

INHALED ANESTHESIA AND COGNITIVE PERFORMANCE

Pravat K. Mandal¹, Daniela Schifilliti², Federica Mafrica² and Vincenzo Fodale²

¹Neurospectroscopy and Neuroimaging Laboratory, National Brain Research Centre, Manesar, Gurgaon, India and

²Department of Neurosciences, Psychiatric and Anesthesiological Sciences, University of Messina, Policlinico G Martino, Messina, Italy

CONTENTS

Summary	47
Introduction	47
Postoperative cognitive dysfunctions	48
Volatile Anesthetics	49
Isoflurane	49
Desflurane	50
Sevoflurane	50
Nitrous oxide	51
Conclusions	51
References	52

SUMMARY

Despite technological advances in surgery and anesthesia during the last few decades, the incidence of postoperative cognitive dysfunction remains a relatively common complication in surgical patients. After surgery, elderly patients in particular often exhibit a transient reversible state of cerebral cognitive alterations. Anesthetics administered as part of a surgical procedure may alter the patient's behavioral state by influencing brain activity. This concise report will address the scientific evidence on the relationship between postoperative cognitive dysfunctions and the most com-

mon inhalational agents currently used in anesthesia (volatile anesthetics: isoflurane, desflurane and sevoflurane, gaseous nitrous oxide). The available literature does not allow definitive conclusions to be drawn on the possible differences between anesthetics in relation to the subsequent occurrence of cognitive dysfunction. However, such information is crucial to improve anesthesia performance and patient safety, as well as outcomes.

INTRODUCTION

The number of elderly people is increasing yearly, and more patients are candidates for anesthesia and surgery (1). After surgery, elderly patients in particular often exhibit a transient reversible state of cerebral cognitive

.....
Correspondence: Dr. Vincenzo Fodale, E-mail: vfodale@unime.it and Dr. Pravat K. Mandal, E-mail: pravat.mandal@gmail.com

alterations. The most frequent symptoms are memory loss and lack of concentration (2), but among these cognitive dysfunctions, a state of delirium may develop (3). Delirium is also associated with higher postoperative mortality and morbidity and with delayed functional recovery. However, whether this worse prognosis is directly caused by delirium, or is caused by neurological damage – of which delirium is simply a symptom – remains unclear (4).

These alterations compromise recovery after surgery; mobilization of the patient is difficult and, therefore, hospital stay is extended. The resulting immobilization is associated with further complications (e.g., decubitus, pneumonia or thrombosis) (5).

Anesthetics given during surgery produce changes in the patient's behavioral state by modifying brain activity via at least two mechanisms: dose-dependent global, and regionally specific, suppression of neuronal activity and disruption of functional interactivity within distributed neural networks (6). Contrary to previous understanding, the clinical state of anesthesia consists of multiple components that are mediated via the interaction of anesthetic drugs with different targets on the molecular-cellular network and structural-anatomical levels (7).

Neurotransmitter-gated ion channels, particularly receptors for γ -aminobutyric acid (GABA), glutamate and *N*-methyl *D*-aspartate (NMDA) channels are modulated by most anesthetics, at both synaptic and extrasynaptic sites, and additional ion channels and receptors are also being recognized as important targets for general anesthetics (8).

Neuronal nicotinic acetylcholine receptors (nAChRs) consist of different subunits, α and β , with different subtype arrangements corresponding to distinct pharmacological and functional properties. In the human brain, nicotinic receptor subtypes have discrete distributions, which are, in part, different from those of other species (9). It has been demonstrated that nAChRs are involved in cognitive processes such as learning and memory and control of movement in healthy subjects. Recent data from knockout animals have extended the understanding of nAChR function. Dysfunction of nAChR has been linked to a number of human disorders such as schizophrenia, Alzheimer's and Parkinson's diseases (10). Although nAChRs are not directly involved in the hypnotic component of anesthesia, there is a modulation of central nicotinic transmissions by inhalational agents. Several intravenous anesthetics, such as barbiturates

and etomidate, exert an inhibitory effect on nAChRs, but propofol exerts effects only at concentrations higher than those necessary for anesthesia (11).

The present article aims to provide a concise review of the available up-to-date information on the effects of common inhalational anesthetic agents on the incidence of postoperative cognitive dysfunction, with a view to decreasing the risk of unwelcome events and increasing anesthesia performance, patient safety and outcomes. The literature search was confined to three databases from 1980 to 2008: the Cochrane Library, MedLine accessed through PubMed and CINAHL. Articles were retrieved for closer screening and were assessed for quality.

POSTOPERATIVE COGNITIVE DYSFUNCTIONS

Postoperative cognitive dysfunctions (POCD) are defined as impairment of the mental processes of perception, memory and information processing, which allow the individual to acquire knowledge, solve problems and plan for the future. POCD represents a common complication in postoperative patients (12-14). Although technological advances in surgery and anesthesia in the last few decades have led to a steady decrease in the mortality and morbidity rate associated with these procedures, the incidence of POCD remains relatively high (15). This complication not only compromises recovery after surgery but, if persistent, minimizes and compromises surgery itself (16). Patients with POCD are at an increased risk of death in the first year after surgery (17).

Risk factors for postoperative cognitive disorders can be divided into age- and comorbidity-dependent, as well as those related to surgery and anesthesia (16). Substance abuse, preexisting psychiatric and neurological disorders, and conditions with high intracranial pressure represent some of the most common risk factors associated with comorbidity (16). Average life expectancy is increasing due to the advancement of science, and studies have demonstrated that the risk of postoperative cognitive deficits increases with age (13).

The incidence of POCD in elderly patients on the first day after minor surgery is higher than previously reported for 7 days after major surgery (18). An international trial [the International Study on Postoperative Cognitive Dysfunction (ISPOCD)] of elderly patients (mean age 68 years, range: 60-81 years) who underwent noncardiac surgery demonstrated a 26% incidence of POCD 1 week after surgery, with 10% having persistent POCD 3 months

later (19). Younger patients (mean age 51 years, range: 40-60 years) showed a lesser incidence at 1 week postoperatively (19%), which decreased to 6% after 3 months (20). Postoperative cognitive deficits are common in adult patients of all ages at hospital discharge, but only the elderly are at significant risk for long-term cognitive problems (17). In this latter study, on discharge, POCD was present in 36.6% of young patients (18-39 years), in 30.4% of middle-aged (40-59 years) and in 41.4% of elderly patients (60 years or older), while at 3 months after surgery, it was present in 5.7% young patients, 5.6% middle-aged, and 12.7% elderly patients (17).

Another important risk factor for POCD is the type of surgery: while a very low incidence is associated with minor surgery, cardiovascular, orthopedic and urologic surgery are characterized by a high risk of postoperative cognitive disorders (13, 16). In cardiac surgery, for example, the incidence of POCD – principally attributed to the use of cardiovascular bypass – is approximately 50-80% at hospital discharge, 20-50% at 6 weeks, and 10-30% at 6 months after operation (15).

Finally, not all areas of the brain are affected to the same degree by anesthetic agents; some brain regions are more sensitive to anesthesia and sedation than others (21). For example, sedative concentrations of anesthetics inhibit activity in multimodal association cortices (such as parietal and prefrontal cortices), determining amnesia and attention deficits. In contrast, activity in unimodal cortices and in the thalamus remains largely unaffected by low doses of anesthetic drugs (21), leading researchers to increasingly investigate the degree of involvement of anesthesia in the incidence of POCD. Many studies have been carried out on the comparison of regional as against general anesthesia, but no significant differences were found (12, 13, 22, 23). Similarly, no difference was found between epidural and general anesthesia after knee replacement (24). The effects of propofol or several opioids, such as fentanyl and tramadol, were also investigated. The results suggest, respectively, that patients should refrain from any participation in road traffic for at least 2 hours after propofol-based anesthesia, while patients receiving tramadol patient-controlled analgesia are better prepared to undergo cognitively demanding tasks (25, 26). Thus, these findings seem to suggest that anesthesia per se is not a risk factor of POCD, but rather, that the incidence of postoperative cognitive disorders is strongly related to the cumulative effects of surgery, stress response to surgery, anesthesia, anxiety, prolonged starvation and so on (18).

Nevertheless, most instruments, such as cognitive failure questionnaires (27) or syndrome short tests (25), which are used to assess cognitive dysfunctions, are subjective and hence are not necessarily the best method for measuring these deficits. Moreover, one of the difficulties of human research in this area is that anesthesia is hardly ever administered as a sole procedure but is almost invariably administered to facilitate surgery (12). Further studies to better understand the contribution of perioperative management on POCD, especially in terms of anesthesia, appear to be necessary.

VOLATILE ANESTHETICS

Used alone, or as a part of balanced anesthesia, for decades inhalational anesthetics have been the most widely administered drugs in most anesthesia communities. The most common inhalational agents used today in anesthesia are volatile anesthetics (isoflurane, desflurane and sevoflurane) and the gas nitrous oxide (N_2O). Nevertheless, only a few studies have investigated the effects of these kinds of drugs on postoperative cognitive outcome (28).

Isoflurane

Isoflurane is an older inhalational anesthetic but is still widely used in clinical practice. The effects of this anesthetic agent on the incidence of POCD have been widely investigated. Already in 1992, in their study in patients undergoing elective orthopedic procedures, Tsai et al. (29) observed how desflurane anesthesia appears superior to isoflurane anesthesia, not only in emergence, but also in the recovery of cognitive functions. These results were confirmed in pulmonary surgery (30) and were considered valid even when desflurane anesthesia was supplemented by premedication, intraoperative opioids and N_2O (31). Similarly, recovery of cognitive and psychomotor functions seems to be faster and more complete after sevoflurane than after isoflurane-based anesthesia (32). In addition, the studies carried out by El-Dawlatly (33) show that anesthesia based on this volatile agent produces inferior recovery – in terms of early time error product scores – compared to anesthesia with sevoflurane. Nevertheless, Kanbak et al. (28) have recently revealed that isoflurane is associated with better neurocognitive functions than desflurane or sevoflurane in patients undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass, whereas Mahajan et al. (34) found that isoflurane and sevoflurane anesthesia result in similar clinical and neurocognitive recovery pro-

files in older patients undergoing ambulatory surgical procedures of short duration. In each case, however, recovery of high cortical and neuromotor functions following isoflurane anesthesia was improved by flumazenil, which reduces shivering and improves the overall quality of emergence, including patients' subjective feelings (35, 36).

Finally, recovery of psychomotor and cognitive ability after isoflurane and propofol-based general anesthesia has been investigated (37, 38). Both types of anesthesia allow early extubation and recovery of basic psychomotor functions, and in both cases a decline of these functions up to 24 hours after administration has been recorded, suggesting that isoflurane and propofol show similar recovery of psychomotor functions after long duration anesthesia; therefore, other factors, such as subjective well-being and costs, may be considered when deciding between these two anesthetic techniques (37).

Desflurane

Desflurane is a recently introduced volatile anesthetic drug with a low blood/gas solubility coefficient, which allows rapid changes in anesthesia depth (39). This agent is generally used toward the end of anesthesia to facilitate rapid emergence. In patients undergoing pulmonary surgery, for example, emergence is twice as fast with desflurane as with other volatile anesthetics, such as sevoflurane or isoflurane (mean times to extubation: 8.9 minutes, 18.0 minutes and 16.2 minutes for desflurane, sevoflurane and isoflurane, respectively) (30, 40, 41). Hence, faster recovery following desflurane may be an advantage especially after long surgical procedures, enabling the patient's full cooperation and facilitating early diagnosis of any potential neurological deficits (42).

Chen et al. (41) have shown that recovery of cognitive functions was similar with both volatile anesthetics in a comparative study with desflurane and sevoflurane in elderly patients (41). Other findings have also failed to detect any differences in emergence and recovery profiles in morbidly obese patients receiving desflurane or sevoflurane, especially when the anesthetic concentration was carefully titrated (43). In contrast, in comparison with isoflurane, desflurane-based anesthesia appears to be superior, not only in emergence, but also in recovery of cognitive functions (29). Recovery up to 45 minutes postoperatively occurs earlier after desflurane, with significantly fewer impaired (i.e., drowsy, clumsy, fatigued or confused) patients (44). These results, however, seem to contradict the findings of Kanbak et al. (28) who, eval-

uating the effect of sevoflurane, isoflurane and desflurane anesthesia on neuropsychological outcome in patients undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass, observed how isoflurane promoted better neurocognitive functions than sevoflurane and desflurane, which are associated with prolonged brain injury. Nevertheless, Loscar et al. (31) have reported that desflurane anesthesia, even when supplemented with opioids and N₂O, seems to offer clinical advantages over isoflurane as far as postanesthetic recovery profile is concerned.

In contrast, patients after prolonged surgical procedures showed an earlier recovery after anesthesia with desflurane/fentanyl- than with propofol/remifentanyl-based total intravenous anesthesia (TIVA), with similar recovery of cognitive functions in both groups (45). However, the latter shows significantly faster emergence and return of cognitive functions than anesthesia with desflurane and N₂O (46).

Sevoflurane

Sevoflurane is currently considered the inhalational agent of choice in anesthesia (47). The effects of this drug in relation to the incidence of POCD have been investigated, but the results are not so clear. In their study on patients undergoing coronary bypass graft surgery, Kadoi and Goto (48) found no relationship between POCD and the use of this anesthetic agent. In contrast, some comparative studies of sevoflurane and other volatile anesthetics, such as desflurane and isoflurane, indicate that the former seems to be associated with the worst cognitive outcomes (28). Recovery of cognitive function is similar with both desflurane and sevoflurane in patients with and without morbid obesity (41, 43), and anesthesia based on this anesthetic agent is associated with a superior recovery – in terms of early time error product scores – compared with anesthesia with isoflurane (33, 38, 49). These results were not confirmed after pulmonary surgery, in which Dupont et al. (30) demonstrated how desflurane, but not sevoflurane, allowed more rapid emergence and earlier recovery than isoflurane.

The effects of sevoflurane anesthesia on POCD have also been evaluated in comparison with intravenous anesthesia with propofol, highlighting how the incidence of POCD levels does not depend on the anesthetic agent used (18). Moreover, total intravenous anesthesia with propofol/remifentanyl- shows no patient benefit over sevoflurane/fentanyl-based anesthesia in terms of recovery and cognitive functions (50). Indeed, recovery

appears to be faster after sevoflurane/fentanyl than after propofol/remifentanyl (51). In addition, anesthesia with these drugs shows that emergence and return of cognitive function are significantly faster than with sevoflurane/nitrous oxide anesthesia, up to 60 minutes after administration (46), whereas sevoflurane/nitrous oxide anesthesia has a good recovery profile for ambulatory colonoscopy, resulting in faster recovery of cognitive function than with the combination of fentanyl, midazolam and propofol (52). Finally, in elderly patients undergoing hemiarthroplasty of the hip, induction and maintenance with sevoflurane provides rapid emergence from anesthesia without further depression of postoperative cognitive functions. This may be a preferred anesthetic to unilateral spinal anesthesia (53).

NITROUS OXIDE

N₂O is a colorless, almost odorless gas and is considered a dissociative drug that can cause analgesia, depersonalization, derealization, dizziness, euphoria, sound distortion and slight hallucinations.

N₂O is still frequently used. Careful consideration of the illustrated contraindications and side effects, as well as the available alternatives, shows that N₂O is still an option in general anesthesia (54). This substance is a weak anesthetic agent, usually not used alone during general anesthesia, but administered in combination with more powerful inhalational anesthetics such as sevoflurane, desflurane or isoflurane.

While the anesthetic/hypnotic mechanisms of N₂O remain largely unknown, the underlying mechanisms of its analgesic/antinociceptive effects have been elucidated in the last few decades. The evidence to date indicates that N₂O induces opioid peptide release in the periaqueductal gray matter of the midbrain, leading to activation of the descending inhibitory pathways, which results in modulation of pain/nociceptive processing in the spinal cord (55).

The use of N₂O is associated with POCD and delirium which is an important clinical concern. High doses of N₂O seem to be associated with impairments in many cognitive central nervous system functions (56).

In clinical practice, volatile anesthetics are normally combined with N₂O and/or opioids, leading to an additive interaction between volatile anesthetics and N₂O, but to a synergistic interaction of volatile anesthetics with opioids. However, there have been relatively few investigations into the interactions between the clinical-

ly widely used combination of volatile anesthetics, N₂O and opioids (57). The development of postoperative delirium after exposure to N₂O has a similar incidence when compared with nonexposure to N₂O (58). N₂O interacts with vitamin B₁₂, resulting in selective inhibition of methionine synthesis, a key enzyme in methionine and folate metabolism. Thus, N₂O may alter one-carbon and methyl-group transfer, which is very important for DNA, purine and thymidylate synthesis. Long-term exposure to high concentrations of N₂O may cause megaloblastic bone marrow depression and neurological symptoms. Exposure to higher doses for less than 6 hours, as in clinical anesthesia, is considered harmless (59).

Cognitive impairment due to vitamin B₁₂ deficiency is rarely dominated by isolated memory disorders and an authentic dementia correlated to B₁₂ deficiency is an exception (60). These clinical results are in accordance with the neurotoxic effects produced by N₂O on brain tissues in animal models (61, 62).

CONCLUSIONS

Previous studies have demonstrated that certain inhalational anesthetics may be associated with postoperative cognitive dysfunction. In the aging brain, subtle cognitive dysfunction can persist long after clearance of the drug and mental processes resembling neurodegenerative disorders may be reported by the patients and analyzed by neurological and neuropsychological testing.

POCD in the elderly is a major health problem after surgery and anesthesia, increasing morbidity, as well as hospitalization and domiciliary costs, and reducing patients' quality of life. Most elderly surgical patients receive inhalational anesthetics and these results call for further evaluation of the interaction among inhalational anesthetic drugs with postoperative cognitive function. Since life expectancy and the number of aged patients undergoing surgical procedures is progressively increasing, future research should be directed to anesthetic agents that may have an impact on postoperative cognitive performance decline and the development of cognitive dysfunctions in elderly patients. We have already demonstrated that amyloid beta peptide interacts with isoflurane and desflurane at clinically relevant concentrations using state-of-the-art nuclear magnetic resonance spectroscopy (63). We presented a molecular model for the oligomerization of amyloid beta peptide based on the NMR studies (63-66). Our NMR studies provide a possible explanation for studies on inhaled anesthetic (halothane and isoflurane)-induced plaques

in transgenic mice (with AD pathology) as reported from other laboratories. Hence, further studies to understand the interactions of different brain proteins with these inhaled anesthetics in a clinical setting are warranted.

ACKNOWLEDGEMENTS

Thanks to Dr. Subbulakshmy Natarajan (NBRC) and Prof. Partha Raghunathan (NBRC) for critical comment and suggestions. Research support from the National Brain Research Centre, Department of Biotechnology, Government of India as well as a grant from the Italian Ministry for University and Research, Program for the Development of Research of National Interest (PRIN Grant No. 2007H84XNH, Scientific coordinator V. Fodale) was very much appreciated.

REFERENCES

- Sear, J.W. *Implication of aging on anaesthetic drugs*. *Curr Opin Anaesthesiol* 2003, 16(4): 373-8.
- van Dijk, D., Dieleman, J.M., Hijman, R. *Postoperative cognitive dysfunction*. *Ned Tijdschr Geneesk* 2007, 151(21): 1163-6.
- Praticò, C., Quattrone, D., Lucanto, T., Amato, A., Penna, O., Roscitano, C., Fodale, V. *Drugs of anaesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium*. *Med Hypotheses* 2005, 65(5): 972-82.
- Cavaliere, F., D'Ambrosio, F., Volpe, C., Masieri, S. *Postoperative delirium*. *Curr Drug Targets* 2005, 6(7): 807-14.
- Engelhard, K., Werner, C. *Postoperative cognitive dysfunction*. *Anaesthesist* 2005, 54(6): 588-94.
- Heinke, W., Koelsch, S. *The effects of anaesthetics on brain activity and cognitive function*. *Curr Opin Anaesthesiol* 2005, 18(6): 625-31.
- Perouansky, M. *General anaesthetics and long-term neurotoxicity*. *Handb Exp Pharmacol* 2008, (182): 143-57.
- Hemmings, H.C. Jr, Akabas, M.H., Goldstein P.A., Trudell J.R., Orser, B.A., Harrison, N.L. *Emerging molecular mechanisms of general anaesthetic action*. *Trends Pharmacol Sci* 2005, 26(10): 503-10.
- Rubboli, F., Court, J.A., Sala, C., Morris, C., Chini, B., Perry, E., Clementi, F. *Distribution of nicotinic receptors in the human hippocampus and thalamus*. *Eur J Neurosci* 1994, 6(10): 1596-604.
- Hogg, R.C., Raggenbass, M., Bertrand, D. *Nicotinic acetylcholine receptors: From structure to brain function*. *Rev Physiol Biochem Pharmacol* 2003, 147: 1-46.
- Tassonyi, E., Charpantier, E., Muller, D., Dumont, L., Bertrand, D. *The role of nicotinic acetylcholine receptors in the mechanisms of anaesthesia*. *Brain Res Bull* 2002, 57(2): 133-50.
- Hanning, C.D. *Postoperative cognitive dysfunction*. *Br J Anaesth* 2005, 95(1): 82-7.
- Rasmussen, L.S. *Postoperative cognitive dysfunction: Incidence and prevention*. *Best Pract Res Clin Anaesthesiol* 2006, 20(2): 315-30.
- Rasmussen, L.S. *Defining postoperative cognitive dysfunction*. *Eur J Anaesthesiol* 1998, 15(6): 761-4.
- Wang, D., Wu, X., Li, J., Xiao, F., Liu, X., Meng, M. *The Effect of Lidocaine on Early Postoperative Cognitive Dysfunction After Coronary Artery Bypass Surgery*. *Anesth Analg* 2002, 95(5): 1134-41.
- Kalezi, N., Dimitrijevi, I., Leposavi, L. et al. *Postoperative cognitive deficits*. *Srp Arh Celok Lek* 2006, 134(7-8): 331-8.
- Monk, T.G., Weldon, B.C., Garvan, C.W., Dede, D.E., van der Aa, M.T., Heilman, K.M., Gravenstein, J.S. *Predictors of cognitive dysfunction after major noncardiac surgery*. *Anesthesiology* 2008, 108(1): 18-30.
- Rohan, D., Buggy, D.J., Crowley, S., Ling, F.K., Gallagher, H., Regan, C., Moriarty, D.C. *Increased incidence of postoperative cognitive dysfunction 24 hr after minor surgery in the elderly*. *Can J Anaesth* 2005, 52(2): 137-42.
- Moller, J.T., Cluitmans, P., Rasmussen, L.S. et al. *ISPOCD Investigators. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study*. *Lancet* 1998, 351(9106): 857-61.
- Johnson, T., Monk, T., Rasmussen, L.S. et al. *ISPOCD2 Investigators. Postoperative cognitive dysfunction in middle-aged patients*. *Anesthesiology* 2002, 96(6): 1351-7.
- Heinke, W., Koelsch, S. *The effects of anaesthetics on brain activity and cognitive function*. *Curr Opin Anaesthesiol* 2005, 18(6): 625-31.
- Newman, S., Stygall, J., Hirani, S., Shaefi, S., Maze, M. *Postoperative cognitive dysfunction after noncardiac surgery: A systematic review*. *Anesthesiology* 2007, 106(3): 572-90.
- Rasmussen, L.S., Johnson, T., Kuipers, H.M. et al. *Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients*. *Acta Anaesthesiol Scand* 2003, 47(3): 260-6.
- William-Russo, P., Sharrock, N.E., Mattis, S., Szatrowski, T.P., Charlson, M.E. *Cognitive effects after epidural vs general anaesthesia in older adults*. *JAMA* 1995, 274(1): 44-50.
- Seidl, S., Hausmann, R., Neisser, J., Janisch, H.D., Betz, P. *Severity and duration of mental deficiency symptoms after intravenous administration of propofol*. *Int J Legal Med* 2007, 121(4): 281-5.
- Ng, K.F., Yuen, T.S., Ng, V.M. *A comparison of postoperative cognitive function and pain relief with fentanyl or tramadol patient-controlled analgesia*. *J Clin Anesth* 2006, 18(3): 205-10.
- Broadbent, D.E., Cooper, P.F., Fitzgerald, P., Parkes, K.R. *The Cognitive Failures Questionnaire (CFQ) and its correlates*. *Br J Clin Psychol* 1982, 21(Pt. 1): 1-16.

28. Kanbak, M., Saricaoglu, F., Akinci, S.B., Oc, B., Balci, H., Celebioglu, B., Aypar U. *The effects of isoflurane, sevoflurane, and desflurane anesthesia on neurocognitive outcome after cardiac surgery: a pilot study.* Heart Surg Forum 2007, 10(1): E36-41.
29. Tsai, S.K., Lee, C., Kwan, W.F., Chen, B.J. *Recovery of cognitive functions after anaesthesia with desflurane or isoflurane and nitrous oxide.* Br J Anaesth 1992, 69(3): 255-8.
30. Dupont, J., Tavernier, B., Ghosez, Y., Durinck, L., Thevenot, A., Moktadir-Chalons, N., Ruyffelaere-Moises, L., Declerck, N., Scherpereel, P. *Recovery after anaesthesia for pulmonary surgery: desflurane, sevoflurane and isoflurane.* Br J Anaesth 1999, 82(3): 355-9.
31. Loscar, M., Allhoff, T., Ott, E., Conzen, P., Peter, K. *Awakening from anesthesia and recovery of cognitive function after desflurane or isoflurane.* Anaesthesist 1996, 45(2): 140-5.
32. Schwender, D., End, H., Daunderer, M., Fiedermutz, M., Peter, K. *Sevoflurane and the nervous system.* Anaesthesist 1998, 47(Suppl. 1): S37-42.
33. El-Dawlatly, A.A. *Sevoflurane vs isoflurane anaesthesia: A study of postoperative mental concentration and fine motor movements.* Middle East J Anesthesiol 2002, 16(4): 397-404.
34. Mahajan, V.A., Ni, Chonghaile, M., Bokhari, S.A., Harte, B.H., Flynn, N.M., Laffey, J.G. *Recovery of older patients undergoing ambulatory anaesthesia with isoflurane or sevoflurane.* Eur J Anaesthesiol 2007, 24(6): 505-10.
35. Weinbroum, A.A., Geller, E. *Flumazenil improves cognitive and neuromotor emergence and attenuates shivering after halothane-, enflurane- and isoflurane-based anesthesia.* Can J Anaesth 2001, 48(10): 963-72.
36. Pregler, J.L., Mok, M.S., Steen, S.N. *Effectiveness of flumazenil on return of cognitive functions after a general anesthetic.* Acta Anaesthesiol Sin 1994, 32(3): 153-8.
37. Münte, S., Münte, T.F., Kuche, H., Osthaus, A., Herzog, T., Heine, J., Leuwer, M., Piepenbrock, S. *General anesthesia for interventional neuroradiology: propofol versus isoflurane.* J Clin Anesth 2001, 13(3): 186-92.
38. Schwender, D., Müller, A., Madler, M., Faber-Züllig, E., Ilmberger, J. *Recovery of psychomotor and cognitive functions following anesthesia Propofol/alfentanil and thiopental/isoflurane/alfentanil.* Anaesthesist 1993, 42(9): 583-91.
39. Bedford, N.M., Girling K.J., Skinner, H.J., Mahajan, R.P. *Effects of desflurane on cerebral autoregulation.* Br J Anaesth 2001, 87(2): 193-7.
40. Heavner, J.E., Kaye, A.D., Lin, B.K., King, T. *Recovery of elderly patients from two or more hours of desflurane or sevoflurane anaesthesia.* Br J Anaesth 2003, 91(4): 502-6.
41. Chen, X., Zhao, M., White, P.F. et al. *The recovery of cognitive function after general anesthesia in elderly patients: A comparison of desflurane and sevoflurane.* Anesth Analg 2001, 93(6): 1489-94.
42. Boisson-Bertrand, D., Laxenaire, M.C., Mertes, P.M. *Recovery after prolonged anaesthesia for acoustic neuroma surgery: Desflurane versus isoflurane.* Anaesth Intensive Care 2006, 34(3): 338-42.
43. Arain, S.R., Barth, C.D., Shankar, H., Ebert, T.J. *Choice of volatile anesthetic for the morbidly obese patient: sevoflurane or desflurane.* J Clin Anesth 2005, 17(6): 413-9.
44. Patel, S.S., Goa, K.L. *Desflurane. A review of its pharmacodynamic and pharmacokinetic properties and its efficacy in general anaesthesia.* Drugs 1995, 50(4): 742-67.
45. Röhm, K.D., Piper, S.N., Suttner, S., Schuler, S., Boldt, J. *Early recovery, cognitive function and costs of a desflurane inhalation vs. a total intravenous anaesthesia regimen in long-term surgery.* Acta Anaesthesiol Scand 2006, 50(1): 14-8.
46. Larsen, B., Seitz, A., Larsen, R. *Recovery of cognitive function after remifentanyl-propofol anesthesia: A comparison with desflurane and sevoflurane anesthesia.* Anesth Analg 2000, 90(1): 168-74.
47. Patel, S.S., Goa, K.L. *Sevoflurane. A review of its pharmacodynamic and pharmacokinetic properties and its clinical use in general anaesthesia.* Drugs 1996, 51(4): 658-700.
48. Kadoi, Y., Goto, F. *Sevoflurane anesthesia did not affect post-operative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery.* J Anaesth 2007, 21(3): 330-5.
49. Delphin, E., Jackson, D., Gubenko, Y., Botea, A., Esrig, B., Fritz, W., Mavridis, S. *Sevoflurane provides earlier tracheal extubation and assessment of cognitive recovery than isoflurane in patients undergoing off-pump coronary artery bypass surgery.* J Cardiothorac Vasc Anesth 2007, 21(5): 690-5.
50. Magni, G., Baisi, F., La Rosa, I., Imperiale, C., Fabbrini, V., Pennacchiotti, M.L., Rosa, G. *No difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanyl in patients undergoing craniotomy for supratentorial intracranial surgery.* J Neurosurg Anesthesiol 2005, 17(3): 134-8.
51. Biedler, A., Juckenhöfel, S., Feisel, C., Wilhelm, W., Larsen, R. *Cognitive impairment in the early postoperative period after remifentanyl-propofol and sevoflurane-fentanyl anesthesia.* Anaesthesist 2000, 49(4): 286-90.
52. Theodorou, T., Hales, P., Gillespie, P., Robertson, B. *Total intravenous versus inhalational anaesthesia for colonoscopy: A prospective study of clinical recovery and psychomotor function.* Anaesth Intensive Care 2001, 29(2): 124-36.
53. Casati, A., Aldegheri, G., Vinciguerra, E., Marsan, A., Frascini, G., Torri, G. *Randomized comparison between sevoflurane anaesthesia and unilateral spinal anaesthesia in elderly patients undergoing orthopaedic surgery.* Eur J Anaesthesiol 2003, 20(8): 640-6.
54. Schönherr, M.E., Hollmann, M.W., Graf, B. *Nitrous oxide. Sense or nonsense for today's anaesthesia.* Anaesthesist 2004, 53(9): 796-812.
55. Fujinaga, M., Maze, M. *Neurobiology of nitrous oxide-induced antinociceptive effects.* Mol Neurobiol 2002, 25(2): 167-89.

56. Mahoney, F.C., Moore, P.A., Baker, E.L., Letz, R. *Experimental nitrous oxide exposure as a model system for evaluating neurobehavioral tests*. *Toxicology* 1988, 49(2-3): 449-57.
57. Kreuer S, Bruhn J, Wilhelm W, Bouillon T. *Pharmacokinetic-pharmacodynamic models for inhaled anaesthetics*. *Anaesthesist* 2007, 56(6): 538-56.
58. Leung JM, Sands LP, Vaurio LE, Wang Y. *Nitrous oxide does not change the incidence of postoperative delirium or cognitive decline in elderly surgical patients*. *Br J Anaesth* 2006, 96(6): 754-60.
59. Weimann, J. *Toxicity of nitrous oxide*. *Best Pract Res Clin Anaesthesiol* 2003, 17(1): 47-61.
60. El Otmani, H., El Moutawakil, B., Moutaouakil, F., Gam, I., Rafai, M.A., Slassi, I. *Postoperative dementia: Toxicity of nitrous oxide*. *Encephale* 2007, 33(1): 95-7.
61. Jevtovic-Todorovic, V., Wozniak, D., Benshoff, N., Olney, J. *A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide*. *Brain Res* 2001, 895(1-2): 264-7.
62. Beals, J.K., Carter, L.B., Jevtovic-Todorovic, V. *Neurotoxicity of nitrous oxide and ketamine is more severe in aged than in young rat brain*. *Ann N Y Acad Sci* 2003, 993: 115-24.
63. Mandal, P.K., Fodale, V. *Isoflurane and desflurane at clinically relevant concentrations induce amyloid beta-peptide oligomerization: An NMR study*. *Biochem Biophys Res Commun* 2009, 379(3): 716-20.
64. Mandal, P.K., Pettegrew, J.W. *Abeta peptide interactions with isoflurane, propofol, thiopental and combined thiopental with halothane: A NMR study*. *Biochem Biophys Acta* 2008, 1778(11): 2633-9.
65. Mandal, P.K., Pettegrew, J.W. *Clinically relevant concentration determination of inhaled anesthetics (halothane, isoflurane, sevoflurane, and desflurane) by 19F NMR*. *Cell Biochem Biophys* 2008, 52(1): 31-5.
66. Mandal, P.K., Fodale, V. *Isoflurane and desflurane at clinically relevant concentrations induce amyloid beta-peptide oligomerization: An NMR study*. *Biochem Biophys Res Commun* 2008, 2009, 379(3): 716-20.