INTRODUCTION

Cognition is defined as the mental processes of perception, memory and information processing. Cognitive dysfunction is thus impairment of these processes ***(Ramaiah and Lam, 2009).***

Postoperative cognitive dysfunction (POCD) is characterized by progressive hypomnesia, personality change or deterioration in cognitive function after surgery ***(Fong et al., 2006).***

In clinical studies of cognitive changes after surgery a distinction is made between delirium and POCD. Delirium is characterized by an acute and transient disturbance of mental functions that may be accompanied by changes in awareness ***(Funder et al., 2010)***. POCD encompasses more subtle cognitive changes that are long lasting ***(Krenk et al., 2010)***.

Specific characteristics of POCD include decline in speed of processing the information and disturbance in executive functioning but the patient typically remains oriented to person, time and place ***(Tsai et al., 2010).*** The decline in POCD is mostly recognized by comparison to the patient's pre-operative capabilities ***(Deiner, 2009).***

Anesthesia ***(Rundshagen, 2014)***. Risk factors for POCD, such as advancing age, the severity of surgery, the duration of anesthesia, the occurrence of complications, pre-existing

cognitive impairments and the level of education, have been determined ***(Price et al., 2008)***.

Age is the main risk factor for POCD, and although it is well recognized that the incidence of POCD is higher in the elderly ***(Monk et al., 2008)*** particularly those undergoing sevoflurane anesthesia, the mechanism is not fully understood ***(Rossi et al., 2014).***

Old age comes with infirmities, many of which can be successfully treated with surgery. Unfortunately, persistent cognitive impairments can develop as a side-effect of these surgical procedures, a phenomenon that is predominantly seen in the elderly ***(Krenk et al., 2010).*** This complication has been termed 'postoperative cognitive dysfunction' (POCD). Surgery-induced cognitive decline leads to an increased risk of disability and mortality ***(Steinmetz et al., 2009).*** As a consequence, patients can lose their employment or independence, which seriously reduces their quality of life ***(Steinmetz et al., 2009).***

Several mechanisms have been proposed to be involved in the development of cognitive impairments after surgery, including changes in cerebral blood flow, sleep disturbances, effects of anesthetics, and inflammation. Hypoperfusion, hypoxia, and the formation of micro-emboli have been shown to occur during and after surgery, and could potentially cause ischemic brain damage, but a clear relationship with POCD has not been found ***(Krenk et al., 2010).*** Sleep disturbances can

occur after surgery or due to the use of medication, such as opioids, and are known to affect cognitive performance ***(Krenk et al., 2010),*** but research on the influence of such disturbances on POCD is scarce and inconclusive ***(Gogenur, 2010).***

Some types of anesthesia have been shown to cause neurodegenerative changes in animal studies ***(Kalenka et al., 2010)***.

Consistent evidence is accumulating only for the role of inflammatory processes arising due to surgical trauma and subsequent complications. Where clinical studies have provided leads to the understanding of this mechanism, most of the studies researching the mechanism in more detail have been performed using animal models. Although low levels of immune activation are necessary for regulating normal cognitive functions, the high levels of proinflammatory factors associated with trauma or infection, have been shown to detrimentally affect cognitive processes ***(Yirmiya and Goshen, 2011).***

There have been several reports that central nervous system inflammation provoked by anesthesia and surgery plays an important role in the pathogenesis of POCD ***(Lili et al., 2013).***

An inflammatory response to postoperative stress may contribute to POCD via disruption of the blood brain barrier ***(Rudolph et al., 2008).***

There are no universally accepted guidelines for the diagnosis and treatment of POCD, and there have been few consensus statements on the subject ***(Monk et al., 2008)***.

The accurate assessment of POCD is difficult with a variety of contributing elements ***(Rasmussen et al., 2001)***. The most often mentioned are variability of examiners, different definitions of POCD, interval between test sessions, mood changes and anxiety, pain, sleep-deprivation, pharmacologic effects, failure of some patients to complete the studies, language and cultural problems, timing of postoperative assessment, differences in the tests used, surrounding environments, dissimilar exclusion criteria, and statistical design ***(McDonagh et al., 2010).***

The Mini-Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) are useful as a surrogate for clinical but not investigational purposes. Though they have a sensitivity of 87% and a specificity of 82% and are less time consuming than neuropsychological testing ***(Price et al., 2014)***.

The increased risk is correlated with elevated S-100β protein. S-100β protein is an acidic calcium-binding protein

found in the central nervous system, In the developing CNS it acts as a neurotrophic factor and neuronal survival protein ***(Li et al., 2012).***

In adults it is usually elevated due to nervous system damage, and when detected in the systemic circulation is considered a biomarker of acute brain injury ***(Peng, 2013).***

Serum levels of S-100β protein increases significantly in patients had POCD ***(Van Den Boogaard et al., 2011).***

Aim of the Work

The aim of this study is to compare the effect of anesthesia under inhalational sevoflurane with and without preoperative methylprednisolone, and under total intravenous anaesthesia with propofol on POCD.

Chapter 1
BRAIN ANATOMY

The nervous system is divided into two components: The central nervous system which is composed of the brain and the spinal cord and the peripheral nervous system, which is composed of ganglia and peripheral nerves that lie outside the brain and spinal cord.

A. The central nervous system: (Figure 1)

The central nervous system consists of six main regions:

I. The cerebral hemispheres:

They consist of the cerebral cortex, the white matter under the cortex and three deeply located nuclei:

- The basal ganglia: The basal ganglia have an important role in regulation of movement, and also contribute to cognitive functions.
- The Hippocampus and amygdala: The hippocampus and amygdala are called limbic system. The hippocampus is involved in memory storage ***(Florio and Huttner, 2014).***

II. The Diencephalon:

It consists of the thalamus and hypothalamus and it lies between the cerebral hemispheres and the midbrain. The

thalamus distributes almost all sensory and motor information going to the cerebral cortex. In addition, it is thought to regulate levels of awareness and some emotional aspects of sensory experiences. The hypothalamus lies ventral to the thalamus and regulates autonomic activity and the hormonal secretion by the pituitary gland ***(Blumenfeld, 2002).***

III. The midbrain:

This is the smallest brain stem component which lies rostral to the pons. The midbrain contains essential relay nuclei of the auditory and visual system.

IV. The pons and cerebellum:

It contains a large number of neurons that relay information from the cerebral hemispheres to the cerebellum. The cerebellum lies dorsal to the pons and medulla. The cerebellum receives somatosensory input from the spinal cord, motor information from the cerebral cortex and balance information from the vestibular organs of the inner ear. The cerebellum plays a major role in the control of posture, head and eye movements.

V. The medulla:

This structure is the direct rostral extension (this means toward the head and nose) of the spinal cord. It resembles the spinal cord in both organization and function ***(Waly et al., 2014).***

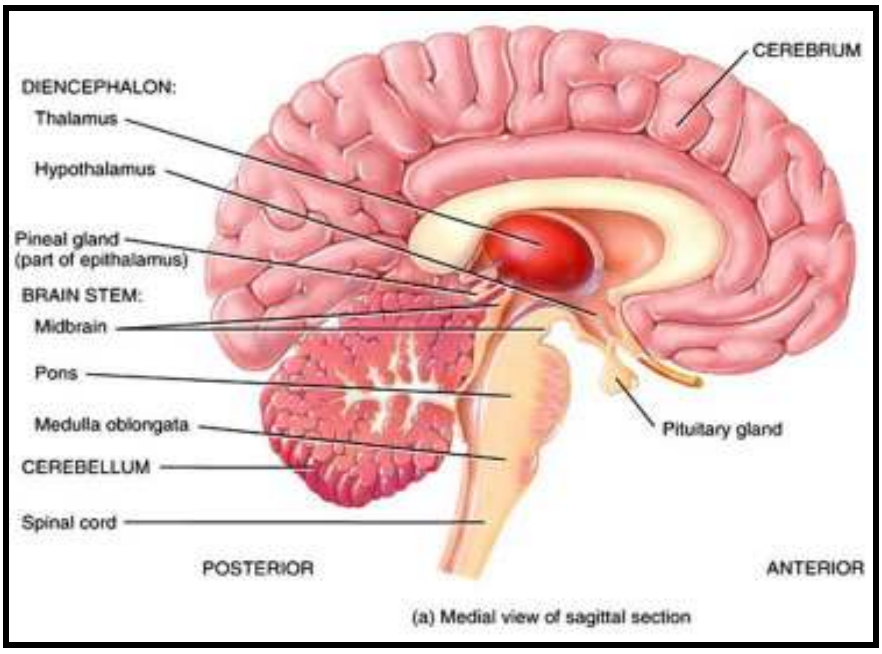

Figure (1): Anatomy of central nervous system ***(Levin, 2000).***

VI. The spinal cord:

It extends from the base of the skull as extension of the medulla oblongata through the foramen magnum then through the first cervical vertebra. The spinal cord receives sensory information from the skin, joints, muscles of the trunk and limbs and contains the motor neurons responsible for both voluntary and reflex movements. It also receives sensory information from the internal organs and control many visceral functions ***(Bullmore and Sporns, 2009).***

B. The peripheral nervous system:

The peripheral nervous system is divided into two subsystems: Somatic and autonomic ***(Blumenfeld, 2002).***

Chapter 2

BASIC BRAIN PHYSIOLOGY

A. Central neurotransmitters:

Neurotransmitters are small molecules that are liberated by a presynaptic neuron into the synaptic cleft and cause a change in the postsynaptic membrane potential ***(Elinore, 2002).***

They are divided into three principal classes. The first class is made up of acetylcholine alone; the second class are the monoamines, that are molecules formed by an amino acid losing a hydroxyl or carboxyl group. The third class is made up of amino acids (Table 1). There is also a specific chain of enzymatic reactions that decompose the transmitter, either for destruction or for recycling ***(Elinore, 2002).***

Neurotransmitters can act as inhibitory or excitatory signals to the postsynaptic cell by either hyperpolarizing or depolarizing its membrane, the same molecule can function as an inhibitor or an excitator. Acetylcholine, for instance can act as an excitator when it binds to one type of receptor, and as an inhibitor when bound on another kind, even if both types of receptors are present in the same cell ***(Carlson, 2001).***

Acetylcholine is the major neurotransmitter in the peripheral nervous system (the other peripheral neurotransmitter is norepinephrine). Acetylcholine is usually (but not always) an excitatory neurotransmitter in contrast to the monoamine

neurotransmitters, which are nearly always inhibitory ***(Elinore, 2002).***

Most brain cholinergic receptors are muscarinic. Cholinergic system in the cerebral cortex is active in both the waking state and in REM sleep but is reduced in non-REM sleep ***(Levin, 2000).***

Table (1): Neurotransmitters.

Neurotransmitter	Function	Synthesis by (enzymes)
Acetylcholine	Mostly excitatory	Acetyl Choline transferase
Bioactive amines 1. Dopamine	Excitatory and inhibitory	Tyrosine hydroxylase
2.Epinephrine	Excitatory	Tyrosine hydroxylase and dopamine B-hydroxylase
3. Norepinepheine	Excitatory	Tyrosine hydroxylase and dopamine B-hydroxylase.
4. Serotonin	Excitatory	Tryptophan hydroxylase
Aminoacids 1. Glutmate	Excitatory	Metabolic amino acid
2. Glycine	Mostly inhibitory	Metabolic amino acid
3.G-amino butyricacid (GABA)	Inhibitory	Glutamate decarboxylase

(Elinore, 2002)

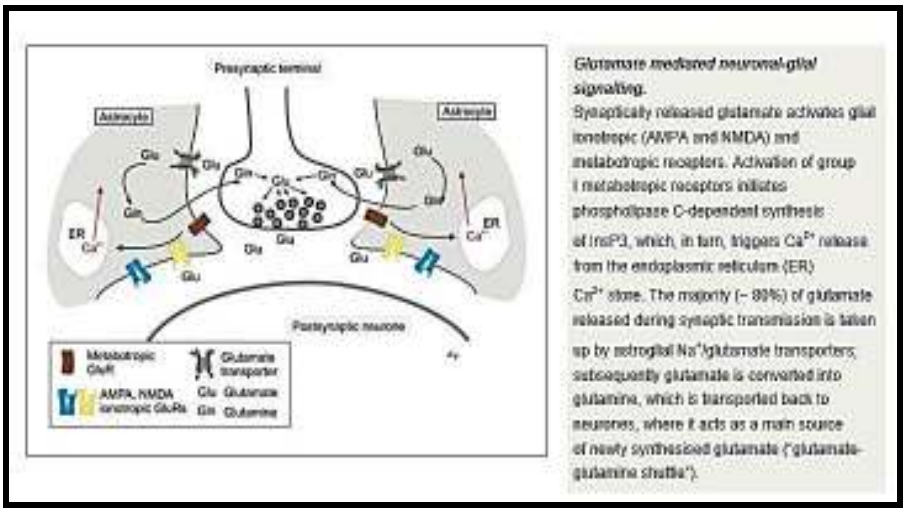

Figure (2): The effect of neurotransmitters at synaptic level ***(La Bar and Le Doux, 2003).***

B. Cognitive functions of the brain:

Cognition is defined as the mental processes of perception, memory and information processing which allows the individual to acquire knowledge, solve problems and plan for the future. It comprises the mental processes required for everyday living and should not be confused with intelligence ***(Hanning, 2005).***

There are three identified association areas of the cortex. One is the parieto-temporal-occipital cortex. This cortex has regions that receive somatosensory, auditory and visual projections, also it receives the high-order input from their respective cortices and is therefore thought to integrate information from these sensory modalities and is necessary for language. The second cortex that is identified is the prefrontal

association area which is believed to control several cognitive behaviors such as provocative behavior and also to control motor planning. The third one is the limbic association cortex which respond exclusively to a combination of the two sensory inputs ***(Elinore, 2002).***

C. Cerebral Blood Flow (CBF):

The adult human brain weighs approximately 1350 g and therefore represents about 2% percent of total-body weight. However, it receives 12% to 15% of cardiac output. This high flow rate is a reflection of the brain's high metabolic rate. At rest, the brain consumes oxygen at an average rate of approximately 3.5-5 mL of oxygen per 100 g of brain tissue per minute. Whole-brain O2 consumption (50 mL/min) represents about 20% of total-body oxygen utilization (Table 2) ***(Michenfelder, 2003).***

Table (2): Normal Cerebral Physiologic Values.

CBF	
Global	45-55 mL/100 g/min
Cortical (mostly gray matter)	75-80 mL/100 g/min
Subcortical (mostly white matter)	≈20 mL/100 g/min
$CMRO_2$	3-3.5 mL/100 g/min
CVR	1.5-2.1 mm Hg/100 g/min/mL
Cerebral venous Po_2	32-44 mm Hg
Cerebral venous So_2	55%-70%
ICP (supine)	8-12 mm Hg

CBF, Cerebral Blood Flow; **$CMRO_2$**, Cerebral Metabolic Rate of Oxygen; **CVR**, Cerebral Vascular Resistance; **ICP**, Intracranial Pressure ***(Michenfelder, 2003)***

1. Chemical Regulation of Cerebral Blood Flow:

A. Cerebral Metabolic Rate (CMR):

Increased neuronal activity results in increased local brain metabolism. This increase in CMR is associated with a well-matched, proportional change in CBF and is referred to as flow-metabolism coupling. The data available implicate local by-products of metabolism (K+, H+, lactate, adenosine and adenosine triphosphate [ATP]). Glutamate, released with increased neuronal activity, results in the synthesis and release of nitric oxide (NO), a potent cerebral vasodilator that plays an important role in coupling of flow and metabolism. CMR is also influenced by several phenomena in the neurosurgical environment, including the functional state of the nervous system, anesthetic drugs and temperature ***(Michenfelder, 2003).***

- **Functional State:**

CMR decreases during sleep and increases during sensory stimulation, mental tasks or arousal of any cause ***(Carlson, 2001).***

- **Anesthetic Drugs:**

In general, anesthetic drugs suppress CMR, with ketamine and nitrous oxide (N2O) being notable exceptions. It appears that the component of CMR on which they act is that associated with electrophysiologic function. Increasing plasma

concentrations of several anesthetics including barbiturates, isoflurane, sevoflurane, desflurane, propofol and etomidate cause progressive suppression of electroencephalographic (EEG) activity and a concomitant reduction in CMR. However, increasing the plasma level beyond what is required to achieve suppression of the EEG results in no further depression of CMR. The component of CMR required for maintenance of cellular integrity (the "housekeeping" component) is unaltered by intravenous anesthetic drugs ***(Peterson et al., 2004).***

- **Temperature:**

CMR decreases by 6% to 7% per degree Celsius of temperature reduction. As is the case with some anesthetic drugs, hypothermia can also cause complete suppression of the EEG (at about 18°C to 20°C) while hyperthermia has an opposite influence on cerebral physiology. Between 37°C and 42°C, CBF and CMR increase. However, above 42°C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may result in protein (enzyme) denaturation ***(Michenfelder, 2003).***

b. $PaCo_2$:

CBF varies directly with PaCo2. The changes in CBF caused by PaCo2 are dependent on pH alterations in the extracellular fluid of the brain. Nitric oxide (NO), in particular