ARE ANAESTHETIC DRUGS RELATED WITH COGNITIVE DISFUNCTION AND ALZHEIMER'S DISEASE? A REWIEV

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Summary

Anaesthesia and surgery will be more and more required in old subjects in future years and Alzheimer disease is frequent in this population. Some uncertainty still exists about the possible cognitive consequences of these procedures in old subjects .We aimed at offering an updated information on the postoperative cognitive dysfunction (POCD) and the relationship between anaesthesia/surgery and the arise or the advance of AD. MEDLINE database was searched for: anaesthesia in Alzheimer Disease, anaesthesia in cognitive decline, postoperative cognitive dysfunction in Alzheimer patients, Postoperative cognitive dysfunction and anaesthesia, cardiac surgery and Alzheimer; cardiac surgery and POCD, Delirium and Alzheimer, surgery and POCD. This systematic review retrieved 12 papers and 5973 patients . They indicate that 1)POCD is frequent in old subjects after both general and local anaesthesia without differences, that it reverts within three months and is unrelated with further impairments. 2) that AD development or progression are unrelated with anaesthesia and surgery

Keywords: anaesthesia, Alzheimer disease, Postoperative cognitive syndrome,

Introduction

As a consequence of the increasing longevity anaesthesia and surgery will be more and more required in old subjects in future years; Alzheimer disease is frequent in old subjects and surgery will be required for these patients. In spite of numerous studies some uncertainty still exists about 1) the possible cognitive consequences of these procedures in old subjects 2) the relationship between anaesthesia and surgery and the exacerbation of cognitive impairments.

In this paper we have considered two conditions: the development of postoperative cognitive dysfunction (POCD) and the relationship between anaesthesia/surgery and the arise or the advance of AD. POCD is a transitory cognitive impairment involving several functions (as memory, language and concentration) which may follow surgery and last a variable period of time, from some days to 2-3 months. POCD patients have also be suggested to be at higher risk of developing AD. Independently from the appearance of a POCD syndrome Alzheimer disease has also been suggested to be related with anaesthesia; through anaesthetics that might interfere with the individual susceptibility as contributing factors of AD development or progression. We performed a systematic review of the literature on the relationship between anaesthesia, surgery, POCD and AD. Data published from 2000 to 2009 were collected and evaluated to give an updated information on these aspects.

Methods

The MEDLINE database was searched for the following keywords: anaesthesia in Alzheimer Disease, anaesthesia in cognitive decline, postoperative cognitive dysfunction in Alzheimer patients, Postoperative cognitive dysfunction and anaesthesia, cardiac surgery and Alzheimer; cardiac surgery and POCD, Delirium and Alzheimer, surgery and POCD. The limits applied were: English language, publications dated from 2000 to 2009, keywords present in the title/abstract. Further research was done on the Cochrane database and Embase. This systematic approach resulted in 11 articles. We excluded those focusing on animal studies and on basic research. The remaining 11 titles were checked independently by us in order to retrieve case series and review articles: eleven case series and four review articles (1,4,5,6) were found. A check of the references of the review articles afforded two more case series (7, 8). An assessment of the quality of the 11 case series was performed according to the Newcastle–Ottawa Scale (NOS) for case–control studies, limited to the items concerning ‘adequacy of the case definition’ and ‘representativeness of the case’. The data of the case series were analyzed in order to investigate their general characteristics, the diagnostic work-up performed used to establish the presence of a relationship between POCD and surgery and between Alzheimer Disease and surgery.

Results

Using the NOS Criteria, the ‘representativeness of the case’ was adequate in 11 case series, and the case definition was adequate in all; in one case

serie, however, the diagnostic evaluation was made through a not validated procedure. Among the 11 case series, 10 focused on POCD and 1 on AD. All the case series concerning POCD except one were prospective, while the case serie focusing on AD and general anaesthesia was retrospective. No differences between prospective and retrospective studies were found in the diagnostic criteria. Each of the series included not less than 100 patients and in nine of them more than 300 patients were included. The recruitment period ranged from 1990 to 2008. The patients mean age ranged from 64 to 74 years. Major non-cardiac surgery was reported in seven case-series: in six of them surgery was performed with general anaesthesia (7, 18, 19, 20, 21, 25), instead, in the other one with general or local anaesthesia (3). One case serie refers to cardiac-surgery in general anaesthesia (16). Major or minor surgery performed in general or local anaesthesia are reported in two case series (8,21). Only one case serie reported minor surgery in general anaesthesia (15). POCD development after general anaesthesia with sulfentanil-xenon or sulfentanil-propofol has been analyzed in one case serie (25). In all the case series patients were out of dementia at the beginning of the study (the exclusion criteria being: alcohol/drugs abuse, antipsychotic drugs use, language ìmpairments). All patients except those recruited in the study of Avidan (19) were recruited from hospitals. Finally in all the case series, except one, a control group was reported. Table 1 shows the main characteristics of the studies, classified by the first author name, the study design, the study period, the number of included patients, their mean age, the surgery and anaesthesia, and the exclusion criteria. The Abilstrom's work (3) considers two groups of subjects : group one (G1) is composed of 177 60-69 years old patients, group two (G2) of 145, 70 years older patients. Both groups had had general anaesthesia for major non cardiac surgery. The presence of POCD was evaluated with different neuropsychological tests (Visual Verbal Learning, Concept Shifting part C, Stroop Color Word Interference, Letter Digit Coding Tests). One week after surgery 21% of G1 patients and 29% of G2 patients had POCD; 3 months later 8% of G1 and 13% of G2 had cognitive symptoms, and 1 year later 5% of G1 and 16% of G2 showed some difficulties. Rasmussen (21) compares general and local anaesthesia. The first group (G1) includes 217 patients and the second (G2) 211, both having had major non-cardiac surgery. The neuropsychological tests were identical to those employed in the previous study, but GDS, Subjective Cognitive Functioning (SCF) and IADL were included too. 19,7% of G1 patients (general anaesthesia) and 12,5% of G2 8 local anaesthesia had some impairment immediately after and non differences were found between general and local anaesthesia

when the cognitive functions were evaluated after three months. Minor surgery has been evaluated by Canet (15) in 199 in-patients (subjects staying in the hospital ward one night after surgery) and 173 outpatients (discharged the same day of surgery); all had general anaesthesia and were evaluated through the same tests reported before. Canet does not find any significant difference between the groups (9,8% of inpatients and 3,5% of outpatients had symptoms) both after one week and three months. Monk (18) considers four groups: 331 patients aged 18-39, 378 aged 40-59, 355 aged more than 60 and a control group composed of 210 subjects illness and surgery free.The three groups had non-cardiac surgery; the tests were similar to those employed by the other authors, and some further scales were included (Beck Depression Inventory, State Trait Anxiety Inventory, Numerical Rating Scale and Daily Living Questionnaire). Monk finds that 36,6% of the first group patients, 30,4% of the second group and 41,4% of the third had some cognitive symptoms, while the percentage in the control group was of 4,5%; and that three months later some cognitive dysfunction was present in 5,7%, 5,6%, 12,6% and only in 3,5% respectively. The tests employed were a bit different in Avidan (2009) study as he included the Visual Retention Test (part C and D), the Weschler Memory Scale, the Weschler Adult Intelligence Scale, the Boston Naming Test, the TMT-A and the Crossing-Off. Avidan sample was composed by 331 patients without surgery, 180 over sixty with surgery and 276 patients with a major illness but no surgery. 5 years later some cognitive dysfunction was present in 23% of the first group, in the 22% of the second, but also in 24% of the subjects who had received none surgical treatment. Hocker (25) compares sulfentanil-xenon and sulfentanil-propofol for major non-cardiac surgery. He found some cognitive impairment in a similar percentage (44% and 50%) six days after surgery and later on (12% and 18%). Robinson (7) analyzes 144 patients for post-operative delirium after major non-cardiac surgery, (through the Charlson Index, the Barthel Index, the Mini-Cog Test and the CAM-ICU) and founds it in 38% of the patients. Rudolph describes 1161 over sixty years patients who had non-cardiac surgery through DSM-IV, MMSE, Stroop Color Word Interference Test, Visual Verbal Learning Test, TMT and Stroop Test. He finds impairments in 8%, 7%, and 6% of them immediately after, one and two weeks later, but further evaluations were missed. Selnes (16) reports patients who had artery bypass graft surgery (CABG) divided in two groups (152 on-pump, 75 off-pump patients) and other two groups of subjects without surgery (99 patients with coronary artery disease and 69 without it).

Tab.1. MAIN CHARACTERISTICS OF THE EXAMINED STUDIES

First Author	Model of Study	Study Period	Number of Patient	Mean Age	Surgery/ Anaesthesia	Exclusion Criteria
Abildstrom 2000	prospective	1994-1997	336	71	non-cardiac major surgery in	diseases of the CNS
Gasparini 2002	retrospective	1990-1997	575	69	surgery in general anaesthesia	
Rasmussen 2003	prospective	1998-2000	428	71		diseases of the CNS
Canet 2003	prospective		372	68	minor surgery in general anaesthesia	diseases of the CNS, alchoolism, drug dependence, visual handicap.
Selnes 2007	prospective	1997-2003	395	64	artery bypass graft surgery	diseases of the CNS, mechanical ventilation, heart's risk factors, stroke/TIA.
Monk 2008	prospective	1999-2002	1203	70	non-cardiac major surgery	diseases of the CNS, visual/auditory handicap, inability to speak English cardiac arrest
Rudolph 2008	prospective	1994-1996	1161	69	non-cardiac elective surgery	diseases of the CNS, visual/auditory handicap, inability to speak English, cardiac/neuro-surgery
Steinmertz 2009	prospective		683	67	major/minor non cardiac surgry	
Robinson 2009	prospective	2006-2007	144	65	major surgery	diseases of the CNS, visual handicap, neurosurgery, inability to speak English
Avidan 2009	retrospective		575	74	major non cardiac surgery	cardiac/carotic/neuro-surgery, stroke, cardiac arrest
Hocker 2009	prospective	2006-2008	101	72	major non cardiac surgery	diseases of the CNS, visual/auditory/motor handicap, alcholism

Table 2 shows the results of the more relevant studies on the topic

First author	Sample	Model of study	Study groups	Surgery	Tests	Setting	POCD
Abildstrom 2000	322	prospective	Group 1 (G1): 177 (60-69 years old) Group2 (G2): 145 (≥70 years old)	major non-cardiac surgery under general anaesthesia	Visual verbal learning test Concept Shifting Test (part C) Stroop Colour Word Interference Test Letter Digit Coding Test	hospital	After 1 week: G1: 21%; G2: 29% After 3 months: G1: 8%; G2:13% After 1 year: G1: 5%; G2: 16%
Rasmussen 2003	428	prospective randomized study	Group 1 (G1): 217 (general anaesthesia) Group2 (G2): 211 (local anaesthesia)	major non-cardiac surgery under general/local anaesthesia	Visual verbal learning test Concept Shifting Test (part C) Stroop Colour Word Interference Test (third part) Letter Digit Coding Test GDS, IADL Subjective Cognitive Functioning (SCF)	hospital	After 1 week: G1: 19,7% G2: 12,5% After 3 months: G1: 14,3% G2: 13,9%
Canet 2003	372	prospective randomized study	Group 1 (G1): 199 (in-patients) Group2 (G2): 173 (out-patients)	minor/major surgery under general anaesthesia	Visual verbal learning test Concept Shifting Test parte C Stroop Colour Word Interference Test Letter Digit Coding Test GDS, IADL Subjective Cognitive Functioning (SCF)	hospital	After 1 week: G1: 9,8% G2: 3,5% After 3 months: G1: 8,8% G2: 4,5%
Monk 2008	1203	prospective	Group 1 (G1): 331 (18-39 years old) Group2 (G2): 378 (40-59 years old) Group 3 (G3): 355 (>60 years) Control Group (CG): 210 (no surgery/illness)	major non-cardiac surgery	Visual verbal learning test Concept Shifting Test /part C) Stroop Color Word Interference Test Letter Digit Coding (WAIS) Beck Depression Inventory State Trait Anxiety Inventory Numerical Rating Scale Daily Living Questionnarie	hospital	After 1 week: G1: 36,6%; G2: 30,4% G3: 41,4% CG: 4,5% After 3 months: G1: 5,7%; G2: 5,65% G3: 12,66% CG: 3,5%
Avidan 2009	575	retrospective cohort study	Group 1 (G1): 331 (no surgery, no major illness) Group2 (G2): 180 (surgery) (>60 years) Group 3 (G3): 276 (major illness)	major non-cardiac surgery	Visual Retention Test (parte C e D) Wechsler Memory Scale Wechsler Adult Intelligence Scale Boston Naming Test TMT-A Crossing-Off	ADRC database	by 5 years from exposion: G1: 23% G2: 22% G3: 24%
Hocker 2009	101	randomized, double blinded, controlled, prospective study	Group 1 (G1): 50 (sulfentanil-xenon) Group2 (G2): 51 (sulfentanil-propofol)	major non-cardiac surgery	Rey's auditorial Verbal learning test TMT-A Stroop color word interference test Digit Symbol Substitution Test Digit Span Test Verbal fluency Test	hospital	After 1 day: G1: 44% G2: 50% After 6 days: G1: 12%; G2:18% After 30 days: G1: 6% ; G2: 12%
Steinmertz 2009	683	prospective		major/minor non-cardiac surgery under general/local anaesthesia	Visual verbal learning test Stroop color word interference test TMT Letter Digit Coding (WAIS)	hospital	After 1 week: 17,00% After 3 months: 8,50%

Subjects were evaluated through many tests, including those more frequently employed (Depression Scale, Functional Status Questionnaire, Rey Auditory Verbal Learning Test, Rey Complex Figure, Block Design, Boston Naming Test) and some others less diffused (Grooved Pegboard Dominant, Grooved Pegboard Non-Dominant, Trial Making Test, Written Alphabet). The results are given as mean values among the different groups. After three months he found some cognitive dysfunction only in some of the tests employed. Finally Steinmertz (8) evaluates 683 patients after major or minor non-cardiac surgery (under general or local anaesthesia) and finds impairments in 17% of them immediately after, but only in 8,50% three months later.

The diagnostic procedures performed in the major parts of the studies included the following neuropsychological test and diagnostic criteria: Visual Verbal Learning Test, Concept Shifting Test (part C), Stroop Color Word Interference Test (Part 3), Letter Digit Coding Test, GDS, IADL, Subjective Cognitive Functioning (SCF), Beck Depression Inventory, State-Trait Anxiety Inventory (STAI), Numerical Rating Scale, Daily Living Questionnarie, Visual Retention Test (part C and D), Weschler Memory Scale, WAIS, Rey Auditory Verbal Learning Test, Digit Symbol Substitution Test, Digit Span Test, Verbal Fluency Test, Mini-Cog Test, CAM-ICU, Barthel Index, Charlson Index, DSM-IV, MMSE, Trail Making Test (TMT-A and TMT-B), Stroop Test, Depression Scale, Functional Status Questionnaire, Rey Complex Figure, Block Design, Boston Naming Test, Grooved Pegboard Dominant and Not-Dominant, Written Alphabeth, Minimental Exam-attention, and Crossing Off.In the following tables (table 3 and table 4) are shown the neuropsychological tests and the diagnostic criteria used for the diagnosis of POCD in the patients in the different studies, and their frequency.

TABLE 3 frequency of the employed neuropsychological tests

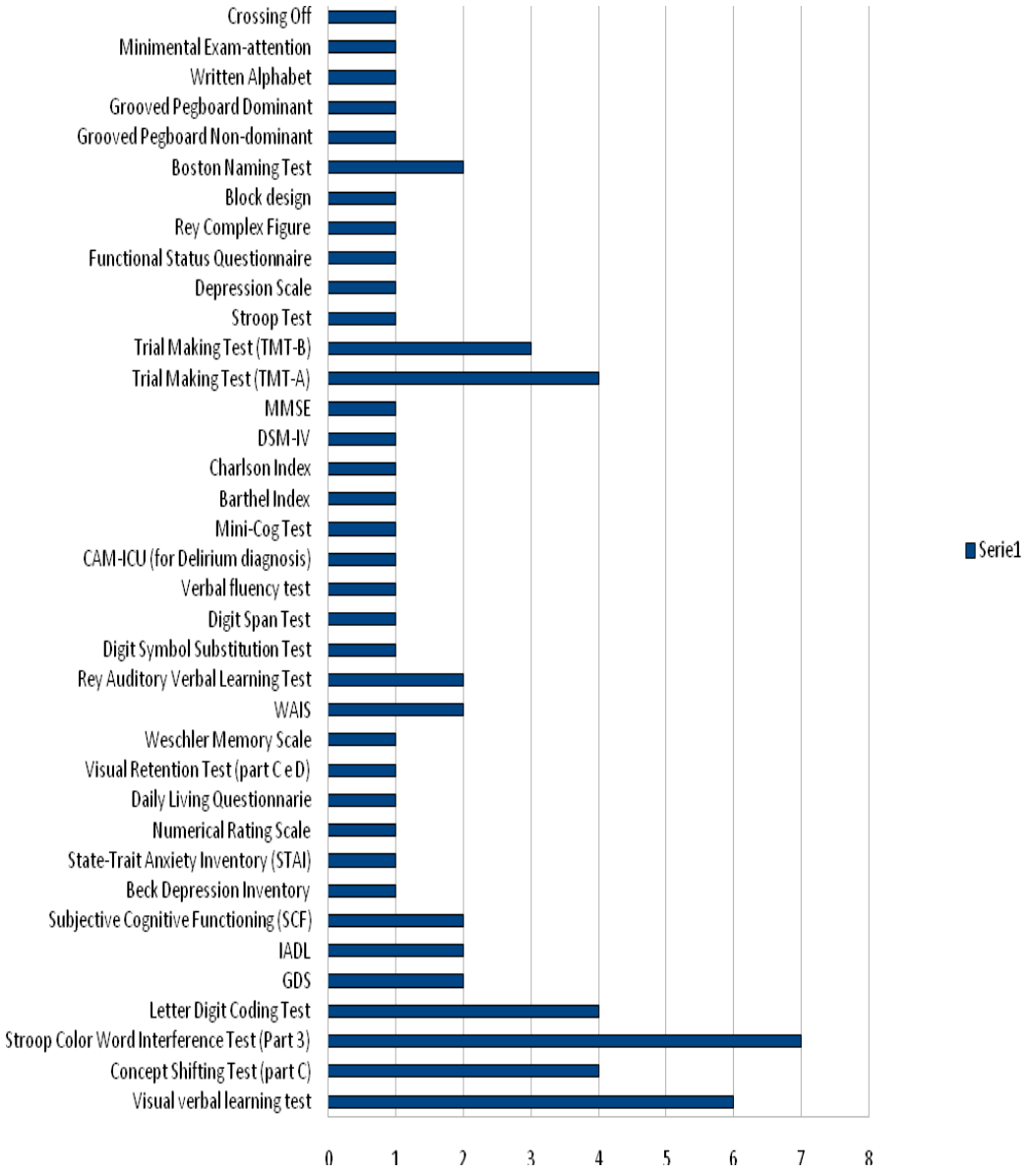

TABLE 4 Tests employed by the different authors

Diagnostic procedures	Abildstrom 2000	Rasmussen 2003	Canet 2003	Monk 2008	Avidan 2009	Hocker 2009	Robinson 2009	Rudolph 2008	Selnes 2007	Steinmertz 2009
Visual verbal learning test	x	x	x	x				x		x
Concept Shifting Test (part C)	x	x	x	x						
Stroop Color Word Interference Test	x	x	x	x		x		x		x
Letter Digit Coding Test	x	x	x							x
GDS		x	x							
IADL		x	x							
Subjective Cognitive Functioning		x	x							
Beck Depression Inventory				x						
State-Trait Anxiety Inventory				x						
Numerical Rating Scale				x						
Daily Living Questionnarie				x						
Visual Retention Test (part C e D)					x					
Weschler Memory Scale					x					
WAIS					x	x				
Rey Auditory Verbal Learning Test						x			x	
Digit Symbol Substitution Test						x				
Digit Span Test						x				
Verbal fluency test						x				
CAM-ICU (for Delirium diagnosis)							x			
Mini-Cog Test							x			
Barthel Index							x			
Charlson Index							x			
DSM-IV								x		
MMSE								x		
Trial Making Test (TMT-A)					x			x	x	x
Trial Making Test (TMT-B)								x	x	x
Stroop Test								x		
Depression Scale									x	
Functional Status Questionnaire									x	
Rey Complex Figure									x	
Block design									x	
Boston Naming Test					x				x	
Grooved Pegboard Non-dominant									x	
Grooved Pegboard Dominant									x	
Written Alphabet									x	
Minimental Exam-attention									x	
Crossing Off					x					

The work of Gasparini et al. was based on finding the existence or not of a correlation between general anaesthesia and AD. In this retrospective case-control study were enrolled 575 patients (115 AD patients, 230 PD patients and 230 patients affected by a non-degenerative neurological disease) exposed to general anaesthesia in the previous 5 years. To diagnose AD were used the NINCDS/ARDRA criteria. Exposition to general anaesthesia 1 year before onset was positive for 39,1% patients in G1, for 56,5% patients in G2, and for 63,5% patients in G3. Exposition to general anaesthesia X years before onset was positive for 77,4% patients in G1, for 82,6% patients in G2, and for 76,9% patients in G3, as shown in table 5.

Tab.5. Study on anaesthesia / surgery and Alzheimer disease

Authors	Sample	Model of study	Study groups	Surgery	Tests	Setting	Correlation Between AD and Anaesthesia/Surgery
Gasparini 2002	575	retrospective case control	Group 1 (G1): 115 (Alzheimer Disease) Group2 (G2): 230 (Parkinson Disease) Group3 (G3): 230 (affected by non-dege-nerative neurological disease)	any kind of surgery with exposion to general anaesthesia (in the previos 5 years)	Nincds/Adrada criteria	hospital	General Anaesthesia 1 year before onset: G1:39,1% G2:56,5% G3:63,5% General Anaesthesia 1 year before onset: G1:77,4% G2:82,6% G3:76,9%

Discussion and Conclusions

This systematic review retrieved 12 papers published from 2000 to 2009; the recruitment period ranged from 1990 to 2008, and the global number of examined patients was of 5973. Data concerned both major and minor surgery and general and local anaesthesia. Two aspects have been examined: 1) the relationship between surgery and anaesthesia and the development of a postoperative cognitive dysfunction (POCD), and 2) the relationship between surgery and anaesthesia and Alzheimer disease development or progression. For the first aspect ten qualified studies are available in the literature, concerning both general and local anaesthesia and both major (cardiac and non cardiac) and minor surgery.

The study designs have been prospective and retrospective ; in two of them a control group has been also included. They indicate that the cognitive disfunction is more frequent in older subjects after general and local anaesthesia without significant differences and that it reverts within three months. POCD is therefore a transitory disturbance unrelated to further impairments. In a neuropsychological perspective, however, we need to highlight that the cognitive tests employed to evaluate the POCD have , in almost all the studies, been directed to the executive functions . This is a particular set of abilities specifically involved in the "control and regulation of other abilities and behaviours " and in the " adapting the behaviour to changing situations." Even if they are essential for goal-directed behaviour, monitoring and changing strategies and planning future actions ,the executive functions are not those found impaired in the first stage of the Alzheimer disease. As a consequence these tests can be inadequate to disclose the appearance of an eventual AD after a POCD , as they do not evaluate the memory functions , whose impairment is the marker of AD. Independently from anesthesia POCD follows essentially major surgery (3,15) probably because of different factors as: the duration of the surgical procedure, an inadequate ventilation and pressure control, the surgical stress by itself. This is a relevant factor as determines a neuro-endocrinological response trough cortisole, renine, ADH and catecolamine increase that may lead to iperglicemia, tachicardia, tachipnea , electrolites and liquids retention. All these aspects, as well known, have significant consequences on brain functions. Our second topic is the possible relationship between anaesthesia and the development or the worsening of Alzheimer disease. It comes from a work by Fodale et al (1) who hypothesize a dose-related reversible interaction of volatile anaesthetics (isoflurane, sevoflurane and desflurane) with the cholinergic nichotinic and muscarinic receptors located in the central nervous system and enrolled in memory. The author highlights furthermore the strong antagonism of barbitures and opioids (with the exclusion of remifentanil) with achetilcholinic receptors of CNS and the possible involvement of thiopental and propofol in Alzheimer disease. Fodale mentions also Palota's article where these two anaesthetics have been studied for their relationship with APP metabolism. In spite of these biochemical data, on a clinical perspective we did not find in the literature any evidence of such a relationship. As a consequence both propofol and thiopental are considered safe with respect to APP metabolism and data do not support any relationship between anesthesia and AD.

In conclusion, in elder patients the risk of developing POCD is higher than in younger subjects after surgery and anaesthesia but it lasts a limited period of time and reverts within three months. The development or progression of Alzheimer disease is not unrelated to anaesthesia and surgery .

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