Comparison of early cognitive function and recovery after desflurane or sevoflurane anaesthesia in the elderly: a double-blinded randomized controlled trial

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Background. Postoperative cognitive dysfunction (POCD) is being recognized as a complication contributing to perioperative morbidity and mortality of the elderly. We hypothesized that the use of the shorter-acting volatile anaesthetic desflurane would be associated with less incidence of POCD when compared with sevoflurane.

Methods. Approved by the local ethical committee, 80 patients (aged 65–75 yr) were enrolled in this randomized, double-blinded study. Patients were allocated to either the desflurane (n=40) or the sevoflurane (n=40) group. The primary outcome was the cognitive Test for Attentional Performance with its subtests Alertness, Divided Attention, Visual Scanning, Working Memory, and Reaction Change. In addition, Paper–Pencil Tests [Well-being Test BF-S, Recall of Digit Span (DST), Digit-Symbol-Substitution Test, Trail Making Tests A and B, and Spielberg State-Trait Anxiety Inventory] were measured. After baseline assessment 12–24 h before operation, patients were followed up 6–8 and 66–72 h after operation. Among other outcome parameters, emergence times from anaesthesia and modified Aldrete scores were recorded.

Results. There was no difference in the incidence of POCD. However, according to the Paper–Pencil Tests, significant improvements for the desflurane group could be detected (Well-being Test at 6–8 h, DST at 6–8 h, and Trail Making Test at 66–72 h). Emergence was significantly faster in the desflurane group for ‘time to open eyes’ and ‘time to extubation’.

Conclusions. The total incidence of POCD showed no differences between the desflurane and the sevoflurane groups. However, the tests Well-being scale, DST, and Trail Making Test, emergence times, and patients’ satisfaction were in favour of desflurane.

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The aim of this study was to compare early cognitive function in the elderly after general anaesthesia with either desflurane or sevoflurane using the computerized and established TAP as the primary outcome. We hypothesized that the use of the less soluble and faster-acting volatile anaesthetic desflurane would be associated with less incidence of POCD when compared with sevoflurane.

**Methods**

The primary outcome parameter was the cognitive function assessed with the computerized TAP (Version 1.7; Psytest, 2002), as reported previously. Of note, in this study, the TAP was performed using an augmented set of subtests. This was implemented to cover a broad range of cognitive domains, including Alertness, Divided Attention, Visual Scanning, Working Memory, and Reaction Change. In addition to the TAP, a selection of ‘classical’ cognitive tests is assessed as secondary outcome parameters, in the course called Paper–Pencil Tests, according to the way of assessment. This selection includes the Digit-Symbol-Substitution Test (DSST), Recall of Digit Span (DST), and the Trail Making Tests A and B. In addition, the short form of the Spielberger State-Trait Anxiety Inventory (STAI) and the Making Tests A and B. This selection includes the Digit-Symbol-Substitution Test (DSST), Recall of Digit Span (DST), and the Trail Making Tests A and B.

POCD was defined as being a 20% decline in 20% of both the Paper–Pencil Tests and the TAP. The TAP assessment was completed by the study subjects in about 45 min.

Eighty patients, aged 65–75 yr, ASA I–III, were enrolled in this clinical trial. The trial was approved by the local ethics committee. Randomization was computer-generated and allocation concealment was ensured by enclosing assignments in sealed, sequentially numbered envelopes. The anaesthetist could not be blinded owing to the different administration methods of the anaesthetics; however, both study investigators and patients were blinded to group assignment (double-blinded observation).

The baseline measurements of the TAP and of the Paper–Pencil Tests were performed 12–24 h preoperative, after obtaining written informed consent. The study subjects were visited by the investigator and were instructed in a standard way on how to use the test battery (TAP) and the Paper–Pencil Tests. To prevent distraction from clinical routine and to guarantee a most identical setting, the room-sharing patients were asked to leave the room and all electronic devices such as telephone and TV were switched off. The 6–8 and 66–72 h postoperative testing were assessed in the same way for each patient. At all test time points, the study subjects first performed the TAP followed by the Paper–Pencil Tests.

For the secondary outcome parameters, the emergence times from anaesthesia were recorded, including the time of tracheal extubation. At a 20 s interval, starting from the time of discontinuation of anaesthetic administration, a blinded investigator asked each patient to open his or her eyes, squeeze the investigator’s hand, and state time (actual day) and spatial orientation until correct answers were given. Every patient was discharged to the postanaeesthetic care unit (PACU) for immediate recovery as soon as they were able to be transported safely to the PACU. At arrival, 5, 10, 15, 30, 45, 60 min, and at discharge, the modified Aldrete scores with a 10-point scale were recorded in the PACU. The patients were asked for nausea and pain at the same time intervals. Additionally, vigilance, well-being, and energy were recorded at the same time. Therefore, an independent investigator assessed the patients’ vigilance; well-being and energy were evaluated by spontaneous patients’ statements. Vigilance was rated as awake, tired, or sleeping. Well-being was classified as excellent, good, fair, and poor. Energy was divided into normal, fair, and poor.

Further, the patients were questioned 6–8 h postoperative for patients’ self-evaluation of the anaesthesia procedure, assessed by marks from one to six (excellent–unsatisfactory). Additionally, the patients were asked whether they would choose the same anaesthesia if necessary for further operations.

The patients underwent elective surgery in traumatology, ear, nose, and throat surgery, gynaecology, urology, or neurosurgery. Of note, neurological interventions were limited to operations on the spine. Chronic alcohol or drug abuse, disturbed renal or liver function, diabetes mellitus, disabling neuropsychiatric disorders, history of stroke, cardiopulmonary resuscitation, or brain trauma in the last 12 months, increased intracranial pressure, anaphylactic reaction to anaesthetics, emergency operations, history of myocardial infarction, adrenal insufficiency, congestive heart failure, and lack of cooperation or legal incapacity were excluded for eligibility. Duration of anaesthesia was planned for at least 60 and up to 180 min. Standard monitoring included three-lead ECG, pulse oximetry, non-invasive arterial pressure measurements, temperature (AS/3 monitor, GE-Datex Ohmeda, Helsinki, Finland), bispectral index monitoring (BIS model A 2000®, Software Version 2.21, Aspect Medical Systems, Boston, MA, USA), and the measurement of end-tidal carbon dioxide, oxygen, and anaesthetic gas concentrations. All mentioned parameters were recorded at fixed intervals of 5 min. For induction of anaesthesia, patients were preoxygenated with oxygen 100% for 3 min followed by a slow i.v. injection of propofol (2 mg kg\(^{-1}\)) and simultaneously given remifentanil at 0.5 µg kg\(^{-1}\) over 60 s. Rocuronium in a dosage of 0.6 mg kg\(^{-1}\) was used to facilitate tracheal intubation. Depth of anaesthesia was controlled by adjusting desflurane or sevoflurane to age-adapted equipotent minimum alveolar concentration (MAC) between 4.2 and 4.5 vol% (desflurane) or 1.1 and 1.4 vol% (sevoflurane) in oxygen 30%. (Cato Draeger, Lübeck, Germany) and administering remifentanil at a base rate of 0.15 µg kg\(^{-1}\) min\(^{-1}\). During surgery, remifentanil was titrated due to clinical needs. On the basis of the patient’s haemodynamic
(systolic arterial pressure or heart rate differing >20% from baseline), autonomic (sweating, flushing, and salivating), and somatic signs (movement and swallowing), the remifentanil infusion was increased successively until symptoms were resolved. Standard treatment of blood loss and fluid replacement strategy were used if necessary.

As part of the post-anaesthetic pain management, piritramide 0.05 mg kg$^{-1}$ i.v. and a short infusion of metamizole 15 mg kg$^{-1}$ were administered 20 min before the estimated end of surgery as part of post-anaesthetic pain management. Ten minutes before the end of surgery, the inhaled anaesthetics were reduced to 0.5 age-adapted MAC. Anaesthesia was maintained until all surgical interventions were completed, the haemodynamics (systolic arterial pressure or heart rate) were stable, and full recovery of neuromuscular block was reached (TOF-Watch SX®, Organon Teknika, Eppelheim, Germany). From this point, return of spontaneous breathing was facilitated by allowing end-expiratory carbon dioxide to increase up to 6.6 kPa. After full recovery of the upper airway reflexes and return of sufficient spontaneous breathing [ventilatory frequency >8 breaths min$^{-1}$ and oxygen saturation ($S_aO_2$) >95% at $F_{iO_2}$ 100%], the patients’ tracheas were extubated.

**Statistical analysis**

Parametric data were tested with one-way ANOVA and presented as means and standard deviation, as means and standard error of the means, as median and range, or as presented as means and standard deviation, as means and 95% confidence intervals, accordingly. Categorical data were analysed with the two-tailed Pearson’s $\chi^2$ test and are given as numbers and per cents of total. Statistical analysis was performed using SPSS Software Version 16.0 (SPSS Inc., Chicago, IL, USA). GraphPad PRISM® (GraphPad Software Inc., La Jolla, CA, USA) was used to generate the figures.

The sample size was calculated for the primary outcome parameters with a power of $\beta=0.9$ and a significance level of $\alpha=0.05$, considering a difference of 20% as relevant. Mean values and standard deviations were taken from a previous study in the elderly assessing the TAP (patients aged 65–75 yr) with the subtests Alertness, Divided Attention, and Working Memory.$^6$ The power was calculated for the subtests of the TAP (Alertness, Divided Attention, and Working Memory) with $n=6–21$ per group. The trial size was determined with a total of 40 patients per group to compensate for possible drop-outs. The power calculation was performed using nQuery Advisor®, Version 4.0 (Statistical Solutions, Saugus, MA, USA).

**Results**

A total of 80 patients were included in this study, 40 in the desflurane group and 40 in the sevoflurane group. Both study groups were comparable with regard to age, height, weight, gender, education level, ASA status, and Apfel score.$^{14}$

At the 6–8 h postoperative assessment, the TAP was completed by 31 patients in the desflurane group and 33 patients in the sevoflurane group, at the 66–72 h assessment by 27 and 30 patients. The reasons for drop-outs were refusal of postoperative testing, not receiving the allocated intervention, and discharge from hospital before the second assessment.

The vital parameters systolic and diastolic arterial pressure, heart rate, and $S_aO_2$ were comparable between the groups, the latter being at least 98% at all times. The mean remifentanil consumption was comparable in both groups. The average anaesthetic gas concentration was 4.32 (0.26)% in the desflurane group and 1.27 (0.11)% in the sevoflurane group. Type of surgery and duration of anaesthesia did not differ between the groups. Baseline assessment and the assessment of the TAP were performed at comparable time points (Table 1).

Patients in the desflurane group recovered significantly faster as indicated by the ‘time to open eyes’ ($P=0.05$) and ‘time to extubation’ ($P=0.05$). No difference was seen between the ‘time to react on demand’ and ‘time to time (actual day) and spatial orientation’. Length of stay in the PACU and intra- and postoperative opioid consumption were comparable between the groups (Table 1). In the PACU, the modified Aldrete scores were similar in both groups. The following scores were in favour of desflurane: vigilance at arrival ($P=0.01$), vigilance at 5 min ($P=0.02$), well-being at discharge ($P=0.03$), and energy at 30 and 45 min ($P=0.05$ and 0.04) (Table 2).

Baseline assessment of cognitive function showed no difference between the two groups. The 6–8 and 66–72 h postoperative tests for cognitive function and well-being assessed with the Paper–Pencil Tests and the ones assessed with the TAP were normalized to the 12–24 h preoperative baselines. The following subtests of the Paper–Pencil Tests showed significant differences in favour of desflurane: Well-being at 6–8 h ($P=0.04$), DST at 6–8 h ($P=0.02$), and Trail making Test A at 66–72 h ($P=0.05$) (Fig. 1). There was no difference for the TAP between the two groups (Fig. 2).

Regarding both, the Paper–Pencil Tests and the TAP, the numbers with a decline of 20% from the 12–24 h preoperative baseline did not differ between the desflurane and the sevoflurane groups at the 6–8 and 66–72 h post-operative assessment (Table 3). Furthermore, the incidence of POCD (defined as being a 20% decline in 20% of both the Paper–Pencil Tests and the TAP)$^{11}$ was similar at the 6–8 h (desflurane 39% and sevoflurane 36%; $P=0.67$) and 66–72 h (desflurane 41% and sevoflurane 47%; $P=0.96$) time points.

The marks for patients’ self-evaluation of the anaesthesia procedure assessed 6–8 h after operation were significant in favour of the desflurane group ($P=0.03$). Also the
question of repetition of the same anaesthesia for further operations showed more positive answers for the desflurane group (P=0.05).

Discussion
In the present study, we compared early cognitive function in the elderly after desflurane or sevoflurane anaesthesia. The TAP showed no differences in incidence and severity between the desflurane and the sevoflurane groups at the 6–8 and 66–72 h assessment. Compared with the baseline, the incidence of POCD was high in both groups (desflurane 39% and sevoflurane 36% at the 6–8 h assessment and at 66–72 h assessment desflurane 41% and sevoflurane 47%). However, in various subtests of the Paper–Pencil Tests, significant improvements for desflurane (Well-being scale, DST, and Trail making Test A) could be detected. Emergence times such as ‘time to open eyes’ and ‘time to extubation’ were faster after desflurane anaesthesia. The scores for vigilance, well-being, and energy in the PACU turned out beneficial to some extent in the desflurane group. Patients’ self-evaluation of anaesthesia was in favour of desflurane.

The power was calculated considering a difference of 20% as relevant. However, a difference of 10–15% might be clinically more realistic. Taking this into account, the

Table 1 Anaesthesia data, emergence from anaesthesia, and time points of testing. Average anaesthetic gas concentration is presented as mean (SD). Type of surgery is given in number and percentage of total in parentheses. Anaesthesia and PACU times are displayed as means with the upper and lower 95% confidence interval. Intra- and postoperative piritramide consumption is presented as mean (SD). Emergence from anaesthesia: all time points are presented in minutes as mean and lower and upper 95% confidence intervals in parentheses. Time points of testing are shown in hours and minutes (h:min) with the upper and lower 95% confidence interval

<table>
<thead>
<tr>
<th></th>
<th>Desflurane</th>
<th>Sevoflurane</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Average anaesthetic gas concentration (%)</td>
<td>4.32 (0.26)</td>
<td>1.27 (0.11)</td>
<td>—</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
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<tr>
<td>Trauma</td>
<td>6 (16%)</td>
<td>7 (18%)</td>
<td>0.48</td>
</tr>
<tr>
<td>ENT</td>
<td>4 (11%)</td>
<td>2 (5%)</td>
<td></td>
</tr>
<tr>
<td>Gynaecology</td>
<td>8 (22%)</td>
<td>5 (13%)</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>7 (19%)</td>
<td>8 (21%)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>12 (32%)</td>
<td>17 (44%)</td>
<td></td>
</tr>
<tr>
<td>Anaesthesia time (min)</td>
<td>127 (105–149)</td>
<td>152 (133–170)</td>
<td>0.09</td>
</tr>
<tr>
<td>PACU time (min)</td>
<td>66 (54–78)</td>
<td>71 (40–80)</td>
<td>0.58</td>
</tr>
<tr>
<td>Intraoperative piritramide (mg)</td>
<td>5.2 (1.9)</td>
<td>5.9 (2.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Postoperative piritramide (mg)</td>
<td>7.2 (4.1)</td>
<td>7.9 (4.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Time to open eyes (min)</td>
<td>7.4 (6.2–8.6)</td>
<td>9.2 (7.8–10.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Time to react on demand (min)</td>
<td>7.7 (6.5–8.9)</td>
<td>9.2 (7.7–10.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>7.7 (6.5–8.9)</td>
<td>9.4 (8.0–10.8)</td>
<td>0.05</td>
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<tr>
<td>Time to (actual day) and spatial orientation (min)</td>
<td>10.8 (9.3–12.2)</td>
<td>13.4 (9.5–17.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Baseline assessment (h:min)</td>
<td>18:12 (17:47–18:37)</td>
<td>18:36 (18:16–18:55)</td>
<td>0.13</td>
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<tr>
<td>6–8 h postoperative assessment (h:min)</td>
<td>15:26 (13:54–16:57)</td>
<td>14:43 (13:05–16:21)</td>
<td>0.52</td>
</tr>
<tr>
<td>66–72 h postoperative assessment (h:min)</td>
<td>15:16 (13:48–14:45)</td>
<td>15:15 (13:55–16:35)</td>
<td>0.98</td>
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Table 2 Post-anaesthetic care unit. All values are recorded after surgery at arrival (A) in the PACU, after 5 (5), 15 (15), 30 (30), 45 (45) min, and at discharge from the PACU (D). Modified Aldrete scores are presented as mean (SD). Vigilance, well-being, and energy after anaesthesia are shown in numbers and per cent of total (in parentheses). Vigilance is rated as awake (A), tired (T), and sleeping (S). Well-being is classified as excellent (E), good (G), fair (F), and poor (P). Energy is divided into normal (N), fair (F), and poor (P)

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<tr>
<td>Vigilance (A/T/S)</td>
<td></td>
<td></td>
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<tr>
<td>4/27/5 (11/27/15)</td>
<td>4/27/6 (11/27/15)</td>
<td>0.01</td>
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<tr>
<td>Vigilance (A/T/S)</td>
<td></td>
<td></td>
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<tr>
<td>5/17/18 (10/44/46)</td>
<td>5/17/18 (10/44/46)</td>
<td>0.23</td>
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<tr>
<td>Well-being (E/G/F)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/16/18 (2/4/71)</td>
<td>9/16/18 (2/4/71)</td>
<td>0.55</td>
<td></td>
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<tr>
<td>Energy (N/F/P)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2/17/17 (6/47/74)</td>
<td>2/17/17 (6/47/74)</td>
<td>0.15</td>
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Pörtgen et al.
study might be underpowered. Further limitations of the study are: patients above 75 yr and those with cardiac and endocrine disease are excluded. However, these patients are at high risk to develop POCD. This fact weakens the external validity of the study. In addition, if the Bonferroni correction is applied, as the study has several outcome parameters, all test results fail to be significant. The average anaesthetic gas concentration was 4.32 (0.26)% in the desflurane group and 1.27 (0.11)% in the sevoflurane group. Both gas concentration ranges are in line with the age-adapted MAC described by Nickalls and Mapleson. As the anticipated operation is a stress factor for the patients, the timing of the baseline assessment is critical and was therefore assessed in a standardized manner 12–24 h before operation in the hospital. Heavner and colleagues used a baseline assessment just before premedication was given, but this could have influenced the baseline testing even more.

Learning by repeated postoperative assessments may represent a strong confounder. Retest reliability for the TAP has been shown before, but not for such a short interval as used in our study. Looking at the Paper–Pencil Tests. All values are shown as mean (SEM) and display the change in per cent at 6–8 and 66–72 h postoperative normalized to the 12–24 h preoperative baseline. All ordinates are in per cent. (a) Well-being Test BF-S (an increase in per cent presents a decline in well-being). For (n–f) an increase in per cent shows an increase in outcome: (n) DST, (c) DSST, (n) Trail Making Test A, (n) Trail Making Test B, and (f) six-item short-form of the Spielberg State-Trait Anxiety Inventory (STAI). Black lines and open diamonds display the sevoflurane group and grey lines and open circles present the desflurane group; *P<0.04; **P<0.02; ***P<0.05. An increase in baseline might be due to a learning effect in (n–f).
Fig 2 Cognitive function assessed with the TAP. All values are mean (SEM) and display the change in per cent at 6–8 and 66–72 h postoperative normalized to the 12–24 h preoperative baseline. All ordinates are in per cent. For (A–J), an increase in per cent shows an increase in outcome. All figure pairs show first reaction time and then valid reaction. (A and B) Alertness; (C and D) Divided Attention; (E and F) Visual Scanning; (G and H) Working Memory; (I and J) Reaction Change. Black lines and black open symbols stand for the sevoflurane group and grey lines and grey open circles display the desflurane group.
Tests, we used complementing versions when available (e.g. Trail Making Test).

In this study, elderly patients underwent surgery known to be associated with a high risk of POCD. The total level of POCD seems to be similar to earlier studies performed in the same age group. However, these data are limited since different methods have been used to measure and define POCD.

By using the DSST, Heavner and colleagues could not find any difference between general anaesthesia with desflurane or sevoflurane in the elderly. Heavner and colleagues attributed their findings to the limitations of the DSST. We used enhanced testing instruments and added the computerized TAP with its subtests Alertness, Divided Attention, Visual Scanning, Working Memory, and Reaction Change in our investigation. The TAP is established to measure attention and was used in previous studies. It was designed to analyse cognitive functions. The increase in the subtest Alertness indicates temporary deficits in attention whereas general slowness can be distinguished. Performing two or more different duties simultaneously is often needed in daily routine. This is examined by dual-tasks in the subtest Divided Attention. The subtest Visual Scanning is important because it measures continuous attention. In the concept of ‘Working Memory’, the short-term memory is the essential instance to control information flow for good attentional performance. Using the subtest Working Memory, a continuous control of the information flow through short-term memory is tested. As mental flexibility seems to be an important aspect of cognitive functioning, this is assessed by the subtest Reaction Change.

In this study, emergence times for ‘time to open eyes’ and ‘time to extubation’ in the elderly with desflurane were faster than those with sevoflurane. Patients’ satisfaction after anaesthesia was in favour of desflurane.

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We would like to thank Jan-Hinrich Baumert and Oliver Kunitz who helped in initiating this trial.

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