EFFECTS OF SEVOFLURANE ANAESTHESIA ON POSTOPERATIVE EXECUTIVE FUNCTION AND VISUAL MEMORY

By

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ABBREVIATIONS

ASA	American Society of Anaesthesiology
BADS	Behavioral Assessment of Dysexecutive syndrome
BLC	Big Little Circle
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFCs	Chlorofluorocarbon
CNS	Central Nervous System
DMS	Delayed Matching Sample
EEG	Electroencephalogram
GABA (A)	Gamma Aminobutyric Acid (A)
GWP	Global Warming Potential
IED	Intra/extradimensional Set Shift
MAC	Mean Alveolar Concentration
MAP	Mean alveolar Pressure
NMDA	N-Methyl D-aspartate
NSAID	Nonsteroidal antiinflammatory drug
MET	Multiple Errands Test
POCD	Postoperative Cognitive Dysfunction
TNF	Tumor Necrosis Factors
WCST	Winconsin Card Sorting Tasks

ABSTRAK

KESAN SEVOFLURANE KE ATAS FUNGSI EKSEKUTIF & MEMORI VISUAL SELEPAS PEMBEDAHAN

Pengenalan: Kadar komplikasi pembedahan dan pembiusan serta kematian semakin menurun sejak akhir-akhir ini. Walaubagaimanapun, POCD atau perubahan terhadap fungsi kognitif masih menjadi isu utama lebih-lebih lagi di kalangan orang-orang tua. Walaubagaimanapun, masih tidak diketahui bagaimana perubahan ini berlaku. Pelbagai kemungkinan telah pun dikemukakan. Kajian yang telah dijalankan juga gagal menentukan sama ada perubahan fungsi kognitif ini berpunca daripada pembedahan ataupun pembiusan. Tidak seperti delirium, perubahan fungsi kognitif ini lebih berpanjangan dan juga mengakibatkan masalah yang lebih konsisten. Sesetengah kajian juga ada menyatakan bahawa perubahan kepada fungsi kognitif ini boleh berpanjangan sehingga lebih daripada 6 bulan apatah lagi apabila melibatkan yang sudah golongan berumur.

Objektif: Menentukan sama ada sevoflurane mengakibatkan perubahan dalam fungsi kognitif dan memori visual.

Metodologi: Pesakit-pesakit yang dijadualkan untuk menjalani pembedahan ortopedik dan memenuhi kriteria yang telah ditetapkan dipilih untuk manjalani kajian kami. Jumlah keseluruhan pesakit yang terlibat ialah 37 orang dan terdiri daripada 28 lelaki dan 9 perempuan. Kesemua data yang kami perolehi adalah daripada Hospital Universiti Sains Malaysia. Pesakit perlu menjalani ujian CANTAB sebelum dan juga selepas pembedahan.

Kami menetapkan 24-48 jam untuk menguji fungsi kognitif pesakit selepas pembedahan dengan mengandaikan bahawa kesan-kesan ubat- ubatan yang diberikan semasa pembedahan telah beransur. Kami menggunakan CANTAB® alatan yang dicadangkan oleh ISO 2006, sebagai di antara alatan yang terbaik untuk memeriksa fungsi kognitif. Data Demografik yang kami perolehi terdiri daripada umur, jantina, bangsa, klasifikasi ASA, dan juga jangkamasa pembedahan dijalankan.

Keputusan: Keputusan yang kami perolehi daripada kesemua tiga ujian yang dijalankan menyokong terhadap tiadanya perubahan dalam fungsi kognitif selepas pembedahan. Keputusan (BLC) menunjukkan peningkatan yang ketara terhadap tempoh reaksi terhadap gambar yang ditunjukkan di mana 32 orang pesakit menamatkan ujian dengan baik dan kami perolehi ($p<.005$) Jumlah kesalahan yang dilakukan dalam ujian (IED) juga berkurangan malah kebanyakan pesakit dapat menamatkan sesi ujian kepada peringkat yang lebih tinggi. . 'IED Completed stage Errors' min 5.1 ($p<0.05$), 'IED Completed Stage Trials' min 8.595 dan ($p<0.037$), 'IED EDS Error' min of 6.595 dan ($p<0.05$) and 'IED Total Errors' min of 5.945 dan ($p<0.05$) Begitu juga dengan ujian DMS dimana memori pesakit diuji. Para pesakit menunjukkan peningkatan yang ketara selepas pembedahan dengan 'DMS Mean Correct Latency' dengan min 566.13 dan ($p<0.05$). Tiada kolerasi di antara kesemua ujian yang dilakukan jika dibandingkan dengan umur, jantina, pelajaran, bangsa dan juga jangkamasa pembedahan.

Rumusan: Kami membuat rumusan bahawa sevoflurane tidak menyebabkan perubahan dalam fungsi kognitif dikalangan pesakit yang sihat dan muda.

ABSTRACT

THE EFFECTS OF SEVOFLURANE ANAESTHESIA ON POSTOPERATIVE EXECUTIVE FUNCTION AND VISUAL MEMORY.

Introduction: Over the last decade, the perioperative morbidity and mortality has been dramatically improved. POCD still represent one of the major adverse events particularly involving the elderly patients. The exact causes of POCD are still uncertain and believed to be multifactorial. It is unknown whether it is the results of surgery or anaesthesia itself. Studies done on regional and general anaesthesia failed to find any difference whether any of these method contribute to POCD. Reports showed that POCD causing more persistent problem and prolonged cognitive disturbance compared to delirium (Bryson GI et al., 2006). Furthermore, certain study reported that postoperative patients especially when it involved the elderly patients can extend up to 6 months and even beyond.

Objectives: To determine the effects of sevoflurane on postoperative cognitive function namely executive function and visual memory.

Methodology: Patients who scheduled for orthopaedic surgery and fulfilled the inclusion criterias were included. A total number of 37 patients with male: 28 female: 9 were enrolled in this study. This is a prospective observational study; all of the datas were collected from Hospital Universiti Sains Malaysia. The same investigator assessed the neurocognitive function of the patients preoperatively and postoperatively. We decided to take 24 to 48 hours postoperatively as we assumed the effects of anaesthetic drugs already subsided. The neurocognitive assessment was done using CANTAB, ISO 2006 recommended tool. The

demographic data collected included age, gender, race, ASA classification, and duration of surgery. Where else the data taken from the CANTAB battery included Big Little Circle (BLC), Intra/extradimensional Set Shift (IED), and Delayed Matching to Sample (DMS).

Results: The reports that we had from all the three tests performed by patients were all directed towards no impairment in cognitive function postoperatively. When compared BLC results postoperatively, patients showed significant improvement with the reaction time with 32 patients completed test successfully and p number obtained was ($p<0.05$). The number of errors made in IED test declined and number of stages completed increased. IED Completed stage Errors mean 5.1. ($p<0.05$), IED Completed Stage Trials mean 8.595 and ($p<0.05$), IED EDS Error mean of 6.595 and ($p<0.05$) and IED total errors mean of 5.945 and ($p<0.05$). Same goes with the DMS test where patient's memory was tested. DMS Mean Correct latency showed significant improvement postoperatively with mean of 566.13 and ($p<0.05$). There were no correlations noted between all these tests with patient's age, gender, education level, race or even duration of surgery.

Conclusion: Sevoflurane anaesthesia does not cause postoperative cognitive impairment in healthy, young adult population**.**

CHAPTER ONE

INTRODUCTION

1.1 Cognitive dysfunction

Postoperative cognitive dysfunction is defined as impairment of the mental processes of memory, perception and information processing. It is a common postoperative complication. Having an intact cognitive function helps a person gaining knowledge, solving obstacles and thinking about future plans. Postoperative cognitive changes can occur in all age groups after illness and surgery, but are more common at the extremes of age (Hanning CD., 2005).

The increased survival of high risk patients after major anaesthetic, surgical and critical care interventions make the preservation of cognition a high priority. The aim is to be able to discharge patient from hospital with intact cognitive function. In fact, postoperative cognitive dysfunction can be severe enough resulting in increased in mortality, risk of losing job and also dependence of social welfare (Steinmets JC et al., 2009).

Sevoflurane was introduced in late 1980s as an inhalational agent for maintenance of anaesthesia. Its favourable pharmacokinetic and pharmacodynamic characteristics such as low blood solubility, rapid induction of anaesthesia and emergence when the agent is

discontinued, and it is also non pungent, thus less likely to provoke airway irritation. Besides its affordable price, Sevoflurane is also being recognised as an inhalational agent with the least green gas effect. Hence, in long running it is no doubt the best inhalational agent to be used widely.

We were conducting this study based on the basis of pharmacodynamics behaviour of the anaesthetics in the brain that has profoundly changed during the last decade. Anaesthetics may even exert multiple effects on a restricted number of molecular targets in the central nervous system.

The main purpose of this study is to compare the effects of Sevoflurane anaesthesia on postoperative executive function and visual memory using Cantab, a software cognitive test as a tool. At the same time we were trying to weigh the risks and benefits with the thinking of developing 'Day Care Anaesthesia Centre' in Hospital Universiti Sains Malaysia in the near future.

Day care or ambulatory anaesthesia which begun in United State has now become a global practice. Patients will be admitted and discharged home on the same day after a few hours postoperative observation in the temporary wards. Day care anaesthesia centre is capable of reducing the hospital stay cost, giving comfort to the patients without significantly disturbed their work or school schedule.

1.2 Rationale of the Study

Despite technological advances in surgery and anaesthesia during the last few decades, the incidence of postoperative cognitive dysfunction remain a relatively common complication in surgical patients. This prospective observational study was designed to investigate the effects of volatile anaesthetic which is sevoflurane as an anaesthetic maintenance agent on the development of POCD (Postoperative cognitive dysfunction) in patients who underwent general anaesthesia

1.3 Objectives

General:

To study the effects of sevoflurane anaesthesia on executive function and visual memory using CANTAB®.

Specific:

1. To study the effects of sevoflurane anaesthesia on executive function using Intra-Extra Dimensional Set Shift (IED) test preoperative and postoperatively.

2. To study the effects of sevoflurane anaesthesia on visual memory using Delayed Matching to Sample (DMS) test preoperative and postoperatively.

1.4 Hypothesis

We hypothesised that the use of sevoflurane anaesthesia may cause short term deterioration in executive function and visual memory in patient who underwent general anaesthesia.

CHAPTER TWO

LITERATURE REVIEW

2.1 General Anaesthesia

Almost ten millions of people have been exposed to general anaesthetic agent for the past decade. General anaesthetic agents are drugs known to cause loss of consciousness. For any given general anaesthetic, it takes specific, well defined concentrations and amount of drug to produce loss of consciousness to the patients (Franks NP et al.,2008).

GABA (A) receptor is one of the most important receptors in the mechanism of loss of consciousness and is found in abundance throughout central nervous system (Macdonald RL et al., 1978). Most general anaesthetic drugs have been found to potentiate GABA- induced Cl currents. However apolar anaesthetic agents like xenon and cyclopropane have only small effect or may not have any effects at all (De Sousa SL et al., 2000).

A drug must cross the blood brain barrier in order to produce anaesthesia or loss of consciousness. Meyer-Overton correlation emphasising on the anaesthetic potency and lipid partitioning. In another words it means that anaesthetic drugs dissolved in the lipid bilayer of nerve membranes and subsequently modify their properties (Seeman P et al.,1972).

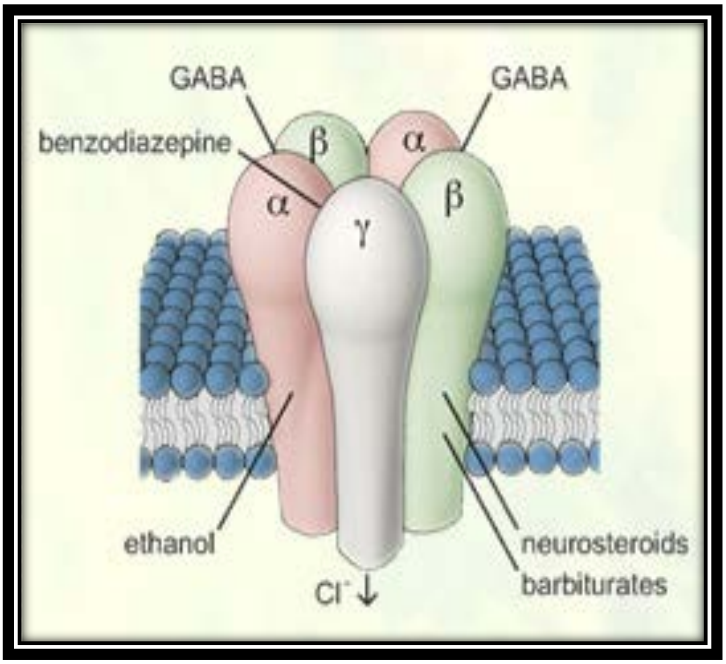

Figure 2.1: GABA (A) receptor

Source: Department of Chemistry and Biochemistry University of Winconsin.

Another important receptor in anaesthetic practice is NMDA (N-methyl-D-aspartate) receptors. Most volatile anaesthetic agent inhibit NMDA receptor to an unknown considerable extent (Yamakura T et al., 2000). At high enough concentration NMDA receptor antagonist will cause sedation and followed by loss of consciousness. However, the period of unconsciousness will be preceded by abnormal behaviour like cataleptic stupor, and followed by brain activity pattern (Langsjo JW et al., 2005).

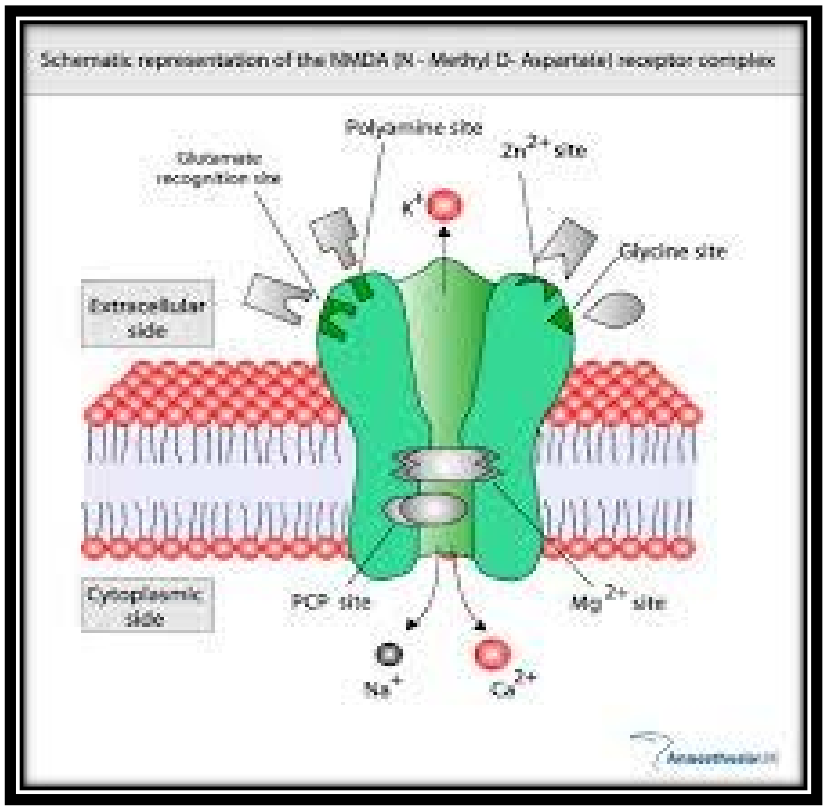

Figure 2.2: Activated NMDA receptor adapted from frca.co.uk

2.1.2 Development of Inhaled Anaesthetics

In 1794-1867, Mary Jean Flourens was conducting her study on depression of central nervous system by using chloroform in dogs. In 1888 and 1890, two Hyderabad commissions were formed concurrent with the use of chloroform in England with regards of its safety when use on patients. Goodman Levy in 1856-1954 was able to prove that in experimental animal models, combination of chloroform and adrenaline produced life threatening ventricular fibrillation. Subsequently nitrous oxide was introduced in anaesthetic practice. In 1863, Colton and Joseph H. Smith a dentist from New haven, Connecticut resumed their 'laughing gas exhibition' for tooth extraction without pain. Then, Edmund Andrews a surgeon, in 1824-1904 succeeded in confirming the analgesic properties of nitrous oxide. He combined the use of nitrous oxide with oxygen and anaesthesia was provided without cyanosis in short surgical procedure. Over the years, the search for satisfactory and potent volatile anaesthetics continues. Until in the early of 1930s, fluorinated volatile anaesthetic became available commercially (Ronald D. MIller, Miller's Anaesthesia, seventh edition).

2.2 Sevoflurane

2.2.1 History of Sevoflurane

Eighteen derivatives of fluoromethylethyl ether including sevoflurane was synthesised by Regan at Travenol Laboratories in the United States in the year of 1968. Subsequently, in 1971 Walin and Napoli found out that sevoflurane has useful anaesthetic properties. Clinical trials performed on sevoflurane in the US by Bruce 1976 and Holaday 1978 revealed that sevoflurane is indeed a favourable anaesthetic agent (Holaday DA, 1981).

Minimum Alveolar Concentration (MAC) represents the potency of volatile anaesthetic agent. Sevoflurane has MAC value of 1.8 which is relatively low, the smaller the MAC value, the more potent and powerful the anaesthetic agent (Kubota Y, 1992).

Sevoflurane can be regarded as volatile anaesthetic of choice with its low blood gas partition coefficient blood:gas of 0.69 and oil:gas 55, makes it one of the most potent volatile agent which facilitate rapid induction of anaesthesia and recovery once sevoflurane is discontinued (Holaday and Smith, 1981). Apart of that, what makes this fluorinated methyl isopropyl ether is so special is that it is non pungent, with minimal odour and thus not irritate the airway and therefore it has high degree of patient's acceptance. Yayuso Kubota, from Dental University of Tokyo, Japan described sevoflurane that has an odour more like a peppermint in his study in 1992. This characteristic is particularly important for paediatric population and also uncooperative adult patients who are unable to tolerate pain with insertion of intravenous line, hence sevoflurane plays a role as an anaesthetic agent for gas

induction and its bronchodilator property adding ease to the anaesthesia in general (Ebert et al., 1998).

In clinical practise, other volatile agents such as isoflurane, enflurane and desflurane are irritating to the airways and resulting in breath-holding, coughing and worst is larygospasm which has life threatening potential. In cases where there is a danger of airway obstruction and to maintain the pharyngeal tone by avoiding any means of intravenous induction agent, sevoflurane has the characteristics that suits the purpose (Kubota Y., 1992).

As for the cardiovascular system, unlike halothane, sevoflurane does not sensitise the myocardium to the arrythmogenic effects of cathecolamines. Compared to isoflurane, it is a less potent coronary arteriolar dilator but more importantly, coronary steal phenomenon does not occur. It also helps to reduce myocardial oxygen consumption and myocardial perfusion by lowering the heart rate (Frink EJ jr., 1992).

Neither sevoflurane nor enflurane resulted in changes in postoperative laboratory test of renal function or even deterioration of renal function although both causing peak serum fluoride of 25 and 13 micromol perlitre respectively. Thus, by exceeding the threshold serum concentration of fluoride ion, it appeared that renal toxicity is not an inevitable consequence (Kharash ED et al.,1995). In one volunteer study involving long hours of anaesthesia, with the MAC value of 3, 6 and 9 sevoflurane, higher peak serum fluoride ion were achieved, and no impairment of ability to concentrate urine demonstrated (Munday IT et al., 1995). Sevoflurane has the ability to react with carbon dioxide absorbents and and producing compound A which is proven toxic to the rats involving renal, hepatic and cerebral damage. Subsequent study showed that at least 200ppm of compound A is required to induce renal injury in rats however the level needed to induce same degree of renal injury in human is still

unknown. In the study done by Bito and Ikeda, patients were exposed to the same concentration of sevoflurane at variable fresh gas flow and was noted that in clinical practice, the concentration of compound A produced is far below the concentration which is toxic in animal (Bito H et al., 1995).

Sevoflurane is decomposed by ultraviolet light while it does not react with metal. There is negligible toxic potential of sevoflurane when it reacts with soda lime, a carbon dioxide absorbent used in general anaesthetic machine. When used within clinical concentration, flammability potential of sevoflurane presents no serious clinical problems (Kubota Y.,et al 1992).

In 1992, new volatile anaesthetic was introduced into clinical practise, known as desflurane (suprane). However, because of its irritant effects on the airway, it is not a suitable and practical induction agent. Futhermore, in order to be administered, it requires specialised electrically heated vaporiser as a tool. Transient increases in heart rate, arterial pressure and even both reported when rapid increment of the concentration of desflurane delivered. In contrast when the level of sevoflurane is adjusted rapidly, these phenomenons were not seen (Smith M et al., 1996).

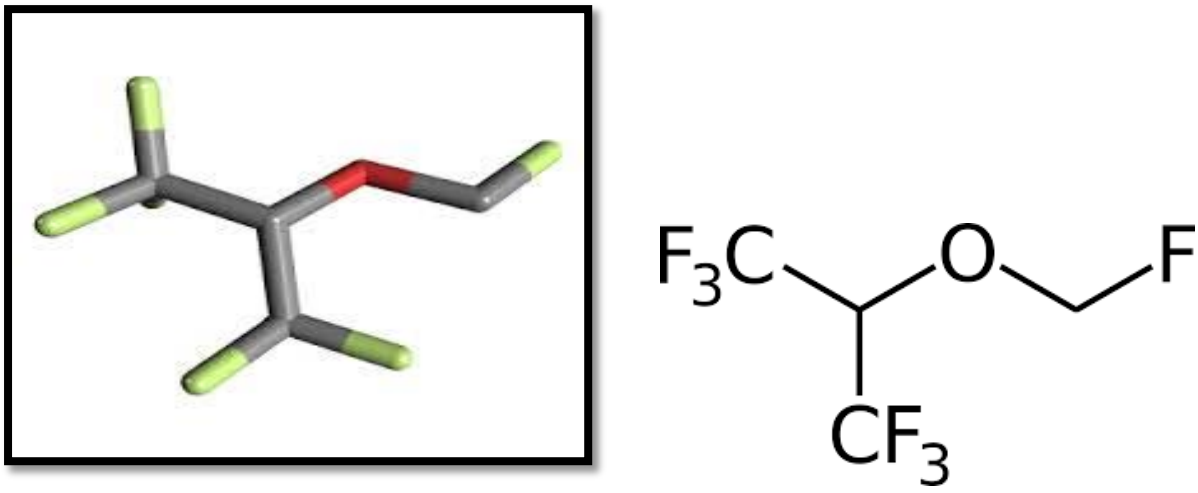

Figure 2.3: Molecular structure of sevoflurane adapted from Pubchem.ncbi.nlm.nih.gov

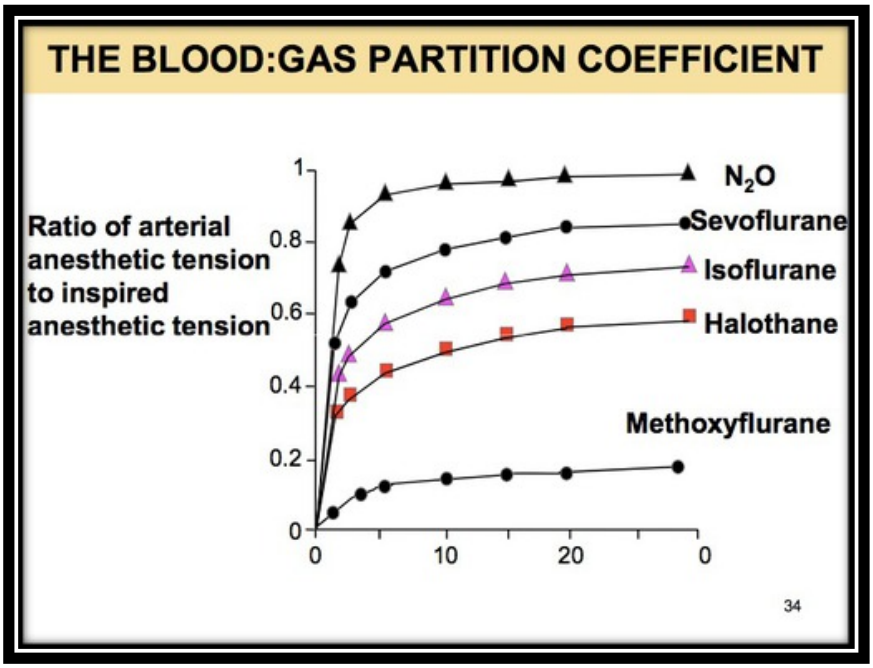

Figure 2.4: Blood gas partition coefficient of volatile agents adapted from frca.co.uk

2.2.2 Central Nervous System Effects

Sevoflurane has variable effects on central nervous system. Inhaled anaesthetic agents including sevoflurane respectively produce characteristic alterations on the electroencephalogram (EEG). At concentrations of about 0.4 MAC, there is a marked shift of high voltage activity from posterior to anterior portions of the brain. Besides, it causes increase in cerebral blood flow in a dose dependent manner that may increase intracranial pressure in patients with space occupying lesions, emphasizing its action as a cerebral vasodilators. Other than that, sevoflurane causes declines in cerebral activity and this has

minimal cerebral oxygen requirements. (Robert KS, Pharmacology in Anaesthetic Practise, 4th edition).

The low solubility in blood of sevoflurane gas allows rapid equilibration between delivered concentration to the central nervous system, the effect site, ability to easily irritate the anaesthetic dose during maintenance and thus resulting in speedy recovery at the end of surgery (Smith M et al.,1996).

In general, neuronal activity in the brain is depressed by sevoflurane, however in deep anaesthesia, sensory information is still being processed by the brain (Kubota Y., 1992). Sevoflurane also possess neuroprotective properties (Popovic R et al.,2000). It is believed due to their ability to reduce neuronal excitability through enhanced inhibitory and depressed excitatory synaptic transmission (Berg-Johnsen J., 1992).

Studies done shown that not every areas of the brain are affected similarly by anaesthetic drugs. Certain areas are more sensitive to the sedative effects than others (Heinke W et al., 2005). Where else, at the cellular level, sevoflurane has been shown to be able to depolarise the mitochondrial membrane gradually at concentration of 1 and 2 MAC respectively (Moe M et al., 2004). Nevertheless, sevoflurane is still preferred in neuroanaesthesia because of its well-maintained cerebral auto regulation (Duffy CM et al., 2000).

2.2.3 Green Gas Effects

The negative impact of anaesthetic gases that has to be taken seriously includes the potential of both global warming and ozone depletion especially when combined with nitrous oxide. This is due to the structure similarity between volatile anaesthetic and chlorofluorocarbon (CFCs). However, the actual contribution of climate changes is small (South Afr J Anaesth, 2011).The molecular structure of sevoflurane which composed of mainly fluorine atoms makes it more stable when compared to other halogenated anaesthetic agent. In fact, in the long run, interesting side benefits of sevoflurane compared with other chlorine containing agent is, it may actually be less destructive to the ozone layer. What is more surprising is that ozone depleting potential of atomic fluorine is only as low as 0.001% when compared to that of chlorine. (Kubota Y et al.,1992).

Futhermore, sevoflurane is the only volatile with the shortest lifetime and the lowest Global Warming Potential (GWP). Where Other gases have greater than two years. This includes isoflurane and halothane which is both intermediate and desflurane has the greatest ability of producing climatic impact (Ishizawa Y et al., 2011).

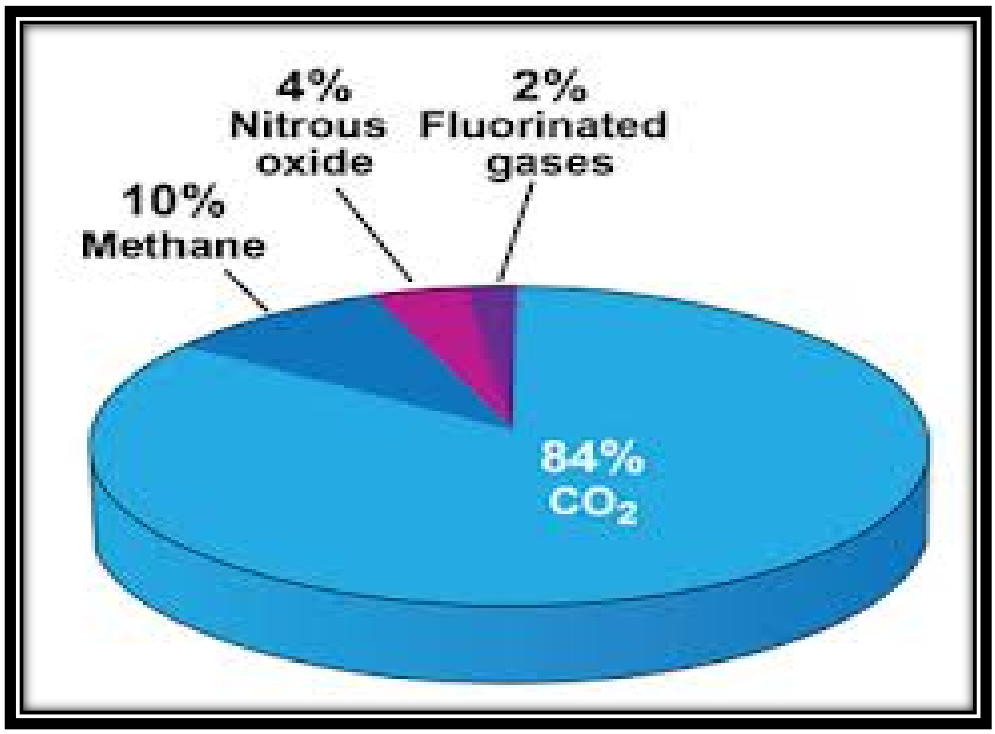

Figure 2.5: Gases and green gas effect adapted from www.ctps.org

2.3 Post Operative Cognitive Dysfunction

2.3.1 Introduction

Impairment of memory and concentration was recognized as features of postoperative cognitive dysfunction and it's proven by neurophysiological testing. Until now, there was no concrete conclusion made on prolonged POCD in patients who underwent non cardiac surgery (Riis J et al., 1983). Results were inconclusive and debatable.

How anaesthetics produced changes in the patient's behavior believed by at least two mechanisms; dose dependent suppression of neuronal activity either globally or regionally and also defect in functional interactivity within neural networks (Heinke W et al., 2005). Previous studies believe that clinical state of anaesthesia consists of interaction of anaesthetic drugs with different targets on anatomical level and on the molecular cellular network (Perouansky M et al., 2008). The incidence of POCD remains high despite revolutionary advanced in surgery and anaesthesia per se (Wang D, Wu X., 2002). The first year of surgery is the most crucial time in POCD patients as the risk of death is at the highest occurrences (Monk TG et al., 2008).

The commonest risks of POCD that are known to be associated with comorbidity includes; high intracranial pressure, preexisting psychiatry and neurological disorders and also substance abuse. The risks of POCD can be further divided according to age and comorbidity dependent, and those related to anaesthesia and surgery (Kalezi N et al., 2006).

Types of surgery also play an important role, as cardiovascular, orthopaedic and urologic surgery is recognized to have high risks of developing POCD (Rasmussen LS et al., 2006). The use of cardiovascular bypass is also known to be the contributing factor for developing POCD (Wang D et al.,2002). POCD is also believed to be related to additive effects of anxiety, anaesthesia, stress response to surgery, surgery, prolonged starvation and so on (Rohan D et al., 2005).

In general clinical practice, it is common to develop postoperative cognitive dysfunction in both group of patients who underwent cardiac or even non cardiac surgery and it is known always to involve the elderly population. Although some researchers hypothesized that POCD may be avoided by choosing regional anaesthesia as an anaesthetic mode, study done by Rasmussen and Johnson also concluded that there were no significant difference respectively between those two groups 1week and also 3 months after surgery (Rasmussen LS et al., 2003).

In different study, the results obtained, showed that anaesthesia and surgery may cause long term cognitive decline and as the age increased, the risks also increased. However the pathophysiology, and also specific risks factor for preventive and also therapeutic purpose were not identified (Moller JT et al., 1998).

2.3.2 POCD and elderly patients

One of the known risk factor for postoperative cognitive dysfunction in both post cardiac and non-cardiac surgery is age. In the first 12 months after major non-cardiac surgery, there were up to 41% of patients aged 60 years and older developing post-operative cognitive dysfunction (POCD) and has an increased risk of death (Monk TG et al., 2008).

Although all adults patients are at risks of developing POCD upon hospital discharged, elderly patients are significantly at risks of long term cognitive decline The percentage goes as high as 12.7% involving the elderly patients (60 years and older) after 3 months of surgery (Monk T.G et al., 2008). Thus, planning for the the best approach managing anaesthetic choice and pain in elderly patients is important although it is still remains debatable. Few considerations need to be taken into account which include, age, underlying medical illnesses, and surgical procedure in the strategy of managing the geriatric patients going for operations.

Elderly patients involved in surgery often develop alterations in cerebral cognitive functions which were usually transient and reversible. Memory loss and lack of concentration were among the most recognizable symptoms present. The most worrying symptom is deliriums which at the same time possess a higher postoperative mortality and morbidity rate and also delayed functional recovery (Van Djik et al., 2007). Subsequently, the delirium state will further compromise recovery; ineffective mobilization and hence prolonged hospital stay and

continues with the vicious cycle of thrombosis, nosocomial pneumonia and various other complications (Engelhard K et al., 2005).

Although survival rates and total number of elderly patients who underwent operations are improving, studies done demonstrated that in elderly patients, cognitive dysfunction still persist and mimicking neurodegenerative disorder. Thus, many more studies need to be done as POCD is regarded as a major health problem, causing increased number of illness and death and also hospital stay and cost, resulting in reduction in quality of life (Mandal PK et al., 2009).

2.3.3 POCD and volatile anaesthetic agent

There were a number of studies done on the prevention of POCD however, so far no significant progress is being observed (Newman S et al., 2007). There were no definitive conclusion and most literatures and studies done were unable to relate between volatile anaesthetic and POCD (Pravat K et al., 2009).

In one study performed by Jan Cremer, and Christian Stoppe in 2011, comparing cognitive function, recovery and also well-being between sevoflurane and noble gas xenon. 40 patients i nvolved were between age 65-75 years (ASA 1-111) were scheduled for elective surgery. Conclusion made at the end of study was, there were no difference in the incidence of POCD in both group. The observation was done and was compared between 66 and 72 hrs after the operation (Cremer JS et al., 2011).

When sevoflurane was compared with intravenous agent which was propofol, the results showed that the incidence of POCD is independent of agent used (Rohan D et al., 2005) In fact, there were no proven benefits shown between combination of intravenous propofol/remilfentanil over sevoflurane on POCD (Magni G et al., 2005). Furthermore, the recovery from sevoflurane was noted to be more rapid. In another study, sevoflurane/nitrous oxide has been shown to produce good recovery outcome for ambulatory colonoscopy when compared with fentanyl, midazolam and also propofol. Despite of having a lower blood level: Gas partition coefficients, Chen et al (Chen X et al., 2001) have managed to show that desflurane have similar recovery of cognitive profile when compared to sevoflurane. There was no difference detected when compared between desflurane and sevoflurane on morbidly obese patients in term of recovery from anaesthesia (Arain SR et al., 2005). In fact, in the current practice, sevoflurane is the volatile agent of choice as an anaesthetic maintenance (Patel S et al., 1996).

In general, only few studies have study the effects of volatile anaesthetic to the development of POCD (Kanbak M et al., 2007). The overall results were vague and sometimes may even contradict each other. Sevoflurane has been shown to have faster and more satisfying recovery in terms of psychomotor and cognitive function when compared to isoflurane (Schewender D et al., 1998). Whereas in different study, it was found that both sevoflurane and isoflurane showed no difference in the short term POCD profile in the day care anaesthesia involving elderly patients (Mahajan VA et al., 2007).

2.3.4 POCD and pain

Pain management is an important aspect of managing postoperative patients. Pain intensity is a contributing factor to the POCD.This is believed to be due to an interactions between cholinergic and dopamine system with glutamergic and gamma amino butyric acid (GABA) pathways (Gaudreau and Gagnon., 2005).

The theory behind pathophysiology of pain inducing POCD is, it could be due to trauma and surgery inducing the release of interleukin and tumor necrosis factors (TNF), which then caused an increase of dopamine and reduction of acetylcholine. Pain intensity is found to be correlated with the increased amount of dopamine (Halaszynski TM et al., 2009).

Adequate pain relief is proven to reduce the risk of developing POCD. In one study done it was found that there was no difference in both group of either intravenous or epidural analgesia on developing POCD (Fong HK et al., 2006). Conclusion made was that the choice of anaesthetic is less likely to influence the incidence of POCD (Bercker et al., 2009). Improper or inadequate pain relief is not only associated with POCD, but also poor surgical outcomes, dissatisfaction among patients and family members and higher medical complications (Apfelbaum JL et al., 1995).

Opioid is the most commonly used agent for pain management either intraoperatively or postoperatively. Opioids are a drug that binds to opioid receptors and these included all exogenous substances, natural and synthetic. They are able to provide satisfactory dose dependent pain relief. However they are also capable of causing physical and psychological

dependence in the long term use by altering CNS activity. Other unwanted side effects included nausea, vomiting, constipation, ileus, dysphoria, and respiratory depressant (Buvanendran A et al., 2009).

Other than opioid, another group of analgesic which was frequently used is Non-steroidal ant inflammatory drug (NSAID). NSAIDs act by inhibiting cycle-oxygenase enzyme, hence reducing the production of prostaglandin, an important pain mediator. It is a potent analgesic for mild to moderate pain. NSAIDs like any other drugs, has their unwanted side effects and being aware of the contraindications beforehand is crucial to ensure patient's safety.
One of the currently and widely used NSAID is Dynastat. It was released to the market in May 2002, and provides satisfactory pain relief intraoperative and postoperatively.

Despite of using single agent for pain management purpose, the combination of drugs or termed as multimodal analgesia, confers a better pain control. For better pain control there should be more than one classes of analgesic drugs used which then act at the different receptors and pathways for their clinical effects. This strategy of managing pain not only gives the benefits of lower medications dose use, but is also able to limit the unwanted side effects of each individual drug (Thomas M., 2013).

Thus, effective preoperative assessment including anaesthetic and analgesic plan should be performed on all patients particularly the elderly patients. A much better postoperative surgical outcome may be achieved by involving a multidisciplinary team approach. Because of the alteration in their normal physiology and also functional reserve, the elderly patients are more prone to develop POCD (Thomas M., 2013).

2.4 Executive function

Executive function is considered as a new subject in neuropsychology. In the book of Clinical Neuro Psychology, edited by Jenifer Gurd and John Marshall described executive function as an ability of a person to adapt in unfamiliar and new surroundings with the thinking strategy and corresponding behavior. Executive function plays an important role in complex social behavior. The results of executive dysfunction can be catastrophic to the person's everyday life and relationship with others. Burgess and Robertson in their study reported that among the components of executive dysfunction include poor abstract thinking 17%, impulsivity 22%, and lack of insight 17%, restlessness 25%, distractibility 32%, poor decision making 26% apathy 20%, lack of insight 17% and few others. With time, some of the symptoms can be resolved well but some may remain (Bugress PW & Roberson IH., 2006).

Trevor in his studies described executive function as the process whereby, an individual is able to optimize his performance in multitasking tasks. These included ability to respond appropriately to new environment, efficient in making plans and suitable actions (Robbins TW et al., 1998).

At the present moment, there are no currently available tests which are capable of assessing every single domains of executive function. Few of the suggested tests included; Behavioural Assessment of Dysexecutive Syndromes (BADS), Cognitive estimate test, Hayling and Brixton test, Multiple Errands Test (MET) , CANTAB®, and others (Bugress PW.,1997).