EFFECT OF SEDATION PROPOFOL WITH TARGET CONTROLLED INFUSION ON COGNITIVE FUNCTIONS ON PATIENTS UNDERGOING OPERATIVE PROCEDURES UNDER LOCAL ANAESTHESIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

BY

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Disclaimer

I hereby certify that the work in this dissertation is my own except for the quotations that have been duly acknowledged.

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May the blessing of the only ONE, be on all.

Abbreviation

ASA	American Society of Anaesthesiology
Ach	Acetylcholine
BP	Blood pressure
BIS	Bispectral index scale
CR	Cognitive reserve
CNS	Central nervous system
ECG	Electrocardiography
GA	General anaesthesia
GABA	Gamma amino butyric acid
HR	Heart rate
LA	Local anaesthesia
MMSE	Mini Mental Status Examination
Mg/ml	Microgram/mililiter
MAC	Monitored anesthetic care
POCD	Post Operative Cognitive Dysfunction
SOMCT	Short Orientatation Memory Concentration Test
SPO_2	Pulse oximetry
TCI	Target controlled infusion

Definitions

Cognition: The term cognition refers to a faculty for the processing of information, applying knowledge and changing preferences. Cognition can be conscious or unconscious Cognition is closely related to abstract concepts such as mind, intelligence, mental functions and mental processes (thoughts).

Abstrak

Pengenalan: Prosedur pembedahan semakin banyak dijalankan dengan menggunakan pembiusan setempat tetapi kebanyakan pesakit suka menggunakan ubat penenang. Gabungan ubat penenang dengan pembiusan setempat adalah satu alternatif selamat berbanding pembiusan umum dalam respirasi spontan, refleks untuk perlindungan dan kerjasama pesakit dapat dikekalkan manakala rasa takut dan bimbang pesakit dapat dikurangkan.

Perubahan dalam fungsi kognitif sering menyukarkan proses pemulihan pesakit-pesakit yang tidak menjalani pembendahan jantung. Sesetengah pesakit mempunyai risiko yang lebih besar daripada orang lain dalam masalah berkaitan kognitif dan apakah dos dadah tersebut? Jika ya, untuk berapa lamakah masalah kognitif akan berlaku? Oleh itu, kita perlu menjalankan kajian untuk menjawab soalan-soalan seperti yang disebut di atas.

Objektif: Tujuan kajian ini adalah untuk menilai perubahan-perubahan kognitif selepas sedatif propofol diberikan melalui TCI sebagai mengesan penjagaan anestetik dan faktor-faktor yang mempengaruhinya.

Metodologi: Penyelidikan ini merupakan kajian perbandingan rawak secara prospektif. Peserta kajian diletakkan dalam blok rawak berganda pra-pembedahan setelah memenuhi kriteria inklusi.

Pemantauan secara berpiawai dilakukan selama tempoh semasa pembedahan dan selepas pembedahan. 104 peserta yang memiliki status fizikal ASA I dan II yang dijadualkan menjalani prosedur pembedahan elektif dengan pembiusan setempat menerima sedatif

seduhan propofol atau hanya pembiusan setempat (tanpa sedatif propofol) sahaja semasa pembedahan oleh penyelidik.

Setelah tiba di kawasan menunggu sebelum pembedahan, pesakit menjalani dua ujian fungsi kognitif (MMSE dan SOMCT) manakala data demografi dijadikan sebagai garis dasar. Ujian ini dilakukan oleh penyelidik “blinded” untuk mengelakkan berlakunya berat sebelah.

Para pesakit kemudian dibawa ke tempat pembedahan dan pemantauan secara berpiawai dijalankan. Garis intravena dijamin dan infiltrasi tempatan di tempat pembedahan dilakukan oleh doktor bedah. Kumpulan “Interventional” menerima sedatif propofol melalui “marsh model” kawalan seduhan propofol untuk tahap kepekatan plasma 0.5ug/ml, dan mereka dalam kumpulan kawalan menerima infiltrasi tempatan sahaja. Seduhan propofol dihentikan pada akhir pembedahan. Pesakit dibawa ke unit rawatan pasca pembiusan (PACU) dan dipantau secara berterusan. Ujian fungsi kognitif untuk MMSE dan SOMCT diulangi pada 20 minit dan 60 minit selepas pembedahan dijalankan untuk kedua-dua kumpulan experimental dan kumpulan kawalan oleh penyelidik “blinded” untuk mengelakkan berat sebelah. Kriteria klinikal berpiawai digunakan untuk membenarkan pesakit dibawa keluar dari bilik pemulihan.

Keputusan: Data demografi dibandingkan dalam kedua-dua kumpulan. Status kognitif meningkat pada akhir 60 minit dalam kedua-dua kumpulan kajian tetapi respon yang lambat didapati dalam kumpulan eksperimental berbanding dengan kumpulan kawalan. Analisis pembolehubah menunjukkan bahawa lelaki menunjukkan perubahan yang ketara berbanding dengan perempuan dalam kumpulan eksperimental manakala lelaki dari

kumpulan kawalan tidak mengalami penurunan skor kognitif. Perubahan yang sama diamati dengan pembolehubah lain seperti bangsa, usia, tabiat merokok dan subjek yang sejarah anestesi umum sebelumnya. Tempoh pemberian sedatif memberi pengaruh ke atas fungsi psikomotorik sebagai prosedur pembedahan yang panjang (> 30 minit) mengalami kehilangan corak pemulihan. Subjek mempunyai taraf pendidikan yang lebih tinggi dan bekerja mempunyai prestasi yang lebih baik dalam ujian kognitif tetapi jangka masa pemulihan mereka masih lebih lambat berbanding dengan kumpulan kawalan. Penilaian untuk kedua-dua ujian kognitif iaitu MMSE dan SOMCT telah dilakukan. MMSE didapati lebih sensitif dalam mengesan perubahan kognitif berbanding SOMCT manakala SOMCT lebih spesifik.

Kesimpulan: Berdasarkan hasil kajian yang diperoleh, kita dapat menyimpulkan propofol merupakan sedatif kerana penggunaannya dapat meningkatan skor kognitif dengan peningkatan masa tetapi corak pemulihan yang lambat dalam kumpulan eksperimental berbanding dengan kumpulan kawalan. Oleh itu, kita menyimpulkan bahawa tiada signifikan defisit dalam fungsi kognitif selepas propofol TCI sedatif diberikan. Pembolehubah yang lain mungkin mempengaruhi penurunan kognitif terhadap selepas pembedahan.

Abstract

Introduction: Surgical procedures are increasingly being performed under local anaesthesia alone but most patients prefer to be sedated. Sedation combined with local anaesthesia is a safe alternative to GA as spontaneous respiration, protective reflexes and patient co operation are retained while fear and apprehensions are reduced.

The changes in cognitive function frequently complicate the post operative course of patients undergoing non cardiac surgery. Some patients are at a greater risk than others of cognitive impairment and what doses of drugs? and if yes then for how long? Hence, the need for experimental study to answer these questions.

Objectives: The aim of this study was to evaluate the cognitive changes after propofol sedation via TCI as monitored anesthetic care and factors influencing it were explored.

Methodology: This was a prospective randomized controlled trial. Study subjects were placed in either arm as per double block randomization preoperative after fulfilling inclusion criteria.

Standard monitoring was done during intraop and postoperative period. One hundred and four consenting ASA physical status I and II patients scheduled to undergo elective surgical procedures with local infilteration were assigned, to receive either sedation propofol infusion or only local infiltration (without propofol sedation) intraoperatively, by the researcher.

Upon arrival in preoperative holding area, patients were to undergo two cognitive function tests (MMSE, SOMCT) beside the demographic data as baseline. These tests were carried out by blinded investigator to avoid bias.

The patients were then taken into operating rooms and standard monitoring was applied. After intravenous line was secured, local infiltration of operative area was done by surgeon. Interventional group received sedation propofol via marsh model target control infusion targeting plasma concentration level of 0.5ug/ml, and those in control group received local infiltration only. Propofol infusion was stopped at the end of surgery. And patients were brought to post anaesthetic care unit (PACU) and monitored continuously. Cognitive function tests were repeated at 20 and 60 minutes postoperatively for both the groups by blinded investigator. Standard clinical discharge criteria were used to discharge patients from recovery room.

Results: Demographic data were comparable in both the groups. Cognitive status was improved, at the end of 60 minutes in both the study groups but slower response was observed in experimental group as compared to control group. Analysis of co variable demonstrated that males showed more marked cognitive decline as compared to females in the experimental group, whereas males of control group had no observed cognitive drop. Similar changes were observed with other co variables like race, age, smoking habits and subjects with history of previous general anaesthesia. Duration of infused sedation seems to have effect on psychomotor functions as longer operative procedures (> 30 minutes) had loss of recovery pattern. Subjects who had higher education and employed had better performance of cognitive tests but still slower recovery as compared to control group.

Also the assessment of both the cognitive tests were done and MMSE was found to be more sensitive in detecting the cognitive changes as compared to SOMCT, while SOMCT was more specific.

Conclusion:

Based on our study results, we can conclude that as propofol is sedative which explain the improvement of cognitive scores with time but a slow recovery pattern had been noted in experimental group as compare to control group. Hence, we conclude that there is no significant cognitive function deficit noted after propofol TCI sedation but trend of slower recovery has been shown when compared to control. Other co variables may have an influence on post operative cognitive decline.

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CHAPTER 1 INTRODUCTION

The term ‘‘cognition’’ comes from Latin indicating ‘‘to know’’ or ‘‘to recognize’’. In recent years, it has come to represent a faculty for the processing of information, applying knowledge, and changing preferences. In the context of research and development, cognition, or cognitive processes, can be natural or artificial, conscious or unconscious. Anaesthesiology, neurology, psychology, philosophy and computer science each brings a distinct perspective to the study of cognition. Alterations in cognition after anaesthesia and surgery have received increased attention in recent years. Indications that some patients were experiencing significant alterations were first reported in the 1950s. Partly because anaesthesia has become safer, because we are anesthetizing an increasingly elder population, and because of advances in cognitive neurosciences, there has been a wealth of recent interest in two major central nervous system disorders, postoperative delirium and postoperative cognitive dysfunction (POCD). In brief, delirium is disordered thinking. The orienting narrative of the patient’s existence may be replaced by a coherent and convincing hallucination. Delirium is a clinical diagnosis made by identifying particular behavioural patterns. POCD, by contrast, is deterioration in the speed and accuracy of executive and memory function. Although there is clearly a clinical correlate of POCD, it is currently a research finding, as opposed to a diagnosis, and can only be defined by preoperative and postoperative testing. In other words, POCD is identified by a decline of a defined magnitude in a patient’s performance during neurobehavioral testing. The timing of testing, content and analysis of the tests are all controversial.

Cognitive impairment can occur following anaesthesia and surgery. While most patients experience some degree of cognitive impairment shortly after emerging from anaesthesia

(Curtis Stevens, 1991). Usually, the impairment is transient, uneventful and does not represent a major clinical problem. However, certain patient population are at risk of developing more pronounced short-term, as well as long-term cognitive postoperative impairment. Such patients include the elderly (Cryns *et al*., 1990, Moller *et al.*, 1998), those with cardiovascular or cerebrovascular diseases (Parikh & Chung, 1995), those with pre-existing cognitive or psychiatric disorders, particularly depression (Ritchie *et al*.,1997, Ancelin *et al*.,2001)

There are multiple aetiologies for short-term cognitive impairment, including exposure to general anaesthesia (Herbert, 1987, Hindmarch & Bhatti, 1987). In fact, studies in young, healthy, volunteer subjects (to whom anaesthesia have been administered without any medical indications) provide strong evidence that GA alone can cause short-term cognitive impairment (Korttila *et al*., 1975, 1977, 1992, Eger *et al*.,1997). The degree and duration of cognitive impairment may be related to the pharmacokinetic properties of the anaesthetic administered (Curtis *et al*.,1991).

There is no universally agreed upon definition for short-term or long-term postoperative cognitive impairment and use of these terms appears somewhat arbitrary in the literature. For instance, some investigators have referred to impairment occurring 1-3 days postoperatively as long-term impairment (Herbert, 1987, Zacny *et al*.,1992, Ritchie *et al*.,1997). In contrast , impairment occurring as long as one month after surgery has been described as short-term by other investigators (Goldstein *et al*.,1998). Nevertheless, there is little argument that impairment within first few postoperative hours is short-term impairment and it will be referred to as such throughout this study.

The significance of short-term postoperative cognitive depends on the patient population, the timing and the severity of the impairment. Inpatients may not be able to leave recovery

room while ambulatory outpatients may not be able to be discharged from hospital as quickly (Zacny *et al*., 1992). This is a financial concern for hospital administration and there is also important safety and legal considerations, for example, premature discharge, particularly in daycare surgery, can lead to accidents and resulting litigation (Korttila, 1986, 1995). So identification of the cause and understanding methods to reduce the short-term cognitive impairment is essential.

But as we are aware that GA is a combination of drugs, we need to study these drugs separately and their effect on cognitive functions,in order to identify the real culprit.

This randomised controlled study is designed to study the effects of propofol sedation, on cognition, on patients undergoing surgical procedures under local anaesthesia.

A variety of intravenous sedative techniques have been used for patients comfort and to achieve stable intra-operative conditions during surgical procedures performed under LA(Sa Rego & Watcha *et al*., 1997, Christian *et al*., 2000). An ideal sedative drug for LA in ambulatory setting should provide not only analgesia, sedation, anxiolysis and amnesia but also a stable hemodynamic status during the procedure, a rapid recovery from sedation, and few side- effects. Propofol is a relatively new sedative hypnotic intravenous agent that can be used to maintain an adequate level of sedation with constant infusion. Favourable characteristics of propofol include a rapid onset of activity, a minimum effect on systemic organs and a low addiction potential without prolonged Central nervous system depression (Smith & White *et al*., 1994). The major advantages of propofol over other sedatives are rapid recovery, few residual effects on awakening and earlier discharge (Pratila & Fischer *et al*., 1993, Sarasin & Ghoneim *et al*., 1996). However, many anaesthetics, including propofol, depress cerebral metabolism which seems to affect cognitive function gradually

in a dose-dependent manner from full consciousness to drug induced unconsciousness (Heinke & Schwarzbauer , 2002) .

Positron emission tomography studies have demonstrated that the effect of propofol is mediated by acting on specific neural network rather than by global decrease in CNS activity (Heinke & Schwarzbauer, 2002), particularly the frontal area is highly sensitive to propofol effect (Veselis *et al*., 2002)

Hence, this randomised controlled study is to assess the effects of propofol sedation on cognition for the safety of subjects under local anesthesia in day care surgery.

CHAPTER 2 LITERATURE REVIEW

2.1 Cognition and cognitive functions

The term “cognition” refers to a faculty for the processing of information, applying knowledge and changing preferences. Cognition can be conscious or unconscious. Cognition is closely related to abstract concepts such as mind, intelligence, mental functions and mental processes (thoughts).

Cognitive function primarily refers to memory, the ability to learn new information, speech and reading comprehension. Humans are equipped with a capacity for cognitive function at birth meaning that each person is capable of learning or remembering certain amount of information. Capacity to learn slows down little by little as one gets older, but overall cognitive function should not be depleted on a large scale in healthy individuals(Ge Y & Grossman *et al*., 2002).

Some research suggests that it is possible to enhance cognitive function and prevent a natural decline in memory and thought when caused by normal aging. Doing activities as word problems, memory problems and mathematics may exercise the brain so that fewer cells die or become inactive over time.

Cognitive function includes alertness, orientation, memory and attention span.

Alertness measures a person`s awareness of his or her environment and situation. Abnormal states range from confusion to lethargy, delirium, stupor or even coma.

Orientation is a person’s ability to describe their knowledge of person, place and time. Disorientation is very often linked with organic brain syndrome like dementia.

Memory is an ability to remember information in the past and the present. This is most important cognitive ability that can be lost. It is the process by which a learning experience is retained over time. Memory can be classified as procedural and declarative or short-term and long-term memory. Procedural memory is related to the knowledge of rules of action and procedure which can become automatic with repetition. This is also called implicit or unconscious memory. The nuclei of cerebellum and spinal cord are necessary for procedural memory to form but they do not intervene in declarative memory. Declarative memory involves explicit information about facts, what we know consciously. Hippocampus and temporal cortex appear to be involved in the declarative memory but not of procedural memory. So, declarative memory is controlled by the higher brain. In a study comparing the effects of midazolam and propofol on cognitive and psychomotor functions, it was concluded that cognitive impairment caused by propofol was shorter and affected explicit memory whereas implicit memory resisted impairment (Sarasin *et al*., 1996)

2.2 Postoperative cognitive dysfunction(POCD)

Postoperative cognitive dysfunction is a subtle disorder of thought process that may influence isolated domains of cognition such as verbal memory, visual memory, language comprehension, visuo-spatial abstraction, attention, or concentration. Post-operative cognitive dysfunction following cardiopulmonary bypass is well described in 25.8% of patients one week after non-cardiac surgery (Moller & Cluitmans *et al.,* 1998). Patients demonstrating POCD one week after surgery experience a decline in their daily activities of daily living (Moller *et al*., 1998) and quality of life (Newmann *et al*., 2001) following hospital discharge and are nearly three times more likely to suffer cognitive decline one to two years postoperatively (Abildstrom & Ramussen *et al*., 2000). The diagnosis of delirium and POCD requires preoperative neuropsychological testing (baseline) and a

determination that defines how much of a decline is called cognitive dysfunction. The spectrum of abilities referred to as cognition is diverse including learning and memory, verbal abilities, perception, attention, executive functions, and abstract thinking. It is possible to have a decrease in one area without a deficit in another. Self-reporting of cognitive symptoms has been shown to correlate poorly with objective testing, so valid pre-operative and post-operative testing is essential for POCD diagnosis (Jorm & Christiansen *et al*., 1997).

During emergence from anesthesia, the patients are cognitively impaired normally because by definition, emergence is the period after anesthesia but prior to return of consciousness of orientation and of response to verbal command. Emergence time is generally short (usually less than 15 minutes) (Curtis *et al*., 1991), because of the rapid rate of elimination of both inhalation and parenteral anesthethics (Mecca, 1999). After emergence, cognitive function is expected to return to baseline levels. However this does not always occur. Some patients experience short-term cognitive impairment, some patients experience long-term cognitive impairment, and some experience delirium. In rare situations patients have experienced permanent neurological deficits(Benzel *et al*., 1990, Porter *et al*., 1994, Hadzic *et al*., 1995, Black *et al*., 1998). The significance of short-term post-operative cognitive impairment depends on the patient population, the timing and the severity of impairment. Inpatients may not be able to leave the recovery room while ambulatory outpatient may not be able to be discharged from the hospital as quickly (Zacny *et al*., 1992). This is more of a economical aspect for administrators (Zancy *et al*., 1992) although there are important safety and legal considerations. For instance, premature discharge particularly in day care surgery can lead to accidents leading to litigation (Korttila 1986, 1995). This is more relevant to younger patients who are less likely to wait for sufficient recovery before returning to work or other daily activities than older or retired individuals.

Delayed physical and emotional recovery particularly in the elderly (Johnson *et al*., 2002) can also delay discharge and increase hospital costs (Parikh *et al*., 1995, Franco *et al*., 2001). In certain patient populations, delayed recovery and short-term cognitive impairment is more than an economic problem, it is an important clinical issue. Neurosurgical patients, for instance, require prompt post-operative neurological assessment (Duffy *et al*., 2000). Delayed recovery from anaesthesia increases the risk of developing serious postoperative complications (Duffy *et al*., 2000). Identification of the causes and understanding methods to reduce the short-term cognitive impairment in these and other high-risk patients is essential.

2.3 Subjects at high risk of developing cognitive impairment

The incidence and severity of cognitive impairment following surgery and anaesthesia differ according to age, type of medical intervention, pre-morbid medical condition, pre-morbid level of cognitive function, affective state, and the period of assessment.

2.3.1 Elderly subjects.

Most studies suggest that elderly patients are at a higher risk than young patients of developing short-term postoperative cognitive impairment (Platzer *et al.,* 1989, Ritchi *et al*., 1997, Dodds *et al.,* 1998, Rasmusen *et al.*, 1999, Litaker *et al*., 2001). The highest incidence of post- operative cognitive impairment occurs in patients that have undergone major cardiac (50-80%) or orthopaedic (30-50%) surgery (Dyer *et al*., 1995). Long-term cognitive impairment is also more prevalent in the elderly. A meta-analytic review 18 studies between 1955 and 1988 indicated that geriatric patients scored approximately one standard deviation lower on postoperative cognitive tests compared to pre-operative test scores (mean postoperative test period was 1.8 weeks in 16 studies and 6.2 months in 5

studies) (Cryns *et al*., 1990). A prospective study of elective, nonemergent, noncardiac, non neurological surgery under general anaesthesia also reported that age was a significant predictor of cognitive impairment one month after surgery (Goldstein *et al*., 1998). Perhaps, the most compelling evidence for long-term cognitive impairment comes from the large scale prospective study by the International Study on PostOperative Cognitive Dysfunction (ISPOCD) group (Moller et al., 1998). These investigators found that cognitive impairment in non-cardiac major surgery patients occurred in approximately 25% of patients one week after surgery and in 10% of patients after three months (Moller *et al*., 1998). Age was one of the risk factors for impairment at three months (Moller *et al*., 1998).

2.3.2 Subjects with preexisting medical conditions

Preexisting medical condition and the presence of concomitant diseases raises the risk of postoperative cognitive impairment, particularly in elderly patients (Parikh *et al*., 1995, Ancelin *et al*., 2001). Studies have shown that elderly patients with pre-existing cardiovascular or pulmonary disorders are at higher risk of developing postoperative cognitive impairment than healthy elderly patients (Crul *et al*., 1992). Preexisting cerebrovascular diseases, particularly arthrosclerosis of the carotid arteries, may also increase risk of postoperative cognitive impairment (Russell *et al*.,2002).

2.3.3 Patients with pre-existing cognitive impairment

A poor preoperative cognitive status is also associated with a higher incidence of postoperative cognitive impairment. Smith *et al*., (1986) found that elderly patients with low preoperative memory score also had greater postoperative memory deficits. Chung *et al*., (1989) reported that low postoperative Mini Mental Status Examination scores were

highly correlated with low preoperative MMSE scores. Smith *et al*., (1991) found that increased choice reaction time variability was predicted by poor preoperative mental status in 48 to 88 years old. Ancelin *et al*., (2001) also found that elderly patients with a recent history of cognitive impairment were at high risk of developing cognitive impairment after orthopaedic surgery.

2.3.4 Patients with pre-existing psychological or psychiatric disorders

Psychological or psychiatric disorders, particularly depression has shown to increase the risk of postoperative cognitive impairment. This is most common in elderly orthopaedic (Berggren *et al*., 1987, Ancelin *et al*., 2001, Galanakis *et al*., 2001) and cardiac patients (Savageau et al., 1982, Strauss *et al*., 1992, Millar *et al*., 2001)

2.4 Possible precipitating factors

The factors causing POCD remain unclear. Some factors are better understood than others, but following are some of possible factors which could be responsible for POCD.

2.4.1 Embolic events during surgery

The high incidence of cognitive impairment in cardiac patients has been attributed to microembolic events during cardiopulmonary bypass pump (Pugsley *et al*., 1994). These microembolic events may cause focal cerebral infarcts leading to POCD (Croughwell *et al*., 1994, Mills, 1995, Murkin *et al*., 1995). The similar incidence of cognitive impairment in both young and elderly cardiac patients also supports this hypothesis (Dyer *et al*., 1995)

Hip replacement and other elderly orthopaedic patients also demonstrate a high incidence of postoperative confusion and cognitive impairment (Rogers *et al*., 1989, Williams Russo *et al*., 1992, William Russo *et al*., 1995). Many of these patients are exposed to fat emboli during surgery, particularly if the surgery involves reaming of bone marrow (Jacobson *et al*., 1986, Edmonds *et al*., 2000). Fat emboli is suggested to be an important factor resulting in POCD in these patients (Jacobson *et al*., 1986, Edmonds *et al*., 2000).

2.4.2 Anticholinergic medications

Use of anticholinergic medications like atropine and scopolamine or medication with anti-cholinergic properties for instance tri-cyclic antidepressants and benzodiazepines , is suggested to be involved in precipitating postoperative cognitive impairment (Gustafson *et al*., 1988, Tune *et al*., 1981, Smith *et al*., 1986, Berggren *et al*., 1987, Miller *et al*., 1988, Parikh *et al*., 1995). Considerable evidence for the involvement of central cholinergic pathway in memory and other cognitive functions supports this argument (Bartus *et al*., 1985, Perry, 1998).

Although anticholinergic medication contributes to POCD in some cases (Tune *et al*., 1981, Smith *et al*., 1986, Berggren *et al*., 1987, Parikh *et al*., 1995), it does not explain the cognitive deficits that occur in studies that do not include anticholinergic medications. Furthermore, recent investigations have indicated that benzodiazepine pre-medications may not be a major risk factor of POCD, even in elderly. Fredman *et al*., 1999 showed that midazolam pre- medication, compared to saline, did not affect emergence, extubation time or orientation time in elderly patients undergoing short urology procedures under propofol/- desflurane anaesthesia. Psychomotor recovery, as tested using Digit Substitution Test, Mini mental status examination and Shape Sorter Test was similarly unaffected.

2.4.3 Opiod medications

Opiate medications, like morphine, codeine and meperidine, that also have anticholinergic properties can contribute to short-term postoperative impairment (Egbert *et al*., 1990, Marcantonio *et al*., 1994, Litaker *et al*., 2001). The effect of opiod on cognition is highly correlated with the pharmacokinetic properties of the drugs. Fentanyl and sufentanil have been shown to result in more rapid return of cognitive functions than morphine or meperidine, as would be expected on the basis of their elimination half-lives (Ghoneim *et al*., 1984).

2.4.4 Other potential perioperative factors

A number of other potential factors that may influence postoperative cognitive recovery have been investigated, but the evidence for most of them is weak. One of the earliest explanation was intraoperative hypotension (Bedford, 1955, Rollason *et al*., 1971, Thompson *et al*., 1978). The investigators of these studies postulated that hypotension could cause a decrease in cerebral perfusion during surgery, hence leading to POCD. However studies using modern anaesthetic technique and more rigorous study protocol have found the relationship to be weak (Towner *et al*., 1986) or nonexistent (Moller *et al*., 1998, William-Russo *et al*., 1999)

Intraoperative and early postoperative hypoxia had been correlated with postoperative cognitive impairment in elderly patients (Hole *et al*., 1980, Berggren *et al*., 1987, Rosenberg *et al*., 1992). Although hypoxia is more common in the elderly, because of greater prevalence of vascular and respiratory disease, a well-designed study by the ISPOCD group did not find an association of hypoxia with postoperative cognitive impairment (Moller *et al*., 1998).

Postoperative pain has been associated with POCD (Smith *et al*., 1991, Duggleby *et al*. 1994, Heyer *et al*., 2000), and delirium (Schor *et al*., 1992 , Lynch *et al*., 1998, Morrison *et al*., 2003) in the elderly. However, under treatment of pain in elderly subjects with pre-existing cognitive impairment may confound the results of these studies (Bell, 1997, Feldt *et al*., 1998). Specifically increased cognitive impairment may relate to pre-existing impairment rather than to increased pain.

A change from a familiar environment can be particularly distressing for elderly patients and is known to impair performance on cognitive tests. This is a possible factor that may contribute to postoperative confusion, at least in the elderly (Nadelson, 1976, Easton *et al*., 1988). Methods to reduce the impact of an unfamiliar environment , by preoperatively orientating patients to the hospital setting providing some of the comforts of home, have been unsuccessful so far (Stromberg *et al*. ,1999).

Sleep deprivation has also been suggested to contribute to cognitive impairment (Ellis *et al*., 1976, Edwards *et al*., 1981, Kaneko *et al*., 1997), but the relationship is complicated. Postoperative pain and anxiety including visits from medical staff and relatives even a change in normal sleeping environment can all disrupt normal sleep, but as discussed above, these factors might also impair postoperative cognitive function. Therefore, it is difficult to differentiate the effect of sleep deprivation from the effect of associated causes of sleep deprivation. A combination of factors is also possible, as one investigator has suggested that postoperative pain may contribute to cognitive impairment indirectly by disrupting the sleep-wake cycle (Lipowski, 1987). Other studies have not found any association between poor sleep and postoperative impairment (Smith *et al*., 1991).

In summary, numerous potential causes of POCD have been suggested, but there are conflicting results for virtually all of them. The evidence for some factors, such as embolic

events in cardiac and orthopaedic patients and postoperative benzodiazepine and opiod use in elderly patients, is more compelling than other factors. However, cognitive impairment is still found in studies of non-orthopaedic and non–cardiac patients, as well in studies without opioid and benzodiazepine use. This suggests that other factors are important. General anaesthesia remains one of the most frequently cited factor associated with cognitive impairment.

2.5 Effect of anaesthesia on cognitive function in volunteer subjects

There is little doubt that anaesthetics can impair cognitive functions in the short term. Particularily strong evidence for this conclusion comes from results of studies conducted in volunteers. The duration and severity of cognitive impairment depends on the dose of anaesthetic administered, the duration of administration, and the type of agent used.

Studies in which sub- anaesthetic concentration of general anaesthetic were administered to volunteers indicate that cognitive impairment can occur (Bruce *et al*., 1974) but does not last longer than 30 minutes. Cheam *et al* (1995) reported that recovery of psychometric tests was completed by 10-20 minutes following inhalation of concentration of 50% nitrous oxide in a small number of healthy male volunteers. Galinkin *et al.,* (1997) showed that administration of either 30% nitrous oxide or 0.6% sevoflurane for 35 minutes did not impair psychomotor function longer than 30 minutes after discontinuing administration. Low concentrations of isoflurane (9.5% and 14.1% of the minimum alveolar concentration (MAC)) administered for 15 minutes to six young healthy volunteers impaired reaction time and critical flicker fusion test (CFFT) but for no longer than 30 minutes (Yoshizumi *et al* ., 1993).

When volunteer subjects have been anaesthetized, longer durations of cognitive impairment occur than following exposure to trace concentration. A series of studies were conducted that used simulated driving skills to assess recovery following anaesthesia. Subjects were impaired for 8 hours after methohexital (Korttila *et al*., 1975), for 6 hours after thiopental anaesthesia (Korttila *et al*., 1975), and 1 hour after propofol anaesthesia (Korttila *et al*.,1992). After a brief inhalational anaesthesia (3.5 minutes), driving skills were impaired for 4-5 hours (Korttila *et al*., 1977). After long (8 hours) duration of anaesthesia with 1.25 MAC desflurane or sevoflurane, psychomotor performance was slower with sevoflurane, 60 and 90 minutes after anaesthesia (Eger *et al*., 1997). Subjects were also given a questionnaire one week after anaesthesia to estimate time required for recovery to specific end-points including mental recovery. Volunteers who received desflurane had reported feeling normal in all aspects by around 12 hours after anaesthesia, whereas those that received sevoflurane did not feel normal for 72 hours (Eger *et al*., 1997).

2.6 Effect of different anaesthetic agents on cognitive recovery in healthy young patients

In young healthy adults, most studies indicate that the type of anaesthetic agents, whether intravenous or inhalational, can influence the speed of emergence and/or recovery (Pollard *et al*., 2003). Older barbiturate anaesthetics such as methohexital and sodium thiopental generally result in delayed emergence and delayed return of psychomotor function compared to propofol (Boysen *et al*.,1989 ,Mackenzie *et al*., 1985) although there are exceptions (Pollard et al., 2003). Recovery following inhalational anaesthesia is generally related to pharmacokinetic properties of the agents. Hence recovery after halothane is

prolonged compared to isoflurane (Eger, II 1981), recovery after isoflurane is prolonged compared to desflurane (Tsai *et al*., 1992, Smith *et al.*, 1994, Fletcher *et al*., 1991, Smily *et al*., 1991, Lee *et al*., 1993, Dupont *et al*., 1999). With sevoflurane recovery is only slightly prolonged compared to desflurane (Nathanson *et al*., 1995, Dupont *et al*., 1999).

2.7 Effect of different anaesthetic agents on cognitive recovery in healthy elderly patients

The type of anaesthetic can also affect the speed and cognitive recovery in healthy elderly patients. Some investigators have shown that in geriatric patients undergoing short ambulatory urological procedures, desflurane was associated with 73% fast track eligibility compared to 43% for isoflurane and 44% for propofol (Fredman *et al*., 2002). Fast track eligibility refers to readiness for rapid hospital discharge of outpatients. In contrast, other studies have shown that while desflurane may lead to earlier emergence and recovery of psychomotor function compared to propofol and isoflurane there is no significant influence on time of discharge from the postanaesthetic care unit (PACU) (Bennett *et al*., 1992, Juvin *et al*., 1997, Solca *et al*., 2000). As expected from the low blood: gas solubilities of both agents, desflurane may result in more rapid emergence than sevoflurane, but by one hour postoperatively the MMSE test did not differ (Chen *et al*., 2001).

2.8 Methods of detecting post operative cognitive impairment

A wide variety of methods have been used to detect POCD, including interviews, questionnaraires, mental status exams and neuropsychological tests (Reviews by Dodds *et al*., 1998, Dijkstra *et al*., 2002). Postoperative interviews and questionnaires are convenient

and quick to administer but provide limited information about more complex cognitive functions. When administered orientation questionnaires, for example, most patients achieve high scores within 15-30 minutes of anaesthesia. Thus a ceiling effect occurs early in the recovery period, which precludes the ability to detect more subtle impairment beyond this time period. Furthermore, take home questionnaires rely on patient self-assessment, which introduces rater bias and do not generally correspond with objective tests of cognitive impairment (Jones *et al*., 1990, Mollar *et al*., 1993).

Tests of mental status are most frequently used methods of assessing cognition in postoperative recovery studies (Chung *et al*., 1990, Prior & Chander, 1982, Mann & Bisset, 1983, Bigler *et al*., 1985, Berggren *et al*., 1987, Chung *et al*., 1987, Chung *et al*., 1989, Knill, 1990, Crul *et al*., 1992). The most common of these is the Mini-Mental Status Examination (MMSE) (Folstein *et al*., 1975). The advantage of MMSE and other mental status tests is their probability and ease of administration. However, the information gained from mental status tests is generally limited to gross changes in cognitive function (de Jager *et al*., 2002).

So in this study the following 2 tests were used

2.8.1 Mini Mental Status Examination (MMSE)

MMSE is a valid test of cognitive function. It separates patients with cognitive disturbances from those without disturbances. Its scores correlate with a standard test of cognition, the Wechsler Adult Intelligence Scale (WAIS)

The MMSE is divided into 2 sections, the first of which requires vocal responses only and covers orientation, memory and attention, the maximum score is 21. The second part tests ability to name, follow verbal and written commands, the maximum score is 9. So total

maximal attainable score is 30. A score of below 24 would indicate a psychological decline of cognitive function and a score of 21 and below denotes significant cognitive impairment.

2.8.2 Short Orientation Memory Concentration Test (SOMCT)

SOMCT investigates the patient`s capacity to know the current year or month and to repeat in numerical order the inverse sequence of the months of the year. These variables permit the assignment of a numerical score from 0 to 28 based upon the patient's cognitive function. Higher scores indicate better cognitive function and scores below 21 indicates significant cognitive decline.

2.9 Propofol intravenous anaesthetic agent - Pharmacology

2.9.1 Physical and chemical properties

Propofol is commonly used intravenous anaesthetic agent, belongs to alkylphenol group that has hypnotic properties.

It is mildly viscous, milky white, lipid soluble oil at room temperature.

1% propofol contains 10% soyabean oil as solubilising agent, 2.25% glycerol to make solution isotonic and 1.2% purified egg phosphatide an emulsifying agent. It has a pKa of 11 and 90% is unionized at pH 7.4 with protein binding of 98% and elimination half life is 0.5-1.5 hours.

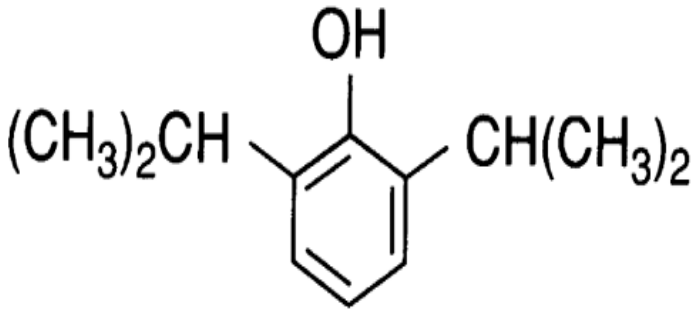

Figure 2.1: Propofol chemical structure – 2,6 diisopropylphenol

2.9.2 Mechanism of action

It acts on GABA receptors and decreases rate of dissociation of GABA and also increases the duration of chloride channel opening resulting in hyperpolarisation. There is evidence that propofol enhances GABA mediated transmission at a site distinct from benzodiazepine receptors (Bryson HM *et al*., 1995, Wagner BJK *et al*., 1997) and such activity may vary depending on plasma propofol concentrations.

2.9.3 Pharmacodynamic properties

Propofol almost affects all systems but most important the central nervous and cardiovascular system.

Central nervous system (CNS) – It causes dose dependent CNS depression from light sleep to deep coma (Fulton B *et al*., 1995). It causes dose-related changes on the electroencephalogram (EEG). Sedative dose of propofol causes activation of beta wave activity while anaesthetic doses are associated with increased slow wave activity in the delta frequency (Bryson HM *et al*., 1995, Langley MS *et al*., 1988). When propofol is administered in anaesthetic doses (2mg/kg), an increases cerebral vascular resistance and a

decreases cerebral blood flow, cerebral metabolic rate for oxygen and glucose are seen (Smith I, White PF *et al*., 1994, Sebel *et al*., 1989) and a anxiolytic.

Cardiovascular effects – When administered in anaesthetic doses (2mg) propofol causes direct myocardial depression and decreases systolic and diastolic BP and 15-30% drop in mean arterial pressure. It also decreases stroke volume, systemic vascular resistance and cardiac output. Heart rate remains fairly stable.

2.9.4 Pharmacokinetics of propofol

2.9.4.1 Absorption and Distribution

Propofol is given intravenously, as it is not effective orally. It is a highly lipid soluble emulsion with a rapid onset of action, with a one arm brain circulation of (30 seconds). It follows 2 or 3 compartment model, has an alpha half-life of 1.8-8.3 minutes and longer beta half-life which is 1-3 hours. It has a protein binding of 98%, volume of distribution is 3.5-4.5 L/kg and clearance is 30-60 ml/kg/minute, which exceeds hepatic blood flow.

2.9.4.2 Metabolism and Excretion

Propofol metabolism is both hepatic and extrahepatic. Hepatic metabolism is rapid and extensive, resulting in inactive, water soluble sulphate and glucuronic acid metabolites which are excreted by the kidneys. Propofol also undergoes ring hydroxylation by cytochrome P-450 to form 4 hydroxypropofol which is then glucuronidated or sulphated. Less than 0.3% of dose is excreted unchanged in urine. The elimination half-life is 0.5-1.5 hours and the context sensitive half time for propofol infusion of 8 hours is less than 40 minutes.

2.10 Propofol as conscious sedation or Monitored Anaesthetic Care (MAC)

Propofol is used alone or in combination with an opiate analgesic and/or a benzodiazepine for initiation and maintenance of MAC sedation in adults undergoing diagnostic procedures or in conjunction with local or regional anaesthesia for surgical procedures (Astra Zeneca, 2001, Baxter, 2001, Bryson HM, Fulton BR *et al*., 1995, Smith I *et al*., 1994). MAC sedation regimes usually provide sedation, analgesia, anxiolysis and /or amnesia without assisted respiration or loss of consciousness (Bryson HM *et al*., 1995, Smith I *et al*., 1994) when administered prior to or during dental, endoscopic, diagnostic, oral or other procedures such as extracorporeal lithotripsy, transvaginal oocyte retrieval, central venous catheter placement, herniorrhaphy and electrical cardioversion (Bryson HM *et al*., 1995, Smith I *et al*., 1994). Propofol is also used with local or regional anaesthesia for surgical procedures including orthopaedic, abdominal and urologic surgery (Bryson *et al*., 1995)

When used for sedation in patients undergoing diagnostic procedures and surgical procedures under local anaesthesia propofol produces less postoperative sedation, drowsiness, confusion and nausea with a more rapid recovery of psychomotor performance than intravenous midazolam. However midazolam has been associated with less pain at injection site and more effective intraoperative amnesia (Smith I et al., 1994, Larijani GE *et al*., 1989).

The best way to administer propofol for MAC is via TCI pump, targeting either plasma or effect site concentration.

2.11 Target Controlled Infusion (TCI) pump

A pharmacokinetic algorithm calculates the necessary doses/ rates to reach and to maintain a desired concentration of a drug in the blood plasma

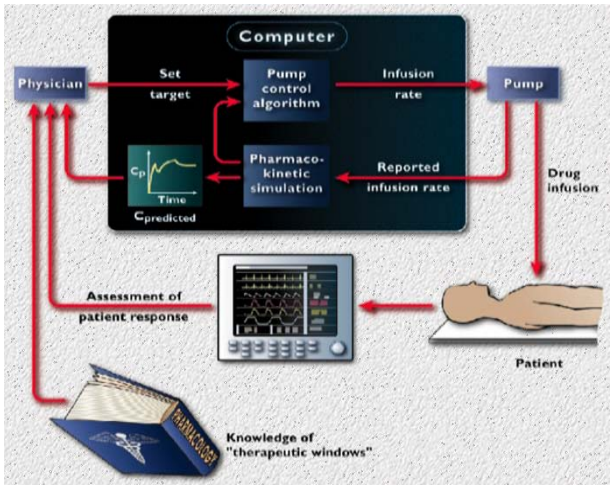

Fig 2.2 Pharmacokinetics of TCI pump

TCI properties

Using the properties of a pharmacokinetic model implemented in an infusion pump then allows:

- To predict the concentration of the drug in the body
- To input a desired target concentration rather than an infusion rate
- To control the pump (rate changes) in dependance of the target
- To target on blood plasma as well as on effect site (bio-phase, pharmacokinetic/ pharmacodynamic model)

Benefits of TCI

- Dose titration to achieve a desired effect is facilitated
- Simplification of dosage and improved ease of use
- Advisory information on the calculated drug concentration is provided
- Improved individualization of dosage if a complex pharmacokinetic model is available using covariates for age or other patient characteristics.
- Provide much more stable concentrations
- Supports to avoid overdosage
- Very quick awakening

CHAPTER 3 OBJECTIVE

3.1 General Objective

To study the effects of sedation with target controlled infusion propofol on cognitive functions in patients undergoing surgical procedures with local anesthesia and monitored anaesthetic care (conscious sedation)

3.2 Specific Objectives

1. To compare the cognitive functions using MMSE and SOMCT scores between Propofol TCI sedation group and Non sedated group at pre-operation, 20 minutes post-operation and 60 minutes post-operation
2. To determine the effects of co-variables with cognitive function assessment at pre-operation, 20 minutes post-operation and 60 minutes post-operation.
3. To compare sensitivity and specificity of MMSE and SOMCT in assessment of post operative cognitive functions.

3.3 Study Hypothesis

H_1: There are cognitive changes following conscious sedation with propofol.