Original Article

Effect of anaesthetic agents on olfactory threshold and identification – A single blinded randomised controlled study

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Access this article online

Website: www.ijaweb.org

DOI: 10.4103/ija.IJA_245_18

Quick response code

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ABSTRACT

Background and Aims: Anaesthetics are implicated in cognitive dysfunction, taste and odour deficits in the postoperative period. We aimed to assess the effect of isoflurane, sevoflurane, propofol and regional anaesthesia on the olfactory threshold, olfactory identification and endocrine regulation of associative memory in the postoperative period. **Methods:** In this observer-blinded randomised controlled study, 164 patients (>50 years) with the American Society of Anesthesiologists I and II status were randomised into one of four groups to receive regional anaesthesia, general anaesthesia with sevoflurane, general anaesthesia with isoflurane and total intravenous anaesthesia with propofol. Hindi Mental State Examination, olfactory threshold and olfactory identification were tested at 12 h preoperatively (T0), at 3 h postoperatively (T1) and at the time of discharge or postoperative day 3 (T2). In addition, serum melatonin levels were estimated at T0 and T1. The olfactory threshold was tested with n-butyl alcohol and olfactory identification with the University of Pennsylvania Smell Identification Test (UPSIT). Data were analysed using the one-way analysis of variance, Kruskal-Wallis or Mann-whitney tests. **Results:** The olfactory identification scores were lower with patients receiving sevoflurane-based anaesthesia at 3 h postoperatively (T1) when compared to preoperative (T0) (median 19.5 vs. 22; $P = 0.01$). This was accompanied by a significant postoperative reduction of plasma melatonin levels in sevoflurane group when compared to other groups (17.34 ± 4.8 pg/ml vs 23.2 ± 3.5 pg/ml; $P < 0.001$). **Conclusion:** Sevoflurane was associated with short-term olfactory identification impairment with a concomitant reduction in melatonin levels illustrating a possible humoral mechanism.

Key words: General anaesthesia, neurotoxicity, olfaction, olfactory identification, sevoflurane

INTRODUCTION

General anaesthetic agents are implicated in producing cognitive dysfunction, taste and odour deficits in the postoperative period. To date, there are several case reports of reversible anosmia and taste dysfunction following surgery and exposure to anaesthetic agents thereby suggesting a possible relationship between anaesthetic agents and altered olfactory function.[1,2] These postoperative manifestations are ascribed to the specific action of general anaesthetics on the brain neuronal system such as modulation of ion channels, mainly Gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptors.[3] Olfaction is mediated by G-protein–cAMP coupled receptors in the cilia of olfactory receptor neurons in the neuroepithelium. Binding of an odorant to these receptors causes depolarization of these cells, leading to the generation of an action potential to the olfactory

How to cite this article: Saravanan B, Kundra P, Mishra SK, Surianarayanan G, Parida PK. Effect of anaesthetic agents on olfactory threshold and identification – A single blinded randomised controlled study. Indian J Anaesth 2018;62:592-8.

bulb. In addition, GABA is the primary inhibitory neurotransmitter found in neuronal synapses involving olfactory bulbs.[4] Thus, the involvement of common GABA pathway implies a possible interaction of the general anaesthetics with olfactory function. However, the evidence for specific aetiology causing olfactory deficit secondary to exposure to anaesthetic agents is still deficient. Olfactory identification is an explicit memory, which in humans is responsible for assigning associative meaning to odours and helps us to respond to previously experienced events. This associative memory is found to be facilitated by the extended hormonal action of melatonin.[5] Also, the presence of common GABA-mediated synaptic inhibition in the transfer of light information from suprachiasmatic nuclei to pineal gland via $GABA_A$ receptor suggests the possible interaction of melatonin and anaesthetic agents.[6] Thus, this study is embarked to assess the effect of anaesthetic agents namely isoflurane, sevoflurane, propofol and regional anaesthesia on the olfactory threshold, olfactory identification and endocrine regulation of associative memory in the postoperative period.

METHODS

This observer-blinded randomised controlled study was conducted after the ethical committee approval and written informed consent. One hundred and sixty-four patients with the American Society of Anaesthesiologists I and II physical status aged >50 years scheduled for elective surgery with the anticipated duration of 60–120 min were enrolled in the study. Patients with recent airway infection, allergic rhinitis, nasal polyps, history of alcoholism, smoking, mental retardation, psychiatric illness, neurosurgical or oto-rhino-laryngeal surgery and patients with the history of olfactory deficits and cognitive impairment were excluded. The patients included in the study were randomly allocated into one of the four groups by sealed envelope technique by the study investigator to receive general anaesthesia with sevoflurane (group SEVO), general anaesthesia with isoflurane (group ISO) and total intravenous anaesthesia with propofol (group TIVA). Patients receiving neuraxial anaesthesia (group RA) were considered as control group. Surgical procedures included hernia repair, varicose vein surgery, incisional hernia repair, minor gynaecological procedures, lower limb orthopaedic procedures and minor urological procedures. All those patients enrolled in the study were subjected to the Hindi Mental State Examination (HMSE), olfactory tests in the form of olfactory threshold and olfactory identification testing at 12 h preoperatively (time point T0), at 3 h after the end of anaesthesia (time point T1) and on the postoperative day 3 or at discharge, whichever was earlier (time point T2). In addition, blood sampling for serum melatonin concentration were drawn preoperatively (time point T0) and 3 h after the end of anaesthesia (time point T1). The second investigator collecting data were blinded to group assignment.

Olfactory threshold was measured using serial dilutions (10 dilutions) of 4% n-butyl alcohol in deionised water. The test consists of 10 steps. In each step, the odorant and a blank were presented to the participant. The test progressed from weaker-to-stronger concentrations of odorant. An odorant bottle was presented to the participant accompanied by an identical bottle that contained distilled water only. The participant sniffed each one for approximately 9 s and then chose which one smelled stronger. If the participant was incorrect at one concentration, the next higher concentration was presented. When the correct choice was made, the same concentration of odorant was presented to the participant until four consecutive correct responses were given. The threshold was defined as the butyl alcohol concentration correctly chosen over water in four consecutive trials, and the corresponding number of the concentration was taken as the threshold value.[7]

Olfactory identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT).[8] The test uses four booklets containing labels impregnated with odorous substances. The test is in multiple-choice format, with four written response alternatives for each odour. The odours are released when the labels are scratched. The examiner scraped each target patch and instructed participants to smell the patch and then select the name of the released odour from among four alternatives. Olfactory identification tested using the UPSIT assessed both the recent memory and the remote memory of the patient as it contained odours which were mixture of both the familiar and unfamiliar ones to the study population. Here, it is not utilised to identify patients with anosmia or hyposmia. Instead, the UPSIT is used as a linear, unbiased unidimensional Rasch measure of human smell recognition abilities.[9]

The patients enrolled in the study were taken to the operating room and standard monitoring (electrocardiogram, non-invasive blood pressure, pulse

oximeter and capnogram) were applied. In all patients in group SEVO, ISO and TIVA, general anaesthesia was induced with fentanyl (2 μg/kg) IV and 1% propofol IV (dose titrated to loss of verbal response). Tracheal intubation was facilitated by vecuronium bromide (0.1 mg/kg) IV. The minute ventilation was adjusted to maintain an end-tidal carbon dioxide between 35 and 40 mmHg. Anaesthesia was maintained in group TIVA with a continuous infusion of propofol 1% (7–10 mg/kg/h) IV, group SEVO with sevoflurane and in group ISO with isoflurane to achieve an end-tidal concentration equivalent to 1 MAC. Intraoperatively, analgesia was supplemented with a bolus dose of intravenous fentanyl (1 μg/kg) in the presence of haemodynamic response (>20% increase in pulse rate and blood pressure from the baseline). At the end of the surgery, the residual neuromuscular blockade was reversed with neostigmine 50 μg/kg and glycopyrrolate 10 μg/kg IV. The trachea was extubated after the patient becomes awake and on return of spontaneous respiration. End of anaesthesia was considered as the time at which the patient could say his name after tracheal extubation. In group RA (spinal anaesthesia) the end of anaesthesia was considered as the end of surgery. The HMSE, olfactory threshold test and UPSIT tests were repeated 3 h following the end of anaesthesia (time point T1) and on the third postoperative day or at the time of discharge (time point T2), whichever was earlier. Blood sampling for serum melatonin concentration was repeated 3 h after the end of anaesthesia (time point T1).

Melatonin levels were measured in plasma by the enzyme-linked immunosorbent assay (ELISA) (IBL, Hamburg, Germany). Analytical sensitivity was at 1.6 pg/ml and specificity at 1.2–2.5%. Intra-assay precision was 8.8–151.7 (3–11.4% of control values) and inter-assay precision was 5.6–134.3 (6.4–19.3% of control values). Calculations were performed on readerfit software, Hitachi using four parameter logistics.

The sample size was calculated using the software nMaster version 2.0. As there are more than two groups in the study and to give allowance for the increase in alpha error by multiple tests, comparison of means by repeated measures analysis of variance method was used for sample size calculation. Kostopanagiotou *et al*.[10] have conducted a study to compare the effect of regional anaesthesia, propofol and sevoflurane on olfactory memory in the immediate postoperative period. In this study, the range of UPSIT score between different groups at immediate postoperative period is 21–38 and within the group is 21–37. Applying the statistical principle shows that 99.7% of values are covered by mean ± 3 standard deviation (SD), we calculated the between-group variance and within-group variance as 8 and 7.13, respectively. For an effect size of 1, the power of 80%, the alpha error of 0.05 and three repeated measurements, we required a sample size of 163.

Descriptive variables of patients such as age and duration of surgery were shown in the form of mean ± SD. These descriptive variables were compared using the one-way analysis of variance (ANOVA). Non-parametric variables such as HMSE, olfactory threshold score and UPSIT score (olfactory identification) were shown in the form of median and interquartile range. These variables were compared with the Kruskal–Wallis test, and the individual differences were found by using the Mann–Whitney post-hoc U test. Serum melatonin levels were shown in the form of mean ± SD and were compared using the one-way ANOVA between the groups. Data analysis were done using the Statistical Package for the Social Sciences (SPSS 16.0). P value <0.05 is considered statistically significant.

RESULTS

One hundred and sixty-four patients were enrolled in the study and randomly allocated into four groups with 41 patients in each group. Seven patients were excluded from the study due to an exceeded duration of surgery (n = 5) and conversion of regional to general anaesthesia (n = 2). Consequently, a total of 157 patients were analysed with 40 patients in group SEVO, 39 in group RA, 40 in group ISO and 38 in group TIVA [Chart 1]. Patients demographic characteristics did not differ between groups [Table 1]. No surgical or anaesthetic complications were noted in any of the patients. Cognitive function evaluated by HMSE scores [Table 2] and olfactory threshold scores (median score 4 in all groups) [Table 3] did not demonstrate any significant variability in patients before and after anaesthesia. Olfactory identification evaluated by UPSIT revealed significantly lower UPSIT score (median 19.5) with patients receiving sevoflurane-based anaesthesia at third hour postoperative period (T1) when compared to preoperative (median 22) and postoperative day 3 value (median 21), P = 0.01 [Figure 1 and Table 4].

Between the group analyses revealed a statistically significant lower UPSIT score in group SEVO at T1 when compared to control group ($P = 0.006$). This was accompanied by a significant reduction of plasma melatonin levels in group SEVO at third hour postoperative period (17.34 ± 4.8 pg/ml) when compared to its preoperative value (23.2 ± 3.5 pg/ml), $P < 0.001$ [Figure 2].

DISCUSSION

Olfaction comprises three different components such as odour threshold, odour identification and odour discrimination. Based on these components, the olfactory function tests can be divided into peripheral and central tests, as the olfactory threshold reflects peripheral olfactory function and the olfactory discrimination and identification reflects central olfactory function.[11] Our study demonstrates that sevoflurane-based anaesthesia produces significant short-term olfactory identification impairment when compared to isoflurane, propofol and regional anaesthesia. This finding was established by significantly low UPSIT score ($P = 0.01$) in the third hour postoperative period in sevoflurane group when compared to isoflurane, propofol and regional anaesthesia group. In addition, a significant reduction in the serum melatonin concentration (26%) was observed in the third postoperative hour with sevoflurane anaesthesia, indicating a correlation between serum melatonin levels and short-term olfactory identification impairment ($P < 0.001$). However, olfactory threshold function was preserved postoperatively in all patients, as the olfactory threshold measured by serial dilutions of n-butyl alcohol was similar to the preoperative values (median score 4 in all groups at all time points). Thus, it is clear that our study finding indicates the involvement of central olfactory function. This finding can be attributed to the central effects of sevoflurane on the neurotransmitters (GABA) in the olfactory memory system and its specific action on amygdala through $GABA_A$ receptors. Since GABA is the primary inhibitory neurotransmitter of the brain involving synapses in olfactory bulbs, the relationship between the general anaesthetics and postoperative olfactory memory impairment can be attributed to the

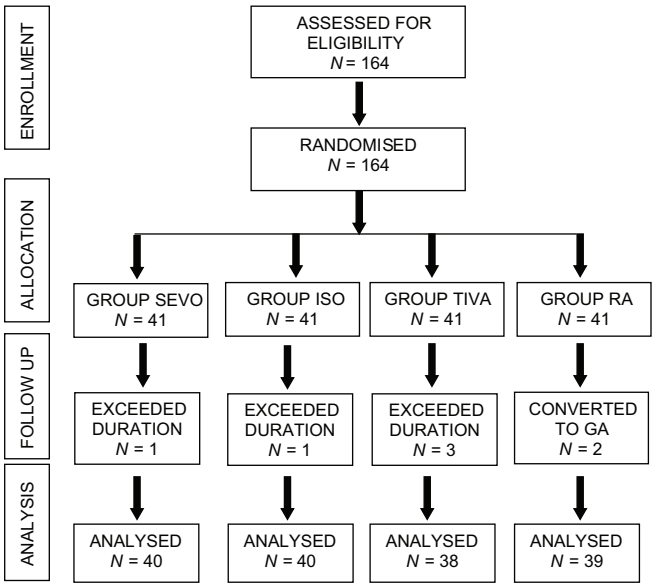

Chart 1: Consort flow chart. Group ISO = isoflurane; Group SEVO = sevoflurane; Group TIVA = propofol; Group RA – regional

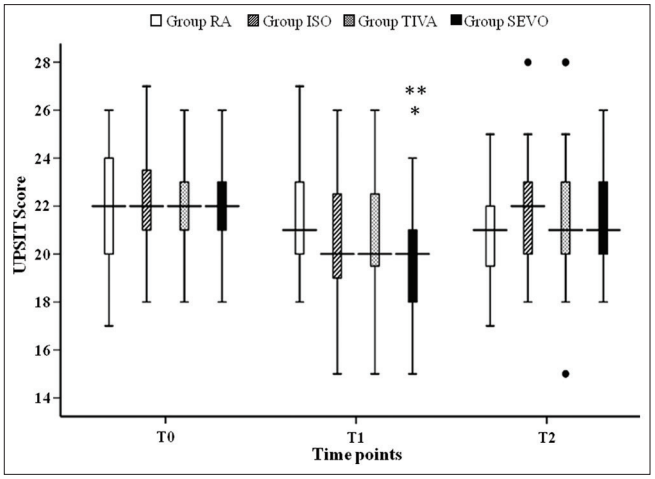

Figure 1: Box and Whisker plots illustrating the University of Pennsylvania Smell Identification Score (UPSIT) in the four groups of anaesthesia at time points T0, T1 and T2. Group ISO = isoflurane; Group SEVO = sevoflurane; Group TIVA = propofol; Group RA = regional. UPSIT = University of Pennsylvania Smell Identification Test. Represents outliers more than 1.5 times the interquartile range. *$P = 0.01$: Significantly reduced UPSIT score within the group SEVO among the three time points. **$P = 0.006$: Significantly reduced UPSIT score in group SEVO at T1 when compared to other groups

Table 1: Descriptive data of patient characteristics with statistical comparisons

Parameter	Group ISO (*n*=40)	Group SEVO (*n*=40)	Group TIVA (*n*=38), *n* (%)	Group RA (*n*=39), *n* (%)	*P*
Age (years)	58.8±7.0	57.6±5.6	57.7±5.6	56.8±6.9	0.65
Male	22 (54.5)	20 (50)	17 (48.3)	20 (51.4)	0.97
Female	18 (45.4)	20 (50)	21 (51.6)	19 (48.5)	0.95
Surgery duration (min)	93.8±17.1	94.1±14.8	99.8±18.5	94.4±17.4	0.44

n=number of patients in each group; values expressed in mean±SD. Group ISO=Isoflurane; Group SEVO=Sevoflurane; Group TIVA=Propofol; Group RA=Regional; SD=Standard deviation

Table 2: Hindi mental state examination scores for the four anaesthesia groups at time points T0, T1 and T2

Groups	HMSE score (T0)	HMSE score (T1)	HMSE score (T2)
Group ISO	29 (28-29)	29 (28-29)	29 (28-29)
Group SEVO	29 (28-29)	29 (28-29)	29 (28-29)
Group TIVA	29 (29-29)	29 (29-29)	29 (29-29)
Group RA	29 (28-29)	29 (28-29)	29 (28-29)

Values expressed as median (inter-quartile range). HMSE=Hindi mental state examination; Group ISO=Isoflurane; Group SEVO=Sevoflurane; Group TIVA=Propofol; Group RA=Regional

Table 3: Olfactory acuity thresholds scores for the four anaesthesia groups at time points T0, T1 and T2

Groups	Acuity threshold score (T0)	Acuity threshold score (T1)	Acuity threshold score (T2)
Group ISO	4 (4-4)	4 (4-4)	4 (4-4)
Group SEVO	4 (4-4)	4 (4-4)	4 (4-4)
Group TIVA	4 (4-4)	4 (4-4)	4 (4-4)
Group RA	4 (4-4)	4 (4-4)	4 (4-4)

Values expressed as median (inter-quartile range). Group ISO=Isoflurane; Group SEVO=Sevoflurane; Group TIVA=Propofol; Group RA=Regional

Table 4: University of Pennsylvania Smell Identification Test scores for the four anaesthesia groups at time points T0, T1 and T2

Groups	UPSIT scores (T0)	UPSIT scores (T1)	UPSIT scores (T2)
Group ISO	22 (18-27)	20 (18-27)	21.5 (18-25)
Group SEVO*	22 (18-26)	19.5 (15-24)	21 (18-26)
Group TIVA	22 (18-26)	20 (15-26)	21 (18-25)
Group RA	22 (17-26)	20.5 (18-27)	21 (17-25)

Values expressed as median (inter-quartile range). *P=0.01: Significantly reduced UPSIT score within the group SEVO among the three time points. *P=0.006: Significantly reduced UPSIT score in the group SEVO at T1 when compared to control group. Group ISO=Isoflurane; Group SEVO=Sevoflurane; Group TIVA=Propofol; Group RA=Regional; UPSIT=University of Pennsylvania Smell Identification Test

general anaesthetics effect on GABA receptor ligand binding.[3,12,13]

The current study established olfactory identification impairment with inhalational agent sevoflurane and not with isoflurane or propofol. This differential effect is explained by the findings made by Salmi *et al*.[14] who demonstrated that propofol affects $GABA_A$ receptor ligand binding to a lesser degree than sevoflurane. Additionally, the author attributed the above said finding to the differences in their allosteric interaction with $GABA_A$ receptor complex. Besides, the difference between sevoflurane and propofol is further substantiated by the higher volume of distribution noted with sevoflurane in the neuronal system when compared to propofol. Similarly, Alkire and Gorski[15] who established extended amnesic potency with sevoflurane when compared to isoflurane describe the difference in the olfactory outcome noted between

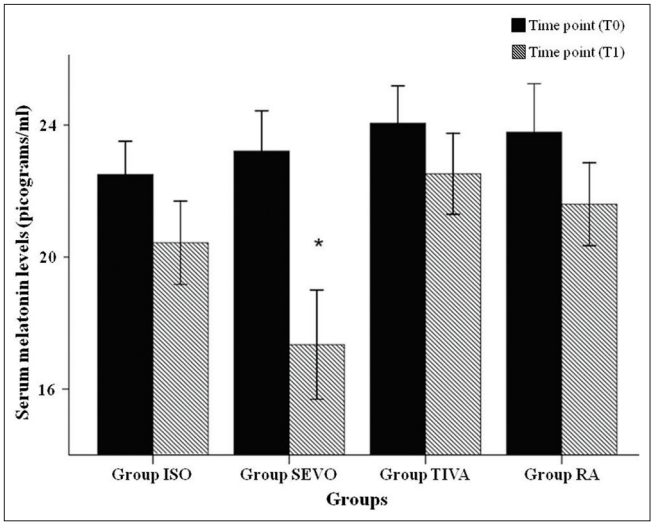

Figure 2: Bar chart showing melatonin serum levels in the four groups of anaesthesia at time points T0 and T1.Group ISO = isoflurane; Group SEVO = sevoflurane; Group TIVA = propofol; Group RA = regional. *P < 0.001: Significantly reduced serum melatonin level in group SEVO at T1 when compared to other groups

sevoflurane and isoflurane. Also, isoflurane required a higher dose (1.5 MAC) for its significant volume of distribution in the neuronal system to exert its effect on GABA receptor ligand binding when compared to 1.0 MAC concentration.[16] The above findings justify the differential effect noted only with sevoflurane in causing short-term olfactory identification impairment. The decline in the central olfactory function (olfactory identification) evidenced in the present study can be attributed to the generalised decrease in the cognitive and sensory alterations as described with conditions such as sleep deprivation, chronic kidney disease and diabetes.[17,18] However, this was overcome in the current study by assessing postoperative cognitive function by using HMSE. Also, spinal anaesthesia has been found not to affect the olfactory function.[19]

General anaesthetic agents are found to desynchronise circadian rhythm via multiple mechanisms within the central nervous system. One such mechanism is through alteration in the nocturnal melatonin secretion.[20] There are several reports of a decrease in the nocturnal secretion of melatonin following anaesthesia with inhalational agents and propofol.[21,22] This finding attributes to the presence of GABA-mediated synaptic inhibition as the transfer of light information from suprachiasmatic nuclei to pineal gland occurs via $GABA_A$ receptor. Several investigators have demonstrated melatonin as a facilitator of memory process especially during stress and its role in the consolidation of memory.[23] Sevoflurane at its

amnestic concentrations inhibit synaptic plasticity of hippocampal cornu ammonis area 1 (CA1) neurons through GABAergic mechanisms and thereby impair memory function by depressing field excitatory postsynaptic potential amplitude and completely blocking long-term potentiation of GABA receptor.[24] Also, the sub-anaesthetic doses of sevoflurane have shown memory loss by its action on amygdala through $GABA_A$ receptor.[25] Thus the relationship between the olfactory identification impairment and reduced blood melatonin concentration could be due to the presence of a notable concentration of melatonin-binding sites in entorhinal cortex and the CA1 in the hippocampus which are sites important in pairing odours with the appropriate memory.[26] The short-term olfactory identification impairment demonstrated with sevoflurane-based anaesthesia suggests a possibility of neurotoxicity which cannot be ruled out in long-term exposure to the patients. This has clinical relevance especially in elderly patients in whom the exposure to such inhalational anaesthetics can act as a risk factor precipitating Alzheimer's disease.[27] Also, the early symptoms demonstrated in these patients were olfactory dysfunction manifesting as impaired olfactory identification with high prevalence upto 100% in Alzheimer's disease.[28,29] However, a long-term follow-up study involving elderly patients is warranted to demonstrate a definitive clinical value.

CONCLUSION

This study demonstrated a short-term olfactory identification impairment in sevoflurane group with concomitant reduction in melatonin levels illustrating a possible humoral mechanism. However, olfactory identification impairment was not found with other inhalational agent such as isoflurane. Additionally, no change in olfactory threshold sensitivity was noted with any of the anaesthesia group.

Financial support and sponsorship

Institutional funding (Jawaharlal Institute of Postgraduate Medical Education and Research) supported this work.

Conflicts of interest

There are no conflicts of interest.

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