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Authors

Kinjo, Sakura
Lim, Eunjung
Magsaysay, Maria Victoria
et al.

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Volatile Anaesthetics and Postoperative Delirium in Older Surgical Patients – A Secondary Analysis of Prospective Cohort Studies

Sakura Kinjo[1] **[Clinical Professor]**, **Eunjung Lim**[2] **[Assistant Professor]**, **Maria Victoria Magsaysay**[3] **[Research Associate]**, **Laura P. Sands**[4] **[Professor]**, **Jacqueline M. Leung**[5] **[Professor]**, and **the Perioperative Medicine Research Group**[*]

[1]Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California, United States of America

[2]Biostatistics Core Facility, Department of Complementary & Integrative Medicine, John A Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, United States of America

[3]Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California, United States of America

[4]Human Development Center for Gerontology, Virginia Polytechnic Institute and State University, Blacksburg, Indiana, United States of America

[5]Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California, United States of America

Abstract

BACKGROUND: Volatile Anaesthetics (VAs) may be associated with postoperative delirium (POD). However, to date, the effects of VAs on POD are not completely understood. The objective of this study was to investigate the incidence of POD in different VA groups.

METHODS: A secondary analysis was conducted using a database created from prospective cohort studies in patients who underwent elective major non-cardiac surgery. Patients who received general anaesthesia with desflurane, isoflurane or sevoflurane were included in the study. POD occurring on either of the first two postoperative days was measured using the Confusion Assessment Method.

[*]Members of the Perioperative Medicine Research Group are listed in Appendix 1.

Corresponding Author Sakura Kinjo, MD, Address: 521 Parnassus Avenue, Box 0648, San Francisco, CA 94143, U.S.A., Tel: 415-514-4346, Fax: 415-514-2999, Sakura.Kinjo@ucsf.edu.

Conflict of Interest: None.

Editorial Comment

Volatile anesthetics may influence postoperative cognitive function. In this observational study, based on a secondary analysis of 2 earlier studies of delirium in the early post-operative period, associations for post-op delirium and 3 different volatile anesthetics were assessed, along with many other factors which might influence risk for post-operative delirium.

Presentation: Preliminary data for this study were presented as an oral presentation at the American Society of Anesthesiologists (ASA) Annual Meeting, 11–15 October 2014, New Orleans, LA.

RESULTS: Five hundred and thirty two patients were included in this study, with a mean age of 73.5 ± 6.0 years (range, 65–96 years). The overall incidence of POD on either postoperative day 1 or 2 was 41%. A higher incidence of POD was noted in the desflurane group compared with the isoflurane group (Odds Ratio=3.35, 95% CI=1.54–7.28). The incidence of POD between the sevoflurane and isoflurane or desflurane group were not statistically significant.

CONCLUSION: Each VA may have different effects on postoperative cognition. Further studies using a prospective randomized approach will be necessary to discern whether anaesthetic type or management affects the occurrence of postoperative delirium.

INTRODUCTION

Postoperative delirium (POD) is defined as an acute confusional state with altered attention and consciousness after surgery. The reported incidence of POD varies from 10% to 65% of older surgical patients after major surgery, depending upon clinical setting and type of surgery.[1–4] Recently, the incidence of POD seems to be declining. The recent meta-analysis on patients who underwent major surgeries including orthopaedic, vascular or abdominal surgeries showed that the incidence of POD was 23.9%.[5] A meta-analysis on total joint replacement patients reported that the incidence of POD was 17%.[6] The possible reasons for this declining incidence of POD may be due to improved patient care such as proactive geriatric consultation program [7]or fast track approach. However, POD is still a common complication after major surgery in older patients. It is associated with increased mortality and morbidity, greater medical expenses, prolonged hospital stays and poor functional outcomes.[8–10] POD is considered a geriatric syndrome. Although the aetiology of POD is not well understood, multiple risk factors for POD have been proposed in previous studies. [1–3] Prior investigations of delirium have focused on risk identification or prophylactic therapy in preventing its occurrence.[11–13] Studies that investigated risks have identified factors that generally cannot be modified readily in the surgical setting such as older age, dementia, gender, or depressive symptoms and etc.[14] Similarly, prophylactic therapies involving pharmacologic agents have not produced definitive results.[14–1617] There is some evidence that the use of a fast-track approach which included multi-modal analgesia (e.g., acetaminophen, non-steroidal anti-inflammatory drugs, gabapentin) in patients undergoing arthroplasty significantly reduces or even eliminates the occurrence of POD[18, 1920] but proper controls were lacking in these studies.

Recently, it has been proposed that deep anaesthetic depth contributes to an increased rate of POD and postoperative cognitive dysfunction.[212223] In fact, some in the anaesthesia field proposed that older patients should be monitored with a processed encephalogram (EEG) to estimate anaesthetic depth. The assumption is that reducing reduction in the amount of anaesthetic will lead to a decrease in the incidence of postoperative delirium. However, this hypothesis is unproven. Furthermore, whether volatile anaesthetics (VAs) by themselves affect delirium risk is also uncertain. To date, only a few clinical studies have investigated the effect of VAs on postoperative cognitive outcomes with no conclusive findings.[24–26] Given the ambiguous results generated thus far, we conducted a secondary data analysis to examine the effect of VAs on POD using a database created for prospective cohort studies in patients examining the pathophysiology of POD in older surgical patients. The aim of the

present study is to compare the incidence of POD in different VA groups. We hypothesize that no particular VA will increase the risk of POD compared with other VAs.

METHODS

The present study is a secondary data analysis of two prospective studies conducted from 2001–2012 at the University of California, San Francisco Medical Center. These clinical studies were approved by the Institutional Review Board (IRB) of the University of California, San Francisco (Study 1: Trial of General Anaesthesia With or Without Nitrous Oxide-Long Term Follow up: IRB number: 10-04658, Study 2: Postoperative Cognitive Function in Elderly Surgical Patients: IRB number: 10-02710).

Written informed consent was obtained preoperatively from each patient. In both studies, the inclusion criteria were 65 years or older, fluent in English, undergoing elective major non-cardiac surgery with an anticipated stay in the hospital of at least 2 days. Patients who were not able to speak English, had brain surgery, or not able to provide a written informed consent were excluded.

Patients who received one of three types of VA: desflurane, isoflurane or sevoflurane as their primary anaesthetic, were included in the analysis. Patients who received more than one VA or patients who did not receive any VA were excluded from this report. In addition, patients kept intubated after their surgeries were excluded. The choice of VA or perioperative care was not controlled. Electroencephalogram (EEG) and/or brain function monitoring were not used in these patients.

Preoperative Assessment

The preoperative interview was conducted by a trained research assistant in the preoperative anaesthesia clinic, typically less than 2 weeks prior to surgery. The patient's health information and any potential covariates associated with cognition, including age, gender, race, level of education, history of central nervous system (CNS) disorders, daily alcohol consumption, ASA physical status, the use of preoperative opioids and benzodiazepine, baseline pain level, preoperative depressive symptoms, history of CNS disorders (delirium, seizure, dementia and other disorders) were obtained. Baseline cognitive status was assessed in person or over the phone preoperatively using the Telephone Interview for Cognitive Status (TICS).[27] TICS is widely used for screening of dementia and correlates well with the Mini-Mental State Examination (MMSE). It consists of 11 tests (maximum 41 points), and subjects with scores below 30 are considered to be cognitively impaired.[8]

Pain level was assessed using the 11-point numeric rating scales (NRS).[28] Preoperative symptoms of depression were measured using the 15-item Geriatric Depression Scale (GDS).[29] The score on the GDS reflects the total number of depressive symptoms reported by the patient. A score of 6 and above suggests depression.

Intraoperative Data

The type of surgery, duration of surgery, dose of opioids, the use of anaesthetic agents and regional anaesthesia techniques (spinal, epidural and peripheral nerve block) were noted. In

addition, surgical risk was determined for each patient based on the perioperative cardiovascular evaluation guidelines from the American College of Cardiology and American Heart Association, which takes into consideration of type and duration of surgery and intraoperative blood loss.[30] Surgical risk was divided into three levels (low, intermediate, and high) and the definition of surgical risk level is provided in Appendix 2. Intraoperative opioid doses were calculated into hydromorphone equivalent using the conversion formulae: 5 mg of morphine sulphate = 1 mg of hydromorphone, 50 mcg of fentanyl = 1 mg of hydromorphone.[31] Age-adjusted Minimum Alveolar Concentration (Aa-MAC)[32] was calculated for each case using the formula provided in Appendix 3.

Postoperative Assessment

Postoperative interviews were conducted in the patient's hospital room by the same research assistant for the first 2 postoperative days. The Confusion Assessment Method (CAM) Rating Scale[33] was used to assess POD. The CAM is a reliable and convenient tool for making a diagnosis of delirium and has high sensitivity (94–100%) and high specificity (90–95%).[33] The research assistants were trained to use CAM by one of the investigators (L.P.S) until they reached a high level of consistency in their assessments. All assessments of POD were validated by the investigator (L.P.S).

Other potential variables expected to be associated with POD such as postoperative pain levels and dose of opioids were also assessed.

Statistical Analysis

To investigate the association between patient or clinical characteristics and VAs, Chi-square tests or Fisher's exact test were used for categorical variables depending on the sample size in each category. For continuous variables, One-way Analysis of Variances (ANOVAs) or Kruskal-Wallis nonparametric tests were used depending on their distribution. In addition to the independent variables found in our previous work,[34] the covariates with a p-value < 0.20 in bivariate association with VAs were included in a multivariable logistic regression model, and the backward stepwise selection method was employed to select variables associated with POD. The Hosmer-Lemeshow test was used to assess model fit, and c-statistics were computed to measure the accuracy of the final model.

Furthermore, to adjust for selection bias and balance between the preoperative and intraoperative variables among the VA groups, a propensity score-weighted method was conducted using inverse probability of treatment weights (IPTW), referred to as the inverse of propensity score. Due to small sample size, instead of using a propensity scoring matching method to assess the unmeasured bias, we used a propensity score-weighted method because the IPTW method does not remove any patients, but bias is adjusted by weight. In IPTW, first propensity scores were computed using multinomial regression models iteratively until all preoperative and intraoperative variables were balanced. Then the IPTW was used in a weighted least squares logistic regression model with the risk factors in the final model to explore any changes in the effects of VAs. All analyses were performed in SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

532 patients were included in this study, with a mean age of 73.5 ± 6.0 years (range, 65–96 years). Table 1 represents patient characteristics, intraoperative and postoperative variables and bivariate associations with VAs. There were no significant differences in preoperative patient characteristics, as well as postoperative variables among the three groups. The type of surgical procedures included orthopaedic or spine (n=309/532, 58%), urologic or gynaecologic (n=92/532,17%), vascular (n=25/532, 5%), and others (such as general, thoracic, ENT, and plastic) (n=106/532, 20%). Among three groups, there were some differences. Overall, 168/532 patients (32%) had combined general and regional anaesthesia. There were a few differences in intraoperative variables among 3 groups (Table 1). The majority of patients (490/532, 92%) received propofol. The dose of propofol was lower in the isoflurane group compared to the desflurane or sevoflurane (p=0.049) populations. However, the difference disappeared in the final model using IPTW (Table 1). There was no difference in the use of spinal or peripheral nerve blocks among the three groups. The use of an epidural anaesthetic was higher in the isoflurane group than the other groups in the original model (p=0.032), however, again the difference disappeared when analysed using IPTW (p=0.536).

The overall incidence of POD on postoperative day 1 or 2 was 41% (n=217/532). The desflurane group had the highest incidence of POD among the three groups (desflurane: n=180/404(45%); isoflurane: n=13/53 (25%); sevoflurane: n=24/75 (32%), p=0.005). The amount of exposure to VAs were compared. Formula for Aa-MAC is listed in Appendix 2. Mean Aa-MAC % (Median (Interquartile Range)) in the isoflurane group was lower than the desflurane or sevoflurane groups (desflurane: 0.73 (0.57–0.90), isoflurane: 0.56 (0.48–0.72), sevoflurane: 0.77 (0.65–0.99), p=0.001). However, the duration of exposure to isoflurane (min, median IQR) was longer than desflurane or sevoflurane (desflurane: 240, isoflurane: 262.5, sevoflurane: 195, p=0.003). Therefore, total amount of exposure (MAC%, median IQR) to VAs were no longer different (desflurane: 10.8(7.8–16.6), isoflurane: 10.3(7.0–15.4), sevoflurane: 10.8(7.0–16.0), p=0.75). All three variables were no longer different in the final model using IPTW. In addition to VAs, variables with P-value<0.2 in Table 1 (race, ASA physical status, surgical risk, type of surgery, use of epidural, use of peripheral nerve block, duration of surgery, intraoperative dose of opioid, mean Aa-MAC, and exposure of MAC) and the risk factors for POD from our prior work[34] (gender, history of CNS disorders, surgical risk, type of surgery, and preoperative TICS) were added to the multivariable logistic analysis. The final model was determined by the backward selection method with removal criterion having significance level of 0.05. Our final model included five variables: gender, history of CNS disorders, preoperative TICS, surgical risk and VAs (Table 2). A Hosmer-Lemeshow test showed a good fit (χ^2=9.13, p=0.331) and the predictive power of our final model was acceptable (c-statistics=0.70, 95% confidence interval [CI]=0.66–0.75). Consistent with our previous findings,[34] female gender, history of CNS disorders, preoperative TICS score <30 (preoperative cognitive impairment) and higher surgical risk were significant predictors of POD. The desflurane group had a higher rate of delirium than the isoflurane group (Odds Ratio [OR]=3.14, 95% CI=1.50–6.57). The delirium rate was not statistically different between the desflurane and sevoflurane groups (OR=0.62, 95%

CI=0.35–1.09) and between the sevoflurane and isoflurane groups (OR=1.93, 95% CI=0.75–4.15).

Similar results were found in the propensity score-weighted logistic regression using IPTW (Table 2). The odds of having POD in the desflurane group is 3.35 times higher than those in the isoflurane group (95% CI=1.54–7.28). No significant differences were found between the desflurane and sevoflurane groups and between the sevoflurane and isoflurane groups.

DISCUSSION

Our study focused on investigating the occurrence of POD in different VA. Desflurane was found to be associated with higher incidence of POD than isoflurane.

To our knowledge, there is no report comparing VAs on POD itself. However, there are some clinical studies comparing each VA on “postoperative cognition”. In these studies, different methodologies in assessing cognitive changes or using different time frames make it difficult to compare results. For example, Chen and colleagues compared the effect of desflurane and sevoflurane on postoperative cognition using the MMSE in elderly patients who underwent total knee or hip replacement,[24] and reported that desflurane and sevoflurane were comparable in terms of their effect on MMSE scores. However, their observations were limited to the first 24 hours. Also, the use of MMSE to measure serial cognitive changes may be limited by the ceiling effects of this test. Mahajan and colleagues conducted a randomized control study comparing the effect of isoflurane and sevoflurane in older patients who underwent ambulatory surgeries.[26] Their postoperative cognitive assessment was even shorter (limited to 6 hours after surgery) and no significant difference was noted in neurocognitive recovery as measured by MMSE in both groups. In the study by Kanbak and colleagues,[25] isoflurane, sevoflurane and desflurane were compared with respect to cognition after cardiac surgery. In their study, MMSE and visual-aural digit span tests were administered on the 3rd and 6th postoperative days. They concluded that sevoflurane was associated with the worst cognitive outcomes as assessed by neurocognitive tests: the postoperative scores (MMSE on 3rd and 6th day and visual-aural digit span scores on 3rd day) in the sevoflurane group were significantly lower than in the isoflurane and desflurane group. They also measured S100 beta protein, an early marker for cerebral injury. The study showed a prolonged increase of this protein in the desflurane group compared to the isoflurane and sevoflurane groups. In addition, a recent small study by Green and colleagues[35] investigated that the effect on cognition comparing desflurane and sevoflurane in short urological procedures. The study showed no statistically significant cognitive decline, except for one of the cognitive tests in desflurane group on postoperative day one.

Previous experimental studies have shown that each VA has different chemical interactions with neurons and suggest that VAs may be neurotoxic and induce cell injury. For example, isoflurane has been shown to induce caspase activation, apoptosis and increase amyloid beta-protein level (Aβ) in vivo.[36] Zhang and colleagues reported that isoflurane, not desflurane increases Aβ levels in cerebrospinal fluid in humans.[37] A study by Dong and colleagues suggests that sevoflurane induces apoptosis and increase Aβ in both vitro and

vivo.[38] Dong's study suggests that sevoflurane may promote neuropathogenesis seen in Alzheimer disease.

On the contrary, some experimental studies have shown that VAs are neuroprotective during brain ischemia. In this context, isoflurane has been studied more than other VAs.[3940–4243] These studies have shown that VAs decrease cell death and improve neurological outcomes. Various mechanisms are proposed for neuroprotective effects of VAs: 1) decreasing the metabolic rate within the brain, 2) reducing glutamate neurotoxicity and 3) regulating signalling molecules such as free radicals, or intracellular calcium.[44] There are only a few clinical studies that investigated the neuroprotective effect of VAs. One study compared the effect of isoflurane, halothane, or enflurane on EEG during carotid endarterectomy. They reported that EEG evidence of brain ischemia was seen more in patients with isoflurane anaesthesia than halothane or enflurane anaesthesia.[45] Another study investigated the effect of desflurane and thiopental on brain ischemia during craniotomy, and the data suggested that desflurane is more neuroprotective than thiopental.[46] Overall, both clinical and pre-clinical studies did not provide any convincing data as to whether VA's differ in terms of their impact on POD.

There are some limitations in our study. First, our study is a secondary analysis of the existing data and is not a randomized control trial. In terms of intraoperative variables, the three groups of patients were relatively matched with respect to perioperative demographics except for a few differences in intraoperative variables (use of epidural, type of surgery). However, the result of multivariable logistic regression using IPTW was not changed even after adjusting for these variables. Second, desflurane has been used more frequently than other agents in our institution. Therefore, the number of patients in the desflurane group is higher than other agents. If there was a larger sample size in isoflurane and sevoflurane groups, the results may be different. Third, processed EEGs were not used in our study. Thus, we cannot differentiate whether it is actually the anaesthetic type or anaesthetic depth that was contributory to different rates of POD. In this study population, propofol was used in almost all the patients and doses were not different in the 3 VA groups. However, we cannot exclude that propofol may have small effects contributing to the depth of anaesthesia and subsequent POD. Fourth, we assessed POD on the first two postoperative days; hence delirium that occurred in later postoperative days would have been missed. However, the incidence of POD is usually higher in the first few days after surgery, and we believe that we have captured results from the most important time period. Fifth, perioperative care may have changed during the long study period and it may have affected the results. Lastly, our studies focused on patients who underwent elective non-cardiac surgery and the results cannot be directly generalized to patients undergoing emergency or cardiac surgery.

In conclusion, our results suggest that desflurane was associated with a higher incidence of POD when compared with isoflurane in older patients who underwent elective non-cardiac surgeries. However, the mechanism as to how different VA's affected the occurrence of POD is unclear. Because our study is hypothesis generating rather than hypothesis testing, future research will need to examine if VAs have an independent effect on POD through a randomized controlled trial. Furthermore, future trials should also investigate whether intravenous-based anaesthetics have varying effects on POD when compared with VAs.

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Appendix 1:: Perioperative Medicine Research Group

The principal investigator is Jacqueline M. Leung, M.D.,M.P.H. Research associates Stacey Chang, B.A., Gabriela Meckler, B.A., Stacey Newman, B.A., Tiffany Tsai, M.D., Vanessa Voss, M.D., and Emily Youngblom, B.A., participated in patient recruitment, cognitive assessments, data entry, and data management.

Appendix 2:: Surgical Risk

High-risk surgery

1. Aortic and other major vascular surgery
2. Peripheral vascular surgery
3. Prolonged procedures associated with large fluid shift and/or blood loss

Intermediate-risk surgery

1. Carotid endarterectomy
2. Head and neck surgery
3. Intraperitoneal and intrathoracic surgery
4. Orthopaedic surgery
5. Prostate surgery

Low-risk surgery

1. Endoscopic procedures
2. Superficial surgery
3. Breast surgery

Appendix 3:: Formulae for Age-adjusted Minimum Alveolar Concentration (Aa- MAC)

$$\text{Aa-MAC}_{\text{desflurane}} = 6.6*10((\text{Age}-40)*(-0.00269))$$

$$\text{Aa-MAC}_{\text{isoflurane}} = 1.17*10((\text{Age}-40)*(-0.00269))$$

$$\text{Aa-MAC}_{\text{sevoflurane}} = 1.8*10((\text{Age}-40)*(-0.00269))$$

$$\text{Aa-MAC}_{\text{N2O}} = 104*10((\text{Age}-40)*(-0.00269))$$

$$\text{Aa-MAC}_{total} = \text{Aa-MAC}_{desflurane} \text{ or Aa-MAC}_{isoflurane} \text{ or Aa-MAC}_{sevoflurane} + \text{Aa-MAC}_{N2O}$$

Aa-MAC_{total}: the sum of age adjusted MAC equivalents when concurrent agents are administered.

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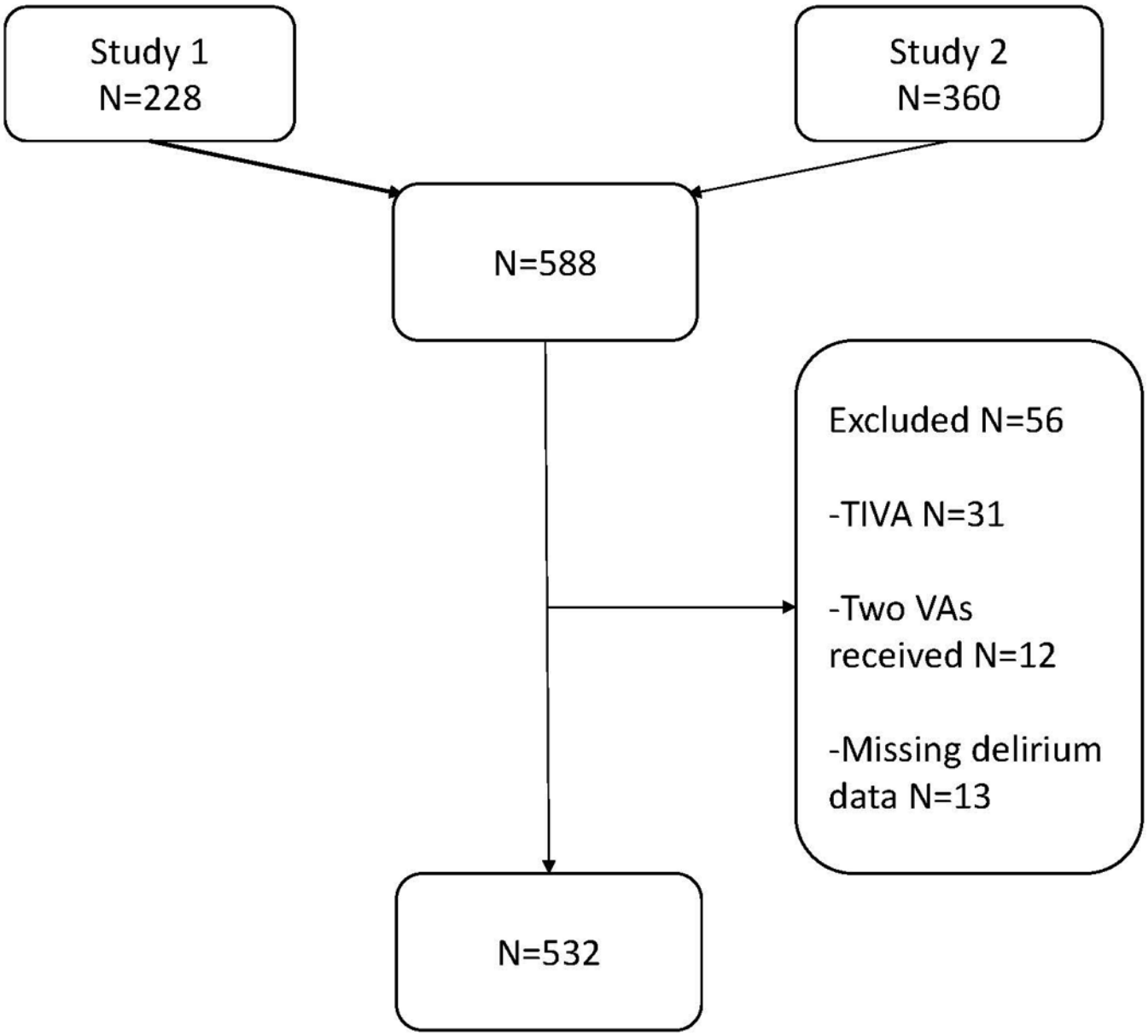

Figure 1:

Consort Diagram Study 1: Trial of General Anaesthesia With or Without Nitrous Oxide-Long Term Follow up: IRB number: 10-04658, Study 2: Postoperative Cognitive Function in Elderly Surgical Patients: IRB number: 10-02710. TIVA=total intravenous anaesthesia, VAs= volatile anaesthetics

Table 1.

Patient Characteristics and Intraoperative and Postoperative Data

Variables	Total (*N*=532)	Volatile Anaesthetics, Unweighted			*P*	Volatile Anaesthetics, IPTW			*P*
		Desflurane (*n*=404)	Isoflurane (*n*=53)	Sevoflurane (*n*=75)		Desflurane	Isoflurane	Sevoflurane	
Patient Characteristics									
Age, yrs, mean ± SD (range)	73.5 ± 6.0 (65–96)	73.4±6.0 (65–96)	72.2±5.7 (65–86)	74.7±5.9 (65–87)	.060	73.5±6.0	72.8±6.3	73.9±5.8	.607
Gender, Female, n (%)	272 (51%)	213 (53%)	25 (47%)	34 (45%)	.417	52%	37%	48%	.154
Education,College or above, n (%)	133 (26%)	104 (26%)	10 (19%)	19 (26%)	.492	26%	26%	27%	.990
History of CNS disorders, n (%)	259 (49%)	200 (50%)	27 (52%)	32 (43%)	.528	50%	53%	47%	.786
Alcohol Intake, ≥2 glasses per day, n (%)	44 (8%)	35 (9%)	5 (9%)	4 (5%)	.615	9%	10%	3%	.175
ASA Physical Status, n (%) I and II III and IV	249 (47%) 283 (53%)	198 (49%) 206 (51%)	22 (42%) 31 (58%)	29 (39%) 46 (61%)	.184	48% 52%	50% 50%	41% 59%	.494
Use of Preoperative Opioids, n (%)	167 (31%)	125 (31%)	18 (34%)	24 (32%)	.899	30%	39%	23%	.146
Use of Preoperative Benzodiazepine, n (%)	80 (16%)	62 (16%)	5 (10%)	13 (18%)	.422	16%	11%	18%	.606
Preoperative TICS, n (%) <30 30–35 ≥35	102 (20%) 254 (51%) 147 (29%)	73 (19%) 195 (51%) 112 (29%)	11 (22%) 23 (45%) 17 (33%)	18 (25%) 36 (50%) 18 (25%)	.710	19% 52% 29%	17% 56% 27%	30% 50% 20%	.235
Preoperative GDS, ≥6, n (%)	81 (16%)	60 (16%)	6 (12%)	15 (21%)	.383	16%	12%	16%	.810
Type of Surgery, n (%) Orthopaedic or Spinal Urological or Gynaecological Vascular Other (General, Thoracic, ENT, Plastic)	309 (58%) 92 (17%) 25 (5%) 106 (20%)	240 (59%) 72 (18%) 14 (3%) 78 (19%)	21 (40%) 12 (23%) 6 (11%) 33 (62%)	48 (64%) 8 (11%) 5 (7%) 14 (19%)	.023	58% 18% 4% 20%	51% 21% 3% 25%	53% 24% 4% 20%	.837
Surgical Risk, High, n (%)	97 (18%)	76 (19%)	13 (25%)	8 (11%)	.112	18%	17%	24%	.425
Intraoperative Variables									
Use of Epidural, n (%)	121 (23%)	89 (22%)	19 (37%)	13 (17%)	.032	23%	28%	27%	.536
Use of Spinal, n (%)	25 (5%)	20 (5%)	1 (2%)	4 (5%)	.685	5%	2%	4%	.647
Use of PNB, n (%)	26 (5%)	18 (4%)	1 (2%)	7 (9%)	.136	5%	3%	6%	.764
Duration of Surgery, hrs. median (IQR)	3.1 (3.1–6.2)	3.1 (3.1–6.2)	6.2 (3.1–6.2)	3.1 (3.1–6.2)	.071	3.1 (3.1–6.2)	3.1 (3.1–6.2)	4.0 (3.1–7.4)	.459

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Variables	Total (*N*=532)	Volatile Anaesthetics, Unweighted			*P*	Volatile Anaesthetics, IPTW			*P*
		Desflurane (*n*=404)	Isoflurane (*n*=53)	Sevoflurane (*n*=75)		Desflurane	Isoflurane	Sevoflurane	
Intraoperative Dose of Opioid, mg,*median (IQR)	6.0 (4.0–10.0)	6.0 (4.0–10.4)	5.5 (3.0–9.5)	6.0 (4.0–9.0)	.143	6.0 (4.0–10.0)	6.0 (4.2–9.5)	5.0 (4.0–10.0)	.526
Mean age-adjusted MAC, %, median (IQR)	0.72 (0.56–0.90)	0.73 (0.57–0.90)	0.56 (0.48–0.72)	0.77 (0.65–0.99)	.001	0.72 (0.57–0.90)	0.70 (0.54–0.96)	0.73 (0.60–0.90)	.931
Exposure of MAC, min, median (IQR)	225 (165–330)	240 (165–345)	262.5 (195–330)	195 (150–270)	.003	225 (165–330)	225 (195–330)	225 (165–435)	.342
Total age-adjusted MAC, %, median (IQR)	10.7 (7.5–15.9)	10.8 (7.8–16.6)	10.3 (7.0–15.4)	10.8 (7.0–16.0)	.750	10.7 (7.5–15.8)	10.8 (7.3–16.0)	11.1 (7.1–24.1)	.256
Propofol, mg, median (IQR)	190 (140–280)	195 (150–300)	150 (100–200)	190 (125–240)	.049	195 (150–280)	150 (120–200)	200 (130–340)	.112
Postoperative Variables									
Pain level at rest on Postoperative Day 1 (NRS), median (IQR)	3 (1–5)	3 (1–5)	2 (0–4)	3 (1–5)	.171	3 (1–5)	2 (2–5)	3 (1–5)	.649
Pain level at rest on Postoperative Day 2 (NRS), median (IQR)	2 (0–4)	2 (0–4)	2 (0–4)	2 (0.5–5)	.801	2 (0–4)	2 (0–4)	2 (0–5)	.266
Dose of Opioid on Postoperative Day 1, mg*, median (IQR)	3.6 (0.6–7.9)	3.6 (0.8–8.2)	3.2 (0.8–8.7)	2.6 (0.4–5.8)	.168	3.6 (0.8–8.0)	3.1 (0.8–8.7)	3.6 (0.4–7.7)	.361
Dose of Opioid on Postoperative Day 2, mg*, median (IQR)	1.0 (0–4.6)	1.0 (0–4.8)	1.4 (0–4.8)	1.0 (0–2.6)	.390	1.0 (0–4.8)	1.2 (0–5.8)	1.2 (0–6.4)	.490
Delirium on Postoperative Day 1 or Day 2, n (%)	217 (41%)	180 (45%)	13 (25%)	24 (32%)	.005	44%	21%	37%	.005

CNS = Central Nervous System. NRS = Numeric Pain Rating Scale. IQR = interquartile range (25 percentile ~ 75% percentile). PNB= Peripheral Nerve Block, IPTW = Inverse probability of treatment weight, calculated as the inverse of the propensity score. Propensity score was computed using multinomial regression with age, type of surgery, surgical risk, mean age-adjusted MAC, exposure of MAC, and interaction between surgery type and mean age-adjusted MAC. *Opioid dose is in intravenous hydromorphone. Conversion formula: 5mg of morphine sulphate = 1mg of hydromorphone, 50mcg of fentanyl = 1mg of hydromorphone.

Table 2.

Odds Ratio and 95% Confidence Interval of Final Multivariable Logistic Regression Model of Postoperative Delirium

		Final Model (unweighted)	**Final Model using IPTW**
Variables		Odds Ratio (95% CI)	Odds Ratio (95% CI)
Gender	Female vs. Male	1.50 (1.01–2.23)	1.46 (0.98–2.18)
History of CNS disorders	Yes vs. No	1.64 (1.11–2.43)	1.45 (0.97–2.17)
Preoperative TICS	<30 vs. ≥35	4.01 (2.26–7.13)	4.26 (2.37–7.65)
	30–35 vs. ≥35	2.09 (1.31–3.34)	1.92 (1.19–3.11)
Surgical Risk	High vs. Low or Intermediate	2.67 (1.64–4.36)	3.03 (1.86–4.93)
Volatile Anaesthetics	Desflurane vs. Isoflurane	3.14 (1.50–6.57)	3.35 (1.54–7.28)
	Sevoflurane vs. Isoflurane	1.93 (0.75–4.15)	1.94 (0.79–4.77)
	Sevoflurane vs. Desflurane	0.62 (0.35–1.09)	0.52 (0.21–1.27)

CI = Confidence Interval, CNS = Central Nervous System, TICS = Telephone Interview for Cognitive Status.

IPTW = Inverse probability of treatment weight, calculated as the inverse of the propensity score.