological testing in 32% of patients and they had a significantly increased risk of postoperative decline, even at 3 months and 12 months [17]. This is remarkable as the authors already excluded the most cognitively impaired patients who had a MMSE test below 26 points or had dementia based on a clinical dementia scale. One could expect that surgery would be offered less commonly to individuals who are demented, but the surgeon may not always be aware of such cognitive impairment.

**Postoperative cognitive complications and dementia**

**Various cognitive complications after surgery**

A number of different types of cognitive impairments after anaesthesia and surgery have been proposed, although the exact relation between anaesthesia and surgery and the cognitive decline is not always well established (box 2). Emergence after anaesthesia is the transition from unconsciousness to being fully awake, and usually this phase is smooth. Inadequate emergence is on the other hand a condition of disturbed activity level in the immediate postoperative period. Inadequate emergence and postoperative delirium are both well-known clinical complications that appear after anaesthesia and surgery, and they are both acute disturbances of attention and cognition that are plausible consequences of surgery and anaesthesia [18,19]. On the other hand, postoperative cognitive dysfunction (POCD) is a more subtle condition as it lacks clinical symptoms and it rarely presents during hospital admission, and therefore it is not readily apparent for the health care personnel. Usually, level of consciousness is unaffected, and POCD can be identified by using a battery of neuropsychological tests, where memory, concentration, and executive function domains usually are mostly affected [20]. A certain level of cognitive performance is required to comprehend most of these neuropsychological tests.

Various tests exist for the detection of delirium but the most widely used is the confusion assessment method (CAM) [21]. Among elderly surgical patients, the incidence of postoperative delirium is roughly 40%, and two of the most important risk

### Box 1

**Cognitive impairment in the elderly according to the fifth edition of Diagnostic and Statistical Manual for Mental Disorders [13]**

- Mild neurocognitive disorder
  - Previously known as “Mild cognitive impairment”
- Major neurocognitive disorder, includes previously known conditions
  - Dementia (several subtypes)
  - Amnestic disorder
- Delirium
Box 2
Postoperative cognitive complications

- Inadequate recovery
- Hypoactive emergence
- Hyperactive emergence (emergence delirium)
- Postoperative delirium
- Postoperative cognitive dysfunction
- Dementia unsubstantiated

Factors are increasing age and dementia. The most important risk factor for POCD is also increasing age, but it is uncertain if preoperative cognitive impairment increases the risk of POCD, since most studies tend to exclude these patients with a low cognitive performance at baseline. Moreover, it is difficult to detect memory deterioration after surgery in patients with a poor level of cognitive functioning preoperatively [22].

Cognitive decline trajectory
It has been suggested that cognitive decline follows a trajectory after surgery (Figure 1) [23]. It is possible that postoperative delirium can cause microstructural abnormalities in the brain that can be associated to the development of subsequent neurodegenerative processes such as dementia. However, such an association could also be explained by an existing preoperative cognitive impairment, hence decrease in cognitive reserve, which increase the likelihood of experiencing postoperative delirium [24]. It seems that patients with impairment of cognitive performance prior to surgery are at a higher risk of postoperative delirium, and later development of dementia [25]. Consequently, this vulnerable population with a preexisting cognitive deteriorating is rather at risk of experiencing cognitive complications, than association can be attributed to anaesthesia (and surgery) itself. Several studies have found an association between the appearances of postoperative delirium and impaired long term functional recovery. One study of 232 patients reported that the 9.1% of patients with postoperative delirium had a significantly poorer functional status 6 and 12 months after orthopedic surgery assessed in a telephone interview [26]. The SAGES study of more than 500 elderly surgical patients showed that postoperative delirium was associated with diminished functional recovery up to three years after surgery [27,28]. However, another study only found an association between postoperative delirium and the development of early postoperative cognitive dysfunction one week after surgery, but not postoperative cognitive decline three months after surgery [29]. The possible association between postoperative cognitive dysfunction and later dementia is more speculative. An observational study of nearly 700 patients with 11-year follow-up did not detect a significant association between postoperative cognitive dysfunction at one week or three months after surgery and later dementia [30]. However, the hazard ratios at both postoperative time points were above one (indicating increased risk of dementia), and the study could not exclude that the
dementia risk was substantially higher in those with POCD. Still, the proportion of patients with dementia was only 4.6%, which is lower than expected in the background population. This seems to be reassuring, but it must be acknowledged that patients in the study constitute a selected group willing to participate in a prospective study. One limitation could be that dementia was not diagnosed (underreported) in some individuals and that 60% died during follow-up.

Currently, we are unaware whether anaesthesia and surgery in itself induce or accelerate structural changes in the brain with a resulting deterioration in cognition, and development of dementia, or if anaesthesia and surgery reveal a preexisting cognitive deterioration that would result in dementia regardless of the anaesthesia and surgery. Nevertheless, frail patients should be screened for cognitive performance preoperatively, as they are at risk of developing postoperative delirium and should be followed closely after discharge.

**Anaesthesia and dementia**

**Limitations of current evidence**

It is well established that cognitive deterioration is a common phenomenon in elderly surgical patients but the relationship with dementia is not simple to assess. The methodology applied in POCD research usually includes a preoperative test to assess baseline performance, and a postoperative test to find out if deterioration from baseline has occurred. Thus, the studies do not include the patients’ or the relatives’ impression or an evaluation of level of functioning, such as activities of daily living. The time perspective is another issue as the short-term changes over days or weeks may not persist and that would be required for a dementia diagnosis to be established. Only a limited number of POCD studies have included a long-term follow-up examination, and it is therefore difficult to say if POCD persist [31]. Some studies have detected POCD several years after major surgery such as coronary artery bypass grafting, but the evidence is limited because control subjects may not have been assessed using the same test battery with the same interval, or deficits are detected at follow-up in patients who had no deficits soon after surgery [32].

It is definitely a possibility that any age-related cognitive decline can be accelerated by major life events, including major surgery. The associated inflammatory response can have an impact on brain function, and the resolution is often prolonged and different in the elderly. The underlying disease can certainly be a contributing factor. However, some surgical patients are expected to decline over time with no relation to exposure to anaesthesia and surgery. This trajectory is difficult to clarify as the single individual and the family tends to connect the experienced decline to any significant event prior to the diagnosis. In a familiar environment, many elderly can compensate for cognitive deficits as they do not have to learn new skills or manage new challenges. Once they are admitted to hospital it can then become obvious that they have memory problems and attention deficits.

More advanced cognitive testing aimed at detecting subtle changes required for research on POCD is often not useful in those with pre-existing cognitive impairment because a low baseline performance precludes detection of a pre-specified magnitude in a score such as the number of words recalled. This is the so-called floor effect [22]. Consequently, these persons that are actually very a relevant group at risk, are often not included in the studies.

**Examples of current evidence**

Several different types of study designs have been used to examine the possibility that exposure to anaesthesia and surgery increases the risk of developing dementia. Cross sectional studies include a single cognitive test session of subjects, who are asked about previous surgery and anaesthesia. In this way, it is possible to analyse whether the level of performance in neuropsychological tests is associated with any exposure, the number of procedures, the type of surgery, age at exposure, and time since exposure. One study included more than 8000 subjects who had psychometric testing done and where information about surgery was obtained from a national registry. Among the participants, 65% had at least one surgery and major surgery was found to be associated with lower performance in the tests but the difference was very small and in patients undergoing knee and hip replacement, a higher cognitive score was found [33].

Longitudinal cohort studies are based on repeated examination of cognitive function over years where some individuals in that population are undergoing surgery. The study then looks at possible differences in the change in level of functioning and the proportion with a dementia diagnosis according to exposure. One such study extracted data from a large database to compare subjects who had surgery, subjects who were admitted to hospital for major illness without surgery, and finally subjects who did not undergo surgery and had no major illness [34]. A total of 575 subjects were included and 180 of these had surgery. The median follow-up time after surgery was around 2 years. Out of 214 persons without dementia, 22% progressed to either very mild dementia or mild dementia after surgery that was not different from the findings in the other groups. Moreover, the annual rate of change in psychometric test performance was not different. Besides, there was no difference according to surgery in the group with dementia. A better design was used in another study where almost 4000 dementia-free subjects over 65 years were prospectively studied every 2 years and followed for an average of 7 years. The participants reported exposure to surgery and anaesthesia, and dementia was diagnosed in 24% of cases. No significant association was found between dementia and exposure to anaesthesia, but high-risk
surgery increased the risk, as compared with other procedures with a hazard ratio of 1.46 [35].

Case-control design is based on a comparison of patients with dementia (cases) and individuals without dementia (controls). It is then examined if a greater proportion of demented patients have been exposed to anaesthesia and surgery. Usually, dementia has been diagnosed carefully as patients in most studies are recruited from dementia clinics, but it is less sure if dementia has been definitely excluded in the controls. Likewise, this study design requires reliable information about exposure and some subjects may not recall important details such as time since exposure, or type of surgery and anaesthesia. A systematic review has summarized 15 case-control studies on this topic and no significant association was found in the meta-analysis based on 1752 patients and 5261 controls [36]. A more recent study included 877 cases of dementia and age- and sex-matched controls without dementia. This was a very impressive study with detailed information about both dementia patients and controls. There was no difference in the proportion that had procedures requiring general anaesthesia (around 70% in both groups) [37]. In contrast, a nationwide study from Taiwan found a significant association between dementia (5345 cases) and exposure to surgery compared to more than 20 000 controls without dementia [38]. The data were analysed using logistic regression and the odds ratio for general anaesthesia as a risk factor was almost 1.5, while risk factors with higher odds ratios were comorbidities, such as stroke and hypertension. In such a large study, it is not possible to describe in detail exactly how dementia was diagnosed.

In a study focusing on mild cognitive impairment no association was found with exposure to general anaesthesia after the age of 40 years where 454 patients were compared with 774 cognitively normal subjects [39]. Few studies have conducted follow-up of patients to determine if dementia develops long time after surgery. In cardiac surgery patients, dementia was detected in 30.8% (95% confidence interval 23 to 40%) at 7.5 years after the procedure. No control group was included so this could be explained as decline unrelated to surgery and anaesthesia [40]. One study included patients undergoing either coronary artery bypass grafting or percutaneous transluminal coronary angioplasty. They were followed for a minimum of 5 years [41]. A total of 9170 patients were included and in an adjusted analysis, surgery was associated with a slightly higher risk of dementia but dementia was only detected in 1.5% in that group and the diagnostic criteria were not very accurate as mentioned by the authors. In a much smaller but detailed prospective study of patients with coronary artery disease, no difference could be found in cognitive function between those 152 patients who had coronary artery bypass grafting and 92 nonsurgical controls who received only medical treatment at follow-up after more than six years [42]. Thus, there is a certain risk of dementia after cardiac surgery but cardiac disease and atherosclerosis seem to be important risk factors as well. Based on the studies summarized above, the role of anaesthesia in cardiac surgery and patients’ subsequent dementia cannot be established.

One study followed patients for a median of 11 years after different types of non-cardiac surgery and national registries were used to identify dementia. In this group of almost 700 patients with a median age of 67 years, POCD was not a significant risk factor for dementia, but the study could not exclude a minor, but still clinically relevant association, as mentioned above [30].

An interesting study was based on randomization of patients with amnestic cognitive impairment to different types of anaesthesia for spine surgery comparing amnestic cognitive impairment persons who did not have surgery. At the 2-year follow-up, patients allocated to sevoflurane anaesthesia more often had progression of cognitive impairment although progression to dementia was not different. The overall group of surgical patients did not differ from controls without surgery as 100 out of 160 had decline as compared with 26 out of 56 controls. Regional anaesthesia seemed to be associated with less progression [43].

A national registry was used in another study where almost 25,000 patients exposed to anaesthesia were compared with more than 110,000 controls not exposed. The risk of dementia was significantly higher in exposed subjects (hazard ratio 1.99) where 2.65% were diagnosed with dementia over the 3 to 7 years of follow-up. Surprisingly, the risk was highest with regional anaesthesia and minor procedures such as eye surgery. Type of anaesthesia was not easy to interpret as the authors distinguished between intravenous/intramuscular, general, and regional, where the latter included not only epidural and spinal anaesthesia but also “local anaesthesia” [44]. The potential neurotoxicity of general anaesthesia that has been shown in several animal studies is not as apparent in the human brain [45,46]. One would logically expect the cognition to be better after regional anaesthesia as compared to general anaesthesia, but this does not seem to be the case. Two reviews including several randomized studies comparing general studies to regional anaesthesia conclude that there is no significant difference in POCD between general and regional anaesthesia [47,48]. Likewise, regional anaesthesia does not seem to reduce the risk of dementia as mentioned above, and a multifactorial aetiology rather than simplifying the risk to general anaesthesia alone appears to be likely.

**Conclusion**

Cognitive deterioration after surgery is a common complication after surgery in the elderly, and with an increasing number of elderly patients undergoing surgery, a potential impact of anaesthesia and surgery on the incidence of dementia would be concerning. Currently, we are unaware whether anaesthesia...
and surgery in itself induce or accelerate structural changes in the brain with a resulting cognitive deterioration, or if anaesthesia and surgery reveal a preexisting cognitive deterioration regardless of the anaesthesia and surgery. While there are several studies showing an increased risk of reversible cognitive impairment after surgery among elderly, the risk of inducing dementia remains speculative. Further studies are needed to elucidate this potential association. Elderly frail patients should be closely followed including cognitive screening preoperatively, as they are at increased risk of experiencing cognitive deterioration after surgery and discharge.

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