Nitrous oxide does not change the incidence of postoperative delirium or cognitive decline in elderly surgical patients

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Background. Postoperative delirium and cognitive decline are common in elderly surgical patients after non-cardiac surgery. Despite this prevalence and clinical importance, no specific aetiological factor has been identified for postoperative delirium and cognitive decline. In experimental setting in a rat model, nitrous oxide (N2O) produces neurotoxic effect at high concentrations and in an age-dependent manner. Whether this neurotoxic response may be observed clinically has not previously determined. We hypothesized that in the elderly patients undergoing non-cardiac surgery, exposure to N2O resulted in an increased incidence of postoperative delirium than would be expected for patients not receiving N2O.

Methods. Patients who were ≥65 yr of age, undergoing non-cardiac surgery and requiring general anaesthesia were randomized to receive an inhalational agent and either N2O with oxygen or oxygen alone. A structured interview was conducted before operation and for the first two postoperative days to determine the presence of delirium using the Confusion Assessment Method.

Results. A total of 228 patients were studied with a mean (range) age of 73.9 (65–95) yr. After operation, 43.8% of patients developed delirium. By multivariate logistic regression, age [odds ratio (OR) 1.07; 95% confidence interval (CI) 1.02–1.26], dependence on performing one or more independent activities of daily living (OR 1.54; 95% CI 1.01–2.35), use of patient-controlled analgesia for postoperative pain control (OR 3.75; 95% CI 1.27–11.01) and postoperative use of benzodiazepine (OR 2.29; 95% CI 1.21–4.36) were independently associated with an increased risk for postoperative delirium. In contrast, the use of N2O had no association with postoperative delirium.

Conclusions. Exposure to N2O resulted in an equal incidence of postoperative delirium when compared with no exposure to N2O.

Br J Anaesth 2006; 96: 754–60

Keywords: anaesthetics gases, nitrous oxide; complications, ageing; complications, cognitive decline; complications, delirium, postoperative

Accepted for publication: March 26, 2006

Postoperative delirium and cognitive decline are common in elderly surgical patients after non-cardiac surgery. Delirium increases the length of hospital stay, rates of nursing home placement, and hospital mortality rates.1,2 A milder form of acute cognitive changes known as postoperative cognitive decline (POCD) is associated with long-term declines in daily functioning in medical patients. Despite this prevalence and clinical importance, no specific aetiological factor has been identified for postoperative delirium and POCD including the choice of anaesthetic types (regional vs general)3,4 or anaesthetic management such as the levels of blood pressure during surgery.5

Nitrous oxide (N2O) has been used as an inhalational anaesthetic for over a century. Although the precise mechanism of how N2O induces general anaesthesia is unknown, there is some evidence that it may be a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist.6 Similar to other NMDA antagonist, N2O has been shown to produce neurotoxic effects in rat brain tissue at high concentrations,6 and in an age-dependent manner.7 Whether this
Nitrous oxide and postoperative delirium

Nitrous oxide was contraindicated. After operation, or those not able to provide informed consent such as those who were expected to remain intubated patients who could not complete the neuropsychological testing with or without N₂O. A secondary aim was to determine if the doses of N₂O (cumulative exposure) influenced the rates of postoperative delirium.

Methods

Patient recruitment

The study was approved by the Institutional Review Board for human research, at the University of California, San Francisco, and informed consent was obtained before operation from each study patient. The study was conducted from 2001 to 2005 at the University of California, San Francisco Medical Centre, an academic hospital.

Study population

Inclusion criteria were consecutive men or women who were ≥65 yr of age, undergoing non-cardiac surgery, requiring general anaesthesia, who were expected to remain in the hospital after operation for ≥48 h. Exclusion criteria were patients who could not complete the neuropsychological testing such as those who were expected to remain intubated after operation, or those not able to provide informed consent. Excluded also were surgical cases in which the use of N₂O was contraindicated.

The sample size calculation was based on results from our pilot study of the incidence of the primary outcome, postoperative delirium rate to be 40%. A sample size of 114 per group was needed to significantly detect a 50% reduction in delirium in the group not receiving N₂O (40–22%), power=0.80, when α was set to 0.05. An intention to treat analysis was planned. POCD was measured as a secondary outcome and not included in the sample size calculation.

Anaesthetic randomization

After sample size calculation and before recruitment of the first patient, a computerized random number list was created by one of the co-investigators (L.P.S.) to designate the two anaesthetic group assignments. The assignment of the anaesthetic group for each study patient was contained in a sealed envelope. The randomization sequence was concealed until the research assistants obtained informed patient consent and interventions were assigned. Before operation on the day of surgery, the research assistant who was blinded to the anaesthetic assignment gave the sealed envelope with the specific anaesthetic assignment to the anaesthetist assigned to the case.

The intraoperative anaesthetic management was randomized to either N₂O with O₂, or O₂ (with or without air) plus a potent inhalational agent for both groups. In order to make the study clinically feasible, we allowed the anaesthetists to adjust the percentages of inspired concentrations of oxygen during surgery as clinically indicated. The inspired concentrations of both N₂O and O₂ were measured throughout surgery and are discussed in detail in the next section.

Clinical management

Pre-medication was limited to fentanyl up to 2 μg kg⁻¹ i.v. During operation, mechanical ventilation was initiated to maintain normocarbia and O₂ saturation ≥95%. Anaesthetists were requested to control intraoperative heart rate and blood pressure to within ±30% of preoperative baseline measurements. Intraoperative monitoring was not controlled by the study but was measured. Additional i.v. morphine sulfate or fentanyl was allowed to be titrated to maintain spontaneous ventilatory frequencies of 10–20 bpm and end-tidal CO₂ between 45 and 55 mm Hg while the inhalational agents were discontinued at the conclusion of surgery.

After operation, patient-controlled analgesia (PCA) was used for pain control for the majority of the patients as indicated by the type of surgery. For those patients who had an epidural catheter placed before operation for postoperative analgesia delivery, local anaesthetic and opioids were permitted to be administered at the end of surgery to allow the patients to awaken in comfort. Postoperative O₂ supplementation was used as clinically indicated to maintain O₂ saturation ≥95%.

Research measurements

The same trained research assistant who was blinded to the anaesthesia assignment conducted three patient interviews in person. The preoperative interview typically occurred <48 h before surgery in the preoperative clinic, and included the assessment of depressive symptoms, medical history focusing on neurological status, and assessment of patients’ cognitive status, pain, and functional status. The two postoperative interviews, which focused on the assessment of cognitive status, were conducted approximately 24 and 48 h after surgery in the patients’ hospital rooms. We focused on the first 48 h after surgery because our previous studies demonstrate the rates of postoperative delirium and cognitive decline to be highest during this period. Although late onset postoperative cognitive changes may occur, aetiologies other than anaesthetic factor may account for these late cognitive changes.
For the occurrence of delirium, we used the confusion assessment method (CAM) rating scale\(^8\) which was developed as a screening instrument based on operationalization of DSM-III-R criteria for use by non-psychiatric clinicians in high-risk settings. This method has a sensitivity of 94–100\% and a specificity of 90–95\% and has a high inter observer reliability,\(^8\) and have convergent agreement with four other mental status tests.

We used four tests to measure cognitive function. This included the telephone interview for cognitive status (TICS), which can be administered in person or over the phone.\(^9\) The additional tests included word list learning, digit symbol test, and the controlled oral fluency test. These tests were conducted before operation and repeated on postoperative days 1 and 2 in patients not determined to be delirious. It is important to distinguish between patients with POCD and delirium because it has not been determined whether risks and outcomes for these two conditions are similar. Also, by incorporating patients with delirium into our estimates of POCD would result in double counting cases of delirium in our estimates of poor cognitive outcomes.

Each of these neuropsychological tests has at least four parallel forms to reduce potential practice effects from memorization of the test stimuli. The TICS is an easily administered test of cognitive function, adapted from the mini mental status examination. It provides an assessment of the severity of dementia and allows serial follow-up of its progression. The digit symbol test is a test of psychomotor performance that is relatively unaffected by intellectual prowess, memory or learning, and has high test–retest reliability.\(^10\) The controlled oral fluency test is a sensitive indicator of brain dysfunction. Reduced capacity to generate words has been associated with every dementing process.\(^10\)

The three neuropsychological tests were selected because of their ease of use, portability and brief time requirement for administration, sample a broad range of cognitive functioning, provide adequate test–retest and inter-rater reliability, and with acceptable sensitivity to detect perioperative changes. These tests specifically target those domains that are known to be impaired in the presence of delirium (orientation, memory and concentration)\(^8\) and those that have shown sensitivity to drug effects (processing and psychomotor speed).\(^11\) Furthermore, these batteries of tests have been used and validated in a large number of geriatric patients,\(^12\)\(^18\)\(^19\) including those with dementia who have been tested successfully and reliably on repeated occasions.\(^12\)

### \(\text{\textit{N}}_2\text{O} \text{ measurements}\)

In addition to the use of \(\text{\textit{N}}_2\text{O}\), we also measured the relative ‘dose’ of \(\text{\textit{N}}_2\text{O}\) by summing the inspired concentrations of \(\text{\textit{N}}_2\text{O}\) that were measured every 15 min throughout the entire anaesthetic duration for each patient. This represented the cumulative exposure of \(\text{\textit{N}}_2\text{O}\) over the entire surgical procedure for each patient.

### Assessment of covariates

The potential covariates associated with postoperative delirium were selected based on the feasibility of measurement in the clinical setting and their possible influence on delirium and cognitive status. A structured interview was conducted before operation to assess patient characteristics, education level, alcohol intake and preoperative living arrangement. The geriatric depression scale was administered to determine the presence of preoperative depressive symptoms.\(^13\) Functional status was measured using the activities of daily living (ADL),\(^14\) and the instrumental ADL.\(^15\) Medical record review was conducted to obtain information about the type and number of co-existent medical conditions. The severity of preoperative co-existent conditions was measured using the Charlson comorbidity index.\(^16\) Other perioperative data obtained from chart review included the type of surgery, and the ASA classification.\(^17\) Surgical risk was estimated using the guidelines from the American College of Cardiology and American Heart Association update for the perioperative cardiovascular evaluation for non-cardiac surgery, which takes into consideration the type and duration of surgery, and intraoperative blood loss.\(^18\)

The method of postoperative pain management, including PCA, neuraxial, orally administered opioid analgesics or combination, was measured. In addition, all medications with central nervous system effects were measured for the first three postoperative days. The adequacy of pain relief was assessed by the same research assistant at the same time of the neuropsychological testing using the verbal version of the visual analogue scale which ranged from 0=no pain, to a maximum of 10=worst pain experienced.

### Statistical analysis

The primary outcome was postoperative delirium and the secondary outcome POCD in patients not determined to be delirious. A diagnosis of delirium requires the presence of acute onset and fluctuating course, inattention, and\() either\) disorganized thinking and/or altered level of consciousness as measured by the CAM rating scale.\(^8\) In non-delirious patients, cognitive decline was defined as significant deterioration on two of the three tests. Significant deterioration for each test was based on prediction intervals developed in earlier research of both cognitively intact and impaired subjects.\(^12\)\(^19\)\(^20\) Prediction intervals allow determination of a range of values that would be expected for a future score based upon an initial score.\(^12\)\(^19\)\(^20\)

Bivariate associations were tested using \(\chi^2\)-tests for categorical variables and Mantel–Haenszel \(\chi^2\)-tests for trend were used for ordinal variables. A multivariate logistic regression analysis was conducted to determine the independent effect of \(\text{\textit{N}}_2\text{O}\) after adjusting for variables that were associated with the onset of delirium in bivariate analyses with a \(P\)-value of \(\geq 0.20\). Variables were eliminated using backward elimination technique.
Results

Two hundred and twenty-eight patients who met the inclusion/exclusion criteria were enrolled between May 2001 and February 2005. There was no significant difference in patient characteristic information, general health status, baseline cognitive function and functional status between patients who did or did not receive N2O (Table 1) except for race, where significantly more patients who received oxygen were white vs those who received N2O (93% vs 77%). Similarly, the intraoperative management was not significantly different between the two treatment groups (Table 2), except for the use of inhalational agents, where significantly more patients in the oxygen group received desflurane rather than isoflurane, compared with those randomized to receive N2O. These two variables were evaluated further and found not to have any significant association with postoperative delirium. Of 180 patients, 74 (41.1%) who were white had postoperative delirium vs 16 of 30 (53.3%) patients who were non-white; P=0.21. For desflurane vs isoflurane: 70 of 155 (45.2%) patients who received desflurane developed postoperative delirium vs 20 of 55 (36.4%) patients who did not receive desflurane; P=0.26, and 7 of 25 (28%) patients who received isoflurane developed postoperative delirium vs 83 of 185 (44.9%) patients who did not receive desflurane; P=0.11. The rates of intra- and postoperative complications and duration of hospital stay also were similar between the two anaesthetic groups (Table 3).

Overall, 46 of 105 (43.8%) patients in the oxygen group developed postoperative delirium on either postoperative day 1 or 2 vs 44 of 105 (41.9%) patients in the N2O group (P=0.78). Cumulative dosing analysis also demonstrates that there is no significant difference in N2O doses between those with postoperative delirium vs those without [59.4 (68.1) vs 53.5 (62.5) min; P=0.55]. Overall, for those without postoperative delirium, 11 of 59 (18.6%) in the oxygen group developed POCD on either postoperative day 1 or 2 vs 8 of 54 (14.8%) patients in the N2O group (P=0.59).

As patients in the two intervention groups may have received different fractional inspired concentrations of oxygen (FiO₂) during the study, we performed additional analysis and found that there was no difference in the mean FiO₂ between the N2O vs the oxygen groups; P=0.48.

By multivariate logistic regression analysis, age [odds ratio (OR) 1.07; 95% confidence interval (CI) 1.02–1.26], dependence on performing one or more independent activities of daily living (OR 1.54; 95% CI 1.01–2.35), use of PCA for postoperative analgesia compared with oral opioids (OR 3.75; 95% CI 1.27–11.01) and postoperative use of benzodiazepine (OR 2.29; 95% CI 1.21–4.36) (Table 4) were independently associated with a greater risk for the development of postoperative delirium. In contrast, the use or the doses of N2O was not significantly associated with the development of postoperative delirium.

Discussion

Our study demonstrates that the use of N2O does not change the risk of postoperative delirium. Of all the co-variates examined, age, loss of the ability to independently perform one or more independent activities of daily living, and postoperative use of benzodiazepines increase the risk of postoperative delirium. In contrast, the use of oral analgesics after operation for pain relief is associated with a lower risk of postoperative delirium when compared with PCA or neuraxial techniques.

Comparison with previous studies

Our study finding is novel as there has been no previous clinical study conducted so far to evaluate the potential influence of intraoperative use of N2O on the development of postoperative delirium and cognitive decline. In contrast to the neurotoxic effects produced by supra pharmacological
level of N₂O on brain tissues in animal models,⁷,²¹ our study cannot confirm that the use of N₂O in clinically relevant doses produces deleterious effects. In an animal model of aged rats, Culley and colleagues similarly could not attribute the spatial memory impairment after exposure to general anaesthesia to the use of N₂O as the impairment appeared to occur regardless of whether N₂O was used.

In the perioperative setting, limited data exist on whether specific intraoperative anaesthetic management strategy precipitates postoperative delirium. The two main areas that have been investigated include anaesthetic techniques (such as general vs regional anaesthesia) or certain drugs that may increase the risk of postoperative delirium or POCD.

### Table 2

<table>
<thead>
<tr>
<th>Types of inhalational agents</th>
<th>N₂O group</th>
<th>Oxygen group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflurane</td>
<td>18</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>19</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Desflurane</td>
<td>77</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>Duration of anaesthesia [min, mean (SD)]</td>
<td>272.9 (106.1)</td>
<td>264.6 (133.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Estimated blood loss [ml, mean (SD)]</td>
<td>527.4 (195.5)</td>
<td>662.9 (954.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Amount of blood transfusion [ml, mean (SD)]</td>
<td>153.9 (382.8)</td>
<td>214.9 (550.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Intravenous vasodilators use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>58</td>
<td>46</td>
<td>0.10</td>
</tr>
<tr>
<td>Neosynephrine</td>
<td>48</td>
<td>50</td>
<td>0.74</td>
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<tr>
<td>Lowest systolic blood pressure [mm Hg, mean (SD)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day of surgery</td>
<td>109.5 (18.1)</td>
<td>108.2 (1.5)</td>
<td>0.59</td>
</tr>
<tr>
<td>POD #1</td>
<td>110.2 (15.5)</td>
<td>112.8 (18.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>POD #2</td>
<td>117.2 (16.9)</td>
<td>115.9 (18.9)</td>
<td>0.60</td>
</tr>
<tr>
<td>POD #1 hemoglobin [g d⁻¹, mean (SD)]</td>
<td>10.3 (1.3)</td>
<td>10.6 (1.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>POD #2 hemoglobin [g d⁻¹, mean (SD)]</td>
<td>10.1 (1.2)</td>
<td>10.4 (1.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>POD #1 sodium [mmol litre⁻¹, mean (SD)]</td>
<td>137.7 (3.7)</td>
<td>136.6 (3.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>POD #2 sodium [mmol litre⁻¹, mean (SD)]</td>
<td>136.8 (3.6)</td>
<td>136.1 (3.2)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Discharge destination</th>
<th>N₂O group</th>
<th>Oxygen group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>75</td>
<td>81</td>
<td>0.39</td>
</tr>
<tr>
<td>Other</td>
<td>39</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Postoperative adverse events</td>
<td>48</td>
<td>44</td>
<td>0.63</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>1</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Other operation within the same hospitalization</td>
<td>5</td>
<td>3</td>
<td>0.72</td>
</tr>
<tr>
<td>Haemodynamic abnormalities</td>
<td>75</td>
<td>85</td>
<td>0.15</td>
</tr>
<tr>
<td>Hospital stay [days, mean (SD)]</td>
<td>5.4 (3.5)</td>
<td>4.8 (2.9)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

### Table 4

| Factors associated with postoperative delirium by multivariate logistic regression. IADL scale, Lawton–Brody instrumental activities of daily living scale; PCA, patient controlled analgesia; POD, postoperative day |
|-------------------------------------------------------------------------------|---------------------------------|---------------------|---------------------|
| Odds ratio | 95% Confidence interval |
| Age | 1.07 | 1.02–1.26 |
| Anaesthetic type (N₂O vs oxygen) | 1.09 | 0.57–2.07 |
| Dependence on performing >1 IADL | 1.54 | 1.01–2.35 |
| Postoperative analgesia | PCA vs oral opioids | 3.75 | 1.27–11.01 |
| Use of benzodiazepines on POD #1 or POD #2 | 2.29 | 1.21–4.36 |

Whether any anaesthetic technique (regional vs general) has an impact on postoperative delirium has not been conclusively determined. Earlier studies suggested an association between a higher incidence of postoperative confusion and general anaesthesia relative to epidural anaesthesia.²³,²⁴ More recent studies, in contrast, have concluded that there is no relationship between anaesthetic technique and the magnitude or pattern of postoperative cognitive dysfunction.⁴,²⁵ Williams-Russo and colleagues²⁶ performed a randomized trial and showed that patients who underwent total knee replacement had similar rates of postoperative cognitive dysfunction at 1 week and at 6 months after surgery regardless of whether they received general vs epidural anaesthesia. A retrospective cohort study of consecutive...
hip fracture patients, aged ≥60 yr, undergoing surgical repair at 20 hospitals in the USA also found that the anaesthesia technique (regional vs general) had no impact on postoperative mental status change.26 More recently, a multi-centre trial of patients ≥60 yr of age, although not adequately powered, reported that the incidence of cognitive dysfunction at 3 months after surgery was not different after either general or regional anaesthesia.4 As a result, the evidence to date does not show that there is a difference in cognitive outcomes after general vs regional anaesthesia.

Although previous studies have demonstrated that certain drugs may be associated with postoperative delirium,27 there has been no prospective randomized clinical trials to determine if the elimination of certain drugs used in the perioperative period will actually lead to a lowering of the incidence of postoperative delirium or POCD. Results from our current study suggest that postoperative use of benzodiazepines should probably be avoided as its use is independently associated with an increased risk of postoperative delirium. This result is corroborated by a recent study of delirium in intensive care unit patients which demonstrated that lorazepam was an independent risk factor for daily transition to delirium.28 The exact mechanism of how benzodiazepines increased the risk of delirium is unclear. It is speculated that as benzodiazepines have high affinity for the γ-aminobutyric acid receptor in the central nervous system,29 this action may alter levels of neurotransmitters believed to be delirogenic.

In addition to benzodiazepines, meperidine is another medication that should be avoided based on results from previous studies.30 Meperidine is infrequently used in recent clinical practice and none of our patients in this study received meperidine as a postoperative analgesic. Meperidine has a relatively long half-life and its metabolite, normeperidine, is a central nervous system stimulant with anticholinergic properties that may induce seizures and delirium.31 Accumulation of normeperidine will occur in patients with renal insufficiency.

In addition to previous studies on anaesthetic techniques and drugs, our present results confirm our previous findings that the method of postoperative pain management has a greater impact on the development of postoperative delirium than preoperative patient characteristic (excluding age and symptoms of depression) or anaesthesia and surgical factors.34 Our present results demonstrate that the use of i.v. opioids increases the risk of postoperative delirium when compared with orally administered opioids. Opioid analgesics administered orally may result in a lower blood level of the drug because of first pass effect when compared with i.v. administered narcotics which may directly cross the blood–brain barrier. Alternatively, the use of oral narcotics for postoperative analgesia may be a marker for a less painful state. However, this result remains significant even when adjusting for the level of pain. This result suggests that future studies are indicated to determine if minimizing postoperative i.v. opioids will result in a lower incidence of postoperative delirium.

Potential limitations

There is concern that the lack of difference between the N₂O vs the oxygen groups was secondary to a lack of power of the study. In fact, the lack of significant differences is best attributed to the very small effect size rather than low power. Specifically, to statistically detect the very small differences we found in incidence of delirium (43.8% in control and 41.9% in N₂O group), one would need more than 20 000 patients. Another way to illustrate that the lack of significance was a result of the small effect size rather than the power of the study is to show that with as many as 1000 in the control group, the 95% CI for postoperative delirium for those assigned to the control group would be 40.7–46.9. The prevalence for the N₂O group falls well within this CI suggesting that the lack of statistical difference is a result of a small effect size, rather than an inadequate sample size.

We focused on measuring delirium in the early postoperative period, as the aim of the study was to determine the effects of N₂O on postoperative delirium. As a result, incidents of later onset delirium may have been missed, but late onset delirium likely will have a different aetiology than early onset postoperative delirium.

Clinical implications

To date, no study has identified any specific anaesthetic type (such as general vs regional) or anaesthetic agent to be deleterious in increasing the risk of postoperative delirium or cognitive decline. The causes for postoperative delirium and cognitive decline are likely to be multi-factorial in which patient factors such as age, educational levels, preoperative symptoms of depression35 etc., increase the vulnerability of the elderly surgical patients, which may lead to the subsequent development of postoperative delirium, cognitive decline, or both. From the evidence to date, if a patient is identified before operation to be at high-risk for postoperative delirium, the avoidance of benzodiazepines or meperidine in the postoperative period appears to be appropriate, as data demonstrating their use with increased risk of postoperative delirium are the strongest. Beside these two medications, further investigations will be necessary to determine if any additional anaesthetic agent, technique, or postoperative pain management strategy is preferred for the patients at risk for postoperative delirium or POCD.

Conclusion

Our study demonstrates that for geriatric surgical patients, exposure to N₂O in clinically relevant concentrations did not result in an increased incidence of postoperative delirium. These results suggest that N₂O may be safely used in a balanced technique in geriatric surgical patients, without
increasing the risk of unwanted postoperative cognitive impairment. Future research should be directed to additional factors beyond intraoperative anaesthetic agent that may have an impact on the development of postoperative delirium and cognitive decline in elderly patients.

Acknowledgements

The authors would like to thank Drs Edmond Eger, II and Philip Bicker, for their advice on study design, and E. Ann Mullen, BS, for technical assistance in research data collection. This project was supported in part by institutional funds and the National Institute of Aging, National Institutes of Health, Grant #1K24 AG00948-05 (Leung).

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