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Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients

L. S. Rasmussen[1], T. Johnson[2], H. M. Kuipers[3], D. Kristensen[4], V. D. Siersma[5], P. Vila[6], J. Jolles[7], A. Papaioannou[8], H. Abildstrom[1], J. H. Silverstein[9], J. A. Bonal[10], J. Raeder[11], I. K. Nielsen[12], K. Korttila[13], L. Munoz[14], C. Dodds[15], C. D. Hanning[16] and J. T. Moller[1] for the ISPOCD2 investigators*

[1]*Department of Anaesthesia, Center of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark;* [2]*Department of Anaesthesia, Hope Hospital, Salford, UK;* [3]*Eindhoven University of Technology, Eindhoven, the Netherlands;* [4]*Department of Anaesthesia, Hillerød Hospital, Denmark;* [5]*Department of Biostatistics, University of Copenhagen, Denmark;* [6]*Department of Anaesthesia, Hospital Universitari Germans Trias i Pujol, Barcelona;* [7]*Brain & Behaviour Institute and Department of Psychiatry & Neuropsychology, Maastricht University, Limburg, Maastricht, the Netherlands;* [8]*Department of Anaesthesiology, University Hospital of Iraklion, Crete, Greece;* [9]*Departments of Anesthesiology, Surgery and Geriatrics & Adult Development, Mount Sinai School of Medicine, New York, USA;* [10]*Department of Anaesthesia, Hospital General Elche, Alicante, Spain;* [11]*Department of Anaesthesia, Ullevaal University Hospital, Oslo, Norway;* [12]*Department of Anaesthesia, Bispebjerg Hospital, Copenhagen, Denmark;* [13]*University of Helsinki Department of Anaesthesia and Intensive Care, Helsinki, Finland;* [14]*Department of Anaesthesia, Fundacion Hospital Alcorcon, Madrid, Spain,* [15]*Department of Anaesthesia, South Cleveland Hospital, Middlesbrough, UK; and* [16]*Department of Anaesthesia, Leicester General Hospital, Leicester, UK*

Background: Postoperative cognitive dysfunction (POCD) is a common complication after cardiac and major non-cardiac surgery with general anaesthesia in the elderly. We hypothesized that the incidence of POCD would be less with regional anaesthesia rather than general.

Methods: We included patients aged over 60 years undergoing major non-cardiac surgery. After giving written informed consent, patients were randomly allocated to general or regional anaesthesia. Cognitive function was assessed using four neuropsychological tests undertaken preoperatively and at 7 days and 3 months postoperatively. POCD was defined as a combined Z score >1.96 or a Z score >1.96 in two or more test parameters.

Results: At 7 days, POCD was found in 37/188 patients (19.7%, [14.3–26.1%]) after general anaesthesia and in 22/176 (12.5%, [8.0–18.3%]) after regional anaesthesia, $P = 0.06$. After 3 months, POCD was present in 25/175 patients (14.3%, [9.5–20.4%]) after general anaesthesia vs. 23/165 (13.9%, [9.0–20.2%]) after regional anaesthesia, $P = 0.93$.

The incidence of POCD after 1 week was significantly greater after general anaesthesia when we excluded patients who did not receive the allocated anaesthetic: 33/156 (21.2% [15.0–28.4%]) vs. 20/158 (12.7% [7.9–18.9%]) ($P = 0.04$). Mortality was significantly greater after general anaesthesia (4/217 vs. 0/211 ($P < 0.05$)).

Conclusion: No significant difference was found in the incidence of cognitive dysfunction 3 months after either general or regional anaesthesia in elderly patients. Thus, there seems to be no causative relationship between general anaesthesia and long-term POCD. Regional anaesthesia may decrease mortality and the incidence of POCD early after surgery.

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Key words: anesthesia; cognitive function; complications; postoperative period; regional anesthesia; surgery.

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Postoperative cognitive dysfunction (POCD) is a common complication in elderly patients undergoing cardiac and non-cardiac surgery under general anaesthesia (1, 2). It has frequently been speculated that POCD might be avoided by performing appropriate surgical procedures under regional anaesthesia. Numerous comparative studies using neuropsychological testing have been conducted to test this hypothesis but no significant difference has yet been found (3–13). There are, however, limitations in several of these studies including low statistical

* *ISPOCD2 Investigators listed at the end of the paper*

power, comparison of group means rather than deterioration in individual test performance, failure to account for practice effects and low sensitivity of tests which may not be suitable for use in surgical patients. These factors may also limit detection of POCD beyond the first postoperative days after non-cardiac surgery (4, 5, 7, 12, 14).

The ISPOCD study (2) demonstrated long-term POCD in elderly patients undergoing non-cardiac surgery. Using this established sensitive test battery, we decided to compare the incidence of POCD in elderly patients randomly assigned to general versus regional anaesthesia in a multicentre study. We investigated early and late POCD as well as subjective reports of cognitive disturbance, testing the hypothesis that POCD would be detected at a lesser incidence after regional anaesthesia.

Materials and methods

Twelve hospitals in seven countries contributed patients to the study, each using the same protocol. All patients were aged over 60 years presenting for major surgery where either regional or general anaesthesia was appropriate. We enrolled subjects with an expected hospital stay of at least 4 days between October 1998 and October 2000 with follow-up until March 2001. The study received ethics committee approval in all institutions and each participant gave informed consent.

Exclusion criteria included diseases of the CNS. After giving informed consent, patients were randomly allocated to general or regional anaesthesia using a centralized dedicated computer program where allocation sequence was concealed. Blinding of patients and data collectors was not considered possible but group assignment was concealed through data processing until the final analysis was performed.

General anaesthesia was performed according to usual anaesthetist and institution practice, however, normocapnia was maintained and neuraxial blockade or regional analgesia were not used.

In the regional anaesthesia group, spinal or epidural anaesthesia was employed and postoperative epidural analgesia was encouraged. Sedation with propofol was permitted during regional anaesthesia at a level compatible with prompt arousal to a verbal stimulus.

Cognitive function was assessed using neuropsychological testing preoperatively (baseline) and at 7 days and 3 months postoperatively; comparing the changes between those at baseline with those after surgery. The evaluation was based on the following seven variables from the four neuropsychological tests: cumulative number of words recalled in three trials and the number of words at delayed recall from the Visual Verbal Learning test (15); the time and number of errors in part C of the Concept Shifting Test (16); the time and error scores from the third part of the Stroop Colour Word Interference Test (17) and the number of correct answers from the Letter Digit Coding Test (18).

We determined mood preoperatively and after 3 months using the Geriatric Depression Scale (GDS) (19). Subjective assessment of cognitive decline was evaluated after 3 months using the Subjective Cognitive Functioning questionnaire (SCF) given to both patients and relatives. Finally, the Instrument for Activities of Daily Living (IADL) score was assessed. The IADL-score was administered to patients as well as relatives preoperatively and at 3 months postoperatively.

Statistical analysis

We calculated the changes in performance of the seven test parameters and using previously collected data from a group of 176 healthy controls (2), we subtracted the average learning effect from these changes and divided the result by the control group SD to obtain a Z score for each individual test outcome. Patients had cognitive dysfunction when two out of seven Z scores in individual tests or the combined Z score were 1.96 or more. The incidence of POCD was compared using the *intention to treat approach* with a chi-squared test.

The results of the questionnaires were compared using Mann–Whitney rank sum test and we assessed the relation between postoperative cognitive dysfunction and the results of the questionnaires by Spearman's rank-correlation analysis on the composite Z score. All data are reported with the 5–95% range or 95% confidence interval where appropriate.

We estimated that a sample size of 1400 (assuming a drop-out rate of 20%) would allow us to detect a difference in POCD after 3 months between 5% after regional anaesthesia and 10% after general anaesthesia with a power of 0.90 at the 0.05 significance level.

Results

When patient enrolment had to be stopped, 438 patients had been included and 428 underwent randomization. The characteristics shown in Tables 1 and

Table 1

Patient characteristics and test intervals.

	General anaesthesia (*n* = 217)	Regional anaesthesia (*n* = 211)
Age (years)	70.8 (61.3–84.1)	71.1 (61.0–83.7)
ASA Physical health class		
I-II/III-IV	191/26	178/33
Sex (M/F)	81/136	94/117
Postoperative hospital stay (days)	8 (2–20)	9 (2–21)
Duration of anaesthesia (min)	140 (59–265)	145 (60–310)
Duration of surgery (min)	100 (30–222)	105 (30–245)
Blood loss (ml)	300 (0–1400)	300 (0–2000)
Interval between operation and 1st postoperative test (days)	7 (3–16)	7 (2–14)
Interval between operation and 2nd postoperative test (days)	102 (76–168)	100 (80–165)
Interval between preoperative test and operation (days)	1 (0–10)	1 (0–14)
Opioids $<$24 h before 1st postoperative test (no. of patients)	38	42

Median (5–95% range) except for ASA class and sex.

Table 2

Type of surgery.

	General anaesthesia (*n* = 192)	Regional anaesthesia (*n* = 187)
Hip replacement	45	35
Hip surgery, other	3	2
Knee replacement	51	56
Gynaecology	45	38
Vascular	15	22
Urology	7	7
Gastrointestinal	2	3
Other	24	24

2 were similar in the two groups. The first postoperative test was omitted in 74 patients (16.9%) and the second postoperative test in 98 (22.4%) (Fig. 1).

There was no significant difference between the groups in the proportion of patients who were missing either the first or second postoperative test data: 29/217 (general) vs. 35/211 (regional), $P = 0.35$ for the first test and 42/217 (regional) vs. 46/211 (general), $P = 0.53$ for the second. The patients who omitted the 3 months' test had significantly lower preoperative scores in the time variable of the Stroop Colour Word Interference Test and in the Letter Digit Coding Test (*P*-value adjusted with Bonferroni correction) but age and education were not significantly different (Table 3).

The incidence of POCD at 1 week after general anaesthesia was 37/188 (19.7%, [14.3–26.1%]) and after regional anaesthesia it was 22/176 (12.5%, [8.0–18.3%]), $P = 0.06$. After 3 months POCD was found in 25/175 (14.3%, [9.5–20.4%]) vs. 23/165 (13.9%, [9.0–20.2%]), $P = 0.93$.

Regional anaesthesia was unsuccessful in 24 patients allocated to regional anaesthesia in whom general anaesthesia was therefore necessary. Also, 35 patients allocated to general anaesthesia actually

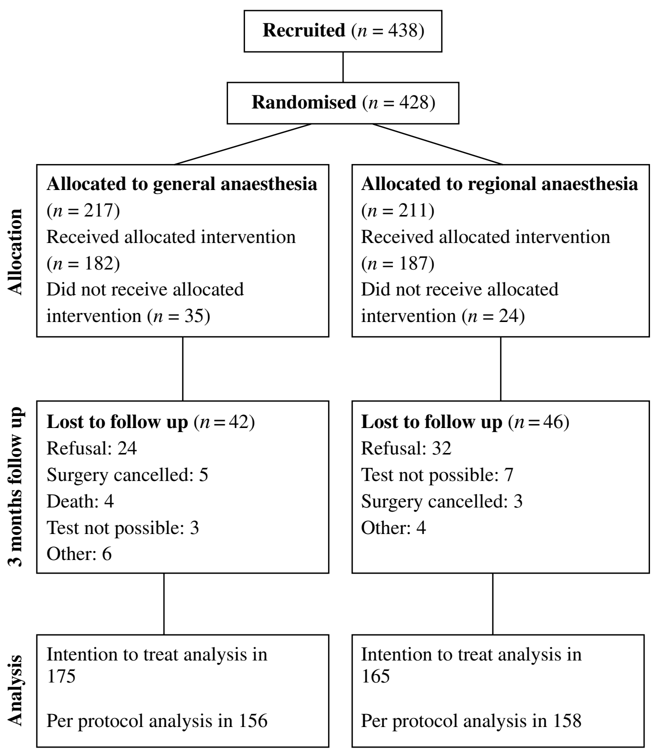

Fig. 1. Flow diagram summarising patient recruitment, randomisation, and follow-up.

Table 3

Patient characteristics and preoperative test result in patients who completed and patients who dropped out.

	Completed ($n = 340$)	Dropped out ($n = 98$)
Age (years)	70.7 (61.0–81.9)	71.6 (62.2–87.2)
Education		
Less than high school	225	65
High school	67	16
More than high school	48	10
Visual Verbal Learning, cumulated recall (number of words)	24 (14–33)	23 (14–34)
Visual Verbal Learning, delayed recall (number of words)	8 (3–12)	7 (3–11)
Concept Shifting Test, Time for part C (s)	48.1 (27.5–98.7)	52.5 (26.9–142.2)
Concept Shifting Test, number of errors in part C	0 (0–5)	1 (0–5)
Stroop Colour Word Test, Time for part 3 (s)	57.5 (37.2–110.2)	67.7 (37.9–125.6)*
Stroop Colour Word Test number of errors in part 3	1 (0–9)	1 (0–8)
Letter-Digit Coding, score	21 (9–35)	18 (6–34)*

Median (5–95% range) except for education.
*$P < 0.05$.

received spinal or epidural anaesthesia. Not all these 59 patients completed the study, but when excluded in a *per protocol analysis*, the incidence of POCD after general vs. regional anaesthesia after 1 week is 33/156 (21.2% [15.0–28.4%]) vs. 20/158 (12.7% [7.9–18.9%]), $P = 0.04$ and after 3 months 19/145 (13.1%, [8.1–19.7%]) vs. 21/147 (14.3%, [9.1–21.0%]), $P = 0.93$.

In the regional anaesthesia group, 37% received propofol sedation. The incidence of POCD in these patients was not significantly different from the incidence in the patients in this group who were not sedated (12.7% vs. 12.4% after 1 week and 10.3% vs. 15.9% after 3 months).

No difference was found between general and regional anaesthesia with regard to the GDS, SCF or IADL.

Mortality was significantly greater after general anaesthesia, 4/217 (1.8% [0.5–4.7%]), vs. 0/211 [0–1.7%]) (Table 4). All four patients received the allocated type of anaesthesia. Pulmonary embolism caused death in two patients at five and 29 days after joint replacement. One patient died 2 days after surgery due to heart failure and cause of death was unknown in one patient who died at home 3 months after surgery. The other postoperative complications were not significantly different between the groups (Table 4).

Discussion

Postoperative cognitive dysfunction was detected in 10–20% of our patients, both at 1 week and after 3 months with no significant difference between general and regional anaesthesia using the *intention to treat* approach ($P = 0.06$ at 1 week). If, however, a *per protocol* approach is used, then POCD is significantly less common after regional anaesthesia at 1 week ($P = 0.04$). A major problem during this study was the poor recruitment rate. Many patients were unwilling to participate because of the random allocation to treatment group, although it was emphasized that both were accepted treatments. We did not record how many patients were asked for consent but it is our estimate that approximately half of all patients refused participation. In our opinion, the low recruitment was a price that had to be paid for randomization of patients. The slow recruitment necessitated a substantial prolongation of the study period, but due to expiration of funding, we had to stop the inclusion when less than half of the calculated sample size was obtained. Having a sample size of 340 after 3 months, the statistical power is approximately 50% if we were aiming at detecting a difference in the incidence of POCD between 5% and 10% (significance level 5%).

We were disappointed that some surgeons and anaesthetists did not adhere to the allocated anaesthetic

Table 4

Postoperative complications.

	General anaesthesia ($n=217$)	Regional anaesthesia ($n=211$)
Respiratory	2	0
Cardiac	2	3
Delirium	5	4
Second operation	8	6
Infectious	7	6
Intensive Care stay for >24 h	3	0
Death*	4	0

*$P < 0.05$.

but insisted on either general or regional. This resulted in a substantial drop-out rate and failure to deliver the allocated treatment. If when comparing two treatments, a proportion of patients received the treatment opposite to that allocated, it is not surprising that a genuine difference between the treatments may be obscured. In this study 14% of patients received the opposite treatment to that allocated and, by excluding these patients, a significant difference became apparent at 1 week postoperatively.

The results should be applied with caution to the general surgical population due to the possible bias, for example we could have selected patients who had less education and whom we have previously demonstrated are more vulnerable to early POCD (2). On the other hand, the present study included nearly twice the number of patients included in the largest previous study of this issue (13). Several studies have compared general and regional anaesthesia and in only one of them has a significant difference been reported in mental function (3–13, 20). However, no neuropsychological testing was applied in that study (20). Neuropsychological test results can be compared in several ways. Examples are group means in postoperative raw scores or changes in raw scores. These approaches tend to overlook a possible difference, because it assumes that a general and uniform deterioration occurs (14). The ability of our testing to pick out a difference between general anaesthesia and regional anaesthesia at 1 week confirms its sensitivity in this patient group. The clinical importance of a neuropsychological deficit can be questioned but our cut-off at a Z-score of 2 is corresponding to a profound deterioration in the neuropsychological test performance, as illustrated in Table 5.

The etiology of POCD is likely to be multifactorial. Our observation of early cognitive impairment in the general anaesthesia group (after per protocol analysis) suggests a negative effect of either the general anaesthetic agents or the postoperative analgesic regimen. Other factors such as inflammatory or metabolic endocrine stress response associated with major surgery may be responsible for the later changes that occurred in both groups.

This study was not designed to assess the incidence of uncommon postoperative complications but we found a significantly greater mortality after general anaesthesia. This may be an incidental finding but we noted also that postoperative respiratory complications and the need for prolonged intensive care occurred only after general anaesthesia. Lower morbidity has been reported with regional anaesthesia, and beneficial effects of regional anaesthesia include lower blood loss and lower risk of postoperative thromboembolic complications (21–23). This is

Table 5

Importance of postoperative deterioration in cognitive function.

Parameter	At 1. Postoperative test	At 2. Postoperative test
Visual Verbal Learning, deterioration in cumulated recall (no. of words)	10	12
Visual Verbal Learning, deterioration in delayed recall (no. of words)	5	6
Concept Shifting Test, slowing for part C	61%	56%
Concept Shifting Test, increase in number of errors in part C	2	2
Stroop Colour Word Test, slowing for part 3	24%	24%
Stroop Colour Word Test, increase in number of errors in part 3	3	3
Letter-Digit Coding, deterioration in score	8	10

For the neuropsychological tests used in the study, we have calculated the deterioration required to obtain a Z score of 2.

compatible with our study's finding of two postoperative deaths in the general anaesthesia group caused by pulmonary embolism. Other factors may therefore also support the choice of regional anaesthesia.

In conclusion, we found no significant difference in the incidence of cognitive dysfunction 3 months after either general or regional anaesthesia. Accordingly, there is no evidence to suggest any causative relationship between general anaesthesia and long-term POCD. We suggest that the choice of anaesthetic, when several options exist, should be based on an open discussion of patients' preference, general postoperative complications, and the experience of the anaesthetist.

Participants in the Second International Study of Postoperative Cognitive Dysfunction

Steering Committee for ISPOCD2:
L. S. Rasmussen, C. D. Hanning, H. M. Kuipers, J. Jolles and J. T. Moller (Chairman of the ISPOCD group)

Data collection centres:
Denmark: L. S. Rasmussen, H. Abildstrom, J. T. Moller, G. Blom, B. Burgdorf (*Copenhagen*); D. Kristensen, E. Hjortsø (*Hillerød*); I. K. Nielsen (*Bispebjerg*)
Finland, Helsinki: K. Korttila, A. Yli-Hankala, E.Castejon
Greece, Iraklion: H. Askitopoulou, A. Papaioannou, O. Fraidakis, F. Haniotaki
Norway, Oslo: J. Raeder, B. Grimsmo
Spain: P. Vila, J. Canet, B. Ysamat, R. Garcia Guasch, R. Llasera, A. Chamero (*Barcelona*); M. T. Ibañez, J. A. Bonal, I. Navarro, P. Santos, M. Ramirez (*Alicante*); L. Munoz (*Madrid*)
UK: T. Johnson, M. Howarth, D. Fines (Salford), Chris Dodds (Middlesbrough)
USA, New York: J. H. Silverstein, J. A. Jalees, R. Cherkezian

Neuropsychology evaluation and monitoring:
J. Jolles, P. Houx, Maastricht, the Netherlands

Statistical support:
V. D. Siersma, L. T. Skovgaard, Copenhagen, Denmark

Data Management Center:
H. Kuipers, H. J. A. vd Meerendonk, G. J. A. vd Boomen, M. Manders, M. Quist, P. J. M. Cluitmans, Eindhoven, the Netherlands

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Address:
Dr L. S. Rasmussen
Department of Anaesthesia
Section 4231
Copenhagen University Hospital
Rigshospitalet
DK-2100 Copenhagen
Denmark
e-mail: lsr@rh.dk