

Effects of sevoflurane and desflurane on early cognitive changes after thyroid surgery: interim results

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The study is being conducted at the 1st Department of Anaesthesiology, the Centre of Abdominal Surgery, the Centre of Anaesthesiology, Intensive Care and Pain Management of Vilnius University Hospital Santaros Klinikos.

Background. These are primary results of a randomized double-blinded study comparing postoperative changes in cognitive functions and the effect of desflurane and sevoflurane on these changes.

Materials and methods. The study includes patients of ≥ 40 years of age undergoing elective thyroid surgery under general anaesthesia. Patients were randomly allocated to either sevoflurane or desflurane group. Cognitive testing (memory, attention, and reasoning tasks) was performed a day before surgery and repeated 24 hours postoperatively. A decrease of 20% in the postoperative score was considered as postoperative cognitive dysfunction (POCD).

Results. At present 38 patients are included in the study. Median decrease in the postoperative score was 2.7% (IQR 16.7). The incidence of POCD was 2.6%. Significantly decreased memory scores were observed in 15.8% of patients. Both study groups were comparable based on demography, duration of anaesthesia, intraoperative opioids, postoperative pain, and satisfaction. No difference was found in the cognitive score comparing sevoflurane and desflurane groups, except for memory tasks where the sevoflurane group performed worse ($p = 0.01$).

The age or the duration of anaesthesia did not affect postoperative scores. Postoperative satisfaction negatively correlated with the memory score ($r = -0.35$, $p = 0.03$). Postoperative satisfaction correlated with the reasoning score ($r = -0.55$; $p < 0.01$) and the total score ($r = -0.42$; $p = 0.03$) in the sevoflurane group. Likewise, temperature in the sevoflurane group correlated with the memory score ($r = -0.58$; $p = 0.02$).

Conclusions. The desflurane group performs better in memory tasks, but no such advantage is found in the total cognitive score. In contrast to the age or anaesthesia duration, intraoperative temperature and postoperative satisfaction may affect postoperative cognitive performance.

Keywords: cognitive disorders, sevoflurane, desflurane, POCD

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is the most common type of cognitive impairment in the postoperative period (1, 2). POCD commonly occurs after cardiac, vascular, and major orthopaedic surgery. The incidence of POCD increases with age (3, 4). Although cognitive dysfunction rarely lasts beyond several weeks to months, it is associated with premature exit from work force, decreased quality of life, and increased mortality (2, 4–6).

Due to their residual effects altering the activity of the central nervous system anaesthetic drugs can affect postoperative cognitive function (7). A rapid recovery from general anaesthesia may reduce the incidence of POCD (3). Desflurane has been associated with faster emergence time, better vigilance, and patient satisfaction (3, 8, 9). However, to this day no clear evidence exists that a certain type of anaesthesia, drug or monitoring technique would reduce the incidence of POCD (2, 3, 10).

We are presenting primary results of a randomized double-blinded study comparing the implications of desflurane and sevoflurane on postoperative cognitive changes.

MATERIALS AND METHODS

This prospective randomized double-blinded study is being conducted at Vilnius University

Hospital Santaros Klinikos. The study protocol was revised and approved by Vilnius Regional Biomedical Research Ethics Committee (Approval No. 158200-17-949-453). Written informed consent was obtained from study participants.

So far 38 patients ≥ 40 years of age and undergoing elective thyroid surgery under general inhalational anaesthesia have been included in the study. The participants were excluded from the study if diagnosed with neurological, cognitive or psychiatric disorders or the follow-up was lost (Fig. 1). The participants were randomly allocated into study groups (desflurane or sevoflurane) by drawing closed envelopes. The envelopes were opened in the operating room by the attending anaesthesiologist (not the researcher). Separate researchers were responsible for cognitive testing and intraoperative data collection.

Preoperative anxiety was evaluated using the Hospital Anxiety and Depression Scale (HADS). Baseline cognitive status was determined a day before surgery using psychometric testing. The tasks focused on three domains: memory, attention, and reasoning. Ten-item test battery consisting of Auditory Verbal Learning, Odd One Out, Sequence of Numbers, Digit Span, Backwards Spelling, Math Processing, Trail-making, Cross-out Paper, and Pencil, and 1-back test was used. The domains were evaluated 45 points each with 135 points as the maximum total score possible. Cognitive

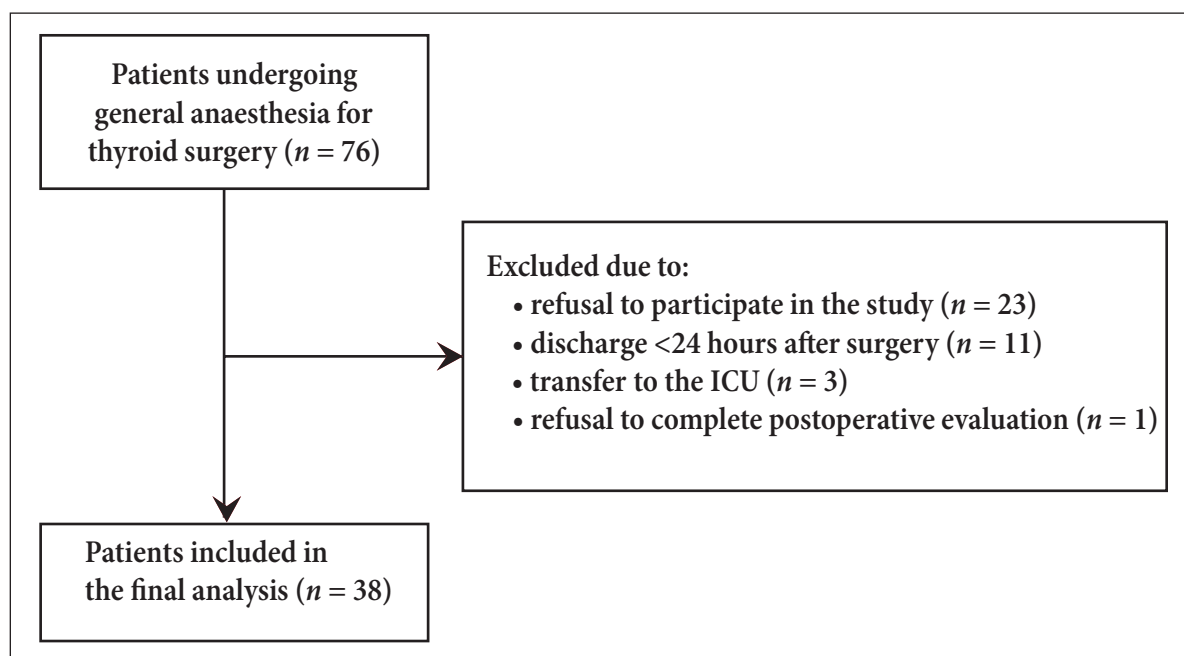


Figure. Flow chart of study participants

testing was repeated 24 hours postoperatively using a modified set of corresponding tests. POCD was diagnosed if total performance score decreased by $\geq 20\%$ from the baseline. Postoperative pain levels were recorded based on the Numerical Pain Scale (NPS) (0–10 points), postoperative satisfaction was evaluated using a five-point Likert type scale (1 – very poor, 5 – excellent).

Anaesthesia induction and maintenance were left at the discretion of the attending anaesthesiologist. During anaesthesia entropy was kept at level between 40 and 60 and the lowest intraoperative nasopharyngeal temperature was recorded.

Data management and statistical analyses were performed with SPSS v23.0 and XLSTAT 2018. Assessment of data normality was done using the Shapiro-Wilk test. Descriptive statistics were used to describe data. The T-test and ANOVA for normal data and the Mann-Whitney-U and the Kruskal-Wallis test for non-parametric data were used for sevoflurane and desflurane group continuous data comparison. χ^2 or Fisher's exact test were used for categorical data where appropriate. Preoperative and postoperative testing results were compared using Paired Sample T-test for normal data and the Wilcoxon signed-rank test for non-normal data. Correspondingly, Pearson and Spearman correlations were used to evaluate the relationship between cognitive test results and perioperative factors. A p value of <0.05 was considered significant. All p -values were two-tailed.

RESULTS

The data of 38 patients were analysed (26 in the sevoflurane group and 12 in the desflurane group). The majority of the participants (84.2%) were female. The mean age of patients was 56.1 years (IQR 16.5). Mean duration of anaesthesia was 142.5 minutes (IQR 30.0) with a range of 85 to 205 minutes.

Median decrease of postoperative cognitive score was 2.7% (IQR 16.7). No significant difference was found between the total preoperative and postoperative cognitive score (94.2 (IQR 28.1) vs. 93.4 (IQR 25.4), $p = 0.98$) in the overall study population. Moreover, no change was observed in memory, attention, or reasoning performance. POCD was diagnosed in one patient (2.6%). However, six participants (15.8%) had significantly lower ($>20\%$) memory scores.

Both study groups were comparable based on education, demographic and intraoperative data, including duration of anaesthesia and intraoperative opioid consumption (Table 1). Likewise, no difference was found between postoperative pain and satisfaction.

Data analysis did not reveal any differences in the cognitive performance between the study groups, except for memory scores which were in favour of desflurane (Table 2). Moreover, the desflurane group demonstrated an improvement in completing memory tasks postoperatively.

A weak negative correlation was discovered between postoperative satisfaction and the total

Table 1. Demographic and intraoperative data of sevoflurane and desflurane groups

	Sevoflurane ($n = 26$)	Desflurane ($n = 12$)	p
Sex	Male – 5 (19.2%) Female – 21 (83.3%)	Male – 1 (8.3%) Female – 11 (91.7%)	0.37
Age, years	55.3 (IQR 17.3)	59.9 (IQR 17.8)	0.51
Body mass index, kg/m^2	29.3 (IQR 7.9)	31.2 (IQR 9.3)	0.34
Duration of anaesthesia, min	137.3 (IQR 35.0)	153.8 (IQR 23.8)	0.09
Fentanyl, $\mu\text{g}/\text{kg}/\text{h}$	1.9 (IQR 0.8)	2.0 (IQR 1.3)	0.95
Morphine, $\text{mg}/\text{kg}/\text{h}$	0.04 (IQR 0.05)	0.02 (IQR 0.04)	0.07
Minimal temperature, $^{\circ}\text{C}$	36.2 (IQR 0.6)	36.1 (IQR 0.4)	0.85
Postoperative pain, pts	3.1 (IQR 4.0)	2.8 (IQR 4.0)	0.77
Postoperative satisfaction, pts	3.7 (IQR 1.0)	3.7 (IQR 1.8)	0.83

Table 2. Median and the range of percentage change from the baseline cognitive score in the study groups

	Sevoflurane	Desflurane	<i>p</i>
Total result	-1.3 (-30.6–17.2)	1.4 (-8.0–24.2)	0.49
Reasoning	0.8 (-26.8–26.2)	-5.1 (-48.3–6.5)	0.19
Attention	-0.3 (-32.2–27.0)	-6.4 (-28.3–11.3)	0.26
Memory	-5.1 (-86.4–48.8)	27.7 (-6.0–154.2)	0.01

score of the entire study population (-0.35 , $p = 0.03$). An identical relationship was found between patient satisfaction and memory performance (-0.35 , $p = 0.03$). Conversely, we failed to identify any correlations between the age, the duration of anaesthesia, or postoperative pain intensity and psychometric testing results.

Analysis of the sevoflurane group revealed a medium negative correlation between the postoperative satisfaction score and performance in reasoning tasks (-0.55 , $p < 0.01$) and a total change in the cognitive score (-0.42 , $p = 0.03$). Furthermore, low intraoperative temperature was also associated with decreased memory performance (-0.58 , $p = 0.02$). On the other hand, no significant correlations were found in the desflurane group.

DISCUSSION

POCD is one of the most common cognitive disturbances occurring after surgery. However, in our study the POCD incidence is rather low – 2.7%. On the one hand, wide variations in the POCD incidence are demonstrated in different studies. Largely, this depends on the type of tests used to make a diagnosis, since no uniform testing methodology exists (4). On the other hand, the type of surgery also plays an important role. POCD is more common after high-risk cardiac, orthopaedic, and vascular surgery (3, 4). Thyroid surgery is considered a low-risk procedure; therefore, the incidence of POCD might be lower than after major operations. Endocrine changes may have an impact on cognitive changes (4), yet pre-existing thyroid abnormalities have not been associated with a higher incidence of POCD (11).

Advanced age is a major risk factor of POCD irrespective of the type of surgery (4). Fairly young age of our participants could have precluded us from finding such an association in this study. Likewise, it may also contribute to a low incidence of cognitive dysfunction in our case.

Apart from the memory score, we failed to find any differences in postoperative cognitive changes between sevoflurane and desflurane groups. Study of Qiao et al. discovered an advantage of propofol over sevoflurane at one week postoperatively. A possible explanation could be that inhalational anaesthetic causes neuronal apoptosis and therefore impedes memory and learning processes (10). Regarding volatile anaesthetics, a recent review by Alalawi et al. did not find any difference between sevoflurane and desflurane in cognitive performance (2). Nevertheless, most of the studies are of an observational nature and evidence from randomized controlled trials is lacking when comparing different anaesthesia techniques or anaesthetics and the incidence of POCD (2, 4).

According to our data, desflurane is superior to sevoflurane in memory tasks. Desflurane is known to have a shorter “time-to-open eyes”, “time-to-extubation”, and better vigilance than sevoflurane (8). Yet this cannot fully explain the result considering no between-group difference found in attention or reasoning tasks. Furthermore, memory performance significantly increased from the baseline in the desflurane group. Postoperatively enhanced cognitive functions could be explained by an overall improvement of health, lower anxiety and stress after surgery (5).

Contrary to the age and anaesthesia duration, poor postoperative satisfaction correlated with a decline in postoperative cognitive performance of the overall study population. Worse wellbeing after surgery decreases the patient’s commitment to complete testing. Similarly, postoperative pain has been found to be associated with postoperative cognitive impairment (4, 12).

Lower intraoperative temperature had a negative impact on the postoperative memory score in the sevoflurane group. No such effect was noticed in desflurane patients. Animal studies reveal neuronal damage caused by rapid rewarming and subsequent inflammation (4). This translates to human

research where hypothermia has been identified as a risk factor of POCD (13). On the other hand, in this study only one patient was truly hypothermic with the lowest recorded temperature of 34.8°C.

One can notice an unequal number of participants in sevoflurane and desflurane groups. This weakness of the study is temporary and caused by the process of randomization. In our case, the participants are allocated to study groups by drawing envelopes from a pool of envelopes. In contrast to 1:1 randomization, we cannot ensure a similar number of patients in both study arms until the end of the study. For this reason, there might be a shift in the final results when the study is completed.

CONCLUSIONS

At the moment, interim analysis demonstrates an advantage of desflurane in accomplishing memory tasks, however, no difference is found between two inhalational anaesthetics in the overall cognitive result. In contrast to the age or anaesthesia duration, intraoperative temperature and postoperative satisfaction may have implications on postoperative cognitive performance.

Importantly, these are only primary results of the study, therefore further analysis is needed to draw more definite conclusions.

CONFLICT OF INTEREST

None declared.

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INHALIACINIŲ ANESTETIKŲ SEVOFLURANO IR DESFLURANO ĮTAKA ANKSTYVIEMS KOGNITYVINIAMS POKYČIAMS PO SKYDLIAUKĖS OPERACIJŲ: PIRMINIAI REZULTATAI

Santrauka

Įžanga. Pateikiami pirminiai randomizuoto dvigubai aklo tyrimo rezultatai, kurie analizuoja kognityvinių funkcijų kitimus po bendrosios nejautos ir inhaliacinių anestetikų sevoflurano bei desflurano įtaką šiems pokyčiams.

Metodika. Į tyrimą buvo įtraukti 40 metų ir vyresni pacientai, kuriems skydliaukės operacijos atliekamos taikant bendrąją nejautrą. Tiriamieji buvo atsitiktinai paskirti į vadinamąsias sevoflurano ir desflurano grupes. Kognityvinių funkcijų (atminties, dėmesio, loginio mąstymo) užduotys buvo atliekamos dieną prieš operaciją ir pakartotinai įvertintos praėjus 24 valandoms po procedūros. Pooperacinė kognityvinė disfunkcija (POKD) diagnozuota, jei testų rezultatai po operacijos pablogėjo bent 20 %.

Rezultatai. Tyrime dalyvavo 38 pacientai. Vidutiniškai pooperacinis testų rezultatas pablogėjo 2,7 % (IQR 16,7).

Nustatytas 2,6 % POKD dažnis. 15,8 % tiriamųjų daug prasčiau atliko atminties užduotis. Abi tiriamųjų grupės nesiskyrė pagal demografinius rodiklius, anestezijos trukmę, opioidų sunaudojimą, pooperacinį skausmą ar savijautą. Pooperaciniai kognityvinių testų rezultatai tarp grupių nesiskyrė, išskyrus atminties užduotis, kurias sevoflurano grupės pacientai atliko prasčiau ($p = 0,01$).

Nei amžius, nei anestezijos trukmė neturėjo įtakos pooperaciniams testų rezultatams. Neigiama koreliacija nustatyta tarp savijautos po operacijos ir atminties užduočių rezultato ($r = -0,35$; $p = 0,03$). Pooperacinė savijauta taip pat koreliavo su bendru ($r = -0,42$; $p = 0,03$) ir loginio mąstymo ($r = -0,55$; $p < 0,01$) užduočių rezultatu sevoflurano tiriamųjų grupėje. Neigiama koreliacija šioje grupėje taip pat pastebėta tarp intraoperacinės temperatūros ir atminties rezultato ($r = -0,58$; $p = 0,02$).

Išvados. Nors desflurano tiriamųjų grupės pacientai geriau atliko atminties užduotis, tačiau bendras pooperacinis užduočių rezultatas tarp grupių nesiskyrė. Skirtingai nei amžius ar anestezijos trukmė, įtakos pooperaciniams kognityvinėms funkcijoms gali turėti pooperacinė savijauta ir temperatūra operacijos metu.

Raktažodžiai: kognityviniai sutrikimai, sevofluranas, desfluranas, pooperacinė kognityvinė disfunkcija