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REPORTS OF ORIGINAL INVESTIGATIONS

Sensitivity to volatile anesthetics in patients with dementia: a case-control analysis

Sensibilité aux anesthésiques volatils chez des patients atteints de démence: une analyse cas-témoin

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Abstract

Background *Patients with dementia are thought to be more sensitive to anesthesia, although volatile anesthetic requirement has not specifically been evaluated in this population. We tested the hypothesis that patients with dementia having non-cardiac surgery have a lower ratio of bispectral index (BIS) to minimal alveolar concentration (MAC) during the five minutes immediately preceding incision, thus exhibiting deeper hypnotic levels at a given MAC fraction.*

Methods *We obtained records from our database registry on patients who had volatile general anesthesia during their most recent operation. We excluded patients premedicated with midazolam. Patients with dementia were identified and their diagnosis was confirmed by chart review. Each patient with dementia was successfully matched with a maximum of five patients without dementia using a multivariate nearest-neighbor distance-matching algorithm restricted to the following criteria: American Society of Anesthesiologists physical status, age, five-minute pre-incision time-weighted average (TWA) estimated effect-site concentration of propofol and fentanyl, and use of remifentanil. Our primary outcome was the TWA BIS-to-MAC ratio during the five minutes immediately preceding incision.*

Results *We analyzed 31 patients with dementia matched with 151 patients without dementia. Median [quartiles] TWA BIS-to-MAC ratios for the matched patients were 85 [73, 100] for the patients with dementia and 78 [73, 84] for the patients without dementia. The percent difference in mean BIS-to-MAC ratios between patients with dementia and patients without dementia was 9% (95% confidence interval: −9% to 29%) ($P = 0.35$, Wald test).*

Conclusions *Our results do not support the hypothesis that patients with dementia are more sensitive to volatile anesthetics than patients without dementia.*

Résumé

Contexte *On estime que les patients atteints de démence sont plus sensibles à l'anesthésie, alors que le besoin en anesthésiques volatils n'a pas été spécifiquement évalué dans cette population. Nous avons testé l'hypothèse selon laquelle les patients atteints de démence subissant une*

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chirurgie non cardiaque auraient un plus bas rapport d'indice bispectral (BIS) à la concentration alvéolaire minimum (MAC) au cours des cinq minutes précédant immédiatement l'incision, présentant ainsi des niveaux hypnotiques plus profonds pour une fraction MAC donnée.

Méthodes *Nous avons obtenu des enregistrements de notre registre de données sur des patients ayant eu une anesthésie générale par des agents volatils au cours de leur plus récente intervention chirurgicale. Nous avons exclu les patients prémédiqués par midazolam. Les patients atteints de démence ont été identifiés et leur diagnostic a été confirmé par l'analyse des dossiers. Chaque patient atteint de démence a été apparié avec succès avec un maximum de cinq patients ne souffrant pas de démence, à l'aide d'un algorithme multifactoriel d'appariements des distances au voisin le plus proche, restreint aux critères suivants: statut physique selon l'American Society of Anesthesiologists, âge, effet estimé/concentration au site moyenne pondérée en fonction du temps (TWA) cinq minutes avant incision pour le propofol et le fentanyl, et utilisation de rémifentanil. Notre critère d'évaluation principal était le rapport TWA BIS sur MAC au cours des cinq minutes précédant immédiatement l'incision.*

Résultats *Nous avons analysé 31 patients atteints de démence appariés à 151 patients indemnes de démence. Les ratios TWA BIS sur MAC médians [quartiles] pour les patients appariés ont été 85 [73, 100] pour les patients atteints de démence et 78 [73, 84] pour les patients sans démence. La différence en pourcentage des ratios BIS sur MAC moyens entre les patients atteints de démence et les patients sans démence a été de 9% (intervalle de confiance à 95%: −9% à 29%) (P = 0.35, test de Wald).*

Conclusions *Nos résultats ne confortent pas l'hypothèse selon laquelle les patients atteints de démence sont plus sensibles aux anesthésiques volatils que les patients indemnes de démence.*

Life expectancy in the United States has progressively improved; consequently, the proportion of geriatric patients needing surgery is increasing.[1] Anesthesiologists are thus faced with an increasing number of patients with dementia because age is a well-established risk factor for neurodegenerative diseases.[2,3] Dementia has been preliminarily associated with postoperative complications, and providing anesthesia to this population imposes an important challenge to anesthesiologists.[4]

Patients with dementia are thought to be more sensitive to anesthesia. Although anesthetic requirement has not specifically been evaluated in this population, there are some published opinions suggesting that the dose of volatile anesthetics be reduced in patients with dementia.[5,6] Sensitivity to volatile anesthetics is important because both excessive anesthesia[7] and anesthetic sensitivity[8] are associated with postoperative mortality.[9]

Accordingly, our goal was to compare volatile anesthetic sensitivity in patients with and without dementia. Specifically, we tested the hypothesis that patients with dementia having non-cardiac surgery have a lower ratio of bispectral index (BIS) to minimal alveolar concentration (MAC) and exhibit deeper hypnotic levels at a given MAC fraction during the five minutes immediately preceding incision.

Methods

We conducted a case-control study with approval from the Cleveland Clinic Foundation Institutional Review Board (IRB) (July 31, 2011). The IRB waived the requirement for informed consent.

Data sources

We obtained records on 77,238 patients who had elective non-cardiac surgery at the Cleveland Clinic Main Campus during January 6, 2005 to September 30, 2010. Prospectively collected data were obtained from the Perioperative Health Documentation System (PHDS) registry. The PHDS contains the entire electronic anesthesia record along with International Classification of Disease (ICD-9) codes, mortality, and a host of other electronic data about every surgical patient at the Cleveland Clinic's Main Campus. We included adults with American Society of Anesthesiologists (ASA) physical status I-III who had volatile general anesthesia during their most recent operations.

We excluded patients premedicated with midazolam because the elderly are intrinsically sensitive to benzodiazepine's sedative effect and can display paradoxical responses.[10] We also excluded patients in whom a full five minutes of anesthetic data immediately preceding incision were unavailable, including minute-to-minute BIS XP™ (A-2000, version 3.21, single disposable 4-Electrode Sensor, Covidien, Dublin, Ireland).

Initially, we used the ICD-9 Clinical Modification (ICD-9-CM) diagnosis codes to identify and match patients with dementia with control patients without dementia. The ICD codes have been validated to identify a diagnosis of dementia with a specificity of 84-85%, a sensitivity of 69%, and a positive predictive value of 81% in a single-center study.[11] In an additional recent systematic review,

an overall specificity of 85% was found for ICD diagnoses of dementia/Alzheimer disease.[12]

We used patients' electronic medical records as well as the Knowledge Project Center for Brain Health database at the Cleveland Clinic Foundation. The Knowledge Project Center has developed an information technology program which is integrated with the electronic medical record to combine data entered by both patient and physician.[13] The diagnosis was based on previous formal testing by neurology staff and classified as Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and senile dementia.[14] Patients whose dementia status could not be confirmed by manual chart review were removed from analysis along with their five matched controls. We similarly deleted any matched control patient from the analysis when manual chart review revealed a clinical diagnosis of dementia.

Our primary outcome was the time-weighted average (TWA) BIS-to-MAC ratio during the five minutes immediately preceding incision. Time-weighted averages are similar to ordinary averages apart from accounting for potential gaps between measurements (specifically, by interpolating observed data pairs and integrating the interpolated profiles). The two are equivalent if measurements are made at equally-spaced time intervals, as was virtually always the case in our electronic records.

Bispectral index was selected as our indicator of anesthetic requirement because it is the best-validated monitor of hypnosis during general anesthesia.[15] We evaluated the five minutes just before skin incision because this period of time is usually stable and avoids the confounding effect of surgical stimulation on the electroencephalogram.[16] Scatterplots and histograms were used to visualize distributions of TWA BIS, TWA MAC, and TWA BIS-to-MAC ratio.

Secondary outcomes were TWA BIS, proportion of the five-minute pre-incision window with BIS < 45, and proportion of the five-minute pre-incision window with hypotension (defined as mean arterial pressure < 60 mmHg). Minimal alveolar concentration-equivalent doses were calculated from end-tidal volatile anesthetic partial pressures using a 1 MAC-equivalent concentration of desflurane (6.6%), sevoflurane (1.8%), and isoflurane (1.17%).[17] Concentrations of plasma fentanyl as well as plasma propofol were estimated using Schneider's pharmacokinetic model.[18]

We matched each patient with dementia with a maximum of five patients without dementia using a multivariate nearest-neighbor distance-matching algorithm. Data were randomly sorted before matching to remove any biases attributable to the ordering of observations (e.g., due to date of surgery). Successful matches were restricted to those with common ASA physical status scores, those with common remifentanil use (yes or no) during the five minutes preceding incision, and those within one standard deviation of each other according to the following factors (removing control patients whose values lied outside the observed range for the patients with dementia): age, five-minute pre-incision TWA estimated effect-site concentration of fentanyl, and five-minute pre-incision TWA estimated effect-site concentration of propofol. The standard deviations among the patients available for matching were 16.2 yr, 0.3 and 0.3 $ng \cdot mL^{-1}$, respectively.

Linear mixed-effect regression modelling was used to compare the matched patients on the pre-incision TWA BIS-to-MAC ratio.[19] This model accounts for the grouped nature of the matched sample by assuming that outcomes among patients within a matched group are correlated (and outcomes among patients in differing matched groups are independent). We used the compound symmetric correlation structure in our mixed-effect model. A logarithmic transformation for the outcome was used prior to modelling in order to model percent differences in medians between groups (technically, percent differences in geometric means under an assumed log-normal distribution for the outcome) and to normalize model errors. We adjusted for any of the above patient- and anesthesia-related factors which exhibited imbalance between patients with and without dementia after matching (Table 1).

We similarly modelled the secondary outcome, mean pre-incision BIS. The percentage of pre-incision minutes with BIS < 45, MAP < 60 mmHg, and systolic blood pressure < 90 mmHg were modelled using a generalized linear mixed model with a quasibinomial link function.[20] The offset term in these models was the number of observations recorded within the five-minute pre-incision window.

Wald tests were used to assess statistical significance of all model parameters for the primary and secondary hypotheses. The type I error rate was set at 0.05 for both the primary and secondary outcomes, and we used the Bonferroni correction to account for three simultaneous tests for the secondary outcomes (specifically, we used nominally-adjusted confidence levels for the confidence intervals and nominally-adjusted significance criteria for tests).[21] R statistical software version 2.14.1 (The R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis.

Power considerations

Our study was retrospective in nature. As such, sample size was fixed (but unknown). In anticipation of analyzing data on 30 patients with dementia and 90 matched controls, we

Table 1 Summary of patient- and anesthesia-related characteristics among patients with and without dementia meeting study inclusion/exclusion criteria before and after matching

Factor	Patients Meeting Inclusion/Exclusion Criteria			Matched Patients*		
	Patients without Dementia ($n = 3{,}778$)	*Patients with Dementia* ($n = 32$)	*ASD*	*Patients without Dementia* ($n = 151$)	*Patients with Dementia* ($n = 31$)	*ASD*
Age (yr), mean (SD)	64 (17)	80 (7)	10.19	79 (7)	80 (7)	0.10
ASA Physical Status (%)						
I	2	0	00.49	0	0	0.01
II	33	15		17	16	
III	65	85		83	84	
Five-minute pre-incision TWA propofol concentration (mg), median [quartiles]	0.21 [0.11, 0.37]	0.13 [0.08, 0.24]	00.40	0.16 [0.07, 0.28]	0.13 [0.08, 0.21]	0.23
Five-minute pre-incision TWA fentanyl concentration (μg), median [quartiles]	0.5 [0.3, 0.7]	0.4 [0.3, 0.6]	00.26	0.4 [0.4, 0.6]	0.4 [0.3, 0.6]	0.03
Remifentanil used during five-minute pre-incision window (%)	4	3	00.07	3	3	0.00

Absolute standardized difference (ASD) scores, defined as the difference in means, mean rankings, or proportions divided by a pooled estimate of standard deviation, are presented. Absolute standardized difference values greater than 0.10 were considered as indicative of imbalance between groups; we adjusted for any of the displayed variables exhibiting an ASD > 0.10 after matching in all comparisons of primary and secondary outcomes

*One patient initially coded as having dementia was actually not demented. This patient and the corresponding five control patients were removed from the matched sample. Similarly, we removed four matched patients without an ICD-9-CM code for dementia who proved to have a diagnosis of dementia

ASA = American Society of Anesthesiologists; SD = standard deviation; TWA = time-weighted average

conducted a power analysis prior to data collection in order to identify the minimal effect size (ratio of median TWA BIS-to-MAC ratios between patients with and without dementia) for which we had 90% power to detect. This power analysis was performed using PASS software version 11 (NCSS, LLC, Kaysville, UT, USA).

For this analysis, we assumed a coefficient of variation of 1.0 for the primary outcome (based on the observed variability in BIS-to-MAC ratio in the PHDS registry), a lognormal distribution for the outcome, and a type I error rate of 5%. Under this setup, we anticipated approximately 90% power to detect a ratio of median TWA BIS-to-MAC ratios between patients with and without dementia of ≥ 1.78 (i.e., 78% larger BIS-to-MAC ratio in patients with dementia).

Results

Among the 77,238 records extracted from the PHDS database, 20,821 (27.0%) received general anesthesia with sevoflurane or isoflurane. Of these, 16,878 (81.1%) receiving midazolam were removed, and 133 (0.8%) of the remaining 3,943 patients had unavailable anesthetic data within the five minutes immediately preceding incision. Thus, data on 3,810 patients (32 with an ICD-9-CM code for dementia and 3,778 without) were available for matching. All 32 patients with an ICD-9-CM code for dementia were successfully matched to five patients without such a code.

Upon reviewing the charts and the Knowledge Project database, we found that one patient initially coded as having dementia was actually not demented; consequently, this patient and the corresponding five control patients were removed from the matched sample. Similarly, we removed four matched patients without an ICD-9-CM code for dementia who proved to have a diagnosis of dementia. To protect against hidden bias, these patients were not included in the dementia group as they did not meet the pre-specified criteria for study inclusion. Our final matched sample thus included 31 patients with dementia and 151 patients without dementia. Among the 31 matched patients with dementia, 26 (84%) had Alzheimer's disease, 2 (6.5%) had dementia with Lewy bodies, 2 (6.5%) had vascular dementia, and 1 (3.2%) had senile dementia.

Median [quartiles] times from induction to incision were 34 [26, 47] min for patients without dementia and 35 [29, 46] min for patients with dementia. All patients received a non-depolarizing muscle relaxant for tracheal intubation and their lungs were mechanically ventilated.

Median [quartiles] TWA BIS absolute values for the matched patients during the five minutes immediately preceding incision were 46.0 [41.6, 53.1] for the patients without dementia and 46.6 [38.6, 55.2] for the patients with

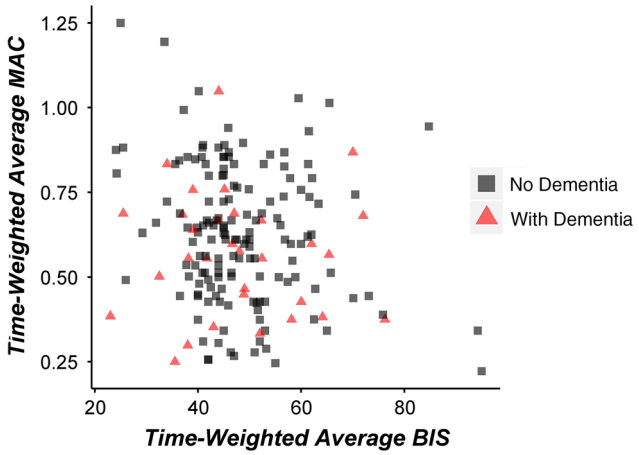

Fig. 1 Scatterplot of time-weighted average minimum alveolar concentration (MAC) *vs* time-weighted average bispectral index (BIS) during the five minutes immediately preceding incision. Patients with dementia are represented as triangles and matched control patients are represented as squares

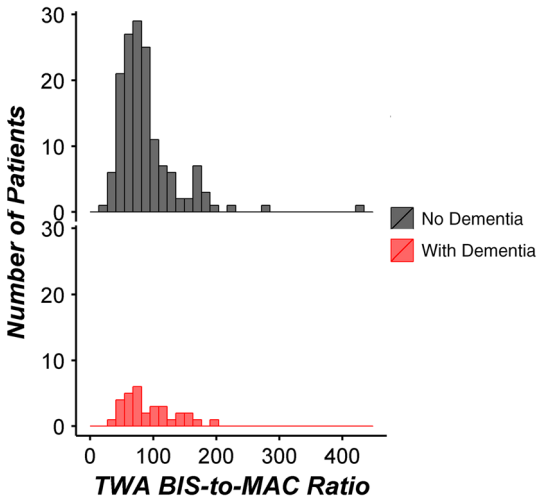

Fig. 2 Histogram of the ratio of time-weighted average bispectral index (BIS) to time-weighted average minimum alveolar concentration (MAC), separately for patients with dementia and matched control patients

dementia. The TWA MAC absolute values at the same time frame were 0.62 [0.49, 0.79] for the patients without dementia and 0.57 [0.41, 0.68] for the patients with dementia (Fig. 1). The TWA BIS-to-MAC ratios were 75 [61, 99] for the patients without dementia and 78 [62, 116] for the patients with dementia (Fig. 2).

The percent difference [95% confidence interval (CI)] in median BIS-to-MAC ratios between patients with dementia and patients without dementia was 9% (95% CI: −9 to 29), which was not statistically significant ($P = 0.38$, Wald test). This univariable result did not control for age and five-minute pre-incision propofol concentration, which continued to show slight imbalance after matching (Table 1). Adjusting for these factors, the estimates were largely unchanged (difference, 9%; 95% CI: −9 to 29; $P = 0.35$).

Secondary outcomes did not differ significantly between patients with dementia and matched patients without dementia. Table 2 summarizes adjusted means for each group and the comparison between groups for all outcomes.

Discussion

By virtue of our multivariate distance matching procedure, our patients with dementia and patients without dementia were well matched on potential confounding factors and anesthetic management. Our results showed a small and non-significant increase in BIS-to-MAC ratio in patients with dementia. We therefore conclude that patients with and without dementia are similarly sensitive to volatile anesthetics. This result is surprising given the widespread view that dementia increases sensitivity to anesthesia.[5,22,23] On the other hand, the result is consistent with recent work showing comparable intravenous anesthesia requirements in patients with cognitive impairment.[24] In contrast, there are two studies showing that a murine model displaying histopathologic and clinical features of Alzheimer's disease has an increased resistance to inhalational anesthetics when compared with their wild-type age-matched controls.[25,26]

The classical definition of inhaled anesthetic potency is MAC (the alveolar concentration needed to prevent movement in 50% of subjects in response to skin incision).[27,28] Minimum alveolar concentration immobility is primarily a spinal reflex and would not be expected to change much with dementia.[29-32] When anesthetic agents are delivered preferentially to the brain excluding spinal cord perfusion, it has been found that MAC immobility increases, emphasizing the critical role of the spinal cord as a target of the inhalational anesthetic action and primary site of motor response to noxious stimuli under general anesthesia.[33] One of the advantages of MAC is its small inter-individual variance. We did not use age-adjusted MAC (MAC years) because the patients were about the same age in both groups. The same linear adjustment would apply to both groups, which would not alter the relative difference or statistical significance.

Bispectral index is a near-instantaneous measure of cortical function.[34] Although BIS is the best-established measure of hypnotic depth,[15,35,36] it is surely imperfect,[9] mainly due to its intrinsic variability. A recent publication proposed a composite variability index comprising BIS and electromyography variability to predict the occurrence of

Table 2 Results of primary and secondary comparisons between matched patients with and without dementia (denoted by *'D'* and *'ND'*, respectively)

	Adjusted Mean (95% CI)		Comparison (*D vs ND*)	Estimate (95% CI)	*P* value
	Patients without Dementia (ND) ($n = 151$)	*Patients with Dementia (D)* ($n = 31$)			
Primary Outcome:					
TWA BIS-to-MAC Ratio	78 (73 to 84)	85 (73 to 100)	% Difference in Means (95% CI)	9% (−9 to 29)	0.35
Secondary Outcomes:					
TWA BIS	48 (46 to 51)	48 (43 to 53)	Difference in Means (95% CI)	−0.28 (−5.72 to 5.17)	0.90
Proportion of five-minute pre-incision window with BIS < 45	0.41 (0.33 to 0.50)	0.41 (0.24 to 0.60)	Odds Ratio (95% CI)	0.97 (0.41 to 2.32)	0.94
Proportion of five-minute pre-incision window with hypotension (*)	0.15 (0.10 to 0.21)	0.20 (0.09, 0.37)	Odds Ratio (95% CI)	1.42 (0.52 to 3.88)	0.41

All results adjusted for age and five-minute pre-incision time-weighted average propofol concentration

(*) Hypotension was defined as SBP < 90 mmHg or MAP < 60 mmHg

BIS = bispectral index; CI = confidence interval; MAC = minimal alveolar concentration; MAP = mean arterial pressure; SBP = systolic blood pressure; TWA = time-weighted average

somatic events during general anesthesia. This index was found to predict the occurrence of somatic events and to be more reliable with respect to the variability of the mean heart rate and blood pressure.[37] Patients with dementia in the awake state show a significantly lower baseline BIS value on average than age-matched controls.[24,38] Whether it is accompanied by a comparable reduction in BIS during inhalational anesthesia and surgery remains unanswered. Anesthesiologists should, as always, titrate volatile anesthesia based on individual responses; but our data suggest that patients with dementia will not have a lesser requirement than other patients.

We excluded patients who received midazolam for induction of anesthesia because the elderly are intrinsically sensitive to benzodiazepine's sedative effect and can display a paradoxical effect.[10] Furthermore, benzodiazepines reduce MAC, which would have compromised our primary outcome.[39,40] Eliminating patients given midazolam markedly reduced the number of patients with dementia available for analysis; however, it presumably improved the reliability of our estimates of the true physiologic effect of dementia on anesthetic requirement. Anesthesia was induced with propofol in virtually all cases. The estimated propofol plasma concentrations at the time anesthetic sensitivity was assessed were similar in the patients with and without dementia and low, i.e., $\approx 0.15\ \mu g \cdot mL^{-1}$, which is less than a tenth of the effective dose of 50% for loss of consciousness (CP_{50}).[41,42] Estimated fentanyl plasma concentrations were also similar and low. Fentanyl reduces MAC by 59% at a plasma concentration of $3\ ng \cdot mL^{-1}$, which is ten times the calculated concentration in our population ($\approx 0.4\ ng \cdot mL^{-1}$).[43] Based on the estimated plasma concentrations, neither drug is likely to have had any substantial effect on MAC.

Our analysis was restricted to the five-minute period just before incision to eliminate the likely influence of the surgical stimulation on BIS. For example, studies reported nociceptive stimuli to have a wide variety of effects on brain electrical activity, either increasing[44] or decreasing alpha frequency.[45] Specifically, the effect of skin incision on the BIS during general anesthesia is an overall tendency for it to become more continuous with significant loss of episodic activity. The changes in BIS after surgical incision depend on the anesthetic technique, with less correlation when opioid analgesics are given.[46] But even moderately deep anesthesia does not consistently obtund BIS response.[16]

The major limitation of our study is that we only had power to identify a relatively large difference of 78% or more in the BIS-to-MAC ratio. Even so, there was not even a trend towards reduced anesthetic sensitivity in the patients with dementia. Low power resulted from the small number of patients with dementia that we were able to identify after applying strict exclusion criteria. Another limitation of this study was using the ICD-9 code for dementia and subsequent chart review as a way to identify the most severe cases of dementia. There may be difficulty in completely uncoupling the relationship between increasing age and cognitive dysfunction in older patients due to the strong correlation that exists between them. Nevertheless, by taking only patients with a formal diagnosis of dementia in the medical record, we were able to identify the patients who had more severe symptoms of dementia. The possibility of undiagnosed

dementia in the controls could not be completely excluded, but these cases were probably mild as they had not yet been clinically diagnosed. Our sample was optimized to collect only the most severe cases of dementia and controls where the likelihood of dementia was low and, if present, mild in severity.

The relatively low proportion of patients with dementia from our database also deserves comment. There are several likely explanations for this finding. Probably the most important is selecting patients without dementia to be eligible for surgery. A second possibility is the presence of undiagnosed patients with mild dementia in the control group. Although this is possible, all elderly patients scheduled for surgery at our institution have a rigorous preoperative evaluation by both internal medicine and anesthesiology. If patients were erroneously identified as not having dementia based on the initial PHDS documentation, it is likely that these patients had mild dementia at most. A subsequent chart review of the detailed medical record failed to disclose a diagnosis of dementia in the control group. A consequence is that prevalence of dementia in our database should not be estimated from our sample.

In summary, our results do not support the hypothesis that patients with dementia are more sensitive to volatile anesthetics than patients without dementia during maintenance of anesthesia. Volatile anesthetics do not appear to be appreciably different based on the limits of the 95% CI for the ratio of means.

Competing interests None declared.

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