Increased incidence of postoperative cognitive dysfunction 24 hr after minor surgery in the elderly

[Incidence accrue de dysfonctionnement cognitif 24 h après une opération mineure chez des gens âgés]

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Purpose: Postoperative cognitive dysfunction (POCD) is evident in 26% of elderly patients seven days after major non-cardiac surgery. Despite the growing popularity of day surgery, the influence of anesthetic techniques on next day POCD has not been investigated. Therefore, we evaluated the incidence of POCD and changes in serum markers of neuronal damage (S-100ß protein and Neuron-Specific Enolase), 24 hr after single-agent propofol or sevoflurane anesthesia in elderly patients undergoing minor surgery.

Methods: Patients (n = 30, mean age 73, range 65–86 yr) coming for cystoscopy or hysteroscopy, were randomized, in an observer-blind design, to receive either single-agent propofol or sevoflurane anesthesia. Changes in neuropsychological tests (the Stroop test and the modified Word-Recall Test), 24 hr postoperatively were compared with age-matched control subjects (n = 15) using Z-score analysis. Changes in S-100ß protein and Neuron-Specific Enolase levels were also documented.

Results: POCD was present in 7/15 [47% (95% confidence interval (CI) 21 to 72%)] patients who received propofol and 7/15 [47% (95% CI 21 to 72%)] patients who received sevoflurane, compared with 1/15 [7% (95% CI 6 to 19%)] control patients, P = 0.03. S-100ß protein and Neuron-Specific Enolase levels were not significantly different in anesthetized patients postoperatively compared with preoperative values.

Conclusion: The incidence of POCD in elderly patients on the first day after minor surgery is higher than previously reported for seven days after major surgery, and is increased after both propofol and sevoflurane anesthesia, compared with age-matched controls. S-100ß protein and Neuron-Specific Enolase levels were unaffected by anesthetic technique.

Objectif : *Le dysfonctionnement cognitif postopératoire (DCPO) se manifeste chez 26 % des patients âgés, sept jours après une opération non cardiaque majeure. Nous avons évalué l'incidence de DCPO et les modifications des marqueurs sériques d'atteinte neuronale (protéine S-100ß et énolase neurospécifique), 24 h après une anesthésie à un seul médicament, le propofol ou le sévoflurane, chez des patients âgés qui ont subi une opération mineure.*

Méthode : *Les patients (n = 30, moyenne de 73 ans, limites de 65–86 ans) opérés pour cystoscopie ou hystéroscopie, ont été randomisés à l'insu d'un observateur pour une anesthésie avec propofol ou sévoflurane. Les changements aux tests neuropsychologiques (test Stroop, test modifié de remémoration de mots) ont été notés 24 h après l'opération et comparés à ceux de sujets témoins appariés selon l'âge (n = 15) au moyen de l'analyse de l'écart réduit. On a aussi noté les changements de niveaux de protéines S-100ß et d'énolase neurospécifique.*

Résultats : *Le DCPO était présent chez 7/15 [47 % (intervalle de confiance de 95 % (IC) 21 à 72 %)] patients qui ont reçu le propofol et chez 7/15 [47 % (IC de 95 % 21 à 72 %)] patients qui ont reçu le sévoflurane, comparativement à 1/15 [7 % (IC de 95 % 6 a 19 %)] témoins, P = 0,03. Les niveaux de protéines S-100ß et d'énolase neurospécifique n'étaient pas significativement différents avant et après l'opération sous anesthésie.*

Conclusion : *Le premier jour après une opération mineure, l'incidence de DCPO chez les patients âgés est plus élevée qu'on ne le rapportait auparavant sept jours après une intervention majeure. Elle est augmentée avec le propofol et le sévoflurane, en comparaison avec des témoins du même âge. Les niveaux de protéines S-100ß et d'énolase neurospécifique ne sont pas modifiés par la technique anesthésique.*

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This study was funded entirely from the resources of the Department of Anesthesia, Critical Care and Pain Medicine, Mater Misericordiae Hospital.

Accepted for publication May 25, 2004.

Revision accepted November 5, 2004.

EARLY postoperative cognitive dysfunction (POCD) and acute confusional states (delirium) are common after major surgery in the elderly.[1] The high incidence of POCD after cardiac surgery, approximately 50% at discharge, has been attributed to the use of cardiopulmonary bypass.[2] In non-cardiac surgery, an international trial of elderly patients (median age 68, range 60–81 yr) demonstrated a 26% incidence of POCD one week after surgery, with 10% having persistent POCD three months later.[3] Younger patients (median age 51, range 40–60 yr) had a lesser incidence of POCD at one week postoperatively (19%), and this decreased to 6% after three months, similar to that of control subjects.[4] These studies were unable to distinguish between the contribution of major surgery and anesthesia to the observed incidence of POCD. Risk factors for POCD identified by these studies included advancing age, duration of anesthesia, and repeat surgery.[1–4]

Serum markers of neuronal injury, S-100ß protein and Neuron-Specific Enolase (NSE) have been evaluated after different kinds of surgery, with conflicting results.[5–8] Levels are elevated after cardiac surgery and S-100ß protein in particular may be correlated to POCD after some types of non-cardiac surgery.[8] However, the role of anesthesia *per se* in contributing to POCD and changes in these serum markers is unclear.

There is no reported evaluation of POCD within the first 24 hr after surgery. Because day case surgery accounts for an increasing proportion of surgical workload in the elderly,[9] evidence of POCD immediately after surgery may have significant implications for their suitability for day surgery and postdischarge care. Propofol and sevoflurane are commonly used anesthetic agents in everyday practice. Therefore, we evaluated the effect of single agent propofol and sevoflurane anesthesia on POCD and serum markers of cerebral insult in elderly patients 24 hr after relatively minor surgery, compared with age-matched control patients.

Methods

After hospital Ethics Committee approval and written, informed consent, elderly patients (age > 65 yr) presenting for minor urological (rigid cystoscopy, transurethral resection of bladder mucosal tumour) or gynecological surgery (hysteroscopy), requiring general anesthesia, and with an anticipated hospital stay of one night postoperatively, were eligible for this study. Within the same hospital, we enrolled an age-matched control group, consisting of in-patients for non-surgical conditions, who had no known evidence of cognitive dysfunction.

Exclusion criteria were diseases of the central nervous system including pre-existing cognitive dysfunction (defined as a Mini-Mental State Examination score below 24), consumption of phenothiazines or antidepressants, cardiac or neurosurgery, previous neuropsychological testing, or poor comprehension of the language used in processing the study tests. Patients with alcoholism or addictive drug dependence were also excluded.

Preoperatively, we recorded the patients' medical history, including medication. After screening patients with a Mini-Mental score, patients undertook two neuropsychological tests: cumulative number of words recalled in five trials plus the number of words at delayed recall,[10] and the error scores from the second part of the Stroop Color Word Interference test.[11] These tests have been validated and used in previous multicentre studies.[3,4] Patients were then informed about what to expect from both anesthesia protocols. A clinical psychologist trained the investigators conducting the tests. All patients were enrolled from a single centre.

Venous blood from a peripheral vein was drawn in a 10-mL sample during preoperative and postoperative tests and centrifuged at 5,000 rpm within 30 min. Serum was aspirated and stored in separate aliquots at -80°C for subsequent determination of S-100ß protein and NSE levels, using an enzyme-linked immunosorbent assay technique (Reovox Chemicals, Amsterdam, Holland).

Patients were randomized (using a sequentially-numbered, sealed envelope technique) in the anesthesia induction room to receive either propofol total *iv* anesthesia or sevoflurane inhalation anesthesia. The investigator who undertook patient enrollment, neuropsychological tests and blood tests did not deliver anesthesia to the patient and, therefore, was unaware of study group allocation. After placement of an *iv* cannula and commencement of a 500 mL infusion of crystalloid solution in all patients, fentanyl 1 $\mu g \cdot kg^{-1}$ was administered *iv*. Propofol patients received total *iv* anesthesia using a Diprifusor™ (Zeneca Pharmaceuticals Ltd., Macclesfield, Cheshire, UK). Target concentrations of propofol were adjusted to maintain adequate depth of anesthesia, at the discretion of the anesthesiologist responsible for the patient. Sevoflurane patients received an incremental dose, tidal volume inhalation induction technique. Once a satisfactory depth of anesthesia was reached after induction, a laryngeal mask airway was positioned in all patients. Fractional inspired oxygen concentration was 0.5, using an oxygen/air mixture in a conventional low-flow breathing system. In all patients, mean

arterial pressure and heart rate levels were kept within 20% of baseline preoperative values, using fluid boluses or ephedrine 3 mg *iv* as required. Paracetamol 10 $mg \cdot kg^{-1}$ was administered for subsequent analgesia. Postoperative tests were administered the following day as close as possible to 24 hr after anesthesia. In practice, all postoperative tests were undertaken between 20 to 24 hr postanesthesia.

The primary outcome measure was the occurrence of cognitive dysfunction on the day following surgery. The definition of cognitive dysfunction was based on agreed protocols from the literature.[12] Changes in neuropsychological tests were compared with a control group, which consisted of a matched group of elderly people, drawn from non-surgical patients within the hospital. Analysis commenced with the control group. Changes in performance of each test for control patients (the difference between the first and second set of values) were calculated for each patient, and the mean and standard deviation (SD) of these differences obtained. The mean difference in performance among controls was taken as a *learning effect* of the control group. For patients, the difference between postoperative and baseline preoperative values was calculated, and the mean learning effect subtracted from these changes. The result was divided by the control group SD, to derive the "Z-score" for that individual's test outcome. Large positive Z-scores indicate deterioration in cognitive dysfunction compared with controls. A composite Z-score for each group was calculated from the mean of all Z-scores in the control group. The SD of this was used to normalize the patients' postoperative Z-scores of the active groups. Patients had cognitive dysfunction when the two Z-scores in the individual tests or the combined Z-score was 1.96 or more.

Continuous data were compared using analysis of variance with post hoc Dunnett's test for multiple comparisons where there is a control group. Interval data, including differences in raw POCD test scores, were compared using the Kruskal-Wallis test. Categorical variables, including the incidence of POCD, was analyzed using Fisher's exact test. $P < 0.05$ was taken as significant.

This was a pilot study to investigate if POCD differed between anesthetic techniques. The International Study of POCD (ISPOCD) showed an incidence of POCD of approximately 26% in patients, taken one week after surgery. Given the relatively higher incidence of postoperative confusion seen in more elderly patients in the first one to three days,[1] we estimated that the incidence of detectable POCD at 24 hr would be in the region of 45%. Taking approximately 5% as the incidence of POCD in control patients from previous ISPOCD studies at one week[3,4] we estimated that $n = 15$ patients in each study group would be needed to show a difference in POCD between 45% and 5%, assuming a type I error of 0.05 and a type II error of 0.2.

Results

Thirty patients (23 men and 7 women) and 15 control subjects (11 men and 4 women) from elderly hospitalized patients who had not undergone anesthesia and surgery in the preceding 12 months were enrolled. The mean age of the control patients was 74.9 yr (range 67–86 yr), compared with 72.9 yr (range 65–83 yr) and 73.8 yr (range 67–86 yr) for propofol and sevoflurane patients, respectively. All patients completed the postoperative assessment. The postoperative tests were carried out a median of 23 hr postoperatively (range 20–24 hr).

In the control group, the criteria for cognitive dysfunction were found in 1/15 patients [7% (95% confidence interval (CI) 6 to 19%)]. This compares with 7/15 [47% (95% CI 21 to 72%)] in both propofol and sevoflurane patients, respectively, $P = 0.03$. Baseline data for the patient and control groups are shown in Table I. Patients were well matched in terms of age, gender distribution, and baseline values of the Mini-Mental State Examination score and the neuropsychological tests. Table II shows the changes in cognitive function tests at the postoperative test session, and the incidence of POCD. The control patient identified as having POCD had a Z-score > 1.96. Of the seven patients given propofol, six had a Z-score > 1.96 on the Stroop test, and one had a combined score > 1.96. Of the seven given sevoflurane, four had a Z-score > 1.96 on the Stroop test alone, the remaining three having combined Z-scores > 1.96.

Table III shows values for S-100ß protein and NSE among propofol and sevoflurane patients. No significant difference between the groups was noted postoperatively, nor did values change within either group in the postoperative period compared with the preoperative period.

Discussion

This study evaluated the effect of different anesthesia techniques on POCD. This was achieved by randomizing patients undergoing only cystoscopy or hysteroscopy, both relatively minor procedures. Two distinct general anesthetic techniques, total *iv* anesthesia with propofol and single-agent inhalation anesthesia with sevoflurane were compared. Irrespective of the general anesthetic technique used, there was a signifi-

TABLE I Patient characteristics and baseline neuropsychological test results

Variable	*Controls*	*Propofol*	*Sevoflurane*
Age, yr, mean (range)	74.9 (67-86)	72.9 (65-83)	73.8 (67-86)
Gender, *n* male	11	12	11
Nocturnal hypnotics, *n*	5	3	4
Non-opioid analgesics, *n*	4	1	2
Duration anesthesia, min, mean (range)	N/A	18 (8-30)	15 (10-28)
Mini-Mental State Examination score median, range	27 (23-30)	27 (25-30)	28 (25-30)
Number of errors for Stroop test (baseline), *n*, median, range	0 (0-2)	1 (0-3)	1 (0-3)
Modified Word Recall Test (number of words)	29 (20-41)	32 (18-50)	33 (20-49)

TABLE II Changes in psychometric test results at 18 to 24 hr postoperatively and incidence of postoperative cognitive dysfunction (POCD)

Variable	*Controls (n = 15)*	*Propofol (n = 15)*	*Sevoflurane (n = 15)*
Change in number of errors for Stroop test, median, range	0 (-1 to 3)	-1 (-4 to 2)	-2 (-4 to 3)
Modified Word Recall Test change in cumulative learning (number of words)	2 (-4 to 9)	4 (-4 to 10)	6 (0-13)
Incidence POCD, *n* (%)	1 (7%)*	7 (47%)	7 (47%)

Data shown is after adjustment for learning effect. *$P = 0.03$ Fisher exact test.

TABLE III S-100ß and Neuron-Specific Enolase levels

Variable	*Propofol (n = 15)*	*Sevoflurane (n = 15)*
Baseline S-100ß ng·mL^{-1}	1.0 ± 0.2	1.2 ± 0.3
Postoperative S-100ß ng·mL^{-1}	1.1 ± 0.4	1.3 ± 0.2
Baseline Neuron-Specific Enolase ng·mL^{-1}	6.7 ± 4.2	6.1 ± 2.4
Postoperative Neuron-Specific Enolase ng·mL^{-1}	6.5 ± 3.4	6.0 ± 4.4

Values shown are mean ± SD.

cant increase in POCD after anesthesia to 47%, higher than the 26% observed in somewhat younger patients in the ISPOCD study at one week.[4] Perhaps POCD is highest in the early postanesthetic period and decreases progressively with time postoperatively. However, our small study differs from the ISPOCD trial in that our patients underwent only minor procedures, were tested within 24 hr of the procedure and were substantially older (mean age 73 yr compared with 68 yr).

Elderly patients are especially susceptible to POCD, which has implications for postoperative care of these patients, particularly if they are being discharged four to six hours postoperatively. Middle-aged patients who's mental status was evaluated one week after surgery had a reported incidence of POCD of 19%.[4] These observations are consistent with the idea that advancing age is a risk factor for POCD.[12] Severe, early POCD is a problem for 15% of patients[12] and may influence rehabilitation. We did not include subjective (self-assessed) measures of POCD because they have been shown to over-estimate its incidence.[13] Furthermore, early POCD seems to resolve rapidly as the time interval after surgery increases.[3,4]

Importantly, our findings do not suggest that anesthesia *per se* causes POCD, rather that the cumulative effects of surgery, the stress response to surgery, anesthesia, anxiety, prolonged starvation etc. induce POCD with the first 24 hr postoperatively.

We used a robust study method, consistent with recent guidance.[12] The age-matched control group allowed us to control for learning effect and patient variability. However, these control patients did not undergo surgery, therefore it is likely that another aspect of the perioperative experience (e.g., surgery

itself, anxiety, fasting) may have contributed to the POCD we observed. It is unlikely that our observations are attributable to minor differences in control patients' medication (use of nocturnal hypnotics, long-term non-opioid analgesics, etc.). This was a pilot study to evaluate the incidence of POCD 24 hr postoperatively, and to investigate if any clear difference emerged between two different anesthetic techniques. All patients underwent minor surgery (cystoscopy or hysteroscopy) of less than 30 min duration. Even with the small numbers used in this study, we were able to demonstrate POCD at 24 hr compared with controls, but a similar incidence was observed in the two anesthetic techniques, suggesting that the choice of general anesthetic agent may not influence the incidence of POCD at 24 hr even in a larger study.

Ours was a single-centre study with two investigators (D.R. and S.C.) conducting the neuropsychological tests: multicentre studies have shown significant inter-centre variation in the incidence of POCD, possibly related to differences in local culture and practice.[3,4] While avoidance of general anesthesia by using regional anesthesia techniques (e.g., epidural analgesia) might have been expected to reduce the incidence of POCD, the reverse has been observed in middle-aged patients,[4] suggesting that plasma concentrations of bupivacaine may be sufficient to cause POCD by acute neurologic toxicity.[14] However, a randomized study of 438 elderly patients compared general *vs* regional anesthesia and found that the latter decreased the incidence of POCD seven days after major non-cardiac surgery.[15]

There was no significant difference between S-100ß and NSE levels in patients receiving either anesthetic technique, suggesting that no structural neurologic insult occurred. In a recent study, S-100ß has been shown to increase after major abdominal surgery, while NSE was decreased. The increased S-100ß correlated with acute confusion (delirium) postoperatively.[5] However, a study in patients undergoing cardiopulmonary bypass recently indicated that much of the observed increase in S-100ß protein and NSE may be attributable to contamination with blood from the surgical field.[6] In contrast, NSE, measured 36 hr after cardiac surgery, was found to correlate with the composite Z-score in POCD tests.[7] A further study evaluating S-100ß protein and NSE after different types of surgery found that POCD correlated well with S-100ß protein but not NSE. However, urological surgery, which accounted for the majority of our patients, did not show any difference in S-100ß protein levels among patients with and without POCD,[8] suggesting that this marker reflects structural neuronal damage and therefore may be of limited value in detecting POCD in this subgroup of patients.

In conclusion, this pilot study of POCD in elderly patients, (mean age 73 yr) has shown significantly higher POCD in patients 24 hr after receiving either propofol or sevoflurane anesthesia for minor surgery, compared with age-matched controls, but no difference between the two anesthetic techniques. This does not imply that anesthesia *per se* causes POCD, rather that the perioperative experience induces POCD early in the postoperative period. No difference in S-100ß protein or NSE was observed either in the postoperative period compared with the preoperative period or between the propofol or sevoflurane patients, suggesting that these markers are not influenced by anesthesia, and may be of limited value in detecting POCD after minor surgery.

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