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ROSSI Ariane

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UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département des Services de Chirurgie et d'Anesthésiologie
Service d'Anesthésiologie

**Serum Anticholinergic Activity and Postoperative Cognitive Dysfunction
in Elderly Patients**

THESE

préparée sous la direction du Professeur Luzius A. Steiner
et du Professeur Christian Kern

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Ariane ROSSI

Médecin diplômée de la Confédération Suisse
Originaire de Trub (BE) et Penthaz (VD)

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***Serum Anticholinergic Activity and Postoperative Cognitive
Dysfunction in Elderly Patients***

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*pour Le Doyen
de la Faculté de Biologie et de Médecine*



*Madame la Professeure Stephanie Clarke
Directrice de l'Ecole doctorale*

Serum Anticholinergic Activity and Postoperative Cognitive Dysfunction in Elderly Patients

Ariane Rossi, MD,* Christoph Burkhart, MD,† Salome Dell-Kuster, MD, MSc,† Bruce G. Pollock, MD, PhD,‡ Stephan P. Strebel, MD,† Andreas U. Monsch, PhD,§ Christian Kern, MD,* and Luzius A. Steiner, MD, PhD*†

BACKGROUND: Cerebral cholinergic transmission plays a key role in cognitive function, and anticholinergic drugs administered during the perioperative phase are a hypothetical cause of postoperative cognitive dysfunction (POCD). We hypothesized that a perioperative increase in serum anticholinergic activity (SAA) is associated with POCD in elderly patients.

METHODS: Seventy-nine patients aged >65 years undergoing elective major surgery under standardized general anesthesia (thiopental, sevoflurane, fentanyl, and atracurium) were investigated. Cognitive functions were assessed preoperatively and 7 days postoperatively using the extended version of the CERAD-Neuropsychological Assessment Battery. POCD was defined as a postoperative decline >1 z-score in at least 2 test variables. SAA was measured preoperatively and 7 days postoperatively at the time of cognitive testing. Hodges-Lehmann median differences and their 95% confidence intervals were calculated for between-group comparisons.

RESULTS: Of the patients who completed the study, 46% developed POCD. Patients with POCD were slightly older and less educated than patients without POCD. There were no relevant differences between patients with and without POCD regarding gender, demographically corrected baseline cognitive functions, and duration of anesthesia. There were no large differences between patients with and without POCD regarding SAA preoperatively (pmol/mL, median [interquartile range]/median difference [95% CI], *P*; 1.14 [0.72, 2.37] vs 1.13 [0.68, 1.68]/0.12 [-0.31, 0.57], *P* = 0.56), SAA 7 days postoperatively (1.32 [0.68, 2.59] vs 0.97 [0.65, 1.83]/0.25 [-0.26, 0.81], *P* = 0.37), or changes in SAA (0.08 [-0.50, 0.70] vs -0.02 [-0.53, 0.41]/0.1 [-0.31, 0.52], *P* = 0.62). There was no significant relationship between changes in SAA and changes in cognitive function (Spearman rank correlation coefficient preoperatively of 0.03 [95% CI, -0.21, 0.26] and postoperatively of -0.002 [95% CI, -0.24, 0.23]).

CONCLUSIONS: In this panel of patients with low baseline SAA and clinically insignificant perioperative anticholinergic burden, although a relationship cannot be excluded in some patients, our analysis suggests that POCD is probably not a substantial consequence of anticholinergic medications administered perioperatively but rather due to other mechanisms. (*Anesth Analg* 2014;119:947–55)

Postoperative cognitive dysfunction (POCD) is an increasingly recognized problem. Age and preexisting cognitive impairment are predisposing factors,^{1–3}

From the *Department of Anesthesia, Lausanne University Hospital, Lausanne, Switzerland; †Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland; ‡Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada; Centre for Addiction and Mental Health, Toronto, Canada; and §Memory Clinic, University Center for Medicine of Aging, Felix Platter Hospital, Basel, Switzerland.

Christoph Burkhart, MD, is currently affiliated with Department of Anaesthesia and Intensive Care Medicine, Kantonsspital Graubunden, Chur, Switzerland.

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The authors declare no conflicts of interest.

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Address correspondence to Luzius A. Steiner, MD, PhD, Department of Anesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland. Address e-mail to luzius.steiner@usb.ch.

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and 25% to 40% of patients aged 60 years or older have POCD 1 week after noncardiac surgery.^{2–4} The etiology of POCD is unclear. Several mechanisms have been investigated,⁵ and although the type of anesthesia does not seem to play a role,^{6,7} the contribution of perioperative medications remains largely unknown.

Cerebral cholinergic transmission plays a key role in cognitive function. A central cholinergic deficit has been demonstrated to be associated with age-related cognitive impairment,⁸ and anticholinergic drugs are associated with impaired cognitive functions^{9–12} and delirium.^{13–15} Elderly people and especially those with altered cognitive functions¹⁶ are sensitive to central anticholinergic side effects, which may already occur at standard doses of frequently prescribed drugs.^{14,17} More than 600 drugs have some anticholinergic activity, and 14 of the 25 most commonly prescribed medications for older adults have detectable anticholinergic effects.¹⁷ During the perioperative phase, many substances with anticholinergic effects are administered, and disturbed cholinergic transmission is considered a possible cause of POCD.¹⁸

Serum anticholinergic activity (SAA) can be measured as a marker of anticholinergic burden in a patient's blood using a radioreceptor assay.¹⁹ Independent of the source of the anticholinergic activity, SAA reflects the binding of all compounds present in a person's serum to muscarinic receptors.²⁰ Increased SAA has been shown to be associated with cognitive impairment or delirium in several studies

involving elderly patients taking anticholinergic drugs regularly,^{16,21–23} although the precise relationship between SAA and cognitive performance is not established. Moreover, SAA seems to be a stronger predictor of cognitive decline than age.²¹

To the best of our knowledge, repeated measurements of SAA in patients with and without POCD have not been used in the perioperative setting to investigate the link between anticholinergic activity and POCD. To explore the role of anticholinergic medication in the development of POCD, we tested the hypothesis that an increase in SAA during the perioperative period is associated with the occurrence of POCD in elderly patients.

METHODS

Subjects

After obtaining approval by the Regional Ethics Committees of Basel and Lausanne and written informed patient consent, 79 patients aged ≥ 65 years scheduled for elective major noncardiac surgery were enrolled in this study. Exclusion criteria were neurosurgery, carotid endarterectomy, a history of cerebrovascular disease, a preoperative Mini-Mental State Examination (MMSE) score $< 24/30$, and long-term psychiatric medication. The study was registered at www.clinicaltrials.gov (NCT00512200). Some of the patients also participated in a study exploring intraoperative cerebral autoregulation and cerebral oxygenation.²⁴

Anesthesia

All patients received standardized general anesthesia using thiopental (3–5 mg/kg) for induction, and sevoflurane, fentanyl, and atracurium for maintenance. All other aspects of the anesthetic management (dosing of sevoflurane and fentanyl, arterial blood pressure targets, use of vasoactive drugs, reversal of the neuromuscular blockade) were left to the discretion of the anesthesiologist in charge. Postoperative management on the ward including analgesia was prescribed by the surgeons and was not affected by this protocol.

Neuropsychological Assessment

Cognitive functions were assessed preoperatively (the day before the operation) and 7 days postoperatively or at hospital discharge using the validated German and French modified versions of the Consortium to Establish a Registry for Alzheimer's Disease-Neuropsychological Assessment Battery (CERAD-NAB).²⁵ This battery, which is an extended version of the original to constitute the CERAD-NAB-Plus, consists of 7 subtests that cover the most commonly affected areas of cognitive functioning in patients with Alzheimer disease. The cognitive domains were assessed, and the corresponding variables were semantic memory/executive functions (animal fluency, naming of as many animals as possible in 60 seconds), confrontation naming (Boston Naming Test, naming of 15 drawn items), general level of cognitive functions (MMSE), verbal episodic memory (Word List—Learning, Word List—Intrusion Errors, Word List—Delayed Recall (after 5–10 minutes), Word List—Savings (%), Word List—Recognition), constructional praxis (Figures—Copy), nonverbal episodic

memory (Figures—Delayed Recall, Figures—Savings), psychomotor speed (Trail Making Test, part A [TMT-A]), executive functions (Trail Making Test, part B [TMT-B], quotient of TMT-B/TMT-A), phonemic fluency (naming of as many words as possible beginning with a specific letter). (Appendix 1, Supplemental Digital Content 1, contains a detailed description of the tests and of the cognitive domains that were explored, <http://links.lww.com/AA/A943>.) Tests were administered by the same 2 research fellows trained under the supervision of a neuropsychologist. The resulting 15 variables (at baseline and follow-up) were converted into demographically (age, education, and gender) corrected standard scores (z-scores) based on a normative sample of 1100 cognitively healthy individuals²⁶ and subtracted from each other (i.e., z-score at follow-up minus z-score at baseline). If the decline was > 1 standard score in 2 or more of the 15 variables, we considered this meaningful and thus diagnosed POCD.

To compare both SAA and cognitive function on a continuous scale, the CERAD-NAB total score as described by Chandler et al.²⁷ was used to quantify global cognitive performance. This total score is obtained by adding CERAD-NAB subtest scores (excluding MMSE and constructional praxis recall; maximal score = 100) and performing a multiple regression analysis to correct for demographic status (gender, age, and education). The Chandler score has been shown to have an excellent discriminability between patients with mild cognitive impairment and those without cognitive deficits²⁸ and to be applicable to the German version of the CERAD-NAB after adapting the demographic correction to an indigenous normative sample.²⁸

Serum Anticholinergic Activity

The anticholinergic activity assay was performed at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. Blood samples for the determination of SAA were drawn preoperatively and 7 days postoperatively or at hospital discharge but always at the time of cognitive testing. After centrifugation (2000g for 10 minutes), serum was taken and stored at -80°C until further analysis. SAA was measured using a radioreceptor assay first described by Tune and Coyle¹⁹ and commonly applied to determine this variable since then.^{21,29,30} The anticholinergic activity assay quantifies the specific binding of tritiated quinuclidinyl benzilate ($[^3\text{H}]\text{QNB}$; Perkin Elmer, Woodbridge, ON, Canada), a potent muscarinic antagonist with specific affinity for the 5 subtypes of muscarinic receptors, to rat striatum muscarinic receptors in the presence of serum. Anticholinergic substances in the serum sample compete with the radioactively marked QNB for muscarinic receptor binding sites. The receptor- $[^3\text{H}]\text{ligand}$ complexes are then isolated by filtration and counted by scintillation spectrometry (Beckman LS 6000 SC; Beckman Coulter, Brea, CA). The result is standardized by comparing the binding exhibited by the sample to that of a standard solution of atropine (Sigma Aldrich, St. Louis, MO) used as a reference compound by measuring its propensity to displace $^3\text{H}\text{-QNB}$ at various concentrations. It is expressed in atropine equivalents (pmol/mL), that is, the amount of atropine that would be needed to achieve the same displacement of $^3\text{H}\text{-QNB}$ from the muscarinic

receptors in 1 mL of serum without anticholinergic activity. The acceptable assay range is 0.5 to 250 pmol/mL.²⁰ The inter- and intraassay reproducibility has a coefficient of variation of 5.3% to 7.5% and 4.0% to 6.8%, respectively.

Sample Size

Assuming 40% of our patients would develop POCD³ and based on the standard deviation (SD) of SAA in a large group of elderly volunteers of 1.25,²¹ 54 patients (22 with and 32 without POCD) would be needed to be able to detect a difference of 1 pmol/mL between groups (power 80%, type I error 0.05). A 1-pmol/mL change in SAA is a very small increase. The estimated peak concentration reached in vitro after a single dose of 10 mg nortriptyline is 0.8 pmol/mL, and that of a single dose of 20 mg citalopram is 1.2 pmol/mL.²⁰

To compensate for loss to follow-up and a possibly increased SD in our patient population, we increased our sample by one-third to ≥ 72 patients.

Statistical Analysis

Patients were divided into 2 groups according to the presence or absence of POCD. Descriptive statistics were calculated for age, educational level, pre- and postoperative MMSE scores, pre- and postoperative CERAD-NAB raw and total (i.e., demographically corrected) scores, interval of cognitive testing, pre- and postoperative SAA values, and perioperative change in SAA. Because most of the variables were not normally distributed, we chose to express results as medians and interquartile ranges (IQRs). After visual assessment of the distribution of each variable, parametric and nonparametric tests were used as appropriate. Pre- and postoperative SAA values were compared between groups using a Mann-Whitney *U* test. Hodges-Lehmann median differences and corresponding confidence intervals (CIs) were calculated using SSC package in Stata. The method used for calculating the CIs is robust both to non-normality and to unequal variability.³¹ Additionally, an independent-samples *t* test was used to compare the amplitude of

perioperative changes in SAA in patients with and without POCD. The comparison of pre- and postoperative SAA values, independent of the occurrence or absence of POCD and within the 2 groups, was performed using a Wilcoxon signed rank test. Median differences and conservative CIs (binomial exact) were calculated for the within-group comparison. Spearman's rank correlation coefficients and the corresponding 95% CI (based on the Fishers transformation) were calculated to check for a bivariate correlation between the SAA values and CERAD scores pre- and postoperatively, respectively. Because this calculation indicated a poor correlation, we did not perform a regression analysis. Statistical calculations were performed using IBM SPSS v20 (IBM Corp, Zurich, Switzerland) and Intercooled Stata version 13.1 for Macintosh (StataCorp, College Station, TX). *P* < 0.05 (2-tailed) was considered significant.

RESULTS

Among the 79 patients initially included, 9 did not complete all follow-up tests (11.4% dropped out). Six had no postoperative SAA value (sample thawed or lost during transport), 2 withdrew their consent and either did not have a postoperative SAA value or had not performed the postoperative cognitive testing, and 1 patient died. Our analysis is based on the remaining 70 patients, whose characteristics are shown in Table 1.

Of the investigated patients, the 32 (45.7%) who developed POCD were significantly older (77 vs 70 years, *P* = 0.01) and less educated (*P* = 0.047) than patients without POCD. Raw baseline cognitive performance was significantly different (*P* = 0.041). No relevant difference was found between patients with and without POCD regarding gender, duration of anesthesia, or demographically corrected baseline cognitive function. Postoperative testing of the cognitive function was performed after a median of 7 days (IQR = 7, 8) and was comparable in patients with and without POCD (Table 1).

Median pre- and postoperative SAA values and the median perioperative change in SAA for all patients,

Table 1. Patient Characteristics

	All patients	POCD	No POCD	P value (POCD/no POCD)
N	70	32	38	
Age (y)	72 (67, 77)	77 (68, 79)	70 (67, 74)	0.01 ^a
Gender: male/female (n [%])	41/29 (59/41)	20/12 (62/38)	21/17 (55/45)	0.540 ^b
Educational level (y)	12 (11, 14)	12 (9, 13)	12 (11, 14)	0.047 ^a
Duration of anesthesia (min)	258 (198, 316)	258 (202, 331)	251 (188, 311)	0.419 ^a
MMSE preop (points)	28.5 (27, 29)	28 (27, 29)	29 (27, 29)	0.210 ^a
MMSE postop (points)	28 (27, 29)	27.5 (25, 29)	29 (28, 30)	0.004 ^a
CERAD raw ^d score preop (points)	77.5 (69, 85)	73.5 (62, 84)	80 (72, 86)	0.041 ^c
CERAD raw ^d score postop (points)	82 (71, 90)	75 (64, 87)	86 (79, 91)	0.001 ^c
CERAD total ^e score preop (points)	92 (86, 99)	91 (81, 99)	93 (87, 100)	0.379 ^c
CERAD total ^e score postop (points)	96 (89, 104)	93 (85, 101)	99 (93, 105)	0.007 ^c
Postoperative cognitive testing (d)	7 (7, 8)	7 (6, 9)	7 (7, 8)	0.388 ^a

Numeric data are expressed as medians (interquartile range).

POCD = postoperative cognitive dysfunction; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; MMSE = Mini-Mental State Examination; postop = postoperative; preop = preoperative.

^aMann-Whitney *U* test.

^b χ^2 test.

^cIndependent-samples *t* test.

^dNot demographically corrected.

^eDemographically corrected.

patients with POCD, and patients without POCD are summarized in Table 2. We did not find any significant differences regarding SAA preoperatively (median difference 0.12 pmol/mL; 95% CI -0.31, 0.57; $P = 0.556$) or SAA postoperatively (median difference 0.25 pmol/mL; 95% CI -0.26, 0.81; $P = 0.373$) between groups. Regarding changes in SAA in patients with POCD and without POCD, a median difference in SAA of 0.08 pmol/mL (95% CI -0.27, 0.59) and 0.02 pmol/mL (95% CI -0.29, 0.29), respectively, was found and there was no statistically significant difference between the 2 groups (median difference 0.1 pmol/mL; 95% CI -0.31, 0.52; $P = 0.624$). Perioperative changes in SAA (Δ SAA) in patients with and without POCD are illustrated in Figure 1.

In the general comparison in all patients, independent of the presence or absence of POCD, there was no difference between pre- and postoperative SAA ($P = 0.73$). The median change from pre- to postoperative in all patients was 0.02 pmol/mL (95% CI -0.18, 0.17). Little changes in SAA values were found in within-patients comparisons. There were no significant differences between the pre- and postoperative SAA values within the groups (POCD: $P = 0.57$; no POCD: $P = 0.89$).

Postoperative cognitive function based on MMSE, CERAD raw scores, and CERAD total scores was significantly different between the groups. The correlation between SAA and CERAD total score pre- and postoperatively, respectively, was low with a Spearman rank correlation coefficient preoperatively of 0.03 (95% CI -0.21, 0.26) and postoperatively of -0.002 (95% CI -0.24, 0.23). However, our data showed an association between pre- and postoperative SAA values (Spearman rank correlation coefficient 0.58 [95% CI 0.40, 0.72; $P < 0.001$]). Figure 2 shows the CERAD total scores in relation to SAA.

All medications administered during the study are listed in the Appendix 2, Supplemental Digital Content 2 (<http://links.lww.com/AA/A944>). Table 3 shows that few patients received anticholinergic drugs, apart from reversal of neuromuscular blockade. Table 4 lists the drugs most commonly used by study patients and shows that few drugs have anticholinergic activity.

DISCUSSION

We measured SAA preoperatively and 1 week postoperatively concomitant with neuropsychological testing to investigate the potential association between perioperative anticholinergic burden and the occurrence of POCD in elderly patients. No association between SAA and POCD

could be established in this group of patients, neither when a classical binary definition of POCD was used nor when cognitive function was expressed using a continuous score. Postoperative SAA values were similar in both groups, and the 95% CI renders clinically relevant differences implausible.

Our data suggest that the assumption that SAA represents inadequate central anticholinergic activity may be challenged. Drugs that do not cross the blood-brain barrier will contribute to SAA without exerting a central anticholinergic effect and without an impact on cognitive performance. However, the fact that several studies have positively correlated SAA levels with cognitive impairment or delirium supports the SAA assay as a reasonable marker for central anticholinergic activity.²⁹ In a small observational study, Plaschke et al.³² found 2.5-fold higher anticholinergic activity in the cerebrospinal fluid than in blood with a close linear correlation between the two and concluded that SAA adequately reflects the central anticholinergic activity measured by cerebrospinal fluid levels. In contrast, SAA will not be able to detect a dysfunction of cerebral cholinergic transmission, which may occur through mechanisms other than anticholinergic side effects of drugs.

In our group of patients, anticholinergic activity was generally low (SAA values between 0.5 and 5 pmol/mL)²⁰ at both times of measurement and in both groups. Whether this was due to a rising awareness of unwanted side effects of anticholinergics or rather a particularity of our group of patients is unclear. The anesthetics used in our protocol are not highly anticholinergic (atracurium and fentanyl), or their anticholinergic activity is unknown (sevoflurane and thiopental). Furthermore, their kinetics make them unlikely to have an impact 7 days postoperatively. Only 2 patients showed moderate anticholinergic activity (SAA values 5–15 pmol/mL),²⁰ one of whom developed POCD. There was a great variability of SAA in individual patients (Fig. 1). We observed increases and decreases in SAA in patients with and without POCD and marked changes in SAA between the 2 examinations in some patients. We have no robust explanation for the decreasing SAA values postoperatively. There was no relationship to cognitive functions. Mulsant et al.²¹ have shown even low SAA to be associated with cognitive impairment. Subjects with SAA ≥ 2.80 pmol/mL (≥ 90 th percentile in their data) were 13 times more likely to have an MMSE score ≤ 24 (≤ 10 th percentile in their data).²¹ However, the occurrence of POCD in our patients seems to be secondary to other mechanisms. SAA is a transient value, reflecting and following

Table 2. Serum Anticholinergic Activity

	All patients	POCD	No POCD	Median difference (95% CI; POCD/no POCD)	P value (POCD/no POCD)
SAA preop (pmol/mL)	1.13 (0.70, 1.82)	1.14 (0.72, 2.37)	1.13 (0.68, 1.68)	0.12 (-0.31, 0.57)	0.556 ^a
SAA postop (pmol/mL)	1.16 (0.65, 2.39)	1.32 (0.68, 2.59)	0.97 (0.65, 1.83)	0.25 (-0.26, 0.81)	0.373 ^a
Change in SAA periop (pmol/mL)	0.02 (-0.52, 0.51)	0.08 (-0.50, 0.70)	-0.02 (-0.53, 0.41)	0.1 (-0.31, 0.52)	0.624 ^b
Increase in SAA periopyes (%)	35 (50)	17 (49)	18 (51)		0.230 ^c

SAA values expressed as medians (interquartile range).

POCD = postoperative cognitive dysfunction; SAA = serum anticholinergic activity; postop = postoperative; preop = preoperative; periop = perioperative.

^aMann-Whitney U test.

^bIndependent-samples t test.

^c χ^2 test.

Figure 1. Perioperative changes in serum anticholinergic activity (Δ SAA) in patients with and without postoperative cognitive dysfunction (POCD). Most patients have small changes in SAA, and patients with and without POCD show both perioperative decreases and increases in SAA, suggesting that SAA is unlikely to be an important factor in the development of POCD in the majority of these patients.

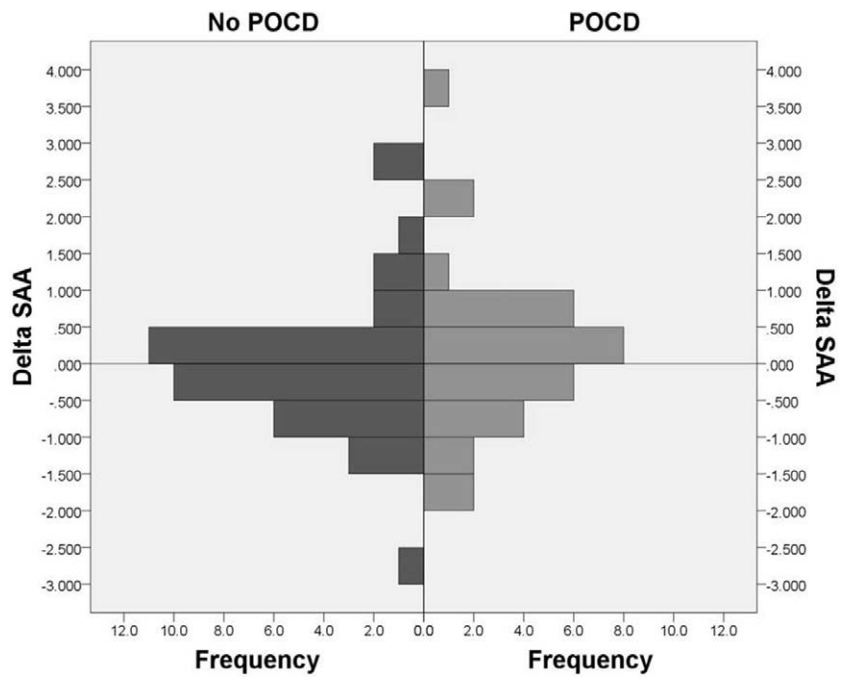


Figure 2. Relationship between serum anticholinergic activity (SAA) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) total score. SAA, CERAD total score: demographically corrected summary measure of cognitive functions on a continuous scale. CERAD total scores are depicted in relation to (A) preoperative SAA and (B) postoperative SAA and (C) changes in SAA (postoperative and preoperative, values >0 denote an increase in SAA) in relation to concomitant changes in CERAD total scores (postoperative and preoperative, values <0 denote a decline in cognitive function). The graphic repartition shows no linear inverse relationship between SAA and CERAD total score, suggesting that there is no association between SAA and CERAD total score, independent of the presence or absence of postoperative cognitive dysfunction (POCD). Furthermore, the test of H_0 demonstrates a high probability that SAA and CERAD total score are independent factors. Spearman rank correlation coefficient: preoperative = 0.03, postoperative = -0.002.

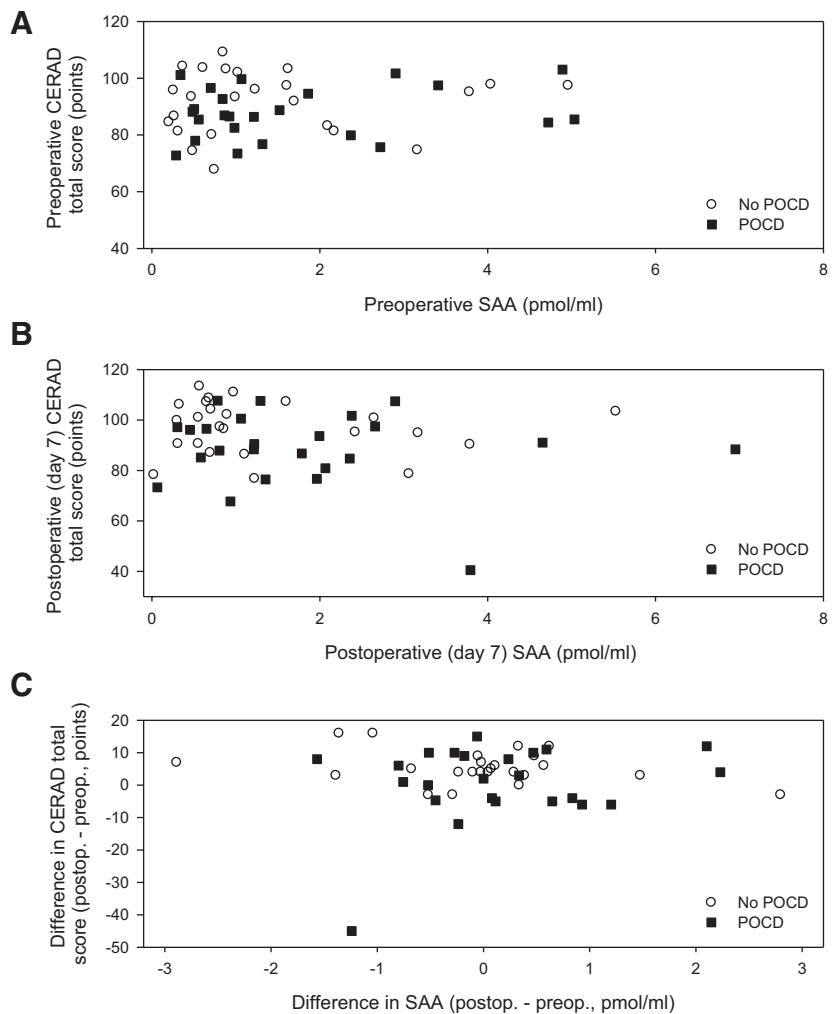


Table 3. Drugs with Anticholinergic Activity (Ranked from High to Low) Used by Participants During the Study

Drugs	Preoperative		Perioperative		Postoperative (day 7)	
	No POCD (N [%])	POCD (N [%])	No POCD (N [%])	POCD (N [%])	No POCD (N [%])	POCD (N [%])
Atropine	0 (0)	0 (0)	1 (2.6)	0 (0)	0 (0)	0 (0)
Robinul/neostigmine	NA	NA	19 (50)	18 (56.2)	NA	NA
Flavoxate	0 (0)	0 (0)	0 (0)	0 (0)	4 (10.5)	1 (3.1)
Ipratropium bromide/tiotropium	2 (5.3)	1 (3.1)	1 (2.6)	1 (3.1)	3 (7.9)	5 (15.6)
Mirtazapine	0 (0)	1 (3.1)	0 (0)	0 (0)	0 (0)	1 (3.1)
Quetiapine	0 (0)	1 (3.1)	0 (0)	0 (0)	0 (0)	2 (6.2)

The number of patients (N) and the proportion (%) related to the total of patients in each group (no POCD = 38, POCD = 32) are reported.
NA = not applicable; POCD = postoperative cognitive dysfunction.

Table 4. Most Commonly Used Medications by Participants (>20%, at One Time or Another [Pre-, Peri-, or Postoperative] During the Study) and Their Anticholinergic Activity

Drugs	Anticholinergic activity	Preoperative		Perioperative		Postoperative (day 7)	
		No POCD (N [%])	POCD (N [%])	No POCD (N [%])	POCD (N [%])	No POCD (N [%])	POCD (N [%])
Protocol drugs							
Thiopental	Unknown	NA	NA	38 (100)	32 (100)	NA	NA
Atracurium	No	NA	NA	38 (100)	31 (96.9)	NA	NA
Fentanyl	Minimal	NA	NA	38 (100)	32 (100)	NA	NA
Sevoflurane	Unknown	NA	NA	38 (100)	32 (100)	NA	NA
Neuromuscular blockade reversal							
Robinul/neostigmine	High	NA	NA	19 (50)	18 (56.2)	NA	NA
Analgesics and antiinflammatory drugs							
Paracetamol	No	2 (5.3)	5 (15.6)	38 (100)	32 (100)	32 (84.2)	24 (75)
Metamizole	Unknown	1 (2.6)	2 (6.2)	34 (89.5)	26 (81.2)	10 (26)	5 (15.6)
Morphine	No	0 (0)	0 (0)	10 (26.3)	8 (25)	1 (2.6)	1 (3.1)
Methadone	Unknown	0 (0)	0 (0)	24 (63.2)	21 (65.6)	0 (0)	0 (0)
Anti-infectives							
Cefuroxime/cefazolin/ceftriaxone	Unknown	1 (2.6)	0 (0)	34 (89.5)	23 (71.9)	1 (2.6)	1 (3.1)
Nervous system							
Benzodiazepines (lorazepam, bromazepam, midazolam, diazepam)	No/minimal	3 (7.9)	5 (15.6)	28 (73.7)	26 (81.2)	4 (10.5)	5 (15.6)
Cardiovascular system/blood							
Antihypertensive drugs							
β-Blockers	No	5 (13.2)	7 (21.9)	7 (18.4)	7 (21.9)	5 (13.2)	7 (21.9)
"Sartans"	No	6 (15.8)	8 (25)	1 (2.6)	2 (6.2)	6 (15.8)	8 (25)
Vasopressors							
Ephedrine	No	0 (0)	0 (0)	24 (63.2)	30 (93.7)	0 (0)	0 (0)
Phenylephrine	No	0 (0)	0 (0)	19 (50)	18 (56.2)	0 (0)	0 (0)
Norepinephrine	No	0 (0)	0 (0)	10 (26.3)	5 (15.6)	0 (0)	0 (0)
Diuretics							
Furosemide/torsemide	Minimal	4 (10.5)	4 (12.5)	2 (5.3)	4 (12.5)	8 (21.1)	6 (18.7)
Hydrochlorothiazide/chlorthalidone	No	8 (21.1)	8 (25)	1 (2.6)	1 (3.1)	7 (18.4)	7 (21.9)
Statins	No	10 (26)	13 (40.6)	1 (2.6)	1 (3.1)	8 (21.1)	11 (34.4)
Acetylsalicylic acid	No	8 (21.1)	3 (9.4)	3 (7.9)	0 (0)	7 (18.4)	3 (9.4)
Heparin	No	7 (18.4)	5 (15.6)	2 (5.3)	2 (6.2)	11 (28.9)	15 (46.9)
Alimentary tract and metabolism							
Proton pump inhibitors (panto-, ome-, and esomeprazole)	No	9 (23.7)	10 (31.2)	6 (15.8)	6 (18.7)	19 (50)	16 (50)
Miscellaneous							
Vitamins and oligoelements (vitamin B, calcium, calcium/vitamin D3, magnesium, KCl, folic acid, thiamine)	No	10 (26.3)	3 (9.4)	2 (5.3)	2 (6.2)	12 (31.6)	5 (15.6)

Anticholinergic activity: no = 0 pmol/mL; minimal = <0.5 pmol/mL; low = 0.5–5 pmol/mL; moderate = 5–15 pmol/mL; high = >15 pmol/mL. The number of patients (N) and the proportion (%) related to the total of patients in each group (no POCD = 38, POCD = 32) are reported.

NA = not applicable; POCD = postoperative cognitive dysfunction.

Adapted from Chew et al.²⁰ and Mintzer and Burns.¹⁴

the pharmacokinetic profiles of the drugs and their metabolites, which collectively contribute to anticholinergic effects. We measured SAA 7 days postoperatively, not necessarily at the time of peak concentration. Conversely, POCD is a phenomenon that can last weeks to months and may even be permanent. It is unknown whether a peak of SAA during the first postoperative week could initiate POCD, which is diagnosed later after SAA has decreased. Our study was not designed to answer this question. However, because performing neuropsychological testing shortly after surgery seems premature,³³ we deliberately chose to measure SAA at a time when relevant information may be gained from concomitant cognitive testing. Even if most studies comparing SAA and cognitive function have found a relationship between an increased level of SAA and cognitive impairment or delirium,^{22,29} some investigations have failed to do so.⁹ Moreover, although the link between SAA and cognitive function is well established, it does not necessarily imply causality.²¹ Also, in many studies, SAA was measured in patients with long-term or regular exposure to anticholinergic medications or suffering from preexisting cognitive impairment.³⁴ This was not the case in our subjects, as marked preexisting impairment of cognitive functions was an exclusion criterion, and 7 days' exposure to anticholinergic drugs may be insufficient to cause cognitive side effects. Furthermore, many other factors in the perioperative setting could be responsible for the development of POCD, for example, the inflammatory response¹ or the stress response.^{35,36}

The serum anticholinergic assay may have some limitations. Cox et al.³⁷ have suggested that this assay may not be an accurate method to quantify SAA because of extensive binding of [³H]QNB to plasma proteins. However, from their brief description, we believe that there were methodological differences. It is not clear whether they allowed the samples to equilibrate to reach a balance between plasma proteins, muscarinic receptors, and unbound drugs. It is also not clear whether they used an atropine standard curve in plasma and whether they filtered the plasma for the standard curve. The CAMH performed an equilibration of the samples and used an atropine standard curve in plasma. The serum anticholinergic assay is based on the amount of [³H]QNB binding to rat brain muscarinic receptors; whether the receptors in human and rodent brains react in the same way is unclear. Moreover, nicotinic receptors are also involved in the cholinergic pathway. They also modulate cognitive function although they are less widely distributed throughout the brain³⁸ and despite the fact that the main cognitive effects are mediated by muscarinic receptors.¹²

Determining the incidence of POCD depends on the numbers and types of cognitive tests, the manner in which they are performed, the definition of how much dysfunction is clinically relevant, the statistical analysis and criteria used for examining change, and the time of postoperative assessment.^{7,39,40} There is no internationally accepted definition for POCD.⁴⁰ Most studies evaluating anticholinergic effects and cognitive impairment used the MMSE to assess the cognitive performance.⁹ This test is neither designed for nor accurate enough to detect POCD. We used the more

precise and more inclusive CERAD-NAB-Plus test battery, which allows the detection of slight changes in cognitive function characteristic of POCD, perhaps explaining our high percentage of patients with POCD compared to some other trials.⁴ A further explanation for the rather frequent incidence of POCD (45.7%) could be the high median age of our patients (72 years), which is similar to that of a group of patients investigated by Monk et al.³ (incidence of POCD 41%, mean age 70 years) but in contrast to the results of the ISPOCD1 study (incidence of POCD 26%, median age 68 years).⁴ There is no consensus regarding the intervals between surgery and postoperative cognitive testing, which is usually chosen for practicality (time of discharge, follow-up visit). Similar to ours, many protocols perform the first postoperative test 7 days postoperatively. This may be criticized and considered early because of the influence of postoperative pain, opioids, or sleep disturbance on cognition. On the other hand, delayed testing increases the risk of overlooking short-term POCD.⁴¹ The lack of a matched control group is a weakness of our study. However, we have a control group of 60 Swiss volunteers who underwent retesting on day 7 (and 90).⁴² The demographic variables and cognitive function at baseline of these volunteers are different from those of our patients (better cognitive function in volunteers). For this reason, we decided to use the methodologically weaker approach of a change from baseline using a demographically corrected baseline based on a large group of volunteers rather than a pure baseline. This approach may have led to an underestimation of the number of patients with POCD. Similar to many other authors, we based our definition of POCD on z-scores. This widely used method determines a certain predefined grade of decline in the cognitive tests but in a binary fashion without considering the severity of the cognitive deterioration. Because SAA is a continuous variable, we used the CERAD total score in addition to a standard definition of POCD to attempt to describe a potential relationship between SAA and cognitive functions and found no association. Defining POCD based on a continuous scale such as the CERAD-NAB total score as an outcome variable and considering the practice effect resulting from the repetition of the neuropsychological testing as described by Burkhart et al.⁴² could be interesting and would be preferable. However, in our opinion, we currently do not have enough data to define POCD based on the CERAD.

CONCLUSIONS

In this group of patients, with low baseline SAA and low anticholinergic burden perioperatively, we were unable to demonstrate an association between POCD and SAA. While a relationship between anticholinergic drug effects and POCD cannot be excluded in some patients, our data suggest that POCD may not be a consequence of anticholinergic medications administered perioperatively but rather due to other mechanisms. Particularly, our methods do not allow for drawing conclusions on the role of an altered central cholinergic transmission because of factors such as changes in transmitter synthesis or apoptosis of cholinergic neurons. ■■

DISCLOSURES

Name: Ariane Rossi, MD.

Contribution: This author helped conduct the study, analyze the data, and write the manuscript.

Attestation: Ariane Rossi has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Christoph Burkhart, MD.

Contribution: This author helped design the study and conduct the study.

Attestation: Christoph Burkhart has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Salome Dell-Kuster, MD, MSc.

Contribution: This author helped design the study, analyze the data, and write the manuscript.

Attestation: Salome Dell-Kuster has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Bruce G. Pollock, MD, PhD.

Contribution: This author helped design the study and analyze the data.

Attestation: Bruce G. Pollock has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Stephan P. Strebel, MD.

Contribution: This author helped design the study and analyze the data.

Attestation: Stephan P. Strebel has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Andreas U. Monsch, PhD.

Contribution: This author helped design the study and analyze the data.

Attestation: Andreas U. Monsch has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Christian Kern, MD.

Contribution: This author helped conduct the study and write the manuscript.

Attestation: Christian Kern has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

Name: Luzius A. Steiner, MD, PhD.

Contribution: This author helped design the study, conduct the study, and analyze the data.

Attestation: Luzius A. Steiner has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

This manuscript was handled by: Gregory J. Crosby, MD.

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