INTRAOPERATIVE MONITORING OF PATIENTS DURING NEUROSURGICAL PROCEDURES: A BIOCHEMICAL AND ELECTROPHYSIOLOGICAL STUDY

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CONTENTS

Abbreviations:

TES	**–** Transcranial Electrical Stimulation
iMEP	– intraoperative Motor Evoked Potential
CMAPs	– Compound Muscle Action Potentials
IOM	– Intraoperative monitoring
IM tumours	– Intramedullary tumours
IDEM tumours	– Intradural Extramedullary tumours
Myelopathy	– Pathological condition of the spinal cord that damage both white and gray matter and / or myelinated fiber tracts that carry sensory and motor signals to and from the brain.
MRC Grade	– Medical Research Council (One of the grading systems used to assess the individual muscles power of both upper and lower limbs).
Nurick	– One of the grading systems used to assess the degree of spinal cord compression in patients undergoing spinal cord surgery.
McCormick	-- Grading system used to assess both sensory and motor functions of the patients undergoing spinal cord surgery.
TA	– Tibialis Anterior
Sol	– Soleus
Quad	– Quadriceps
EAS	– External Anal Sphincter
Supratentorial	– In anatomy, it is the brain region part located above the tentorium cerebelli.
Craniotomy	– A kind of neurosurgery in which part of the skull is removed in order to access the brain for the removal of tumour.
Perioperative	– Periods including preoperative, intraoperative and postoperative.
MAP	– Mean Arterial Pressure
CBV	- Circulating Blood Volume

CHAPTER 1

GENERAL INTRODUCTION AND REVIEW OF LITERATURE

1.1. Introduction:

Intraoperative electrophysiological monitoring of the nervous system is used to prevent complications arising during the course of neurosurgical procedures. Various electrophysiological monitoring techniques such as EEG (Electroencephalogram), EP (evoked potentials), EMG (Electromyography) and NCV (Nerve conduction velocity) are used during the course of surgery. The principal goal of intraoperative electrophysiological monitoring is (1) prompt identification of nervous system impairment during surgery and prevent permanent postoperative deficits. (2) provide relative reassurance to the surgeon that no identifiable complication has been detected up to that point, allowing the surgeon to proceed further and provide a more thorough or careful surgical intervention than would have been provided in the absence of monitoring (3) modify surgical strategy when any change occurs in the recordings.

The common neurophysiological techniques that are used for intraoperative monitoring are sensory evoked potentials (SEPs) where the stimulus varies depending on the modality that is being stimulated such as auditory pathway (brainstem auditory evoked potentials), somatosensory pathway (somatosensory evoked potentials) and visual pathway (visual evoked potentials). These methods evaluate the integrity of the sensory pathways and the potential generators. Similarly, motor pathways are evaluated using motor evoked potentials (MEPs) where motor areas/pathways are stimulated by using either electrical or magnetic stimulation methods.

1.1.1. Spinal cord Monitoring:

1.1.1.1. Somatosensory evoked potential (SSEP):

Peripheral nerves such as median nerve at wrist or posterior tibial nerve at ankle are stimulated by a brief electrical pulse repeatedly and responses are recorded along their path in the spinal cord and on the scalp (contra lateral to the side of stimulation). . Since sensory evoked potentials are of small magnitude and to improve signal to noise ratio these responses are averaged. For more than two decades somatosensory evoked potentials have been used to monitor the status of the spinal cord during spinal surgery. In 1996 a survey of more than 60,000 monitored operations (1) the overall incidence of "true positives" (patients in whom correctly predicted the occurrence of a postoperative deficit) was 0.42%. The incidence of "false negatives" (unpredicted deficits) was 0.063%. Many of them would be included in 1.15% of "false positives" patients whose somatosensory evoked potentials (SSEPs) showed a change but who had no postoperative sequel. Unfortunately we do not know the exact proportion of "false positives" that represented real neurophysiological changes, which are reversed in time to prevent the occurrence of neurological deficits, and how many were actual "false alarms". The largest single centre survey of SSEP monitoring during kyphoscoliosis surgery is that of Forbes et al in 1991(2). They used a more invasive method to record spinal SSEPs from the epidural space above the levels of surgery, rather than non invasive cortical SSEPs. In this single centre study the incidence of "false negatives" was 0% but that of "true positives" was at 2.7%. Probably because of the strict criteria they have used to define significant postoperative impairments as compared to other studies. Epidural SSEP

recording technique affords greater stability to systemic factors such as blood pressure and the level of anaesthetic agents.

In 1980s a number of case reports appeared suggesting that postoperative deficits might occur in spite of unchanged SSEPs. A collection of these studies was published by Lesser et al., 1986 (3). One group (4) reported a 9% incidence of "false negative" SSEPs during the performance of thoracic vertebrectomy, while a second group (5) more specifically reported a case of an anterior cord syndrome following a 3-level thoracic spondylectomy, during which SSEPs remained unchanged. A recent study (6) found SSEPs to give "false negative" indications in 4.1% of 658 neurosurgical procedures involving the spine and/or the brain. In the context of spinal surgery it might be argued that any procedure where the cord is approached from the anterior side might potentially endanger the anterior spinal artery, and that such a compromise may possibly go undetected if only SSEPs are monitored. Even in routine procedures such as anterior cervical discectomy, two cases of temporary postoperative quadriparesis have been reported, which were not detected by peroperative SSEP monitoring (7).

1.1.1.2. Motor Evoked Potential (MEPs):

It is also widely acknowledged that SSEPs may be abolished during resection of intramedullary tumours, recovering again during closure or in the immediate postoperative period (8). This is presumably due to neurapraxia of dorsal column axons when a midline myelotomy is performed to access the tumour. Under these circumstances motor evoked potential (MEP) monitoring is considered essential by some surgeons, although there are only anecdotal reports testifying to its effectiveness.

MEPs are commonly used to monitor motor tracts during the course of spinal cord surgery. MEP's can be elicited by electrically stimulating either motor cortex or spinal cord. MEPs can also be elicited by trancranially stimulating the cortex using Transcranial Electrical Stimulation (TES) or Transcranial Magnetic Stimulation (TMS) methods. The responses can be recorded from the spinal cord or peripheral nerves or muscles, known as compound muscle action potentials (CMAPs).

Currently there are five methods that are adopted to do MEP monitoring.

(1) Electrical stimulation of the spinal cord and recording from spinal cord either from the epidural space or outside the vertebral column. This would result in activation of both motor and sensory tracts (9). Due to this relative contribution of both motor and sensory at another level it may be difficult to assess.

(2) Stimulating the spinal cord and recording CMAPs. This did not result in reliable responses from a single electrical shock above the mid-thoracic level. However, double pulse stimulations with stimulus interval of about 2 ms were highly effective (10).

(3) The other method is to stimulate the spinal cord and record from the peripheral nerve known as neurogenic motor evoked potential (NMEP) (11). These are commonly recorded from tibial nerve at popliteal fossa which is a mixed nerve. Hence, there is a possibility that NMEP could be due to antidromic sensory fiber activation which is a serious drawback (12, 13).

(4) Transcranial stimulation and epidural recording. In this the cortex is transcranially stimulated and recorded from the spinal cord using epidural electrodes (14 -16). Currently there appears to be no methodological problems for transcranial stimulation of the cortex and recording from spinal cord or CMAPs. However when

recording from the spinal cord it is not possible to differentiate left side and right side leg responses as stimulation cannot be directed to one leg only.

(5) Transcranial stimulation and CMAP recording. This involves transcranially stimulating the cortex and recording from the muscles (16-18). Transcranial stimulation of the cortex and recording responses from the muscles seem to give better advantage over the other methods mentioned above. Transcranial magnetic stimulation (TMS) is pain free in conscious state but is not relevant in patients under surgical plane. The disadvantage of using TMS is that they are capable of activating only cortical interneurons and the pyramidal cells directly (19, 20). This will make recording CMAPs to multipulse stimulation less easily recordable than electrical stimulation. The other reasons being the size of magnetic coils which are bulky and placement will be cumbersome when there are head pins.

1.2. TES and monitoring of the Spinal cord:

The scientific foundation for MEP monitoring was laid by Patton and Amassian in 1954 by discovering that a single electrical pulse applied to monkey motor cortex could evokes several motor corticospinal tract volleys (21). Electrical stimulation to the spinal cord produces direct generation of first and largest non-synaptic discharge of corticospinal axons volley and that was named as the D-wave. Followed by the excitation of cortical synaptic circuits that discharge of 1-5 volleys by corticomotor neurons with 1.3 to 2.0 ms periodicity and these are called as I waves, being indirectly generated by the electric pulse (Figure-1A). D-wave monitoring is applicable to assess the fast corticospinal tract (CT) axons. Deletis (2008) reported that monitoring of D-wave is less specific below the Thoracic 10-11 spinal cord level, since there are not enough fast CT

axons to generate D-wave responses (16). The other disadvantage of D-wave monitoring is the high percentage of false positive and negative results (22).

In 1980, Merton and Morton used single pulse TES and successfully evoked a muscle MEPs in conscious humans (23). Taniguchi et al. made a significant step forward in 1993 by showing that a short train of 3-5 electric pulses with an inter stimulus interval of 2-4 ms applied directly to human motor cortex evokes muscle MEPs under general anaesthesia. In 1996, three independent research groups studied and showed that multipulse-train of TES is also effective to elicit muscle MEPs (24-26).

In the present study we focused on monitoring iMEPs (intra operative compound muscle action potentials / Compound muscle action potentials (CMAPs)) during the course of removal of spinal cord tumours. Even though this method seems to suggest that this technique is superior over the above mentioned techniques there are several factors that seem to affect iMEPs resulting in false alarms. Some of these factors are (1) poor quality of recordings due to preoperative clinical status of the patients, (2) depth of anaesthesia, (3) guidelines for change in iMEPs to predict postoperative morbidity (4) systemic changes during surgery that affect iMEPs.

1.2.1. Poor quality of recordings due to preoperative clinical status of the patients:

Preoperative clinical status of the patients makes it difficult to record the baseline iMEP responses during the course of spinal cord surgery. It also affects the success rate of MEP monitoring and the postoperative neurological outcome. Chen et al., 2007 (27) could record 39.1% iMEP responses from lower limbs with preoperative neurological deficit. Morota et al., 1997 (8) reported that moderate to severe postoperative deteriorated outcome may occur if the patients had preoperative neurological deficit as

compared to neurologically intact patients. Preoperative weakness (myelopathy) also affects the iMEP threshold voltage change during the course of surgery (28).

1.2.2. Depth of Anaesthesia:

Stimulation of the motor pathways with a single-pulse electrical stimulus delivered transcranially to the motor cortex proved to be less specific, because of the high stimulus intensity. Review of literature also showed that depth of anaesthesia could affect the quality of iMEP recordings during the course of surgery (29). Numerous experimental and clinical studies have shown that general anaesthetics particularly volatile agents have a stronger depressant effect on iMEPs (17, 30-33). Most of these agents suppress the excitability of either cortical and spinal alpha motor neurons or the muscles relaxants on the neuromuscular junction (29). Anaesthetic agents affect the MEP responses in a dose dependent fashion (34). Studies have shown that multipulse transcranial electrical stimulation can overcome anaesthetic effects (24, 35 and 36). In overall, to improve the quality of the iMEP recordings, anaesthesia management is of equal importance along with the electrical stimulation and recording protocols.

1.2.3. Guidelines for change in iMEPs to predict postoperative morbidity:

A number of centres in the world routinely use transcranial electrical stimulation to record motor evoked potentials during the course of neurosurgical procedures. Different techniques have been developed by various centres; each has its advantages and disadvantages to predict the postoperative clinical outcome. Some centers have adopted an “all or none” MEP responses to predict the postoperative clinical outcome (24, 37 and 38). Other centers have used an increase in latency by 10% and drop in 50% amplitude (39) or a drop in amplitude by 50% (17) as the cut-off threshold to indicate postoperative

morbidity. Calancie 2001 & Quinones-Hinojosa 2005 (40, 41) have suggested that an increase in stimulus strength by 100V in eliciting iMEP responses can predict postoperative motor outcome. However, there are no proper guidelines for correlating intraoperative MEP responses to postoperative morbidity (42).

1.2.4. Systemic changes that affects iMEPs:

Surgical manipulation and anaesthesia causes changes in physiologic environment which plays an important role in normal functioning of the nervous system. (43). Maintenance and control of the patient's blood pressure is part of the anaesthetic management during the course of surgery. Under general anaesthesia, intraoperative neurophysiological techniques are used not only for the spinal cord surgeries but also for the tumours within or in close proximity to the brain stem, in intracranial aneurysms and excision of tumours in and around eloquent cortex or epilepsy surgeries. Studies have shown that there is a threshold relationship between regional blood flow and cortical evoked responses (44). Elevated systemic blood pressure and intracranial pressure are associated with reduction in amplitude and increase in latency of cortically generated SSEPs (45) and MEPs (43).

The occurrence of systemic hypertension in intracranial procedures (46-48) causes frequent complications during and after the surgery. Hypertension in intraoperative period may be associated with a number of pathophysiological consequences, when cerebral auto regulation is disturbed.

The anaesthetist would respond to an increase in blood pressure by increasing the depth of anaesthesia. i.e. by increasing the concentration of inhalational agents or by administration of narcotics or intravenous anaesthetics. These inhalational, intravenous

anaesthetic agents and narcotics have effect on the evoked potentials and would result in a drop or disappearance of the potentials, and could hence act as a confounding factor in interpretation of the electrophysiological event. This resulted in having a wide margin of safety in determining postoperative outcome, which makes intraoperative monitoring less specific and less effective.

1.3. Hypertension in Craniotomy neurosurgical procedures:

Craniotomy is a surgical operation in which part of the skull is removed in order to access the brain to remove the tumour. Hypertension in the context of craniotomy neurosurgical procedures constitutes a challenging clinical situation with unique and important implications for anaesthetic management because of the interactions between blood pressure and cerebral physiology and pathophysiology. Pharmacotherapies used to treat acute and chronic systemic hypertension may have undesirable effects on cerebral perfusion pressure (49). Therefore, planning an appropriate and effective anaesthetic regimen are needed for patients undergoing neurosurgery in order to avoid the pathophysiologic changes, such as surgical manipulation that could alter systemic blood pressure and cerebral blood flow.

1.3.1. Pathophysiology of Hypertension:

The relation between primary pathophysiologic mechanisms to intraoperative hypertensive complications is not clear. Some of the pathophysiologic consequences attributes to this intraoperative neurosurgical hypertension are (i) Sympathetic over activity (ii) Surgical stress (iii) Renin – Angiotensin - Aldosterone System and (iv) Salt sensitivity. In many surgical procedures, operative factors may be associated with an

increased risk of hypertension through increase jn the sympathetic activity that could cause intraoperative hypertension.

1.3.1.1. Sympathetic over activity:

It is well known that increase in sympathetic response and cardiovascular abnormalities are interlinked to each other in many disease condition. Sympathoneuronal activation and parasympathetic inhibition is observed primarily in hypertensive patients (50, 51). Increased norepinephrine spill over rate and augmented muscle sympathetic nerve activity were also observed in hypertensive patients (52). The autoregulatory mechanism between sympathetic over activity and catecholamine (epinephrine and norepinephrine) spill over rate are not clearly understood in the intraoperative hypertensive patients.

1.3.1.2. Surgical stress:

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system (53). The endocrine response is activated by sensory neuronal impulses from the site of injury. There has been a great deal of interest in the modification of the stress response with respect to the potential beneficial effects on surgical outcome. However, Desborough, (2000) reported that few studies only dealt with surgical stress responses to complications during and after surgery (54). The anaesthesia and surgical stress affects the plasma level of many vasoactive substances. Artru (1980) and Rupp (1989) also suggested that intraoperative acute hypertension episodes might also occur due to surgical stress during cerebellar retraction and resection in posterior fossa approach of brain manipulation (55, 56)**.**

1.3.1.3. Renin – Angiotensin - Aldosterone System:

Renin is an acid protease that catalyzes angiotensinogen to produce angiotensin-I. Angiotensin-I is further metabolized to the physiologically active angiotentsin-II by angiotensin converting enzyme. As shown in the figure -1B, angiotensin-II could have wide variety of action and stimulates aldosterone secretion via adrenal cortex, enhances sodium and water reabsorption in the kidney and intestine. These processes activates through central nervous system that enhances the vasoconstriction in vascular smooth muscles (57).

1.3.1.4. Salt sensitivity:

Electrolyte abnormalities are common during and after the surgery. This may be due to fluid shifts caused by osmotic diuretics and inappropriate fluid administration. Hyponatremia is the usual cause during neurosurgical procedures that happens due to excessive hypothalamic-pitutary release of antidiuretic hormone (ADH) and excessive production of atrial naturetic peptide (ANP). A rise in ANP levels causes sodium excretion and hyponatremia in neurosurgical procedures (58). This hyponatremia condition is also a possible factor that could trigger the hypertension during the course of surgery.

1.4. Methods to maintain the blood pressure in patients undergoing craniotomy procedures:

Prys-Roberts et al., 1971 (59) showed that the anaesthesia maintenance is poorly controlled in hypertensive patients due to extensive variable and fluctuating of blood pressure and heart rate. The important clinical question regarding the impact of hypertension on surgical outcome has not been addressed well by controlled and randomized studies. Colombo et al., 1999 extensively reviewed on perioperative

hypertension and its outcome and reported that, very little data is available to confirm that preoperative treatment to chronic hypertension reduces surgery related risk (60). This could be particularly true for neurosurgical procedures.

Olson et al., 2002 (61) showed that activation of Renin-Angiotensin-Aldosterone-System (RAAS) may be a primary event that facilitates the stimulation of the sympathetic nervous system and amplifies the vasoconstrictive effect of the catecholamines. This suggests that the potential for a preventive and therapeutic role of angiotensin converting enzyme (ACE) inhibitors; angiotensin antagonists and β-blocking drugs may be useful in maintenance of uniform blood pressure during the surgery. This could in turn help the anaesthetist to maintain the stable anaesthesia, and neurophysiologists to predict the postoperative outcome better manner.

In the present study we (1) Standardized TES and iMEPs in patients undergoing surgery for spinal cord tumours (2) Compared two anaethetic protocols (isoflurane Vs propofol) to see which is better for monitoring iMEPs: A randomized study (3) iMEPs for predicting postoperative outcome: Prospective study (4) Factors that trigger intraoperative hypertension: A prospective study (5) . Manitenance of uniform anaesthetic levels during surgery using Atenolol (β_1-adrenergic receptor blockade) and Lisinopril (Angiotensin Converting Enzyme Inhibitor): A randomized study.

CHAPTER 2

GENERAL METHODS

2.1 Introduction:

The objective of electrophysiological monitoring of patients during surgery is to enable the intraoperative monitoring (IOM) team to give a feed back to the surgeon when necessary. Since patient safety is a priority the IOM team would require considerable experience in dealing with many problems and compromises that faces the monitoring team in the operating room (OR).

The intraoperative environment provides many technical challenges to successful monitoring that are not present in diagnostic laboratory. The principal goal of monitoring is to warn the surgeon of significant change, rather than delineate diagnosis, thus altering the approach to evoked potential testing.

The Goals of Intraoperative Monitoring are

1. To establish a reliable and recordable montage where the evoked potential recording reflects function of the nerve tracts that are at risk.
2. To re-establish continuously to compensate for baseline changes reflecting varying physiologic and anaesthetic states.
3. The continuous use of consistent stimulating and recording parameters, preoperative to postoperative status to be correlated with intraoperative results.
4. The evoked potential monitoring must be able to alter surgical or anaesthetic technique if deterioration occurs without compromising patient safety.

2.2. Challenges in the Operating Room:

Several challenges force IOM team to compromise the evoked potential monitoring techniques in the operating room, since operation theatre (OR) is an hostile environment for electrophysiological recordings. Some of the limiting factors in the OR

are (1) Limitation of access to the stimulation and recording sites (2) Interference from other OR equipment (3) Pre-existing pathology.

2.2.1. Limitation of access to stimulating sites:

In many circumstances placement of stimulation electrodes depends on the type of modality that is being monitored and the type of surgery. For example in aneurysm or epilepsy surgery placement of reference electrodes and ground electrodes needs to be relocated depending on the site of incision. Any movement in skin flap will introduce artifacts into the recordings. These electrodes need to be firmly anchored and it may not be possible to access these sites after draping the patients. Hence it is important to discuss with the surgeon regarding the placement of electrodes and ensure that the electrodes are properly anchored after skin preparation.

Similarly placement of the usual recording electrodes may pose problems in certain cases. For example the placement of epidural electrodes may interfere with the surgical field in spinal cord surgery. Similarly access to electrodes, placed in sphincter muscle in tethered surgery cases may be not possible.

In general, well placed disc electrodes with collodion often provide an optimal impedance but this can produce more noise contaminated records in electrically hostile environments. Sub dermal needle electrodes which are used to record CMAPs (compound muscle action potentials) have low impedances and are practically quite acceptable during the course of surgery (64).

2.2.2. Intereference from other OR equipments:

One major challenge to the earlier recording period is the use of eletrocautery instruments (monopolar and bipolar) and its grounding plate. This produces some

electrical interference that prevents the monitoring during the course of surgery. Since electrocautery is usually used extensively at the beginning of surgery, it forces prompt establishment of baseline responses prior to interference or it forces to stay around to disconnect for establishment of baseline responses.

In general, the electrical environment as well as the physical environment of the operating room serves challenges on the equipment and accessories that are used for IOM. The sources of high voltage interference in the OR are many such as air conditioners, (AC) mains, Electrocardiogram (ECG) recordings, intravenous (IV) lines, operation table, pump used for infusion of anaesthetic drugs etc. Generally, IOM machine must have its own electrical outlet. The outlet should have a separate ground that is not linked with other OR equipment. Since OR is always crammed with various equipment, it will not be possible to keep the machine close to the operation table. So it is important to consider the length of the cables between the machine and the amplifiers, stimulators etc that are placed close to the patient.

The monitoring equipment must have good noise suppression filters in its power supply and its amplifiers, since there is constant high frequency contamination of the power lines and recording wires. Amplifiers are the most important part of the IOM machine.

It is important that amplifiers connected to the IOM machine have good rejection of noise occurring at both the inputs (common mode rejection). In general, the incoming signal will contain electrical activity in a wide range of frequencies. For purposes of extracting the evoked potential, filters are set to a particular range to record an evoked potential free from extraneous signals (noise) in the operating room. Unfortunately, the

frequency spectrum of the noise normally overlaps with that of the biological signals which is to be analyzed. Generally, the frequency is set to exclude frequencies below 10 and above 1000Hz. Some of the common precautions that are taken are: (1) Prevention of cross talking of other electrical cables with IOM cables. (2) Usage of shielded or twisted pair of cables to reduce interference from other electrical sources. (3) Coiling of cables. (4) Prevention of ground loops which is caused by earthing cables from different machines that are hooked on to the patient. (5) proper skin preparation do not only reduce impedance but also to reduce impedance difference between active and reference electrodes.

2.2.3. Pre-existing Pathology:

Patients themselves often present challenges, particularly in those cases with pre-existing neurological deficits. Preoperative neurological deficit may produce poor evoked potential, which decreases signal-to-noise ratio. The physiologic and anaesthetic state may also decrease the signal-to-noise ratio in these patients than in neurologically intact subjects.

2.3. Recording Method:

There are two methods to record and monitor the corticospinal tract integrity during the spinal cord surgery. They are (1) D-wave monitoring of the spinal cord using epidural electrode. More recently, these two methods are used to monitor the spinal cord integrity. However, there are several disadvantages in recording the D-wave than iMEPSs* (intraoperative motor evoked potentials/ intraoperative compound muscle action potentials) in the spinal cord surgery especially in intramedullary tumours.

Note: The abbreviation iMEPs is used instead of compound muscle action potential (CMAPs) to specifically refer them to recordings done during the intraoperative period.*

(1) D-wave monitoring is applicable to assess the fast corticospinal tract (CT) axons. Deletis, reported that monitoring of D-wave is less specific below the Thoracic 10-11 spinal cord level, since there are not enough fast CT axons to generate D-wave responses (16). Since many studies reported that central pattern generators for locomotion were highly present in the thoracolumbar region that could be monitored by iMEPSs.

(2) The other disadvantage of D-wave monitoring is the high percentage of false positive and negative results (65).

(3) McDonald, 2002 (66) reported that spinal cord gray matter function may easily be detected with iMEPS responses than with D-wave in spinal cord surgery.

(4) Another relative disadvantage of D-wave monitoring is the epidural placement of electrodes that may disturb the surgical field.

2.4. Randomization and prospective study methodology:

In the past two decades many studies were published on transcranial electrical stimulation and recording of iMEPSs. Similarly, a number of papers reported the intraoperative hypertension and its treatment during and after the surgery in neurosurgical procedures. However, there were no known randomized prospective studies in this regard.

Our study has two major parts. (1) To study the transcranial electrical stimulation and recording of iMEPS in patients undergoing surgery for spinal cord tumours. (2) To

study the factors associated with intraoperative hypertension and develop methods to control it during the course of surgery.

2.5. Effect of anaesthetic agents on intraoperative neurophysiological monitoring:

The impact of anesthetic agents on neurophysiologic monitoring increases with the number of synapses in the monitored motor tracts. All anaesthetic agents can produce effect by altering neuronal excitability through changes in synaptic function or axonal conduction. Inhalational and intravenous anaesthetic agents depress the evoked potential amplitude and increase the latency in a dose dependent manner. iMEPS responses obtained under general anaesthesia show a large inter-patient and intra patient trial-to-trial amplitude variability. Higher levels of neuromuscular blockade also cause smaller amplitude potentials with greater degree of trial-to-trial variability (29). This has made it difficult to develop common guidelines to predict postoperative outcome.

2.6. Systemic factors that influences on intraoperative monitoring:

In addition to changes resulting from the anaesthetic effects, the physiological milieu plays an important role on IOM during the course of surgery. Several factors like blood pressure, intracranial pressure, temprature and vasoactive biochemical factors affect the intraoperative neurophysiologic monitoring.

Maintenance and control of blood pressure is part of the anaesthetic management during the course of surgery. Several studies reported the relationship between blood pressure and evoked responses (43, 44). Evoked responses are more sensitive to both brain and spinal cord ischemia (43). Elevated intracranial pressure is also associated with reduction in amplitude and increase in latency during the course of surgery (45).

Hypothermia associated alterations in SSEPs and iMEPs have been observed by many authors. Hypothermia associated increase in stimulation threshold in the intraoperative period were also reported (44). This is consistent with both cortical initiation and peripheral conduction being affected by the drop in temperature (67).

Changes in vasoactive biochemical factors may produce alterations in the evoked potentials during intraoperative period. Marked reduction in total blood volume increases superior vena cava pressure during surgery has been related to SSEP changes. Other changes in the neurochemical environmental like sodium, potassium and other electrolytes could also result in the intraoperative evoked potential changes (43).

2.7. Statistical Methods:

In our study various parametric statistical tests were used to predict the results. For two group comparison, student independent‘t’ test was used. For the preoperative to postoperative stimulus strength treatment paired‘t’ test was used for the analysis. Pearson’s correlation co-efficient was used to correlate the two independent factors in this study. Linear regression analysis was used to predict the postoperative outcome in all the study.

In order to eliminate these common methodological problems in the hostile environment we have taken some of the precaucious and preventive methods in the operating room for the intraoperative monitoring (IOM). They are,

1. To avoid movement after the skin flap to reference and ground electrodes, reassurance of electrodes placement was made with surgeon after the skin preparation.

2. We used subcutaneous needle electrodes instead of epidural electrodes for the iMEPS recordings to avoid the interference with surgical field and also it eliminates the background noise during monitoring.
3. The cable outlets used for the IOM machine was properly grounded to avoid the electrical interference used in OR
4. To avoid the artifacts, we separated out the amplifier cables from other electrical lines to reproduce the recording results.
5. To eliminate the high skin impedances, skin preparation is necessary for intraoperative monitoring. We cleaned both stimulation and recording skin area twice with skin preparative gel (Omniprep, D.O. Weaver & Co, USA) and followed by twice with surgical sprit. Then we applied conducting gel (Ten 20 conductive gel, D.O. Weaver & Co, USA) on the stimulation site to reduce the impedances.
6. We adopted to monitor the iMEPS responses than D-wave since it will not be able to assess the spinal cord gray matter function that could lead to false positive results during the course of surgery.
7. We used multipulse stimulation technique to overcome the effect of anaesthesia.
8. Anaesthesia has major effects on the intraoperative monitoring during the course of surgery. In our study, we maintained inhalational anaesthetics ranges between 0.8% to 1% endtidal concentrations of isoflurane. Propofol was used as intravenous anaesthesia ranging between 6-8 mg/kg.hr. To minimize the intraoperative trial to trial variability in amplitudes we used constant vecuronium

infusion as muscle relaxants. The infusion rate was maintained to obtain partial neuromuscular blockage.

9. To understand intraoperative hypertension and to maintain stable blood pressure during the course of surgery, preoperatively we treated craniotomy patients with either β-adrenergic receptor blocker (Tab.Atenolol-50mg) or Angiotensin converting enzyme inhibitor (Tab.Lisinopril-5mg) and analyzed the levels of vasoactive biochemical substances in the perioperative period.

2.8. T**he common functional scoring methods that are employed to assess clinical status of the patients in our study.**

2.8.1. Nurick's Grading System: (68)

Grade – 0 Root Involvement; No Cord involvement

Grade – 1 Signs of cord disease; No difficulty in walking

Grade – 2 slightly difficulty in walking, not preventing full time employment

Grade – 3 Difficulty in walking preventing full time employment

Grade – 4 Gait aided

Grade – 5 Wheel chair bound or bed ridden.

2.8.2. Medical Research Council (MRC) grading system for Lower limbs: (69)

Grade – 0 No Movements

Grade – 1 Flickering of muscles; but no joint movement

Grade – 2 Movement of Joints with out elimination of gravity of the muscles.

Grade – 3 Movement of Joints with elimination against the gravity but not against resistance

Grade – 4 Movement of Joints against the elimination of gravity and moderate resistance.

Grade – 5 No dysfunction or Normal

2.8.3. McCormick's Grading system: (70)

Grade-1 Neurologically normal; mild focal deficit not significantly affecting function involved limb; mild spasticity or reflex abnormality; normal gait

Grade-2 Presence of sensory motor deficit affecting function of involved limb; mild to moderate gait difficulty; severe pain or dysesthetic syndrome impairing patient's quality of life; still functions and ambulates independently

Grade-3 More severe neurological deficit; requires cane / brace for ambulation or significant bilateral upper extremity impairment; may or may not function independently

Grade-4 Severe deficit; requires wheelchair or cane / brace with bilateral upper extremity impairment; usually not independent.

CHAPTER 3

STANDARDIZATION OF TRANSCRANIAL ELECTRICAL STIMULATION AND RECORDING PARAMETERS

3.1. Introduction:

Transcranial electrical stimulation (TES) is routinely used by many centres to record intraoperative motor evoked potentials (iMEPs) for monitoring spinal cord during the course of surgery. In the history of IOM, iMEPs are relatively new. As mentioned in the first chapter to predict postoperative outcome different stimulation (cranial or spinal) and recording techniques (epidural, neurogenic and compound muscle action potentials (CMAPs)) have been developed by different centres and each technique has its advantages and disadvantages. With regard to transcranial electrical stimulation and recording, some of the factors that were studied are stimulation site (16, 18), stimulus intensity (71), interpulse intervals, number of pulses (16), frequency of stimulation (76, 77), averaging of the responses (15), frequency filters (28, 82), time base (28) and recording muscles (24, 37, 75). To improve the quality of iMEP (intraoperative motor evoked potential) recordings, free running electromyography with TES-MEP was also done to predict the postoperative outcome (82). Mercuri et al., 1997 suggested that H-reflex enhances iMEP responses after the TES and it is possible to predict intraoperative changes to postoperative outcome (83). Stimulation and recording parameters published by many authors for intraoperative monitoring are very rare to compare and there are no reference values to predict clinical outcome (18). Table-3.1 shows a list of parameters and criteria used by different authors to predict postoperative clinical outcome.

A safety concern for the TES monitoring includes seizures, cardiac arrhythmia, scalp burns, pain or headache, and hormonal or haematological disturbances (72). It is necessary that design and development should take into consideration safety stimulation protocols for the excitable nervous tissue during TES-MEP monitoring in the

intraoperative period (18, 84). A major disadvantage of MEP monitoring using iMEPs is the marked jerking of proximal muscles during multipulse TES (72). This would require surgeon to pause during the course of surgery. Tongue biting is a recognised complication which can be minimised when stimulating electrodes are medially placed (24, 75). Variations in amplitudes that occur from trial to trial in recording iMEPs during the course of surgery reduce sensitivity and specificity in order to predict postoperative outcome. Anaesthetic agents also have depressive effect over iMEPs when used for prolonged period of time (28). Studies have shown that iMEP cannot be reliably elicited above mid-thoracic level with single pulse stimulation, but double pulses with interpulse interval of 2ms are highly effective (10). In 1996, three groups independently studied and reported that multipulse-train TES is effective to elicit iMEPs (24-26).

The selection of appropriate muscles to record iMEP responses is an important issue for intraoperative monitoring. Choosing non-optimal muscles can give misleading results. Deletis, 2008 (16) has suggested that for lower extremities, the abductor hallucis (HA) and tibialis anterior (TA) are the optimal muscles for intraoperative monitoring during the removal of intramedullary tumours. In the present study we used eight channels to record iMEPs. We chose to record bilaterally from quadriceps, TA and soleus muscles for monitoring the lower extremities as knee function and foot drop are of potential surgical complications. In addition to this, External Anal Sphincter (EAS) muscles were also monitored to prevent postoperative urinary incontinence complication.

In this chapter, data is presented on the standardisation of procedure for spinal cord monitoring and the factors that influence baseline iMEP recordings.

3.2. Patients and Methods:

Patients undergoing spinal cord surgery for the removal of intramedullary (IM) or intradural extramedullary (IDEM) tumours were considered for the study. Informed consent of all the patients was taken in accordance with the Institutional Review Board. Stimulation and recording methods were standardised on 20 patients who were undergoing excision of spinal cord tumours (IM and IDEM tumours). Correlation of preoperative clinical status with intraoperative baseline iMEP responses was done on 75 cases.

The following are the common functional scoring methods that are employed to assess clinical status of the patients in our study.

1) Nurick's Grading System:

Grade – 0 Root Involvement; No Cord involvement

Grade – 1 Signs of cord disease; No difficulty in walking

Grade – 2 Slightly difficulty in walking, not preventing full time employment

Grade – 3 Difficulty in walking preventing full time employment

Grade – 4 Gait aided

Grade – 5 Wheel chair bound or bed ridden.

2) Medical Research Council (MRC) grading system for Lower limbs:

Grade – 0 No Movements

Grade – 1 Flickering of muscles; but no joint movement

Grade – 2 Movement of Joints with out elimination of gravity of the muscles.

Grade – 3 Movement of Joints with elimination against the gravity but not against resistance

Grade – 4 Movement of Joints against the elimination of gravity and moderate resistance.

Grade – 5 No dysfunction or Normal

3) McCormick's Grading system:

Grade-1 Neurologically normal; mild focal deficit not significantly affecting function involved limb; mild spasticity or reflex abnormality; normal gait

Grade-2 Presence of sensory motor deficit affecting function of involved limb; mild to moderate gait difficulty; severe pain or dysesthetic syndrome impairing patient's quality of life; still functions and ambulates independently

Grade-3 More severe neurological deficit; requires cane / brace for ambulation or significant bilateral upper extremity impairment; may or may not function independently

Grade-4 Severe deficit; requires wheelchair or cane / brace with bilateral upper extremity impairment; usually not independent.

3.3. Results:

3.3.1. Standardisation of TES-iMEP stimulation and recording parameters (20 patients):

The equipment used for stimulating and recording, was Viking IV (Nicolet Biomedical Inc, Madison, Wisconsin, USA) and this was linked to D185 (Digitimer Ltd., Welwyn Garden City, UK) for TES. The delivery of stimulus was through pregelled flat silver disc of 2 cm in diameter, which was used as anode and cathode being an EEG disc

electrode of 8mm diameter. The iMEP responses were recorded from the belly of the muscles with a pair (5cm apart) of uninsulated subcutaneous needle electrodes.

In this study, the following parameters were standardized: (1) Stimulation electrode placement (2) Stimulus Voltage (3) Rate of stimulation, (4) Number of pulses (5) Interpulse interval and (6) Averaging of responses.

iMEPs were recorded bilaterally from quadriceps, tibialis anterior (TA), soleus and external anal sphincter. Patients with MRC grade-4 and 5 and normal urinary voiding conditions were only considered for standardisation of stimulation and recording parameters. iMEP amplitude was measured peak to peak between two largest peaks. The first deflection from baseline was taken as latency.

There were 12 males and 8 females. Their age ranged from 22 to 51 years (mean±SD, 33±18). 16 patients had intradural extramedullary (IDEM) tumours and 4 intramedullary (IM) tumours. Isoflurane anaesthesia was used in these patients with, air and oxygen and no nitrous oxide was used.

3.3.2. Stimulation electrode placement:

Survey of literature showed that stimulating electrodes are placed at one of the three locations on the scalp. They are C1-C2 or C3-C4 or Cz-Fpz (in accordance with International 10-20 EEG system). To standardise stimulation we chose (1) C3-C4 and (2) Cz-Fpz electrode placement. When stimulating electrodes are placed at C_3-C_4 (n=4) and responses are recorded bilaterally from the lower limbs there seem to be considerable amount of difference in latency and amplitudes between left and right side muscles. This difference is attributed to the direction of stimulus flow between anode and cathode. This would mean that in order to correlate between two similar muscles it would require

continuously switching anode and cathode after each recording. This kind of difference is not seen when stimulating electrodes are placed medially i.e. Cz' (1cm behind Cz)-Fpz (n=5) (Figure 3.1A & 3.1B). Besides this placement of stimulating electrodes at Cz'-Fpz montage also elicited iMEP responses from external anal sphincter muscles. It was noticed that the amplitudes of Tibialis anterior muscle (TA) are relatively larger than from other muscles and they could be elicited at a lower stimulus threshold. Hence TA muscle was chosen and data presented accordingly in the standardisation procedure.

3.3.3. Stimulus Voltage:

Transcranial electrical stimulation was delivered using Digitimer 185 (Digitimer Ltd., Welwyn Garden City, UK). In all the patients the starting stimulus voltage was set at 100V (n=20). This was increased in steps of 10 volts till the surgeon informs us that there was visible movement in the surgical field or we could record responses from all the muscles, which ever happens earlier. In this standardization procedure, we observed that there was a direct correlation of amplitudes to stimulus strength (Figure.3.2A). The mean stimulus strength used to elicit the baseline responses was mean±SD, 300±35V. However voltage required to elicit iMEPs depend on the clinical status of the patient.

3.3.4. Number of Pulses:

Digitimer 185 transcranial electrical stimulator was used for all the surgical procedures (n=20). It can deliver 1 to 9 pulses. In the present study the numbers of pulses were increased from 2 to 5 pulses. As shown in the figure-3.2B, an increase in number of pulses, decreases latency in TA muscle and increases its amplitudes. A delivery of 5 pulses seems to elicit maximum iMEP response (100%) as compared to two pulse stimulation. The pulse width is constant for digitimer which is 50μsecs.

3.3.5. Interpulse interval:

Interpulse interval can be adjusted from 0.5 to 5 ms in digitimer. An increase in interpulse interval caused corresponding increase in latency and drop in amplitude (Fig-3.2C) (n=20). In the present study interpulse intervals were increased from 1ms to 2.5 ms. As shown in the figure, an increase in interpulse interval increases the TA latency by more than 10% (36.2ms to 41.4 ms) and decreases its amplitude by 33% (From 7.3μV to 4.88μV). However, since we could obtain satisfactory responses at 2 ms interpulse interval and is the standard practice in majority of centres this was adopted in our study.

3.3.6. Rate of stimulation:

Rate of stimulation is controlled by the IOM equipment (Viking IV, Nicolet Biomedical Inc, Madison, Wisconsin, USA). In each trial of stimulation, frequency rate was varied from 0.7 Hz to 1.9 Hz (n=17). We observed that increase in rate of stimulation decreased latency of TA muscle by 10% (From 42.5 ms to 38 ms) and increased the amplitude by 52% (From 2.7μV to 4.1μV) (Fig-3.2D). However since we could elicit technically adequate responses at 0.7 Hz, we used this as a standard rate of frequency of stimulation. Survery of literature showed that investigators have used only train of pulses to elicit iMEPs. In our study we not only delivered a train of five pulses but we went on to deliver five such trains of five pulses at 0.7Hz.

3.3.7. Averaging of Responses:

Each sweep has the following parameters, number of stimuli 5 pulses, interstimulus interval 2 ms and rate of stimuli 0.7Hz. As shown in the figure 3.2E, averaging also has an effect on the responses. It was noticed that very often in the first two or three sweeps of stimuli no responses could be elicited but by third or fourth sweep

of stimuli responses starts appearing. By fifth sweep of stimuli responses appeared more consistently and hence this was kept as constant. Summarized stimulation and recording parameters are shown in table 3.2.

3.3.8. Correlation of preoperative clinical factors with baseline iMEP responses (75 Patients):

80 patients were considered for the study. In five patients baseline responses could not be elicited and they were excluded from the study. There were 57 males and 18 females in this group. Their ages ranged from 10 to 72 years, (mean±SD, 38±15 years). 53 patients had intradural extramedullary (IDEM) tumours and 27 had intramedullary (IM) tumours. In these 75 patients parameters that could affect iMEP recordings under general anaesthesia were studied. They are (1) correlation of preoperative clinical status of the patients with baseline iMEP recordings (2) correlations of functional motor status with stimulus strength, (3) duration of symptoms and (4) age.

3.3.8.1. Statistical Analysis:

Statistical analysis was done to see the cumulative pattern of baseline iMEP responses in all 75 patients. The analysis showed that latency falls in to the normal distribution and amplitude falls in to the non-normal distribution pattern. Based on this, latency was taken as mean value and amplitude as median for the further analysis. The linear regression analysis was used to predict the baseline iMEP response with the functional grading systems (MRC, Nurick's & McCormick grading system). Pearson's correlation coefficient analysis was used to see the effect of stimulus strength, duration of symptoms, age with baseline iMEP responses. A $p < 0.05$ was considered as statistical significance for all the analysis.

3.3.8.2. Percentage of muscles recorded with clinical scoring systems:

Patients undergoing spinal cord surgery are routinely assessed by either one or more clinical scoring methods. They are (1) Nurick grading system, (2) Medical Research Council (MRC) grading system and (3) McCormick's grading system. Each scoring system reflects it own functional integrity of either motor or sensory or both. Table 3.3(A-E) shows percentages of muscles (TA, Quadriceps, Soleus, APB and EAS) recorded with respect to different scoring methods.

3.3.8.3. Success Rate of TES-iMEP monitoring:

The success rate for eliciting the iMEP responses in various spinal cord procedures using TES-MEP with different stimulation sites are shown in table 3.4. In our study, the iMEP responses were elicited in 100% (responses from any one muscle) of the patients (n=75) with Cz-FPz stimulation montage.

3.3.8.4. Correlation of preoperative clinical status of the patients with baseline iMEP responses:

Patients were preoperatively assessed using Nurick's, MRC and McCormick grading systems. The linear regression analysis showed that the ability to record baseline iMEPs correlates highly with the preoperative Nurick grade ($p< 0.01$) followed by MRC grading system ($p<0.05$) and least by McCormick functional grading system ($p = 0.44$) (Table-3.5). Baseline iMEPs were most likely to be obtained in patients with Nurick's grade 0 to 3 and less likely in those with grades 4 and 5. Similarly baseline iMEPs could be most often recorded from tibialis anterior, soleus and followed by quadriceps muscles with MRC grades 3/5 to 5/5 power.

3.3.8.5. Correlation of functional motor status with baseline iMEP responses and stimulus strengths:

The regression analysis showed that the ability to record baseline iMEPs correlated with the preoperative Nurick grade ($p< 0.05$) but not with the McCormick functional grading system ($p = 0.44$). Baseline iMEPs were most likely to be obtained in patients in Nurick's grade 0 to 3 and less likely in those in grades 4 and 5. The amount of mean stimulus strength required to elicit baseline responses also increases with the degree of weakness (Table 3.6A). While the stimulus strength correlated with patients' preoperative Nurick's grades ($r = 0.91$; $p<0.05$) there was no such correlation with the preoperative McCormick ($r = 0.075$) grade. The stimulus strength required to elicit iMEPs showed a direct correlation ($r = 0.98$, $p<0.01$) with the degree of muscle weakness (MRC); stimulus strength increases with the degree of muscles weakness (Table3.6B).

3.3.8.6. Duration of symptoms and baseline iMEP responses:

Duration of symptom (myelopathy) is an important key factor which could affect the elicitation of base line iMEP responses. In our study, pearson's correlation was used to see if there is a correlation between duration of symptoms (deficits) and ability to elicit baseline iMEP ($n =75$) responses. The analysis showed that there was a negative correlation of -0.63 suggesting that duration of symptoms also effect baseline responses ($p<0.01$) (Figure-3.4).

3.3.8.7. Age and baseline iMEP responses:

The effect of age (ranged from 10 to 72 years, (mean±SD, 38±15 years)) on baseline iMEP responses were analysed in all 75 patients. The result showed that percentage of baseline iMEP recordings decreased with increase in age (years). The

Pearson's correlation analysis showed that there was a negative correlation between baseline iMEP responses and age (r = - 0.62) and the value is statistically significant (p <0.01) suggesting that age also has an effect on baseline iMEP responses.

3.3.8.7.1. Age inter-variability and percentage of muscles recorded:

Analysis was done between different age groups and percentage of successful responses that could be record from a muscles in neurologically intact patients (Nurick Grade-0, No=17). The result shows that generally the percentage of muscles recorded was less in younger age group and increased in middle age group and again it decreased in the older age groups (Figure 3.6). Quadriceps seems to be an exception which seems to decrease with increase in age.

3.4. Discussion:

3.4.1. Techniques of TES

3.4.1.1. Stimulation Technique:

Different centers used different techniques to elicit iMEPs to monitor and predict postoperative outcome. Some centers used C3-C4 stimulation (Jones et al., 1996, Calancie et al., 1998) or C3 (C4)/ Cz method (85, 86) to record the iMEP from lower limb muscles. However, C3-C4 stimulation showed marked trial-to-trial variability (17) and switching of anode to cathode with Cz area (C3-C4/Cz) is necessary for monitoring the leg area (86). Recently, Szelenyi et al., 2007 (18) empirically studied different types of montages and parameters for optimal TES-iMEP and suggested that, lower extremity muscles can be achieved with montage of Cz/Cz+6cm. Our study suggests several advantages of using Cz'-Fpz montage over C3-C4/CZ montage. They are (1) Right and left side can be stimulated and recorded in one trial, hence would not need switching

between sides (2) Midline placement of stimulating electrodes would enables us to stimulate leg area hence would be useful for monitoring spinal cord below cervical level. (3) This montage also enables us to record consistently from external anal sphincter muscles. (4) Tongue biting was not seen in any of our cases. However placement of TES electrodes in the midline would prevent placement of SSEP (somatosensory evoked potentials) electrodes over the sensory cortex of the leg area. Even if one manages to place them the amplifiers will get saturated because of the closeness of TES electrodes (stimulating electrodes) and SSEP electrodes (recording electrodes).

3.4.1.2. Stimulus intensity:

Calancie et al., 1998 (38) showed that the threshold level stimulation can be used for monitoring spinal cord during surgery and they could record from 95% of the cases. We adopted similar technique but used Cz'-Fpz montage as compared to C3-C4 montage by Calancie group. Our results show that we could record in 100% of the cases. Calancie et al., 1998 (38) also observed that when using C3-C4 montage the upper limbs require lower stimulus strength to elicit responses as compared to lower limb muscles. We observed that among the muscles that we monitored tibialis anterior requires least stimulus strength followed by soleus, quadriceps and sphincter muscles.

3.4.1.3. Number of Pulses and Interpulse Interval:

It is known that patients with poor clinical status would require higher stimulus strength. Taniguchi et al. made significant contribution to TES in 1993 by showing that a short train of 3-5 electric pulses applied directly to human motor cortex will evoke iMEPs under general anaesthesia (32). Current literatures on TES-iMEP monitoring also suggested that a short train of 5-7 pulse stimuli could be useful to elicit the iMEPs (15,

16). Bartley et al., 2002 (85) reported that more than 5 train pulses usage did not improve any iMEP responses and shortened the latency in spinal cord surgery patients. These studies closely supported our results where we used 5 train pulses for TES monitoring under general anaesthesia and they produced technically adequate responses.

The interpulse interval in the multipulse stimuli is dependent on the stimulus intensity. Novak et al., 2004 (87) suggested that higher stimulus intensity requires shorter inter pulse interval and suggested that 4 ms would be optimal for the TES. A 4 ms interpulse interval parameter could be applied for a single pulse TES in moderate anaesthetized patients to elicit a single D wave response (16). Studies on effects of interpulse interval on transcranial electrical stimulation are limited in literatures. Bartley et al., 2002 suggested that 2 ms interpulse interval could be compact for recording iMEP responses. When interpulse interval is increased the responses are more complex and dispersed (85). Most of the authors used interpulse interval of 2 ms in TES-iMEP monitoring (20, 24, 25, 37 and 88). Our study also supports the usage of 2ms interpulse interval and we could record satisfactory responses.

3.4.1.4. Rate of Stimulation:

There are no studies that have reported on rate of stimulation. Our study shows that rate or stimulation does increase the amplitude. However keeping in view of the net amount of charge that is being delivered to the cortex and no studies that are available on long term effect of TES we chose the least stimulus rate and found that the recordings are technically adequate. 0.7 Hz stimulation rate falls well within the safety limits (156).

3.4.1.5. Averaging of iMEP responses:

It is well known that, trial-to-trial variation in iMEP responses make it difficult to predict the postoperative outcome. In order to obtain quality recordings and minimise the trial-to-trial variation in amplitude, averaging of responses have been attempted by some authors (15, 41). Bartley et al., 2002 (85) empirically used 4-8 repeated averaging technique to reduce iMEP amplitude variability in spinal cord surgery patients. Kothbauer, 2007 reported that iMEP signals do not require averaging; however they varied rate of stimulation to maintain the iMEP responses for each trial during the course of surgery (15). There are no known prospective studies correlating with postoperative outcome using averaging method. In our study, iMEP responses were averaged with 5 stimuli in all the patients to get reproducible results from each trial of stimulation. In our study a combination of 0.7 rate of stimulation showed that responses starts appearing only on second or third sweep and averaging those responses seem to show more consistent results. This method also showed that it would require lesser stimulus strength to elicit responses as compared to other studies and success rate is 100% in patients above MRC grade 3. The reason for this could be attributed to the priming of the cortex due to multipulse stimulation.

3.4.2. Feasibility of obtaining TES-iMEPs

The main problem associated with intraoperative TES monitoring to iMEP responses is the success rate during the course of surgery. Preoperative clinical factors that could affect the success rate of TES monitoring of iMEP responses are neurological status, duration of symptoms (myelopathy) and age. A careful consideration of these factors may help to improve the success rate and better predict postoperative outcome.

The warning signs and criteria of TES-iMEP monitoring to spinal cord tumours (especially in intramedullary cases) is still controversial. Presence or Absence criteria were used because compound muscle action potential amplitudes showed marked trial-to-trial variation and because of reports that only iMEPs loss consistently correlated to postoperative motor deficits (81).

3.4.3. Success Rate of TES-iMEP monitoring:

Many authors used different stimulation technique to establish the baseline iMEP responses during the spinal cord procedures. It is true that this establishment of iMEPs depends on the modality of the stimulation and the pre-existing clinical and neurological statuses. Due to these variations, it is difficult to produce 100% baseline iMEPs from all the lower limb muscles. In our study we had higher success rate for lower limbs as compared to others and this could perhaps be attributed to priming of the cortex by giving multiple sweeps (5 sweeps) of stimulation at 0.7Hz.

3.4.3.1. Preoperative neurological status and prediction of baseline iMEP responses:

The main problem or factor in the intraoperative spinal cord monitoring to elicit iMEPs is the preoperative neurological status (27). We assessed the patients with three different functional scoring methods (Nurick's, MRC and McCormick's) preoperatively and correlated with elicitation of baseline iMEPs responses. Our study showed that baseline iMEP responses are highly dependant on nurick's grading method, followed by MRC grading method. McCormick's scale did not predict elicitation of baseline iMEP responses. Generally, Nurick's grading is used to assess severity of the spinal cord compression and the degree of walking difficulties in spinal cord injury patients (68). MRC grading system is used to assess the motor power of the joints to individual muscles

in both upper and lower limbs against the elimination of gravity in spinal cord injury patients (69). Our study suggests that baseline iMEP responses were highly dependant on degree and severity of the spinal cord compression. The McCormick's scale is used to evaluate both sensory and motor functions in intramedullary tumours especially with removal of ependymoma pathology (70, 90). This grading system may not be fully applicable to the resection of IM tumours and other spinal cord procedures due to some unfavourable neurological and non-neurological perspectives (76). One possible reason is that both sensory and motor functions are taken into account to arrive at the McCormick grade whereas the Nurick functional grade is based solely on the motor function of the lower limbs and the MRC grades is for grading of the motor power.

3.4.3.2. Duration of Symptoms and Baseline iMEP responses:

The stimulus strength required to obtain iMEPs highly correlates with the Nurick's grade followed by MRC grading. The central motor conduction pathways are substantially damaged in patients with longer duration of cord compression than in those with shorter duration of symptoms. Our study shows that duration of symptoms in patients with spinal cord tumours correlates with the percentage of muscles from which baseline responses could be obtained. This could be explained by prolongation of refractory periods that occurs damaged axons under general anaesthesia (43). These damaged axons could easily undergo fatigue state at faster rate as compared to intact fibers (80). Lyon et al., 2004 found it difficult to record iMEP responses in myelopathic patients (51%) as compared to normal subjects (100%).

3.4.4. Age and Baseline iMEP responses:

Age significantly affected the success rate in eliciting baseline iMEP responses for lower extremities (27). In our study the maximum percentage of responses that could be recorded are in the age group of 31-40 years. One possible reason for recording lesser percentage of responses from younger age group could be due to immaturity of the corticospinal tracts innervations to muscles in the younger age groups (8-18 years). While age related loss of nerve fibers, medical problems such as cervical myelopathy or peripheral neuropathy could be attributing factors to decrease iMEPs in the elderly group (27).

Conclusions:

In the present chapter, we standardized the stimulation and recording parameters in the spinal cord tumour surgery.

This study suggests that,

(1) Stimulation at Cz'-Fpz with 5 pulses and inter pulse interval of 2 ms and five such stimulations at 0.7 Hz gave reliable iMEP responses throughout the study.

(2) Stimulation frequency rate at 0.7Hz with averaging of 5 stimuli seems to give consistent responses with less variability from trial to trial.

(3) This technique has enabled us to stimulate the cortex at sufficiently lower voltages with lesser degree of interference.

(4) This in turn caused lesser degree of movement, allowing the surgeon to perform surgery without interruption.

CHAPTER 4

EFFECT OF INHALATIONAL AND INTRAVENOUS ANAESTHESIA ON iMEP RECORDINGS

4.1. Introduction:

Transcranial electrical stimulation is commonly used to elicit iMEP (intraoperative motor evoked potentials/ intraoperative compound muscle action potentials) under general anaesthesia. It is well known that iMEPs are highly suppressed by most of the anaesthetic agents in a dose dependent fashion (29). iMEPs are affected by most of the inhalational, intravenous and muscle relaxants at clinically relevant doses. Inhalational anaesthetic agents inhibit the pyramidal activation of spinal motor neurons at the level of the ventral horn (91, 92) or in the cortex internuncial synapses (43). Most of the intravenous agents suppress the activation of the alpha motor neurons at the spinal gray matter. Hence, in order to improve the quality of recordings, and to arrive at a meaningful conclusions it is important that stimulation, recording and anaesthesia management must be standardised.

In 1980, Merton and Morton used single pulse TES and successfully evoked iMEPs in conscious humans (23). Later, it has proved to be difficult to obtain iMEPs reliably under general anaesthesia. However, this suppressed effect caused by anaesthesia can be overcome by paired electrical pulses to the motor cortex (10). Subsequent studies have reported a significant increase in the rate of successful iMEPs using multi pulses that could eliminate the anaesthetic effects during the course of surgery (24, 25, 32, 35, 37).

The iMEPs (CMAPs) are affected not only by the inhalational/intravenous anaesthesia but also by the muscle relaxants. When the patient is being anaesthetised a bolus of muscle relaxant is administered. This will approximately lasts about an hour. During this time it is not possible to record any iMEPs. To know the extent of

neuromuscular blockage the anaesthetist gives a train of four stimuli (stimulus strength 40 mA) at 2Hz to a peripheral nerve like tibial nerve at ankle or median nerve at wrist. If no muscle twitch occurs then the neuromuscular block is considered to be complete. We usually wait till two twitches could be elicited to a train of four stimuli. This will indicate a partial neuromuscular block which we found to be ideal for eliciting iMEPs. Once we could achieve partial neuromuscular block, infusion of muscle relaxant is started to maintain partial neuromuscular blockage. As shown in table (4.1) some centres adopt this method (17) while others manage anaesthesia without any neuromuscular block (24).

The choice and management of anaesthesia for these surgeries are still a great deal of interest to neurophysiologist and anaesthesiologists.

Survey of literature showed that there were no randomised studies regarding the effect of different anaesthetic agents on iMEPs (29). Pelosi et al, 2001, compared inhalational (isoflurane) versus intravenous anaesthesia (propofol) intraoperatively, using nitrous oxide in both the groups (17). The supplementation of nitrous – narcotic anaesthetic technique is useful during the course of surgery. This technique is an accepted method for most of the evoked potential monitoring procedures (43). Nitrous oxide is context sensitive in that the actual effect may vary with combination of other anaesthetics already present. It is well known that nitrous oxide also reduces iMEP amplitudes in a dose dependent manner (93). Studies have shown that less than 50% of nitrous oxide is better with propofol anaesthesia while using train of five pulses for recording iMEPs (94). While >50% decreases the iMEP amplitude significantly (95). Nitrous oxide induced iMEP suppression can be reversed by supplementation of propofol (93). However, other studies have shown that it is difficult to reverse the nitrous oxide induced

iMEP suppression even with multipulse stimulation when used with propofol anaesthesia (96). To date, there are no guidelines regarding ideal anaesthetic conditions for monitoring iMEPs.

Some studies showed “anaesthetic fade” to occur in iMEP monitored cases (28, 71). Anaesthetic fade is the phenomenon when anaesthesia deepens or accumulates and produces additional lower motor neuron suppression that may cause fading or disappearance of the iMEP responses to the initially chosen stimulus parameters.

In the present study we did a prospective randomized analysis to see the effect of propofolbased anaesthetic (intravenous anaesthesia) with that of an isoflurane (inhalational anaesthesia) based anaesthesia. Nitrous oxide was not used in these cases. Partial neuromuscular block was used to do continuous monitoring of the patient during course of surgery. In the present chapter, we also looked in to the effect of anaesthesia and preoperative clinical factors that could affect baseline iMEP responses.

4.2.1. Electrophysiology:

The equipment used for stimulating and recording, was Viking IV or Endeavour (Nicolet Biomedical Inc, Madison, Wisconsin, USA) and this is linked to D185 (Digitimer Ltd., Welwyn Garden City, UK) for transcranial electrical stimulation.

4.2.1.1. Transcranial Electrical Stimulation:

Transcranial electrical stimulation (TES) was delivered by placing anode at Cz’ (1 cm behind the Cz position) and cathode at Fpz (EEG 10-20 electrode system). A train of 5 (each pulse 50 μsec duration) pulses with 2msec time interval between them was delivered. Five such sweeps at 0.7Hz were delivered and responses were averaged. To establish baseline responses, stimulus intensity was started at 100V and gradually

increased in steps of 10V. Stimulus intensity was increased until all muscles being monitored were recruited or until the surgeon warned of patient movement due to stimulation or perceptible movement seen through a TV linked to the operating microscope. Stimulus strength was reduced until no movement was observed. This was done to enable continuous monitoring during the course of surgery without affecting the surgical manoeuvres. When a drop in amplitude is noticed then the stimulus strength is increased till either they reach the baseline amplitude or patient movement is noticed. Despite this if amplitudes do not reach the baseline levels then the level of anaesthesia is checked. If none of these are the factors for drop in amplitude then surgeon is warned.

4.2.1.2. iMEP recordings:

Patients were clinically assessed by MRC, Nurick's and McCormick's grading scales prospectively. Clinical assessment was done before surgery and on 8^{th} day after surgery. iMEPs were recorded bilaterally from the following muscles: tibialis anterior, soleus, quadriceps and external anal sphincter. Compound muscle action potentials were recorded from the belly of these muscles with a pair (5cm apart) of uninsulated subcutaneous needle electrodes. The time base was set at 100 ms and the filter band pass was 30Hz – 500Hz.

4.2.2. Maintenance of Isoflurane and Propofol anaesthesia:

60 patients were randomly assigned in to either Isoflurane anaesthesia or Propofol anaesthesia, 30 patients in each group. This study was approved by Internal Review Board. Patients were explained about the study who agreed to participate in the study and written consent was obtained in their native language.

4.2.2.1. Isoflurane Anaesthesia: (Mean ± SD)

There were 30 patients in this group and the patients mean age was 41±3 years (ranges from 15 – 65 years). Anaesthesia was induced with thiopentone (mean dose 220±16mg, range 70-250mg) and supplemental fentanyl was used as required (mean dose of 164±10mg, range 70-250mg). Anaesthesia was maintained with isoflurane mean end tidal of 0.75±0.1% during the course of surgery and vecuronium was used as a muscle relaxant by the infusion of 0.040±0.005 mg/kg/hr (total mean dose of 14±0.7mg, range of 8.5-20mg).

4.2.2.2. Propofol Anaesthesia: (Mean ± SD)

There were 30 patients in this group and the mean age was 36±3 years (ranges 17 – 59 years). Propofol anaesthesia was induced with thiopentone (mean dose of 171±32mg, range 50-250mg) and supplemental fentanyl was used as required (mean dose of 186±13mg, range 90-360mg). A mean total 1520±76mg of propofol was required and the infusion rate of 6.6 mg/kg/hr (ranges 6-8 mg/kg/hr) was given as maintenance dose. Vecuronium was used as a muscle relaxant and infusion rate of 0.042mg/kg/hr (total mean dose used was 15±0.1mg, range of 8-20mg) was maintained during surgery.

4.2.3. Statistical Analysis:

Pearson correlation was used to see the relationship between preoperative clinical factors and baseline iMEP recordings in both isoflurane and propofol groups. For two group comparison, we used student's independent sample t-test. To analyse change in stimulus strength from preoperative to postoperative period paired't' test was used. For all tests, a $P < 0.05$ was considered as a statistical significant.

4.3. Results:

4.3.1. Anaesthetic effect on preoperative clinical factors and baseline iMEPs:

In the previous chapter it was mentioned that the preoperative clinical factors (neurological status, duration of symptoms and age) affected the baseline iMEPs. Besides these factors baseline iMEPs also seem to be affected by anaesthesia.

4.3.1.1. Effect of Propofol on iMEPs responses in neurologically intact and deficit patients:

Preoperative neurological status (Nurick's and MRC scoring system) influenced the baseline iMEP responses under isoflurane and propofol anaesthesia. In our study, 16 / 30 patients were neurologically intact (either nurick's grade-0 and / or MRC grade-5) under isoflurane anaesthesia and 17 / 30 patients were under propofol anaesthesia. iMEPs were recorded from TA, Soleus, Quadriceps and EAS (bilaterally). Comparision between these two anaesthetic groups showed that responses could be recorded in 62% (n=16) of the muscles under isoflurane and 75% (n=17) of the muscles under propofol anaesthesia (Figure 4.1). Statistical analysis showed that there was significant difference between the groups and isoflurane has more suppressive effect than propofol anaesthesia.

4.3.1.2. Effect of anaesthesia on duration of symptoms and baseline iMEPs:

Our study in the previous chapter showed that longer the duration of symptoms, reduces the elicitation of baseline iMEPs responses. Analysis of correlation of duration of symptoms with elicitation of baseline iMEP responses under two anaesthetic conditions showed that both anaesthetic agents have a negative correlation with the duration of clinical symptoms. Isoflurane anaesthesia seem to have a greater degree of negative correlation ($r = -0.66$) than under propofol anaesthesia ($r = -0.50$). The pearson's

correlation analysis showed significance at the level of $p<0.01$ in both anaesthetic regimens (Figure-4.2). The correlation line shows isoflurane has more effect at 8 months than under propofol, which slightly decreased but retains its status at 40%.

4.3.1.3. Effect of anaesthesia on age and baseline iMEP responses:

Similarly, age also seem to significantly affect the elicitation of baseline iMEP responses in both anaesthetic regimens. The result showed that increase in patient's age decreases the elicitation of baseline iMEP responses. High degree of negative correlation was found in patients under isoflurane anaesthesia ($r = -0.71$) than under propofol anaesthesia ($r = -0.60$). The pearson's correlation analysis showed significance at the level of $p<0.01$ in both anaesthetic regimens (Figure-4.3). The correlation line shows isoflurane has more profound effect after 30-40 years in age. Under isoflurane anaesthesia in patients over 40 years responses could be recorded in less than 50% of the muscles while under propofol group responses could be recorded in about 60% of the muscles.

4.3.2. Effect of anaesthesia on stimulus strength:

The mean stimulus strength required to elicit baseline iMEPs was more under isoflurane (mean 274±60Volts) than under propofol anaesthesia (mean±SD= 205±55Volts) (Fig-4.4). The student independent't' test analysis showed statistically significant at the level of $p<0.01$.

4.3.2.1. Anaesthesia fading effect and stimulus strength:

Preoperative to postoperative increment in stimulus strength is considered to be anaesthetic fading effect. In the present study, analyses was done to see the drop in amplitude (potential fading) caused by isoflurane and propofol anaesthesia. The results

shows that increase in stimulus strength from preoperative to postoperative stage was present under both anaesthetic regimens and it was higher under isoflurane (from 274±60V to 299±61V) than under propofol (from 205±74V to 220±50V) anaesthesia (Fig-4.5). The paired't' test analysis showed statistical significant difference between the two groups ($p<0.01$).

4.3.3. Maintenance and Usage of Anaesthetics:

4.3.3.1. Maintenance of Isoflurane and Propofol during surgery:

Maintenance of Isoflurane (n=30) and Propofol (n=30) anaesthesia during the course of surgery was studied. In isoflurane group the mean end tidal was 0.75%±0.1% (ranges 0.7%-0.9%) and in propofol group it was 6.6±0.47mg/kg/hr (range 6-8 mg/kg/hr). In both groups during induction period, anaesthesia requirement was high and it was gradually decreased and maintained till laminectomy was completed. Anaesthesia requirement increased again while opening of the dura and it was reduced at the end of tumour resection (Figure 4.6a&b).

4.3.3.2. Maintenance of Fentanyl in Isoflurane and Propofol anaesthesia:

The maintenance of fentanyl dose in isoflurane group and propofol group was studied. In isoflurane group a mean dose of 35.5± 20µg of fentanyl and in propofol group the mean dose was 34.6±51µg (Figure.4.5c) was used.

During the induction period the amount of fentanyl requirement was high and then it was gradually decreased until the end of the laminectomy. Fentanyl requirement increased again during tumour resection and it gradually reduced after tumour resection. However there were no statistical differences between the two anaesthetic groups.

4.3.3.3. Maintenance of Vecuronium between Isoflurane and Propofol anaesthesia:

The maintenance of vecuronium under isoflurane and propofol anaesthesia was analyzed. In isoflurane group, vecuronium maintenance range was 0.04±0.005 mg/kg/hr and in the propofol group it was 0.04±0.02 mg/kg/hr.

The maintenance of vecuronium infusion was not uniform during the course of surgery in the isoflurane group (Figure.4.6d). In the propofol group, vecuronium infusion could be maintained relatively at a constant rate during surgery. However, there was no statistical difference between the two anaesthetic groups.

4.3.3.4. Correlation of mean arterial pressure (MAP) and Heart Rate under isoflurane and propofol Anaesthesia:

In our study, MAP seems to increase gradually over a period of time during surgery. Under propofol anaesthesia the increase in MAP is more uniform than under isoflurane anaesthesia (Figure.4.7a). Analysis of data showed that the mean MAP under isoflurane anaesthesia was 81±5 mmHg while under propofol it was 87±3 mmHg and there was statistical significant difference between the two ($p<0.05$)

Similarly, heart rate was analysed between isoflurane and propofol anaesthesia. In isoflurane group the mean heart rate was 89±3 / min and in the propofol group it was 88±3 / min. However, there was no significant difference in heart rate between the two anaesthetic groups (Figure.4.7b).

4.4. Discussion:

4.4.1. Anaesthesia effect on baseline iMEP responses in neurologically intact patients:

iMEPs were monitored in 100% and 90% of the operations under propofol and isoflurane anaesthesia respectively when supplemented with nitrous oxide (17). In our

study, there is a considerable improvement in recording the baseline iMEPs (100%) in both isoflurane and propofol anaesthesia. However, in the present study we do not know the reason for this improvement in being able to record more number of muscles. It could be due to absence of nitrous oxide in the anaesthesia or the stimulation technique that we adopted. Studies have shown that usage of multipulse stimulation is more effective than the single pulse stimulation (17). Studies also showed that there is a great degree of variation from trial to trial (17, 97). In order to overcome these variations some studies have used priming the cortex with a prepulse stimulation (98). This does suggests that priming the cortex will bring down the threshold response. In awake conditions when the muscles are voluntarily contracted the stimulus threshold is lesser than under a relaxed condition (99). In our technique we delivered a train of five pulses as is the common practice by the many centres, in addition to this we gave five such sweeps stimuli at 0.7Hz. In this condition in the first two sweeps no responses are noticed but they start appearing by third or fourth sweeps. Perhaps the first two act as priming stimulus that may result in lowering the threshold at cortical / spinal level. This could also be the reason for us being able to record responses in all the study cases.

4.4.2. Effect of anaesthesia on preoperative clinical factors and baseline iMEPs:

The central motor conduction pathways are substantially damaged in patients with longer duration of cord compression than in those with shorter duration of symptoms. In this condition, anaesthesia caused prolongation of refractory periods in damaged axons (43). These damaged axons could easily undergo fatigue state at faster rate as compared to intact fibers (80). Lyon et al., (2004) found it difficult to record iMEP responses in myelopathic patients (51%) as compared to normal subjects (100%) when used with the

combination of desflurane and propofol anaesthesia (28). In our study we found that elicitation of baseline iMEP responses in myelopathic patients are also affected by anaesthetics and the degree of suppression was higher under isoflurane anaesthesia than under propofol anaesthesia.

4.4.3. Effect of Anaesthesia on age and baseline iMEPs:

Age significantly affected the success rate in eliciting baseline iMEP responses from lower extremities under general anaesthesia. One possible reason could be that age related loss of nerve fibers, medical problems such as cervical myelopathy or peripheral neuropathy could be attributing factors to decrease iMEPs in the elderly group under propofol anaesthesia (27). Our study is in accordance with this observation and showed that in general isoflurane affected all age groups to a greater extent than under propofol anaesthesia.

4.4.4. Effect of anaesthesia on Stimulus strength:

It is well known that stimulus strength depends on depth of anaesthesia in transcranial electrical stimulation procedures to elicit iMEP responses (17, 29, 37). Pelosi et al 2001 who used nitrous oxide in combination with inhalational (isoflurane) and intravenous anaesthesia (propofol) suggested that under isoflurane anaesthesia it would require more stimulus strength in order to overcome the level of background suppression of iMEP responses than propofol anaesthesia (17). In our study the results are similar even though no nitrous oxide was used. The effect of inhalational anaesthesia (isoflurane) is more in our study than under intravenous anaesthesia (propofol). Studies have shown that prolonged exposure to anaesthetics (anaesthesia fading) affect iMEPs under the combination of desflurane-propofol anaesthesia (28). In their study, increase in

stimulus strength by 12volts / hour is needed to maintain the baseline iMEP responses. In our study, the stimulus strength increased by 22 volts and 14 volts per hour under isoflurane and propofol anaesthesia respectively during entire surgical procedures and isoflurane produced more fading effect than propofol anaesthesia. In general isoflurane seem to have more suppressive effects on iMEPs (30, 31 and 101) than propofol anaesthesia (17).

4.4.5. Maintenance and usage of Anaesthetics:

Our study shows that, isoflurane maintenance highly varied during the course of surgery as compared to propofol anaesthesia. Based on the trend analysis, during different surgical periods vecuronium shows high variations between two anaesthetic groups. Propofol anaesthesia required constant maintenance of vecuronium infusion during the surgery but was not the case with isoflurane anaesthesia. The reason for this could be that isoflurane itself could be having muscle relaxant effect (102).

Conclusion:

In the present randomized prospective study, we examined the inhalational and intravenous anaesthetic effect on iMEPs.

This study suggests that,

(1) Preoperative clinical factors like neurological status, duration of symptoms and age suppressed iMEP responses more under isoflurane than under propofol anaesthesia.

(2) Stimulus strength required to elicit the baseline iMEP responses was higher under isoflurane than under propofol anaesthesia.

(3) The anaesthetic potential fade on stimulus strength from preoperative to postoperative stage was higher under isoflurane than under propofol anaesthesia.

CHAPTER 5

INTRAOPERATIVE MOTOR EVOKED POTENTIAL (iMEP) CHANGES TO PREDICTION OF POSTOPERATIVE OUTCOME

5.1. Introduction:

Spinal cord monitoring using TES and recording of iMEPs is increasingly recognized as an appropriate tool for spine surgeries. Since it has been realized that changes in intraoperative SSEPs do not necessarily correlate with postoperative motor outcome (42), iMEP monitoring has gained ascendancy in recent years. The sensitivity of TES-iMEPs to spinal cord manipulation during surgery suggests that postoperative neurological deficits may be predictable by intraoperative monitoring (8, 37, 38, 40 and 103).

Some authors have adopted an "all or none" iMEP responses in the intraoperative period to predict the postoperative outcome (17, 24, 104 and 105). Sala et al., 2006, used presence or absence criteria (81), because iMEP amplitudes showed marked trial-to-trial variation and based on the previous reports that only muscle iMEPs loss consistently correlates to postoperative motor deficits (24, 106 and 107). In contrast, some other centres have used an increase in latency by 10% and drop in amplitude by 50% (39) or a drop in amplitude alone by 50% (17) as the cut-off threshold to indicate postoperative morbidity.

Calancie (2001) & Quinones-Hinojosa (2005) have suggested that an increase in stimulus strength by 100V in eliciting iMEP responses predict postoperative motor morbidity (40, 70). At present there is no common consensus on the correlation between iMEP responses and postoperative clinical outcome. To date, quantitative criteria for the interpretation of results of muscle-recorded iMEP monitoring have not been established.

We did a prospective study on the predictive value of iMEPs on different muscles to determine the best indicator for overall postoperative change in clinical status (Medical

Research Council (MRC) scoring system). We also studied sensitivity and specificity of our TES-iMEP to postoperative clinical outcome in IM and IDEM patients.

5.2. Patients and Methods:

115 consecutive patients undergoing spinal cord surgery were considered for intraoperative neurophysiological monitoring. 30 patients were omitted from the analysis as they did not meet inclusion and exclusion criteria. Five patients declined to participate in the study and were excluded from the study. In five patients with intramedullary tumours responses could not be elicited and hence were excluded from further analysis. Final analysis was done on 75 patients.

Patients with MRC grade-3 / 5 and above were included in the study. Patients with MRC motor power of < 3 / 5 and those with history of seizures, head injury and stroke were excluded from the study. There were 57 males and 18 females. Their ages ranged from 10 to 72 years, (mean±SD, 38±15 years). 53 patients had intradural extramedullary (IDEM) tumours and 22 had intramedullary (IM) tumours.

Institutional Review Board and Ethical committee clearance was obtained to perform the study. The study was explained to the patients. The written consent was obtained in their native language from all the patients those willing to participate in the study. Patient's demographic details with IM and IDEM tumours, pathological, surgical and postoperative clinical outcome were shown in the table-5.1.

5.2.1. Electrophysiology:

The equipment used for stimulating and recording, was Viking IV or Endeavour (Nicolet Biomedical Inc, Madison, Wisconsin, USA) and this is linked to D185 (Digitimer Ltd., Welwyn Garden City, UK) for transcranial electrical stimulation.

5.2.1.1. Transcranial Electrical Stimulation:

Transcranial electrical stimulation (TES) was delivered by placing anode at Cz' (1 cm behind the Cz position) and cathode at Fpz (EEG 10-20 electrode system). A train of 5 (each pulse 50 μsec duration) pulses with 2msec time interval between them was delivered. Five such sweeps at 0.7Hz were delivered and responses were averaged with 5 stimuli. To establish baseline responses, stimulus intensity was started at 100V and gradually increased in steps of 10V. Stimulus intensity was increased until all muscles being monitored were recruited or until the surgeon warned of patient movement due to stimulation or perceptible movement seen through a TV linked to the operating microscope. Stimulus strength was reduced until no movement was observed. This was done to enable continuous monitoring during the course of surgery without affecting the surgical maneuvers. When a drop in amplitude is noticed then the stimulus strength is increased till either they reach the baseline amplitude or patient movement is noticed. Despite this if amplitudes do not reach the baseline levels then the level of anaesthesia is checked. If none of these are the factors for drop in amplitude then surgeon is warned.

5.2.1.2. iMEP recordings:

Patients were clinically assessed by MRC, Nurick's and McCormick's grading scales prospectively. Correlational analysis of iMEPs with postoperative (8^{th} postoperative day) clinical grading showed that only MRC grading correlated and not Nurick's grading and McCormick's grading. Hence the data that is presented and analysed in this chapter is only with MRC grading. Clinical assessment was done before surgery and on 8^{th} day after surgery. iMEPs were recorded bilaterally from the following muscles: tibialis anterior, soleus, quadriceps and external anal sphincter. Compound

muscle action potentials were recorded from the belly of these muscles with a pair (5cm apart) of uninsulated subcutaneous needle electrodes. The time base was set at 100 ms and the filter band pass was 30 – 500Hz. TES was done after being able to record at least two twitches to a train of four stimuli (TOF) to a peripheral nerve like tibial nerve at ankle or median nerve at wrist. This would indicate a partial neuromuscular block. It usually takes about 40 min to do the first recording after intubation of the patient. From the point where we could record iMEPs to the point of completion of laminectomy is considered as baseline responses. These responses are used for comparison with responses that are elicited during and after completion of surgery.

5.2.2. Anaesthesia

Anaesthesia was maintained with either isoflurane (mean±SD endtidal 0.8±0.1%, n = 45 patients) and or propofol (mean ±SD, 6.6 ±1.2 mg/kg/hr, n = 30 patients) supplemented by oxygen and air (1:2 ratios) during the surgery. Anaesthesia was induced with thiopentone (mean dose of 220±16mg, range 70-250mg). Analgesia was provided by intravenous fentanyl bolus (mean 164±10µg, range 70-360µg).

5.2.2.1. Neuromuscular Block

Vecuronium (67 patients) or atracurium (8 patients) muscle relaxant was used to facilitate the tracheal intubation and ventilation. Further doses were given by infusion. The relaxant was titrated so as to give 2 to 3 clearly visible twitches on stimulation of a peripheral nerve (posterior tibial nerve at ankle or median nerve at wrist). Vecuronium infusion was used in the range of 0.045±0.05 mg/kg/hr and atracurium was used in the range of 0.15 mg/kg/hr.

5.2.3. Statistical analysis

iMEP amplitude was measured peak to peak between the two largest peaks. The first deflection was taken as latency. Statistical Analysis was done using Statistical Package for Social Science software (SPSS 10.0 version). Pearson's correlation co-efficient were used to assess relationship between percentages of amplitude changes to postoperative clinical outcome. TES-iMEPs sensitivity and specificity and likelihood ratio were calculated based on the postoperative clinical outcome. ROC (Receiver Operative Characteristic curve) analysis was done to predict the iMEP cut-off changes to predict the postoperative outcome. A $p < 0.05$ was considered as a statistical significant.

5.3. Results:

5.3.1. Baseline iMEP responses in IM and IDEM tumor patients:

As shown in Table 5.2 greater proportions of baseline responses could be recorded from tibialis anterior muscle followed by external anal sphincter and soleus muscle and the least from the quadriceps muscle. This is true for both intramedullary (IM) and intradural extramedullary (IDEM) tumour cases. Tibialis anterior muscle responses could be elicited with lower stimulus strength followed by soleus muscle. Responses could also be consistently elicited from these two muscles than from quadriceps.

5.3.2. Tumor level

29 patients had tumours in cervical region, 27 patients had tumours in thoracic region, and 19 patients had tumours in thoracolumbar region. As shown in figure 5.1, the percentage of muscles from which responses could be recorded increases when the lesions are more caudally located. When the lesions are present in the thoracolumbar

region responses could be elicited from more number of muscles as compared to other regions in the spinal cord ($p<0.01$).

The iMEP amplitudes that could be elicited in patients with thoracolumbar tumors are higher when compared to those with tumors in the thoracic and cervical regions ($p< 0.05$). The latencies did not show any statistical significant difference.

5.3.3. Intraoperative iMEP changes

5.3.3.1. Intradural Extramedullary tumours (IDEM tumours):

There were 53 patients in this group and none of the patients had any worsening in their clinical status after surgery. In 53 patients, iMEPs dropped by more than 50% in 15 patients (8 patients improved and 7 showed same clinical status postoperatively). iMEPs were lost during the course of surgery in 4 patients and none of them deteriorated clinically in the postoperative period.

iMEPs improved by more than 50% in 48 patients and postoperatively all of them improved clinically. Intraoperative MEP changes with respect to the tumour level and its postoperative clinical outcome are shown in table-5.3. Statistical analysis showed that there is no correlation between intraoperative iMEP changes to postoperative clinical status in these patients. This is true for both amplitude and latency changes irrespective of the level or site of the tumour. Although there was no correlation between iMEP changes and postoperative clinical status of the patients, there were no false negative responses.

5.3.3.2. Intramedullary tumours (IM tumours):

There were 22 patients in this group. Data was analyzed from individual muscles and correlated with postoperative clinical outcome using MRC grading.

5.3.3.2.1. Tibialis anterior

Responses from tibialis anterior muscle could be recorded from 17 patients. None of the patients showed any improvement in amplitude during the course of surgery.

Six patients showed postoperative deterioration by one grade. In five of these cases the lesion was in the thoracolumbar region and one in the thoracic region. Analysis of the data showed that in these patients the amplitude drop ranged from 45% to 100% (Figure 5.2). Figure 5.2 shows only those patients whose TA amplitude dropped by 10% or more.

Correlation of iMEP amplitude with clinical outcome ($r = 0.49$) showed that a drop in amplitude by 45% or more could indicate a deterioration of muscle power by one grade. In one case (T10- L1 level tumour) the amplitude dropped bilaterally by 47% and 60% and postoperative clinical assessment showed both the muscles deteriorating by one grade. In the other five cases where there were postoperative deficits there was a unilateral drop in amplitude.

5.3.3.2.2. Soleus

Soleus muscle responses could be recorded from 13 patients. In four patients, postoperatively the soleus muscle power deteriorated by one grade. In these patients the amplitude drop ranged between 68 to 100%. In all four patients, there was unilateral drop in amplitude. Of these, in three patients the lesion was in thoracolumbar region and one in thoracic region (Figure 5.3).

The correlation analysis with postoperative outcome ($r = 0.75$) showed that a drop in amplitude by 68% or more could indicate a deterioration of muscle power by one grade. Figure 5.3 shows amplitude of those patients who showed a drop in amplitude by 10% or more.

5.3.3.2.3. Quadriceps

Quadriceps responses could be recorded from 5 patients. Of these, four patients muscle power deteriorated by one grade in the postoperative period. In these patients the amplitude drop ranged between 60 to 100%. One patient with lesion in the mid thoracic region (T5-T8) and one patient with lesion in thoracolumbar region (T10-L1), the amplitude dropped bilaterally (60% and 100%, 63% and 81% respectively). However in both the cases muscle power reduced only by one grade. In the other two patients, with thoracolumbar tumors, there was unilateral drop in amplitude. The correlation analysis with postoperative outcome ($r = 0.48$) showed that a drop in amplitude of 60% or more could indicate deterioration by one grade. Figure 5.4 show amplitudes of those patients who showed a drop in amplitude by 20% or more.

5.3.3.2.4. External Anal Sphincter

Responses from external anal sphincter muscles could be recorded from 7 patients. Postoperatively three patients required catheterization and in these cases the amplitude drop ranged between 61 to 100% (Figure 5.5). In these cases the lesion was in thoracolumbar (T10-L1) region. Of these three patients in one case the amplitudes dropped bilaterally (100%). The correlation analysis with postoperative outcome ($r = 0.74$) showed that a drop in amplitude of 61% or more could indicate that the patients would require postoperative catheterization.

An illustrative example of postoperative iMEP changes in bilateral TA (47% and 60%) and Soleus (38% and 68%) were shown in figure 5.6A and 5.6B.

5.3.4. Sensitivity and specificity of iMEPs:

Table 5.4 summarizes the relation between changes in the iMEPs and surgical outcome. The sensitivity and specificity in all the 75 patients was 1 and 0.46 respectively; in patients with IDEM tumours it was 1 and 0.32 and in those with IM tumours it was 1 and 0.73. In our study, there were no false negative cases.

5.3.4.1. Likelihood Ratio of the TES-iMEP monitoring:

We assessed the reliability of TES-iMEP monitoring technique in patients undergoing spinal cord surgery for removal of tumours based on likelihood ratio (LR+ve) of positive relationship. Likelihood ratio, is derived by combining sensitivity and specificity and arriving at a single number. A higher value indicates a better sentivity and specificity than a lower value. We calculated the LR+ve for 75 patients (both IM and EM) and also separately based on the 40% and 50% amplitude changes to see which offers a better cut-off point to predict postoperative out come i.e is 40% -45% cut-off point or 45%-50% cut-off point (Table-5.5). As shown in table a 45%-50% cut-off point offers a better prediction of postoperative outcome for IM patients.

5.3.4.2. ROC analysis in IM patients:

The receiver operative characteristic (ROC) curve analysis was used to see the percentage changes in iMEP amplitudes (tibialis anterior) with postoperative deterioration in IM tumours. Tibialis anterior was chosen for this analysis as it seem to be more sensitive to changes as compared to other muscles. The postoperative motor status did not change with the baseline amplitude diminution from 25% to 40%. However, the possible cut-offs for postoperative motor adverse outcome was 45% amplitude diminution from baseline in IM patients (Table 5.6 & Figure 5.6).**5.4. Discussion:**

5.4.1. iMEPs under general anaesthesia:

In general, we could obtain more responses from IM tumours as compared to IDEM tumour patients from all the individual muscles under general anaesthesia. In our study, we observed that the tumour location could affect the elicitation of iMEP responses. In our patient population, the percentage of muscles from which iMEPs could be recorded increases when the lesions are more caudally located. Higher amplitudes were also obtained when the lesions are more caudal than in the rostral spinal cord region.

5.4.2. Number of muscles to monitor:

iMEPs were most consistently obtained from the TA. TA is the optimal muscle to monitor the pyramidal tract because of its dominant corticospinal tract innervation like the abductor hallucis (16). Other authors have reported that the postoperative motor outcome can be predicted with 100% sensitivity and 81% specificity on the basis of intraoperative changes in TA-iMEPs (106). Our study results demonstrated that different lower limb muscles have different thresholds that predict a postoperative deterioration in motor power. It also shows that if there is deterioration in iMEPs in one particular muscle postoperatively it may not reflect in another muscle. Thus suggesting that it is important to monitor more number of muscles than monitoring only one muscle.

5.4.3. Threshold of significant change in iMEPs:

5.4.3.1. Intramedullary (IM) patients:

The sensitivity of TES-iMEPs to spinal cord manipulation during surgery suggests that postoperative neurological deficits may be predictable by intraoperative monitoring (8, 38, 40 and 103). Though many studies described about different warning

criteria on iMEP changes to predict the postoperative outcome (17, 24, 104 and 105) and each has its own advantages and disadvantages. Burke et al, 1995 suggested that if iMEP response is no longer evocable, irreversible neurological compromise may have already occurred (108). Current literature suggests that compared with monitoring of D and I-wave, iMEPs are a more sensitive method of monitoring possible ischemic and compressive insults to the spinal cord during the surgical procedures (76, 109).

In our patients with IM tumors individual muscles had different cut-off point in their amplitude change to predict postoperative deterioration. In tibialis anterior, a decline in the amplitude of iMEP of >45% was reflected in a postoperative loss of muscle power by 1 MRC grade. For soleus and quadriceps muscles a drop in amplitude of iMEP of 68% and 60% respectively was associated with postoperative deterioration in the motor power of the respective muscles by 1 grade. For the external anal sphincter muscles a worsening of the amplitude of iMEP of >61% was associated with the need for postoperative urinary catheterization. Hence, in patients with IM tumors, we suggest that amplitude deterioration by more than 45% from the baseline may be considered as an initial baseline warning criteria for the iMEP responses.

5.4.3.2. Intradural extramedullary (IDEM) patients:

In our patients with IDEM tumors, a wide range of variations in latency and amplitude was observed and the increase in 10% latency and/or decrease in 50% amplitude criteria (17, 39) did not correlate with the postoperative clinical outcome. In these patients >50% improvement in amplitude of iMEPs was reflected in improvement of monitored muscles. However, > 50% drop in amplitude or complete loss of the iMEP response did not result in any weakness in the postoperative period. Lang et al (1996(a),

who studied iMEPs in patients undergoing thoracic spinal instrumentation suggested that decrement in amplitude by more than 60% - 80% from the reference value (analyzed in 8 patients) may not be reflected in development of postoperative weakness (106).

5.4.4. Sensitivity and Specificity of TES technique:

The sensitivity and specificity of iMEPs in predicting postoperative outcome (40) differed for patients with IM and IDEM tumors. A decrease in iMEP of > 45% shows high positive likelihood ratio in predicting postoperative outcome in patients with IM tumors (positive ratio = 5.9) than in patients with IDEM tumors (positive ratio = 1.9). The ROC curve analysis also showed that with 45% in iMEP deterioration as the cut of point to predict the postoperative deteriorated outcome. In our study, we did not find any false negative cases in both IM and IDEM tumours. Due to trial to trial wide amplitude variations in the IDEM tumour patients, we may exclude the warning criteria of 50% amplitude changes to TES-iMEP monitoring technique in IDEM tumour patients.

Conclusions:

This prospective study suggests that,

(1) Tibialis anterior should be the first choice to monitor as it not only had lower stimulus threshold but also a drop in amplitude of 45% could indicate postoperative deterioration.

(2) It is important to monitor more than one muscle on a particular side.

(3) The degree of change in iMEP amplitude and correlation to postoperative change in clinical status is different for each muscle.

(4) In patients with IM tumours, amplitude deterioration of more than 45% from the baseline may be considered as critical to postoperative deterioration.

(5) iMEPs changes correlated better in patients with IM tumours than IDEM tumours.

(6) Sensitivity and specificity analysis correlated with patients having IM tumours than in patients with IDEM tumours.

CHAPTER 6

INTRAOPERATIVE HYPERTENSION IN CRANIOTOMY

6.1. Introduction:

Patients undergoing certain neurosurgical procedures are routinely monitored using neurophysiological techniques. Under general anaesthesia these neurophysiological techniques are used not only for the spinal cord surgeries but also for the tumours within or in close proximity to the brain stem, in intracranial aneurysms and excision of tumours in and around eloquent cortex or epilepsy surgeries.

Studies have shown that patients undergoing intracranial procedures in general have been reported to have systemic hypertension during these procedures (110-113) and they have frequent complications during and after the surgery. Hypertension in intraoperative period may be associated with a number of pathophysiological consequences, when cerebral auto regulation is disturbed.

A systemic reaction caused by injury encompasses a wide range of endocrinological, immunological and haematological factors (114). The stress response to surgery is characterized mainly by increased secretion of pituitary hormones and activation of the sympathetic nervous system (115). Cerebral autoregulation disturbance caused by altered baroreceptor reflexes which lead to a decrease in the vasomotor center action, enhanced central sympathetic outflow, directs an increase in the blood pressure (116).

The anaesthetist would respond to an increase in blood pressure by increasing the level of anaesthesia (depth of anaesthesia). i.e. by increasing the concentration of inhalational agents or by administration of narcotics or intravenous anaesthetics. These inhalational, intravenous anaesthetic agents and narcotics have effect on the evoked potentials and would result in a drop or disappearance of the potentials, and could hence

act as a confounding factor in interpretation of the electrophysiological event. This results in having a wide margin of safety in determining postoperative outcome, which makes intraoperative monitoring less specific and less effective.

In clinical practice, intraoperative preparations of local anaesthetics (Lidocaine, Cocaine and Bupivacaine) often contain a vasoconstrictor; usually epinephrine which will increase the blood pressure (117, 118).

Most of the studies indicated that pain stimuli could be the possible factor which causes surgical hypertension. In one study, 35% of the patients had hypertension caused by pain in various surgical procedures. In this same study, reaction to endotracheal tube induced pain had a hypertensive effect in 15% of the patients. (119). A review of literature reported that pain induced acute postoperative hypertension occurs in 57-91% of the neurosurgical procedures (120). Besides blood loss, duration of surgery and emergence are some of the intraoperative operative factors that could have effect on intraoperative hypertension (119-121). Pain is treated indirectly by increasing either inhalational anaesthesia or addition of analgesics during the course of intracranial surgery (120).

Majority of studies have focused on postoperative hypertension alone since intraoperative hypertension is controlled by inhalational and narcotic anaesthetics. Vasoactive biochemical modulators are known to be markers of surgical evidence for the intraoperative hypertension in various surgical procedures (122, 123). It was also suggested that hypertension may have started in the preoperative period and persisted to the postoperative follow up period and RAAS and sympathetic stimulation have been implicated for the hypertension process (123).

Hence, in order to maintain stable anaesthesia during the course of surgery it is important to identify the preoperative and intraoperative clinical and biochemical factors that are responsible for intraoperative hypertension.

Based on these views, we did a prospective study and analyzed the preoperative and intraoperative clinical factors responsible for intraoperative hypertension in 25 patients undergoing craniotomy procedures.

6.2. Patients and Methods:

Patients undergoing craniotomy surgery for excision of supratentorial masses (tumors) were included in the study. Informed written consent was obtained from all the 25 patients. Patients with no evidence of raised intracranial pressure on preoperative evaluation were considered for the study. Patients who had hypertension or any co-existing vascular, pulmonary, endocrine or renal dysfunction were excluded from the study. All the patients underwent surgery in a particular protocol of anaesthesia (see below) with standard haemodynamic (mean arterial pressure and heart rate) and vital monitoring (et.Isoflurane, et.CO2 and BIS).

BIS: Bispectral index: Used to asses depth of anaesthesia. The scale ranges from 0-100. A value of 100 means patient is completely awake. A value below 60 is considered to be under surgical plane.

6.2.1. Anaesthesia Protocol:

The patients were premedicated with diazepam 0.2mg/kg and metaclopromide 0.15mg/kg, one hour before induction of anaesthesia. Radial artery of the non-dominant arm was also cannulated to monitor the blood pressure. Anaesthesia was induced with thiopental 4-5mg/kg/hr and fentanyl 1-2μg/kg. Vecuronium 0.06-0.1 mg/kg was

administered to facilitate intubation and to maintain muscle relaxantion. The end tidal CO_2 pressure was maintained between 30-35mmHg. The anaesthesia was maintained using isoflurane as appropriate. The anaesthetists were aware that the study is in progress but were instructed to continue/intervene as appropriate for maintenance of anaesthesia that the patient would require. When mean arterial pressure (MAP) increased they compensated by increasing the isoflurane concentration or by using vasodilators like metaprolol. A decrease in MAP was compensated by reducing the isoflurane concentration or administration of ephedrine in small doses (2.5-4mg) as they would routinely do. Isoflurane concentration was monitored by end tidal gas analyzer. Bispectral Index (BIS) monitor was used to monitor the depth of anaesthesia, which was maintained in the range of 35 – 45 in all the patients. Administration of Isoflurane was stopped after the last suture, and the endotracheal tube was removed when the patients responded to verbal stimulation or when they coughed. The total amount of blood loss for each patient was estimated at the end of the surgery.

The mean arterial pressure, heart rate, et.isoflurane, et.CO_2 were recorded every 10mins from the induction to the end of extubation period.

Hypertension was defined as mean arterial pressure (MAP) of more than 20% of the preoperative value. Blood samples for estimation of renin, aldosterone, norepinephrine and sodium levels were collected at three time points: pre operative (12hrs before the surgery), intra-operative (during dural opening) and at immediate postoperative period (after extubation). Serum was separated immediately and stored at -70° C for analysis.

6.2.2. Measurement of biochemical Markers:

6.2.2.1. Renin:

The Gamma coat [^{125}I] radioimmunoassay kits were used for the determination of plasma renin activity (PRA) by the radioimmunoassay (based on competitive binding principle) of generated angiotensin-I (124, 125). The PRA determination involves an initial incubation of plasma to generate angiotensin-I, followed by quantitation of angiotensin-I measured by using gamma counter as counts / min. Values are expressed in ng/ml/hr.

6.2.2.2. Aldosterone:

Aldosterone was analyzed by the solid phase ^{125}I radioimmunoassay method (126) using a diagnostic kit based on solid phase radioimmunoassay principle. Briefly, the aldosterone-specific antibody was immobilized to the wall of the coated tube. ^{125}I labelled aldosterone competes for a fixed time with aldosterone in the sample for antibody sites. The tube is decanted, to separate bound from free, and counted in a gamma counter. The amount of aldosterone present in the sample was determined from a calibration curve. Values are expressed in pg/ml.

6.2.2.3. Norepinephrine:

Quantitative determination of Plasma norepinephrine analyzed by using diagnostic kits based on the Enzyme immunoassay (ELISA) method (127). Norepinephrine was determined by the Solid-Phase enzyme linked immunosorbent assay (ELISA) based on the sandwich principle. Results of the samples can be determined directly using the standard curve. Values are expressed in ng/ml.

6.2.2.4. Sodium (Na+):

Quantitative estimation of serum Sodium (Na+) analyzed by using Flame Emission Photometry method (128). When a sample of an inorganic salt (sodium) is sprayed into the flame, the elements in the compound are partly converted into the atomic state. By comparison of the intensity of light emitted by standards containing known amount of the test substance, with the intensity of light emitted from the test samples, it is possible to calculate the concentration of the test substance in the sample.

6.2.3. Statistical Analysis:

Among the 25 patients 17 patients were hypertensive (H) (>20% of preoperative MAP) after extubation. The other 8 patients were normotensive (N). Comparisons between groups N and H was carried out using student's independent sample t-test. Paired't' test was used to analyze preoperative to postoperative levels in biochemical factors. Linear regression analysis was used to assess the relationship between preoperative factors and MAP. For all test, a $P < 0.05$ was considered as a statistical significant.

6.3. Results:

6.3.1. Preoperative factors and hypertension:

6.3.1.1. Effect of age and weight on group N and H patients:

Preoperative factors (age and weight) responsible for intraoperative and postoperative hypertension were analyzed in group N (n=8) and H (n=17). In group N the mean±SD was 33±5 years (8 cases) and in group H it was 41±6 years (17 cases). The mean±SD weight was 59±3 Kgs, 66±9 Kgs in group N and H respectively. In group N, age and weight did not show any relationship with MAP. However in group H, age and weight had an effect on the intraoperative MAP. The prediction based linear regression analysis

showed age and weight significantly affects ($p < 0.05$) intraoperative MAP in group H patients (Table-6.1).

6.3.2. Intraoperative factors affecting N and H patients:

The N group patients (n = 8) required et.Isoflurane 0.71±0.1% and fentanyl of 2.4±0.4µg/kg. The H group of patients (n = 17) required et.Isoflurane of 1.2±0.1%, and 3.4±0.6µg/kg fentanyl to maintain the stable haemodynamics. These two groups were statistically different ($p<0.01$) regarding usage of isoflurane and fentanyl. (Table-6.2) Total blood loss during surgery was also estimated between group N (mean±SD, 488±68ml) and H (mean±SD, 756±164ml) patients. The total intraoperative blood loss was significantly higher in group H ($p<0.01$) as compared to group N. Durations of surgery ($p<0.01$) and anaesthesia ($p<0.05$), Extubation and Emergence times ($p< 0.05$) during the course of surgery (Table.6.2) were also significantly higher in group H as compared to group N patients.

6.3.3. Systemic haemodynamics between group N and H patients:

Haemodynamic parameters were analyzed at different time periods (pre-operative, intra-operative & immediate post-operative) in group N (n = 8), (mean±SD, 90±3, 95±2, 108±4 mmHg) and group H (n = 17) (mean ±SD, 93±2, 104±3 and 129±7 mmHg) patients. In group N patients, MAP (Mean arterial pressure) and heart rate did not differ during the surgical periods. In group H, both MAP and heart rate significantly increased in the intraoperative ($p < 0.05$) and immediate postoperative periods ($p<0.01$) as compared to preoperative period (Figure6.1A& B).

6.3.4. Vasoactive biochemical factors between group N and H patients:

The plasma and serum spill over rate of all vasoactive modulators levels between group N and H are shown in table 6.3. The temporal profiles of plasma renin and aldosterone levels were analyzed in groups N (n=8) and H (n=17). One-way ANOVA was used to analyse the renin and aldosterone levels. The one way ANOVA results show that renin (Figure 6.2A) and aldosterone (Figure 6.2B) levels were significantly higher in intraoperative ($p<0.05$) and postoperative periods ($p<0.001$) as compared to preoperative period in group H patients. There were no such significant differences found among the surgical periods in group N patients. The preoperative renin and aldosterone (base line) levels were also significantly higher in group H patients as compared to group N patients.

6.3.5. Sympathetic stimulation between group N and H patients:

An increased secretion of norepinephrine in plasma is a good indicator of an increased stimulation of sympathetic nervous system. In our study, serum norepinephrine levels were measured during the course of surgery. The result shows an increased secretion of norepinephrine levels in intraoperative ($p<0.05$) and immediate postoperative periods ($p<0.01$) as compared to preoperative period in group H patients (n = 17) (Figure 6.3). However, there were no fluctuations observed during the surgical period (Preoperative, intraoperative and postoperative) in group N patients (n = 8).

6.3.6. Shift of fliud balance by altering Sodium levels:

Serum sodium levels were analyzed among the surgical periods. Decreased serum sodium levels were observed in both intraoperative and immediate postoperative periods in H group patients. The inter group one way ANOVA analysis showed statistical significance at the level of $p<0.05$ in both intraoperative and postoperative periods (Figure 6.4) as compared to preoperative period. While in group N patients it was

reversed during the surgical period and there was no statistical difference between the surgical periods.

6.3.7. Vasoactive modulators changes in group N and H patients:

Preoperative to postoperative changes (%) in vasoactive modulator levels were analyzed in group N (n = 8) and H patients (n = 17). The results show that group H significantly differed from group N in all the vasoactive factors that were studied. Among these vasoactive factors in group H, the renin and aldosterone levels increased by 70% from preoperative to postoperative periods and the serum norepinephrine levels increased by 100%. While the serum sodium levels dropped postoperatively by 13% from the preoperative levels (Figure 6.5).

6.3.7.1. Possible Scenarios for Hypertension:

In our study we analysed pain induced MAP (mean arterial pressure) and percentage change in vasoactive modulator levels in hypertensive patients (n=17). Three subgroups were observed in our hypertensive patients. (1) Group 1: Pain induced increase in blood pressure which started after the craniotomy procedure and sustained till the end of the surgery (n=10, brown line). (2) Group 2: In this group (n=4, red line), MAP declined after the craniotomy procedure. (3) Group 3: In this third group, MAP declined after the craniotomy procedure (n=3, blue line) but increased again while excising tumour and sustained till the end of the surgery (Figure-6.6A). The preoperative to postoperative percentage change in vasoactive modulator levels also increased in group1 as compared to group 2 and 3. The plasma norepinephrine level was increased from preoperative

levels (606%) especially in the group-1 as compared to renin (507%) and aldosterone (455%). While the serum sodium level decreased by 480% (Figure 6.6B).

6.4. Discussion:

Hypertension is a common systemic occurrence during and after the neurosurgery that has important implications in the intraoperative period. The main intraoperative concern for patients who are hypertensive prior to surgery is the protection of the major organs that have potential dysfunction. A guideline will be useful to assess the blood pressure during intraoperative period to avoid unnecessary complications. The main aim of intraoperative management of the hypertensive patient should be to diminish the large increases in blood pressures often seen at time of intubation, incision and at completion of surgery.

6.4.1. Factors causing intraoperative hypertension:

Many preoperative patient characteristics (advanced age, weight etc) and intraoperative factors (Blood loss, duration of procedures and pain) may be associated with an increased risk of intraoperative hypertension (119). These factors may be associated with increased sympathetic activity and cause hypertension in the intraoperative period (120). In general, the autonomic nervous system, and water and electrolyte balance are frequently altered by aging (129). Our present study also showed that higher age group tend to have greater degree of intraoperative hypertension. Besides this weight also has an effect on intraoperative hypertension.

6.4.2. Intraoperative factors and intraoperative hypertension:

Studies have suggested that pain could be a key factor that could trigger intraoperative hypertension (119). De Beneditis et al (1996) did a pilot study in brain

surgery and reported 60% of the patients suffered due to pain in the immediate postoperative period. Similarly, 50% of the patients had pain induced immediate postoperative hypertension during craniotomy neurosurgical procedures (123). In our study, 68% of the patients had intraoperative hypertension. Blood loss in the intraoperative period will make a complicated situation during the course of surgery. Hirasawa et al., 2000 reported that there is a direct relationship between loss of circulating blood volume (CBV) i.e. blood loss and the hypertension in craniotomy procedures (130). In agreement with this study, our result supported that increase in blood loss increases the blood pressure during the course of surgery.

It is well known that increase in vasoactive substances (modulators) directly correlate with postoperative hypertension, which could be due to various factors like Pain, Stress, Emergence excitement (110, 119).

Vasoactive substances (modulators) like Renin, Aldosterone, Catecholamines and Atrial Natriuretic Peptide (ANP), Endothelin and Cortisol are thought to be possible contributors for hypertension and Renin – Angiotensin – Aldosterone System (RAAS) is mainly responsible for postoperative hypertension (123). Similarly, several non-cranial surgeries also revealed that changes in these substances during and after surgery (131-133)

High renin and aldosterone levels were observed in the intraoperative and postoperative periods exclusively in group H patients (123). These results are similar in our study in intraoperative and immediate postoperative periods. The lower in CBV levels could activate the RAAS pathway and stimulated the renin release in aortic abdominal surgery (137). In our study, severe blood loss was observed exclusively in

group H patients. This could be one of the possible reasons for the increase in renin levels in the intraoperative and postoperative period in our group H patients. Many of the studies indicated that, there is a synergism between renin and alsodosterone in the developing of hypertension following the surgical procedures (123, 130 and 131). Hirasawa et al., (2000) studied different plasma concentration of hormones in response to circulating blood volume (CBV). They reported that aldosterone levels increased significantly with decrease in CBV ($r = -0.30$) suggesting that it could also be the possible reason for developing hypertension in our craniotomy procedures (130).

6.4.3. Systemic evidence of sympathetic stimulation:

The stress response to surgery was characterized by the increased secretion of pituitary hormones and direct activation of sympathetic nervous system (114). Increased norepinephrine spill over rate is a good indicator to assess the degree of sympathetic stimulation during the course of surgery (134). Increased sympathetic activity may be due to reduction in CBV (130). Increased sympathetic activity results in tachycardia and hypertension (135). This was reflected in our study where both MAP and heart rate were increased in the intraoperative and postoperative periods exclusively in group H patients. Norepinephrine levels did not differ significantly in the intraoperative period as compared to postoperative period from baseline levels (123, 130). However in our study, serum norepinephrine levels were elevated in both intraoperative and postoperative levels as compared to baseline exclusively in group H patients.

6.4.4. Shift of fluid balance in hypertension:

RAAS activation leads to sodium retention, causing shift of fluid in to the circulation (130). CBV decreased due to the reabsorption of solute free water. The

response of these RAAS hormones during surgery may be complex, affect each other, and influence the fluid retention in the body but not in the circulation (130). Loss of CBV (hypovolemia) could be suspected from a postoperative decrease in serum sodium levels exclusively in group H patients. This hypovolemic hyponatremia may be induced by the shifts of fluid caused by osmotic diuretics, primary neurosurgical disease, adrenal insufficiency and syndrome of inappropriate antidiuretic hormone secretion where there is an excessive hypothalamic release (129).

Renin may play a key role or even prerequisite for hypertension either through a direct vasopressor effect or through the amplification of the vasopressor effect of norepinephrine (136). In many of the surgical procedures, catecholamines often considered as most important factors in surgical hypertension (Kataja et al., 1988, Crozier et al., 1992, Hirasawa et al., 2000). Pain induced increase in MAP and changes in vasoactive hormone levels are common in surgical procedures (119, 120, 123 and 131) and these were observed and analyzed in 10 patients of the H group. The plasma norepinephrine level seems to be higher in these patients as compared to renin and aldosterone. The serum sodium levels decreased in these patients. Pain seems to be the common pathophysiological response during the course of surgery (119, 120) which induces the increased secretion of norepinephrine levels thus causing hypertension. Our study shows that in majority of the cases the source of hypertension is more due to pain and to a lesser degree it is due to blood loss.

Conclusion:

(1) Blood loss and duration of surgery are some of the factors that are responsible for intraoperative hypertension in H group patients.

(2) Stronger correlation between MAP and biochemical factors was found during and after supratentorial craniotomy surgery in hypertensive patients.

(3) The percentage change in secretions of aldosterone and norepinephrine was higher in H group as compared to N group patients. Renin, aldosterone and norepinephrine seem to have a possible role in inducing intraoperative hypertension in H group patients.

(4) However, an increased secretion of plasma norepinephrine suggests that it may play a primary role associated with increased sympathetic activation in H group patients than the factors like renin and aldosterone in supratentorial craniotomy surgeries.

CHAPTER 7

COMPARISON AND THERAPEUTIC EFFECT OF β_1ADRENERGIC RECEPTOR BLOCKADE AND ANGIOTENSIN CONVERTING ENZYME INHIBITOR ON INTRAOPERATIVE HYPERTENSION

7.1 Introduction:

Strict control of systemic hypertension can be of paramount importance during neurosurgical procedures. Systemic hypertension in intraoperative period frequently complicates patients with a number of pathophysiological consequences, when cerebral autoregulation is disturbed. Intracranial haemorrhage can be a serious and fatal complication when it occurs during intracranial surgery (121) which could affects the intraoperative monitoring as well as tumour removal (43).

Anaesthesia for craniotomy procedures must be administered with emphasis on haemodynamic stability, a sufficient cerebral perfusion pressure, avoidance of agents or procedures that increase the intracranial pressure (138). Experimental and clinical studies on cerebral haemodynamics reported that, it is well controlled by isoflurane anaesthesia in supratentorial neurosurgical patients (139).

The pathogenesis of intraoperative hypertension in craniotomy procedure is not known. Blooemfield et al., 1996 reported several mechanisms that activate the cerebrovascular reflexes and liberation of neurohumoral factors in the intracranial procedures (140). Literature on neurosurgical procedures and neurohumoral factors in association with intraoperative hypertension are few in craniotormy neurosurgical procedures (123, 131 and 140).

It is generally preferred to avoid the occurrence of hypertension by preemptive therapy. Blood pressure control may be best achieved by using longer acting drugs as a single dosage than multiple and/or infusion during the intraoperative period (141). Many antihypertensives have been used during neurosurgical procedures, but some have

complicated cerebral effects, such as cerebral vasodilation, that may preclude their use in certain situations.

Olson et al (2002) showed that activation of Renin-Angiotensin-Aldosterone-System (RAAS) may be a primary event that facilitates the stimulation of the sympathetic nervous system and amplifies the vasoconstrictive effect of the catecholamines (123). This suggests that the potential for a preventive and therapeutic role of angiotensin converting enzyme (ACE) inhibitors; angiotensin antagonists and β-blocking drugs may be useful in maintenance of uniform blood pressure during the surgery. This could help the anaesthetist to maintain stable anaesthesia which in turn will help the neurophysiologists during intraoperative monitoring to predict better postoperative outcome.

In order to consider the feasibility of having a uniform blood pressure throughout the course of surgery it is necessary to use drugs that could break into the chain of sympathetic events that lead to hypertension. However, it is also very important to use only those drugs that have been used and proved to be safe for the patients. Keeping the safety of the patient in view we chose the drugs of proven safety record that is (1) Atenolol, a cardio selective β1-adregenic receptor blocker that could lower cardiac output, to inhibit renin release, (2) Lisinopril that inhibits the angiotensin converting enzyme (ACE). Drugs acting on ACE inhibit the conversion of angiotensin-I, a weak vasoconstrictor to angiotensin-II, a potent vasoconstrictor.

A double-blinded randomized trial study was done to study the effects of β-adrenergic blocker (Atenolol) and Angiotensin converting enzyme (ACE) inhibitor

(Lisinopril) on intraoperative hypertension. Effects of these agents on clinical and biochemical factors responsible for hypertension were also studied.

7.2. Patients and Methods:

Patients undergoing craniotomy for excision of supratentorial masses (tumors) were selected for the study. The study was approved by the Institutional Review Board and Ethical Committee clearance was obtained. 50 patients were selected for the study. The study was explained to the patients and informed written consent was obtained from all the patients by the anaesthetist on the eve of the surgery. These patients were randomized and divided into two groups. One group (25 patients) received Tab. Atenolol (50gms) and other group (25 patients) received Tab. Lisinopril (5mg) packed in a opaque sealed white cover by the pharmacy and are labelled as A and B. The anaesthetists, surgeon, neurophysiologist were blinded to the drug. Patients with no evidence of raised intracranial pressure on preoperative evaluation were considered for the study. Patients who had hypertension or any co-existing vascular, pulmonary, endocrine or renal dysfunction were excluded from the study. All the patients underwent for the surgery with a particular protocol of anaesthesia with standard haemodynamic (mean arterial pressure and heart rate) and vital monitoring (et.Isoflurane, et.CO2 and BIS).

Hypertension was defined as mean blood pressure of more than 20% of the preoperative value. Blood samples for estimation of renin, aldosterone, norepinephrine and sodium levels were collected at three time points: pre operative (12hrs before the surgery), intra-operative (during dural opening) and at immediate postoperative period. All the blood samples centrifuged and serum was separated, stored at -70° C for the analysis.

7.2.1. Anaesthesia Protocol:

The patients were premedicated with diazepam 0.2mg/kg and metaclopromide 0.15mg/kg one hour before induction of anaesthesia. Along with the premedication, the sealed opaque cover containing either Tab. Atenolol or Lisinopril was given to the patients. Before induction of anaesthesia, a radial artery of the non-dominant arm was cannulated to monitor the blood pressure. Anaesthesia was induced with thiopental 4-5mg/kg/hr and fentanyl 1-2μg/kg. Vecuronium 0.06-0.1 mg/kg was used to facilitate intubation and maintenance during the course of surgery. The end tidal CO_2 pressure was maintained between 30-35mmHg. The anaesthesia was maintained using isoflurane as appropriate. The anaesthetists were instructed to continue / intervene as appropriate for maintenance of anaesthesia that the patient would require. An increase in mean arterial pressure (MAP) was compensated by increasing the isoflurane concentration or using vasodilators like metaprolol. A decrease in MAP was compensated by reducing the isoflurane concentration or administration of ephedrine in small doses (2.5-4mg). Isoflurane concentration was monitored by end tidal gas analyzer. Bispectral Index (BIS) monitor was used to observe the depth of anaesthesia, which was maintained in the range of 35 – 45 in all the patients. Administration of Isoflurane was stopped after the last suture, and the endotracheal tube was removed when the patients responded to verbal stimulation or when coughed. The mean arterial pressure, heart rate, et.isoflurane, et.CO_2 were recorded every 10mins from the induction to the end of extubation period.

7.2.2. Measurement of biochemical Markers:

Renin:

The Gamma coat [^{125}I] radioimmunoassay kits were used for the determination of plasma renin activity (PRA) by the radioimmunoassay (based on competitive binding principle) of generated angiotensin-I (Haber et al, 1969, Yalow et al, 1971). The PRA determination involves an initial incubation of plasma to generate angiotensin-I, followed by quantitation of angiotensin-I measured by using gamma- scintillation counter in a counts / min. Values are expressed in ng/ml/hr.

Aldosterone:

Aldosterone was analyzed by the solid phase ^{125}I radioimmunoassay method (Mayes D et al, 1970) using a diagnostic kit based on solid phase radioimmunoassay principle. Briefly, the aldosterone-specific antibody was immobilized to the wall of the coated tube. ^{125}I labeled aldosterone competes for a fixed time with aldosterone in the sample for antibody sites. The tube is decanted, to separate bound from free, and counted in a gamma counter. The amount of aldosterone present in the sample was determined from a calibration curve. Values are expressed in pg/ml.

Norepinephrine:

Quantitative determination of Plasma norepinephrine analyzed by using diagnostic kits based on the Enzyme immunoassay (ELISA) method (Westermann et al, 2002). Norepinephrine was determined by the Solid-Phase enzyme linked immunosorbent assay (ELISA) based on the sandwich principle. Results of the samples can be determined directly using the standard curve. Values are expressed in ng/ml.

Sodium (Na+):

Quantitative estimation of serum Sodium (Na+) was done using Flame Emission Photometry method (Tietz NW, 1986). When a sample of an inorganic salt (sodium) is sprayed into the flame, the elements in the compound are partly converted into the atomic state. By comparison of the intensity of light emitted by standards containing known amount of the test substance, with the intensity of light emitted from the test samples, it is possible to calculate the concentration of the test substance in the sample.

7.2.3. Statistical Analysis:

Comparisons between preoperative to postoperative vasoactive modulator levels in N and H groups were carried out using student's independent sample t-test. Linear regression analysis was used to assess the relationship between perioperative factors and MAP (at the immediate extubation period). For all test, a $P < 0.05$ was considered as a statistical significant.

7.3. Results:

On the basis of MAP difference (>20%) between preoperative and at immediate postoperative period, 11 patients (44%) had postoperative hypertension (H group) and 14 patients (56%) had normotension (N group) in atenolol administered group. None of the patients were hypertensive in lisinopril administered group.

MAP, heart rate, clinical factors and biochemical markers between hypertensive and normotensive patients in atenolol and lisinopril administered groups are discussed.

7.3.1. Preoperative factors in atenolol administered patients:

In atenolol group (25 patients), mean age were 36±8 years, 43±13 years and mean weight were 59±7 Kgs, 62±6 Kgs in group N and H respectively. Increase in blood loss,

duration of surgery, duration of anaesthesia was observed in H group patients as compared to N group patients; however, there was no significant difference between them. Vasoactive modulator levels after the treatment with atenolol and lisinopril were showed in table-7.1A & B.

7.3.2. Systemic haemodynamics in supratentorial craniotomies:

Systemic heart rate and MAP were analyzed between N and H group patients in atenolol administered group. In N group patients, the MAP and heart rate did not differ significantly in intraoperative and immediate postoperative periods as compared to preoperative period in the atenolol administered group. In H group, atenolol controlled the heart rate well in the intraoperative and postoperative periods (Figure 7.1A). However, MAP was not controlled by atenolol in the immediate postoperative period and it is significantly increased ($p<0.05$) as compared to preoperative and intraoperative periods (Figure 7.1B).

In lisinopril administered patients, MAP was maintained well during the course of surgery. However, heart rate showed changes which increased in the intraoperative period (Mean±SD = 84±8/min, $p=0.08$) and immediate postoperative period (94±7/min, $p<0.05$) as compared to preoperative period (81±8/min) (Figure 7.1C & D).

7.3.3. Renin and Aldosterone levels:

Temporal profiles of plasma renin, aldosterone levels were analyzed in both N and H groups in atenolol administered patients. In our study, decreased serum renin levels were found in both H and N group during and after the surgery (Figure.7.2A). On the other hand high intraoperative ($p<0.05$) and postoperative ($p<0.001$) aldosterone

levels were found as compared to the preoperative period in H group patients (Figure.7.2B).

In lisinopril-administered group, a significant increase ($p<0.05$) in intraoperative and immediate postoperative renin levels was observed as compared to preoperative level (Figure.7.2C). However, aldosterone levels showed an opposite effect ($p<0.01$) as compared to preoperative levels (Figure.7.2D) .

7.3.4. Norepinephrine levels

In group H patients, serum norepinephrine levels were increased in intraoperative ($p<0.05$) and postoperative periods ($p<0.01$) as compared to preoperative period in atenolol administered patients. In group N, there were no changes in the plasma norepinephrine levels among perioperative periods (Figure.7.3A). In lisinopril treated group, norepinephrine levels were significantly decreased in intraoperative and immediate postoperative periods ($p<0.01$) as compared to preoperative period (Figure.7.3B).

7.3.5. Sodium levels:

Serum sodium levels were decreased intraoperatively in both N and H group (not significant, $p = 0.09$) as compared to preoperative levels. This sequential sodium decremental effect was significantly observed ($p<0.01$) in the immediate postoperative period in H group patients. While, sodium levels returned to baseline in N group patients postoperatively (Figure 7.3C). In lisinopril administered patients, sodium levels barely decreased in intraoperative period and returned to baseline in the immediate postoperative period. However, these differences did not have any significant effects among the three surgical periods (Figure 7.3D).

7.3.6. Percentage changes in vasoactive modulators in atenolol and lisinopril administered patients:

Preoperative to postoperative percentage changes in vasoactive modulators were analyzed in atenolol and lisinopril administered group patients. The result shows that in atenolol administered group plasma renin level increased by 16%. Aldosterone and norepineohrine levels were increased by 64% and 100% respectively. Serum sodium levels were decreased by 13% from the preoperative to postoperative period (Figure.7.4A).

In lisinopril administered group, postoperatively the renin and sodium levels increased by 43% and 15% respectively. But the aldosterone and norepinephrine levels were dropped by 30% and 67% respectively.(Figure 7.4B).

7.4. Discussion:

Hypertension in the context of neurosurgical procedures plays a challenging clinical situation with unique and important implications for anaesthetic management because of the interaction between blood pressure and cerebral physiology and pathophysiology. Hypertension during neurosurgery may result in bleeding and cerebral edema after the surgery (142). Pharmacotherapy to acute and chronic systemic hypertension may have undesirable effects on cerebral physiology (143). Therefore, planning an appropriate and effective treatment for hypertension is required in patients undergoing neurosurgery. The occurrence of neurosurgical hypertension is to be avoided by pre-emptive therapy (46, 141 and 144). Blood pressure control may be best achieved by combining longer acting drugs of slow onset with faster acting drugs of short duration

141). The use of β-adrenergic blocking drugs is contraindicated or occasionally ineffective in controlling the hypertension (145). In the present study we used atenolol and lisinopril to see the effect on intraoperative associated postoperative hypertension. In atenolol administered group, 44% of the patients had hypertension. However, in lisinopril group none of the patients were hypertensive in the intraoperative and postoperative period.

7.4.1. Systemic haemodynamics after the administration of atenolol and lisinopril:

In general, β-adrenergic blocking action of atenolol was estimated by the decrease in heart rate. However, a decrease in heart rate could not account for the antihypertensive effect of atenolol where the blood pressure remains unchanged after the treatment with atenolol in the renal impairment patients (146). This is in close support to our study showing that atenolol controls heart rate well in all the patients (100%) while lisinopril failed to control the heart rate during the course of surgery. A double blinded, randomized, parallel multicentric study on 490 essential hypertensive patients shows that lisinopril (100%) is effective in controlling the blood pressure than atenolol treated patients (72%) (147). Similarly, in our study the MAP was controlled in 56% of the patients in atenolol administered group (n=14) as compared to lisinopril administered group (100%). This could be the reasons that lisinopril inhibits the ACE activity and decreases the angiotensin-II induced increase in sympathetic activity and electrolyte balance and reabsorption process in the kidney.

7.4.2. Renin and Aldosterone response in atenolol and lisinopril administration:

The hypertensive effect of atenolol could be related to decrease in the renin secretion in renal impaired patients (146). In mild to moderate essential hypertensive

patients plasma renin levels are well controlled by atenolol but was not the case with lisinopril treated patients (148). These investigators also showed that plasma aldosterone levels are not altered by atenolol in 100% of the patients with mild to moderate hypertension but, it was significantly decreased in lisinopril group (100%) (148). These studies support our results where the plasma aldosterone was controlled in only 56% of the patients administered with atenolol as compared with 100% in lisinopril administered group. Thus suggesting that atenolol controls the renin level in a better way through inhibitory action of decreased renal perfusion induced secretion of renin levels from the kidney. Lisinopril controls aldosterone levels in a better way through the inhibition of ACE activity. This inhibitory process leads to decreases the angiotensin-II induced secretion of aldosterone in adrenal gland of the kidney.

7.4.3. Sympathetic response in atenolol and lisinopril administration:

Pre-treatment with carvedilol and atenolol on sympathetic plasma norepinephrine response were studied in normal subjects in rest and after the regular exercise (149). This study suggests atenolol could not decrease the plasma norepinephrine spill over rate after the exercise as compared to carvedilol after the exercise in normal subjects. In our study norepinephrine levels remained elevated in the atenolol administered group since its main action on β_1-adrenrgic receptor on kidney and independent to the norepinephrine levels Lisinopril well controlled the plasma norepinephrine levels by inhibiting the conversion of angiotensin-I to angiotensin-II through ACE, a potent stimulator for the norepinephrine release.

7.4.4. Shift of fluid balance in hypertension:

RAAS activation leads to sodium retention, causing shift of fluid into the circulation (130). Cerebral blood volume (CBV) decreased due to the reabsorption of solute free water. The response of these RAAS hormones during surgery may be complex, affecting each other, and influencing the fluid retention in the body but not in the circulation (150). Loss of CBV (hypovolemia) could be suspected from a postoperative decrease in serum sodium levels exclusively in group H patients. Hypovolemic hyponatremia may be induced by the shifts of fluid caused by osmotic diuretics, primary neurosurgical disease, adrenal insufficiency, syndrome of inappropriate antidiuretic hormone secretion due to excessive hypothalamic release of hormones (58). In the present study, the shift of fluid balance by osmotic diuretics was not maintained by atenolol in the treated group, so that sodium levels were not maintained well as compared to preoperative levels. Many studies on the effect of lisinopril in serum sodium levels are still controversial. Some reports show the hyponatremia and normal serum sodium levels observed in normal and essential hypertensive condition (151-153). In our study, serum sodium level was maintained well by lisinopril in the intraoperative and postoperative period. This may be the reason that, lisinopril inhibits the shift of fluid balance by osmotic process and adrenal insufficiency mechanisms under hypertension conditions.

7.4.5. Changes in renin and noepinephrine levels after the administration of atenolol and lisinopril:

7.4.5.1. Renin:

The hypertensive effect of atenolol could be related to profound decrease in renin secretion in renal impaired patients (146). However, lisinopril induced marked increase in

plasma renin levels were observed in mild to moderate essential hypertensive patients (154). Renin may play a key role or even be a prerequisite for hypertension either through a direct vasopressor effect or through the amplification of the vasopressor effect of norepinephrine (136).

7.4.5.2. Norepinephrine:

Plasma spill over rate of norepinehrine levels was not controlled by atenolol in our study as reported by another study (149). Plasma norepinephrine levels were significantly reduced after the treatment with lisinopril in 100% of the essential hypertensive patients (155). This result is very similar to that found in our lisinopril administered patients (100%) from the preoperative to postoperative period.

Conclusion:

This randomized double-blinded study suggests that,

(1) 44% of the patients had an intraoperative controlled hypertension but not postoperatively after the administration of atenolol in supratentorial craniotomy procedures.

(2) In lisinopril-administered group, none of the patients had intraoperative and immediate postoperative hypertension.

(3) Surgical evidence on fluctuation of MAP and biochemical factors was well correlated during and after the craniotomy surgery.

(5) However, sympathetic response to plasma norepinephrine spill over rate was controlled by lisinopril as compared to atenolol.

(6) In this study, lisinopril had potential therapeutic and beneficial effects to control intraoperative hypertension in craniotomy neurosurgical procedures.

CHAPTER 8

GENERAL DISCUSSION AND CONCLUSIONS

The principal goal of intraoperative monitoring is prompt identification of nervous system impairment during the course of neurosurgery. Intraoperative monitoring can identify new systemic impairments, identify or separate nervous system structures (e.g. in or around a tumour), and can demonstrate which tract or nerves are still functional. Even though the objectives are clear the outcome can be affected by several factors such as (1) sensitivity and specificity of the technique that is employed for a particular surgery (2) clinical status of the patient (3) anaesthesia

iMEPs:

Motor evoked potentials are relatively new in the field of Intraoperative monitoring and hence there are several factors that need to be addressed and standardised. The depth of anaesthesia which is maintained under surgical plane is also altered in response to changes in blood pressure and heart rate. These changes affect the potentials making it difficult to predict postoperative outcome. Hence, it is important to be able to maintain uniform anaesthetic levels without compromising the safety of the patient. In the present study we tried to address these factors.

Patton and Amassian set the scientific platform for MEP (Motor evoked potential) monitoring in 1954 by discovering that a single electrical pulse applied to monkey motor cortex evokes several descending corticospinal tract volleys (21). Later in mid 1980's Merton and Morton found that single pulse TES (Transcranial Electrical Stimulation) produces an iMEP (CMAP) in conscious humans (23). After the discovery of this technique, intraoperative electrophysiological monitoring of the nervous system has acquired a powerful and a non invasive tool to monitor cortical, subcortical and corticospinal tracts during the course of surgery. Somatosensory evoked potentials which

are being used till then for monitoring spinal cord have been sidelined as some cases reports have shown that postoperative deficits might occur in spite of unchanged SSEPs (3). These false negative reports are a bothersome resulting iMEPs gaining more importance.

Many methods have been developed with the hope of better evaluating the functional integrity of the spinal cord motor pathways. They are (i) Spinal cord to spinal cord technique (ii) Spinal cord to peripheral nerve technique and (iii) spinal cord to muscle technique.

However, in the course of developing the clinical use of these methods, it has been shown that most of them cannot evaluate corticospinal tract (CT) functional integrity. Since these are not specific to the fast neurons in the CT, which are essential elements for implementation of precise voluntary movements.

Single pulse of TES is effective to elicit iMEP (CMAPs) responses in conscious humans. However, under general anaesthesia it is difficult to obtain iMEP responses using single pulse stimulation. Inghilleri et al., 1990 showed that double pulse stimulation technique is superior to single pulse stimulation to elicit iMEPs (10). Taniguchi et al. made a major breakthrough in 1993 by showing that a short train of 3-5 electric pulses with an inter stimulus interval of 2-4 ms applied directly to human motor cortex evokes muscle MEP (CMAPs) under general anaesthesia (32). Finally in 1996 three independent groups showed that pulse-train TES is also effective to elicit iMEPs (CMAPs) (24-26). Although the methodology for eliciting and recording of iMEPs by transcranial electrical stimuli became available for intraoperative monitoring use a decade ago (32), neither the montage of the stimulating electrodes used for TES, nor the stimulation parameters were

standardized within the neurophysiological community (24, 25, 37, 61 and 88). Szelenyi et al., 2007, empirically studied and reported on optimal stimulation montages, intrepulse interval, individual pulse duration and optimal recording site for the upper and lower limbs in various neurosurgical procedures (18). However, there are some additional parameters necessary to increase the sensitivity and specificity to predict the postoperative outcome to the transcranial electrical stimulation technique. In general, stimulation and recording parameters used by different authors are rarely comparable and no reference values for motor thresholds exist. It is necessary to standardize the optimal TES stimulation and recording parameters in a neurosurgical procedures especially where the higher postoperative neurological deterioration occurs. Factors that have greatly affected for effective use of iMEPs are (1) TES causing marked jerking of movement due to paraspinal muscle contraction (2) trial to trial variation in amplitude that occurs during the course of surgery (3) management of anaesthesia (4) guidelines for predicting postoperative outcome. Some authors used total disappearance of potentials and others used 50% drop in amplitude as the criteria for the prediction of postoperative outcome. Some studies have shown that priming the cortex as way for reducing the stimulus threshold to elicit iMEPs and some have used averaging method to get more uniform responses to follow during the course of surgery. But there were no prospective studies on these two parameters. In the present thesis work, effort has been made to standardize the optimal stimulation and recording parameters in patients undergoing surgery for spinal cord tumours. This has been dealt in our study with different clinical scoring systems and elicited iMEP responses (100% success rate) with our standardized stimulation and recording parameters. Studies have shown that multiple pulse stimulation

is superior to single pulse stimulation in order to overcome anaesthetic effect. In the present study we have taken one more step where we gave 5 such multi pulse stimuli which perhaps resulted in lowering the response threshold much further. This has helped us in being able to continuously monitor the patient through out the course of surgery.

Depth of anaesthesia is another major causative factor which could affect success rate of iMEPs. To date, ideal anaesthetics for iMEP monitoring remains under investigations. In our study comparison of isoflurane and propofol anaesthesia without nitrous oxide on iMEP responses has been done. Our results suggest that propofol was better than isoflurane anaesthesia for iMEPs. Since patients under propofol needed (1) lesser stimulus strength to elicit responses (2) patients with longer duration of symptoms responses could still be recorded (3) responses could be elicited in more older age group as compared to patients under isoflurane anaesthesia.

The intraoperative change in iMEP amplitudes and prediction of postoperative clinical outcome has been of great deal of interest to neurophysiological monitoring community. This is particularly true in patients with IM (intramedullary) tumours where there is a high chance of postoperative neurological deterioration. Many studies that has been dealt with all or none iMEP responses (24, 27, 38) or increase in latency by 10% and drop in 50% amplitude (39) or a drop in amplitude by 50% (17) or increase in stimulus strength by 100V (40, 41) as the cut-off threshold to indicate postoperative morbidity. In our study, we propose the iMEP amplitude changes (%) for monitored muscles have different cut-off thresholds for each muscle (sensitivity) to show postoperative outcome in IM tumours. Tibialis anterior showed earlier postoperative deterioration, followed by EAS, quadriceps and soleus muscles. However, IDEM

(intradural extramedullary) tumours did not show any cut-off thresholds to postoperative clinical outcome due to higher iMEP trial-to-trial variations. More studies need to be done in order to understand this difference between these two groups. One would expect better predictive outcome in patients with IDEM cases as compared to IM cases.

Some of the patients showed postoperative deterioration even though their iMEPs did not totally disappear. Suggesting that total disappearance of the iMEPs should not be taken as the criteria for predicting postoperative deterioration. Our study also clearly suggests that it is important to monitor more than one muscle as changes in one muscle do not reflect in another muscle.

Intraoperative hypertension:

In general anaesthesia this neurophysiological technique are used not only for the spinal cord surgeries but also for the tumours within or in close proximity to the brain stem, in intracranial aneurysms and excision of tumours in and around eloquent cortex or epilepsy surgeries. Studies have shown that patients undergoing intracranial procedures in general have been reported to have systemic hypertension during these procedures (46-48) and they have frequent complications during and after the surgery. Hypertension in intraoperative period may be associated with a number of pathophysiological consequences, when cerebral auto regulation is disturbed.

The anaesthetist would respond to an increase in blood pressure by increasing the level of anaesthesia (depth of anaesthesia). i.e. by increasing the concentration of inhalational agents or by administration of narcotics or intravenous anaesthetics. These inhalational, intravenous anaesthetic agents and narcotics have effect on the evoked potentials and would result in a drop or disappearance of the evoked potentials, and could

hence act as a confounding factor in interpretation of the electrophysiological event. This results in having a wide margin of safety in determining postoperative outcome, which makes intraoperative monitoring less specific and less effective. In our study, we identified the preoperative factors like age and weight and intraoperative factors (pain, blood loss, durations of anaesthesia and surgery) which cause intraoperative hypertension during the course of surgery. Compared to preoperative to postoperative period an increase in renin, aldosterone, norepinephrine and sodium levels directly correlated to an increase in MAP (mean arterial pressure). An elevation norepinephrine level indicates that pain could have triggered hypertension process.

Olson et al (2002) showed that activation of Renin-Angiotensin-Aldosterone-System (RAAS) may be a primary event that facilitates the stimulation of the sympathetic nervous system and amplifies the vasoconstrictive effect of the catecholamines (123). This suggests that the potential for a preventive and therapeutic role of angiotensin converting enzyme (ACE) inhibitors; angiotensin antagonists and β-blocking drugs may be useful in maintenance of uniform blood pressure during the course of surgery. This could help the anaesthetist to maintain stable anaesthesia which in turn will help the neurophysiologists during intraoperative monitoring to predict better postoperative outcome.

In order to consider the feasibility of having a uniform blood pressure throughout the course of surgery it is necessary to use drugs that could break into the chain of sympathetic events that lead to hypertension. However, it is also very important to use only those drugs that have been used and proved to be safe for the patients. Keeping the safety of the patient in view we chose the drugs of proven safety record that is (1)

Atenolol, a cardio selective β1-adregenic receptor blocker that could lower cardiac output, to inhibit renin release, (2) lisinopril that inhibits the angiotensin converting enzyme (ACE). Drugs acting on ACE and inhibit the conversion of angiotensin-I, a weak vasoconstrictor to angiotensin-II, a potent vasoconstrictor.

Our study showed that, atenolol controls heart rate alone, it was failed to control the MAP and 44% of the study patients had intraoperative hypertension associated with postoperative period. All the vasoactive hormones (Serum norepinephrine, sodium and plasma aldosterone) except plasma renin levels were elevated in the intraoperative and postoperative periods in these patients. In contrast to this lisionpril controlled the intraoperative and postoperative MAP and none of the patients were hypertensive in the study group. Except plasma renin levels all the other vasoactive modulators were controlled by lisinopril in our treated patients.

CONCLUSIONS:

Our study shows that intraoperative neurophysiologial monitoring needed specific care and attention during the course of surgery to avoid the permanent postoperative neurological deteriorations. The study also concludes that

(1) Usage of multipulse stimulation and multiple sweeps of stimulation (0.7Hz) is very effective in eliciting iMEPs. More studies need to be done to understand this phenomenon.

(2) Averaging of these responses can used for more consistent responses.

(3) Intravenous anaesthesia (propofol) is more ideal than inhalational anaesthesia (isoflurane) for iMEPs.

(4) It is important to monitor more than one muscle to predict postoperative outcome.

(5) Pain is the main cause for intraoperative hypertension and it is mediated by increased norepinephrine levels in the circulation.

(6) Intraoperative maintenance of stable haemodynamics by pre-emptive therapy with lisinopril (angiotensin converting enzyme inhibitor) would be beneficial and prevent the intraoperative associated postoperative neurological complications. This is particularly important if the patient requires intraoperative neurophysiological monitoring.

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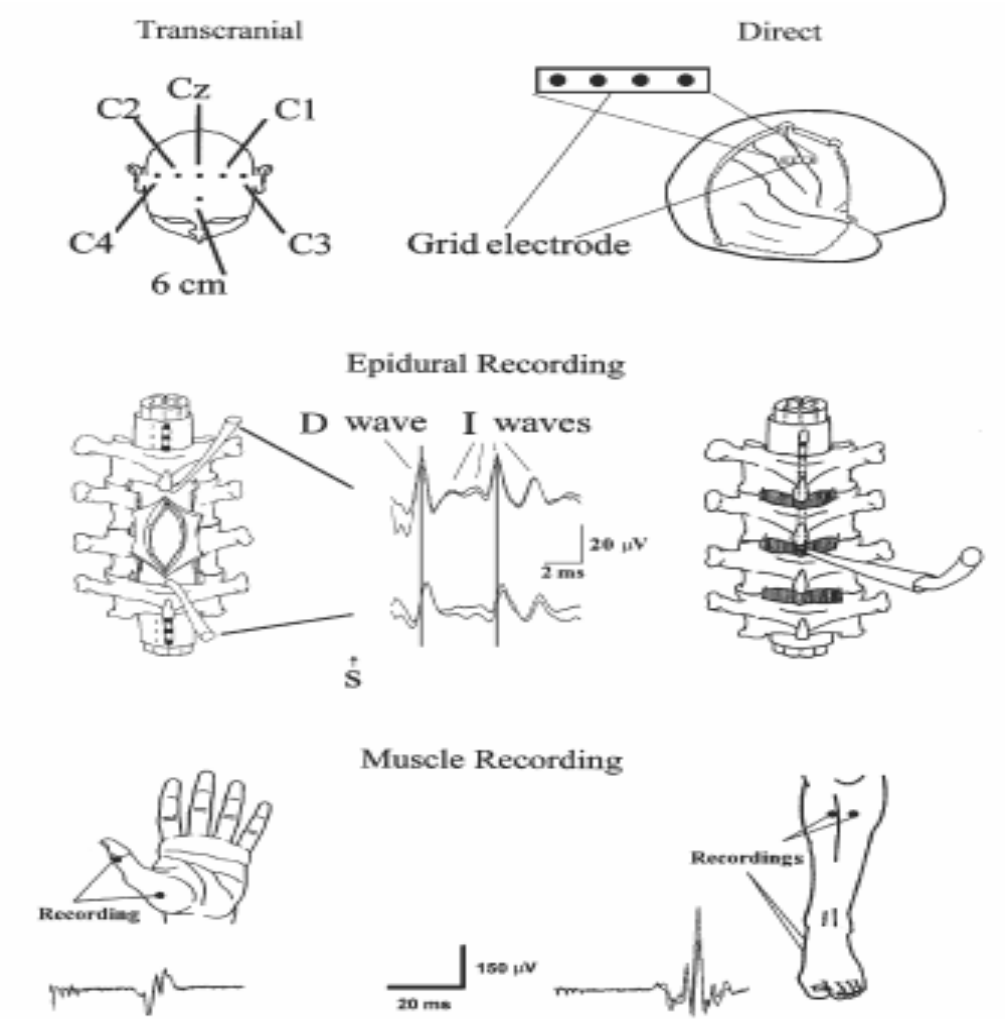


Figure-1A

Schematic representation of intraoperative methodology for stimulating and recording motor evoked potentials from the spinal cord and limb muscles (Reproduced with permission from Deletis 2008).

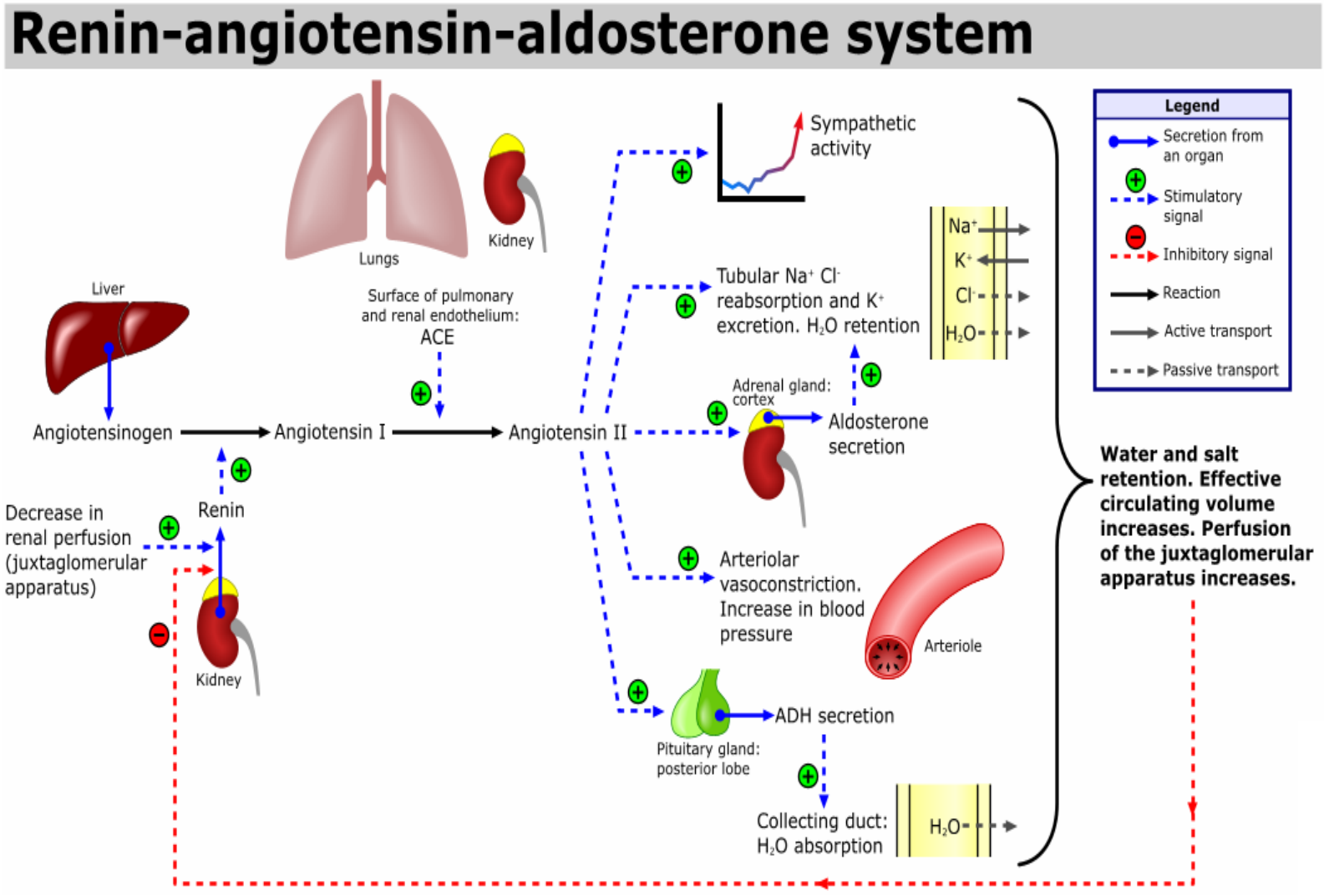


Figure-1B

The schematic pathway of the Renin-Angiotensin-Aldosterone System (RAAS)

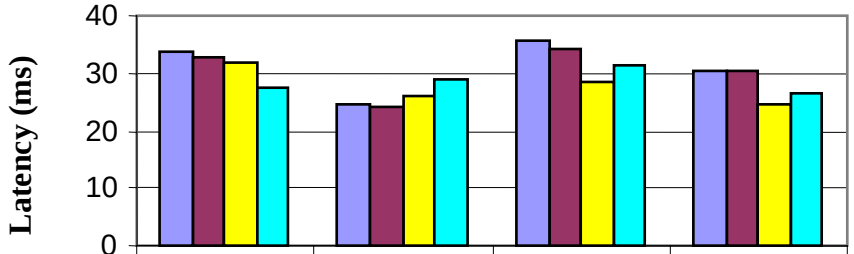
Table.3.1. shows the list TES stimulation and recording parameters used by different authors to predict the postoperative outcome in various surgical procedures

Authors	Type Of Surgery	Stimulation Site	Stimulation Intensity	Number of Pulses / IPI	Muscles Recorded
Jones et al., 1996	Spinal surgery	Cz-C3,C4	300 V to 1000V	1-6/ 1-6 ms	ADM and AH
Calancie et al., 1998	Spine surgery	C3-C4	500V	1-9/ 2 ms	APB, Quad, TA and AH
Kothbauer et al.,1998	IM tumours surgery	Cz – C1,C2 and Cz - C3, C4	200 mA	5/4 ms	APB and TA
Calancie et al., 2001	Cauda Equina, Brain Stem and Spinal cord	C3-C4	100V in 10V increments	2-4/2-3 ms	Thenar and Hypothenar, Quad, TA and AH
Pelosi et al., 2001	Orthopaedic spine	Cz-C3, C4	700V	4/2 ms	TA and AH
Pelosi et al., 2002	Orthopaedic spine	Cz – C1,C2 and Cz - C3, C4	700V	4-5 / 2-4 ms	TA and AH
Quinones-Hinojosa et al., 2005	IM tumours surgery	C1-C2	100V	5-6/2.5-3.5 ms	Thenar,Hypothenar, TA and EDH
Sala et al., 2006	IM tumours surgery	Cz-FPz	240 mA	5-7/ 4 ms	APB and TA
Our study	IM and IDEM tumours surgery	Cz'-FPz	150 V to 350V	5 / 2ms	TA, Soleus, Quadriceps, EAS

TA – Tibialis Anterior, Quad-Quadriceps, AH-Abductor Hallucis, APB-Abductor Pollicis Brevis, EHS-Extensor Hallucis Longus, ADM-Abductor Digiti Minimi.

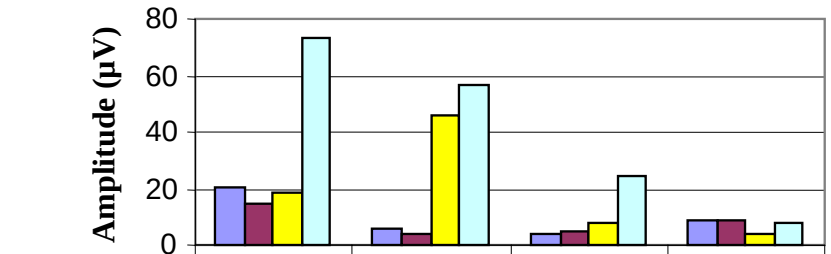
IPI= Interpulse interval. IM= Intramedullary, IDEM = Intradural extramedullary, V= Volts, ms = milli second, mA = milli amphere

Figure-3.1A:



	TA	Quadriceps	Soleus	EAS
Cz-Fz Right	33.6	24.6	35.9	30.5
Cz-Fz Left	32.6	23.9	34.2	30.4
C3-C4 Right	31.8	26.2	28.4	24.7
C3-C4 Left	27.3	28.8	31.5	26.4

Figure-3.1B:



	TA	Quadriceps	Soleus	EAS
Cz-FPz Right	20.6	6	3.8	8.4
Cz-FPz Left	14.2	4.1	5.1	8.3
C3-C4 Right	18.3	46.2	8.21	3.6
C3-C4 Left	73.4	56.2	24.5	7.4

The above figures shows the difference in latency (Fig-3.1A) and amplitude (Fig-3.1B) between C3-C4 and Cz'-Fpz stimulation sites in MRC grade-5 patients.

Table-3.2 shows the summarized TES stimulation and recording parameters used in our study

Stimulation: Anode	Cz’ region
Stimulation: Cathode	Fpz region
Number of Pulses	5 pulses
Inter Pulse Interval	2 msec (500Hz)
Rate of Stimulation of each sweep	0.7Hz
Average	5 sweeps

Table 3.3A-3.3E showed the percentage of muscles recorded from all the monitored muscles with respect to the Nurick's, McCormick and MRC clinical scoring methods. --- = iMEP responses not obtained,.

Table.3.3A (Tibialis Anterior)

Grades	Nuricks	McCormick
Grade-0	87%	NA
Grade-1	71%	71%
Grade-2	59%	59%
Grade-3	32%	21%
Grade-4	---	---
Grade-5	---	NA

Table.3.3B (Soleus)

Grades	Nuricks	McCormick
Grade-0	81%	NA
Grade-1	69%	65%
Grade-2	58%	41%
Grade-3	30%	18%
Grade-4	---	---
Grade-5	---	NA

Table.3.3C (Quadriceps)

Grades	Nuricks	McCormick
Grade-0	61%	NA
Grade-1	49%	65%
Grade-2	32%	41%
Grade-3	18%	18%
Grade-4	---	----
Grade-5	---	NA

Table.3.3D. (EAS)

Grades	Nuricks	McCormick
Grade-0	67%	NA
Grade-1	45%	55%
Grade-2	31%	33%
Grade-3	19%	15%
Grade-4	---	----
Grade-5	---	NA

Table.3.3E (MRC Scoring system):

MRC Grade	Percentage of Tibialis Anterior responses	Percentage of Soleus responses	Percentage of Quadriceps responses
5	96%	91%	71%
4	77%	79%	63%
3	50%	38%	34%
2	35%	22%	---
1	---	---	---
0	---	---	---

Table 3.4 showed the success rate of percentage of muscles recorded (iMEPs) in various spinal cord procedures with different stimulation site

Authors	Stimulation site	Stimulus strength (Volts)	Type of surgery	Monitored Muscles	MEP Success Rate (%)	
					With Weakness	Without Weakness
Kothbauer et al., 1997	C1-C2, Cz-C3 / C4	200 mA	IM tumours	APB and TA	---	100%
Calancie et al., 2001	C3-C4	100V in 10V increments	Spine	APB, Quad, TA and AH	---	95%
Pelosi et al., 2001	Cz-C3, C4	700V	Orthopaedic spine	TA and AH	20%	80%
Pelosi et al., 2002	Cz-C3, C4, Cz-C1 / C2	700V	Orthopaedic spine	TA and AH	---	84%
Bartley et al., 2002	Cz-FPz	500V	Spine surgery	TA and Soleus	---	66%
Fukuoka et al., 2004	Cz-FPz	200 mA	Cervical spine	BCP, ADM, FHB	---	50%
Sala et al., 2006	C1-C2, Cz-Fpz	240 mA	IM tumours	APB, EDL, TA, AH	60%	100%
Chen et al., 2007	C3-C4	400V	Neurosurgery and orthopaedic spine	Thenar and TA	39.1%	78.9%
Our study MRC grades 3-5	Cz-FPz	150 V – 350V	IM and IDEM tumours	TA, Soleus, Qaudriceps, EAS	100%	100%

--- = iMEP responses not obtained. TA – Tibialis Anterior, Quad-Quadriceps, AH-Abductor Hallucis, APB-Abductor Pollicis Brevis, EHS-Extensor Hallucis Longus, EDL-Extensor Digitorum Longus, ADM-Abductor Digiti Minimi. IPI= Interpulse interval. IM= Intramedullary, IDEM = Intradural extramedullary, V= Volts, mA= milli amphere

Table 3.5

Functional grading system	**'p' value**
Nurick's grade**	0.003
MRC grade*	0.028
McCormick classification	0.363

Table-3.5 shows the predictive relationship between different functional classification systems and eliciting the baseline iMEP responses with its 'p' value. (** = $p < 0.01$, * = $p<0.05$).

Table 3.6A

Functional Grading System	**Mean Stimulus Strength (Volts)**	
	Nurick's **	**McCormick's**
Grade-0	199 (91%)	NA
Grade-1	202 (89%)	223 (79%)
Grade-2	229 (83%)	249 (66%)
Grade-3	220 (76%)	228 (63%)
Grade-4	252 (59%)	271 (51%)
Grade-5	308(51%)	NA

Table-3.6B:

MRC Grade	**Mean stimulus strength (Volts) / Percentage of Tibialis Anterior responses ***	**Mean stimulus strength (Volts) / Percentage of Soleus responses ***	**Mean stimulus strength (Volts) / Percentage of Quadriceps responses***
5	227 (96%)	229 (91%)	242 (71%)
4	241(77%)	241 (79%)	254 (63%)
3	252 (50%)	254 (38%)	269 (34%)
2	259 (35%)	271 (22%)	---
1	---	---	---
0	---	---	---

Table-3.6A (Nuricks and McCormicks scoring system) & **Table 3.6B** (MRC scoring system) shows the relationship between different functional classification systems and amount of mean stimulus strength required to eliciting the baseline iMEP responses. Values in bracket indicate percentage of muscles from which iMEP responses could be elicited. (** = $p < 0.01$, * = $p<0.05$). --- = iMEP responses not obtained, NA= Not Applicable.

Figure-3.3:

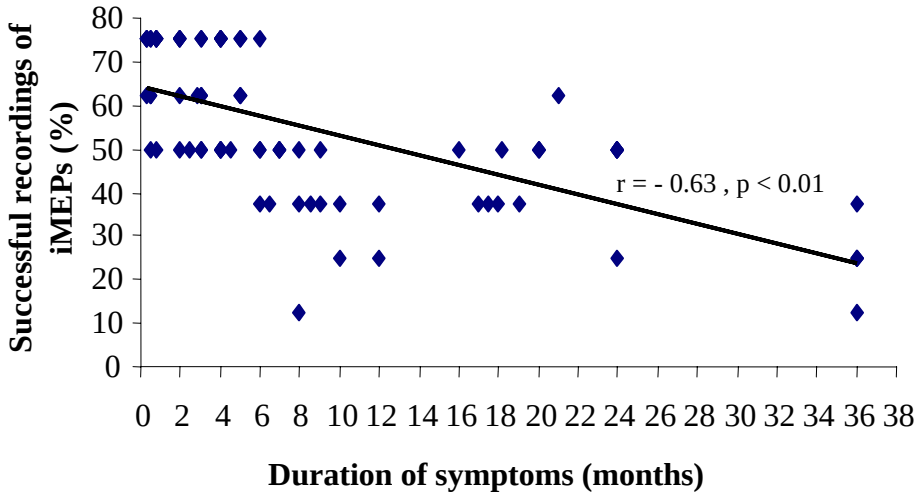
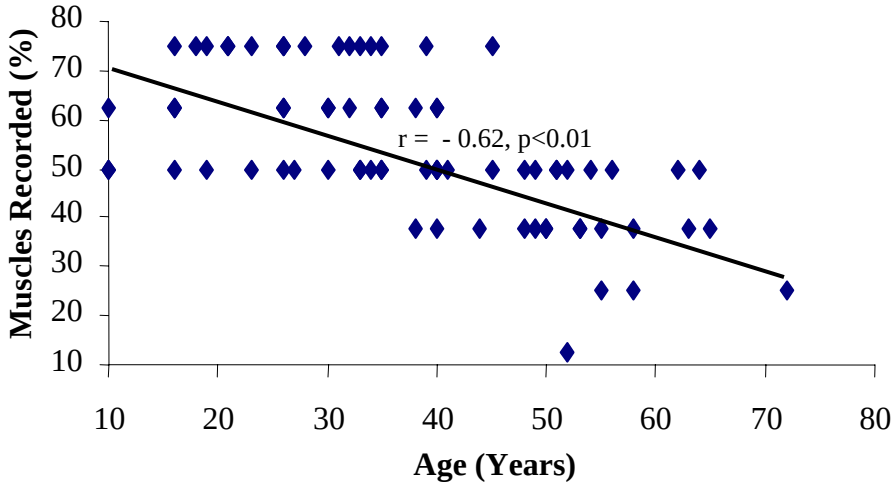


Figure – 3.4:



Percentage of muscles could be recorded with duration of symptoms (months) (**Figure-3.3)** and with age (years) (**Figure-3.4).** Both the graph shows a negative correlation (straight line) between number of muscles that could be recorded and duration of symptoms ($p < 0.01$) and age ($p<0.01$). r = correlation.

Figure 3.5.

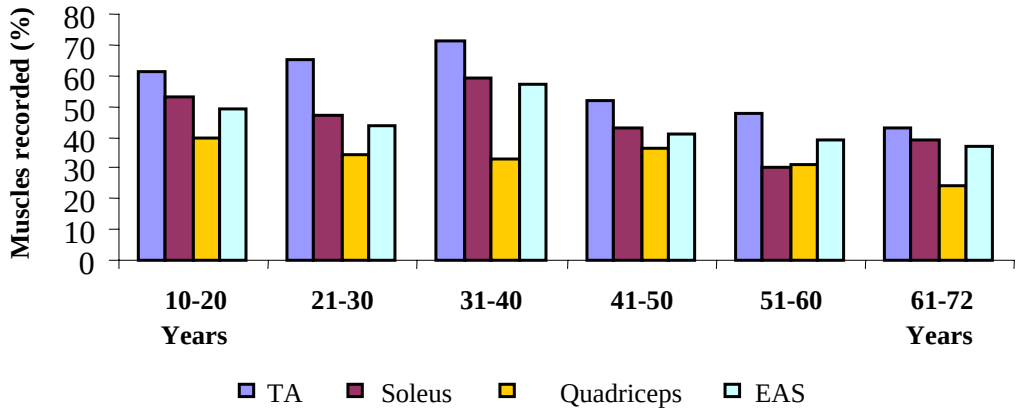


Figure-3.5. Percentage of muscles (iMEPs) could be recorded with age variability (years) in neurologically intact patients (Nurick;s grade-0).

Figure 4.1

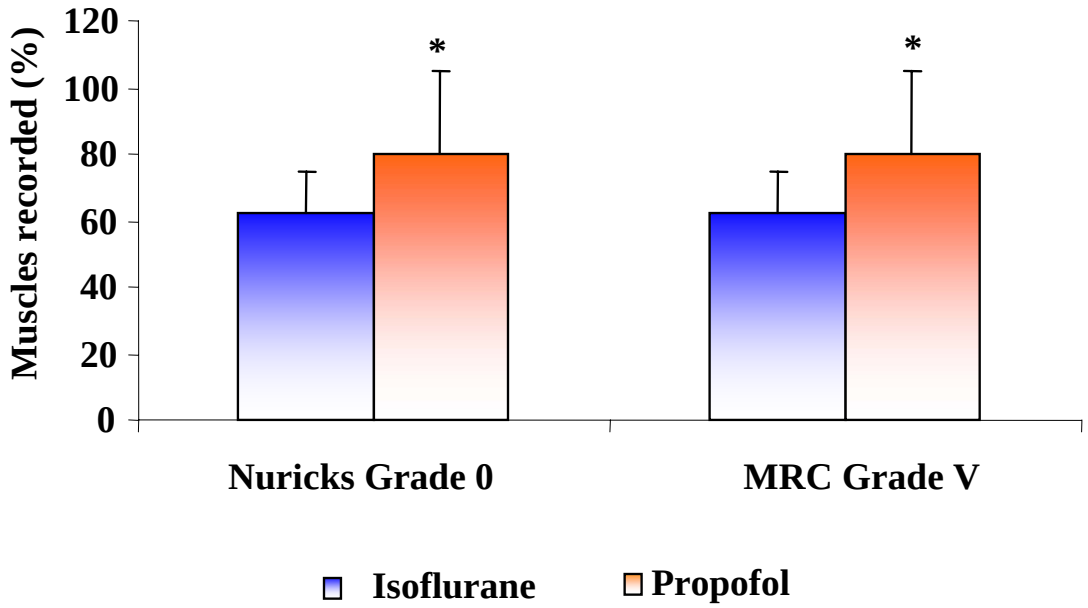


Figure4.1 shows the percentage of muscles (iMEPs) that could be recorded under isoflurane and propofol anaesthesia in neurologically intact patients. * = $p<0.01$, * = $p < 0.05$.

Figure4.2:

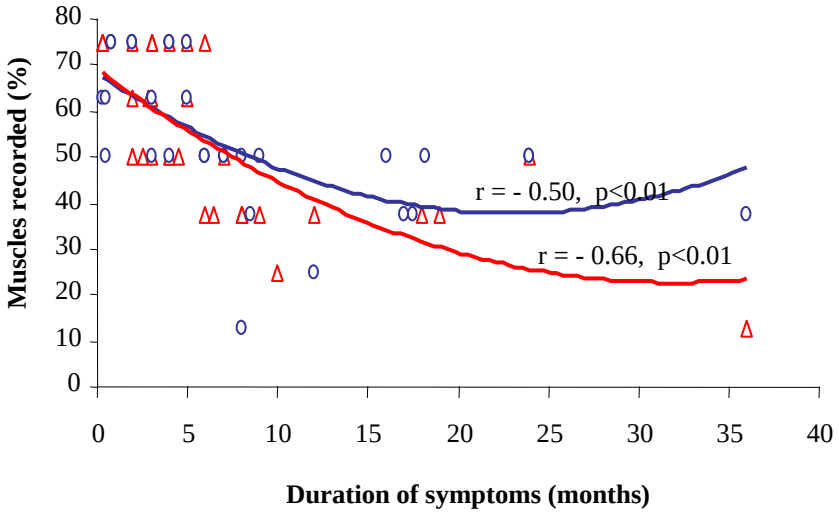
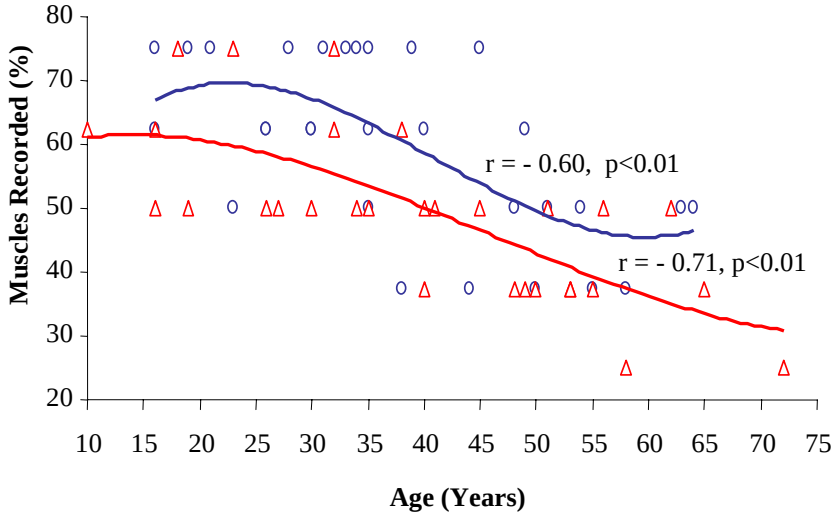


Figure4.3:



Δ **Isoflurane Anaesthesia**

o **Propofol Anaesthesia**

Percentage of muscles recorded (iMEPs) with duration of symptoms (myelopathy) **(Figure-4.2)** and age (years) **(Figure-4.3)** in isoflurane and propofol anaesthesia. r = correlation with negative values. Red line indicates correlation of isoflurane anaesthesia and blue line indicates for propofol anaesthesia.

Figure 4.4:

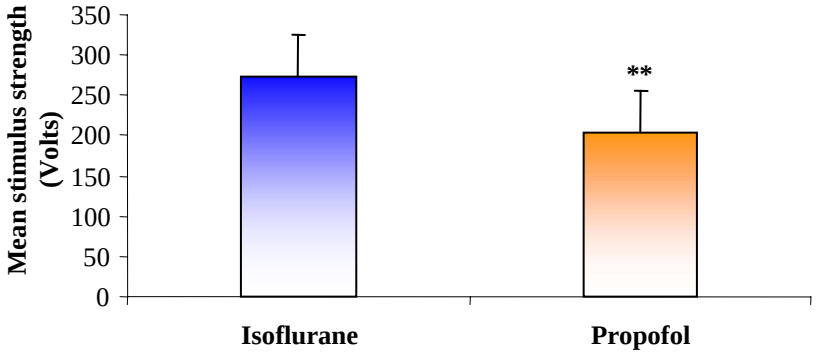


Figure 4.5:

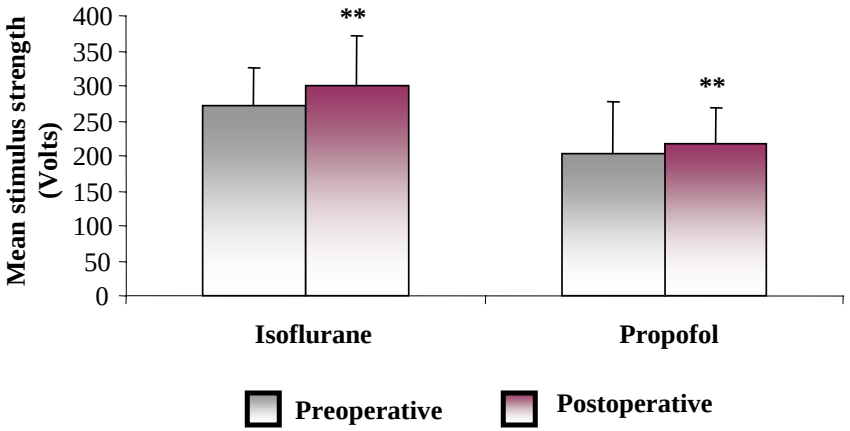


Figure-4.4 show the mean stimulus strength used to elicit the baseline iMEPs and **Figure-4.5** show the preoperative to postoperative stimulus strength increment in isoflurane and propofol anaesthesia. ** = $p < 0.01$.

Figure 4.6A:

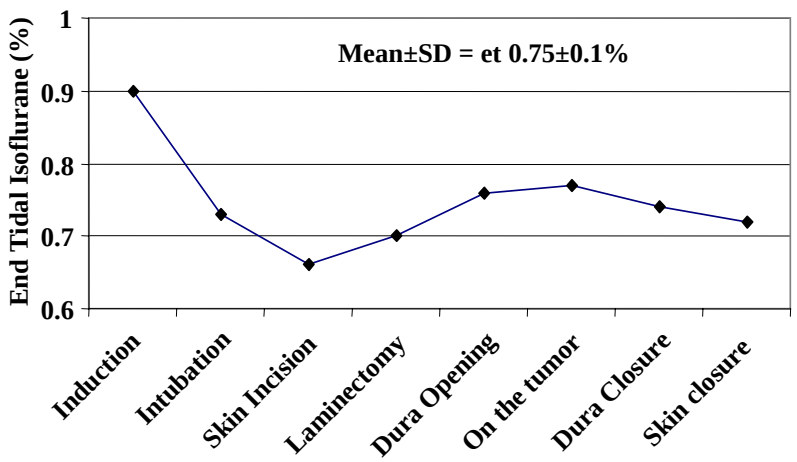
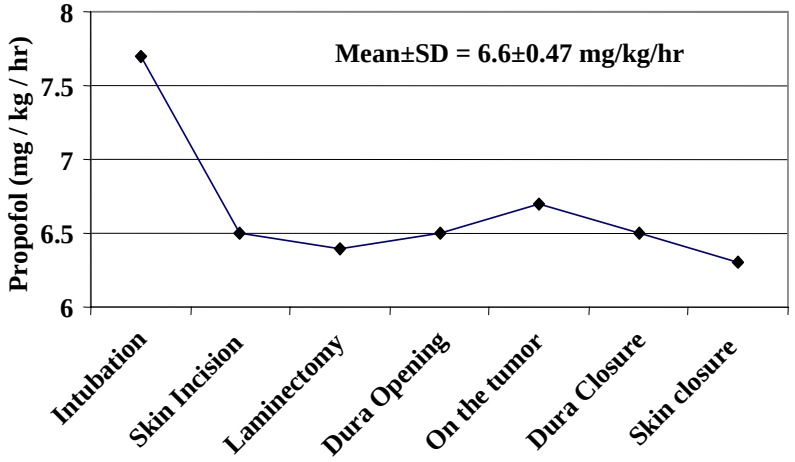


Figure 4.6B:



The above line plot shows the maintenance of end tidal Isoflurane (Figure-4.6A) and propofol (Figure-4.6B) during different stages of surgery

Figure-4.6C:

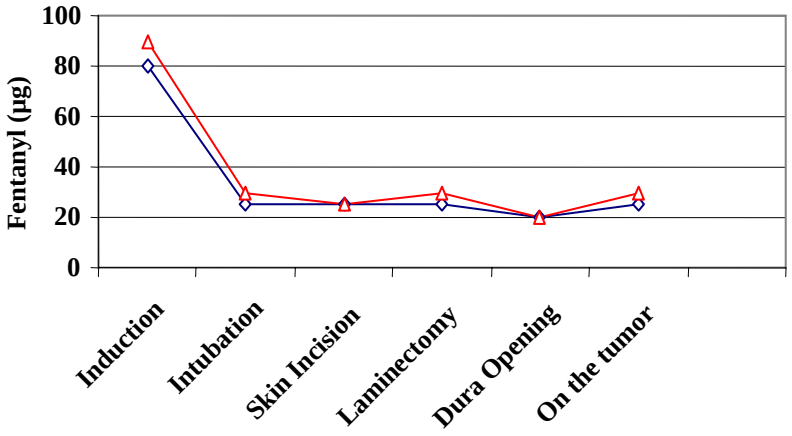
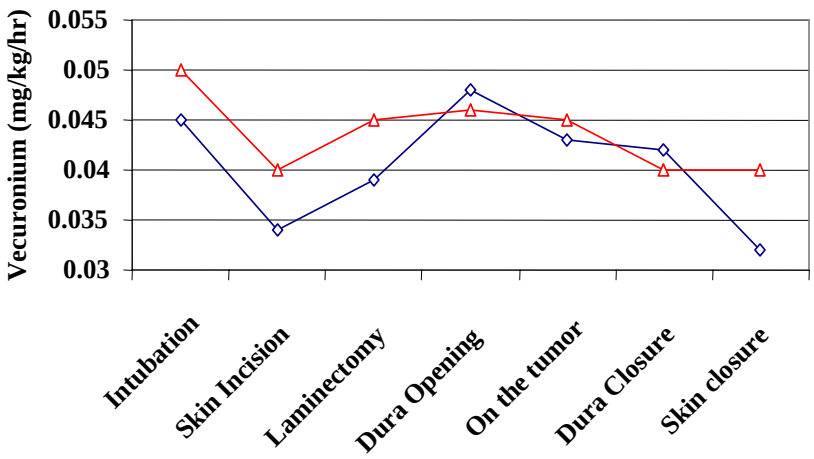


Figure-4.6D:



Isoflurane Anaesthesia **Propofol Anaesthesia**

Line plot graph shows the maintenance of fentanyl (Figure 4.6C) and vecuronium (Figure 4.6D) during the course of surgery in isoflurane and propofol anaesthesia

Figure.4.7A:

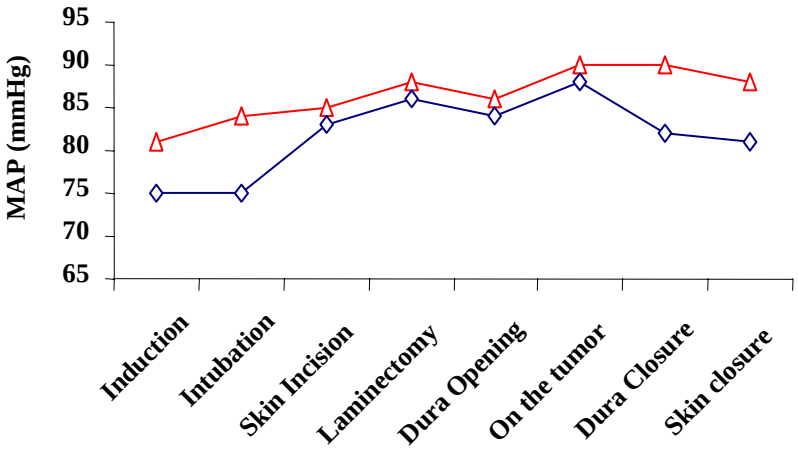
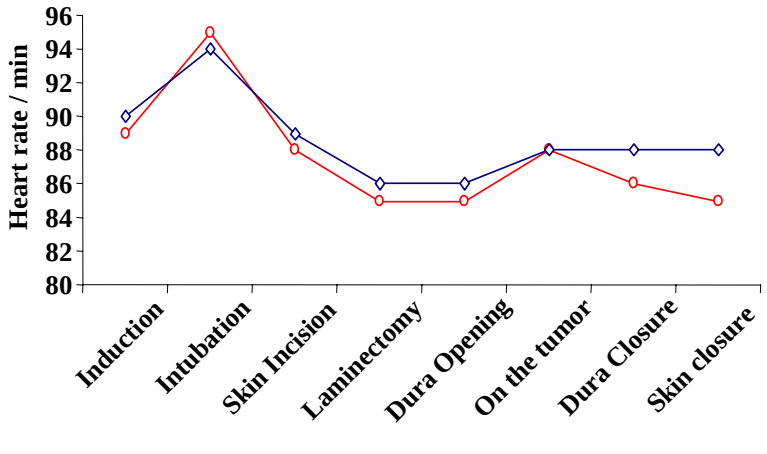


Figure.4.7B:



Isoflurane Anaesthesia **Propofol Anaesthesia**

Line plot graph shows the maintenance of MAP (Figure 4.7A) and Heart rate (Figure 4.7B) during the course of surgery in isoflurane and propofol anaesthesia

Table 4.1 show the different centers TES to iMEP success rate with and without neuromuscular blockade during the course of surgery

Authors	Anaesthesia used	Intraoperative Muscle relaxants Used	Muscles Recorded	MEP success rate
Kalkman et al., 1992	Nitrous oxide / Sulfentanyl	Yes, Succinyl Choline	TA	60%
Lang EW et al.,1996	Nitrous oxide / Oxygen / Etomidate	Yes, Succinyl Choline infusion	TA	95%
Pelosi et al., 2001	Isoflurane / Propofol / Nitrous oxide	Yes	TA and AH	100%
Bartley et al., 2002	Propofol / Fentanyl / Sevoflurane /	Yes (Atracurium)	TA and Soleus	66%
Pelosi et al., 2002	Isoflurane / Propofol / Nitrous oxide	Yes, infusion used	TA and AH	84%
Fukuoka et al., 2004	Propofol / Fentanyl	Vecuronium Infusion used (0.02-0.04mg/kg)	BCP, ADM, FHB	50%
Our study	Isoflurane / Propofol / Oxygen	Vecuronium infusion used (0.04-0.05mg/kg/hr)	TA, Soleus, Quadriceps, EAS	100%
Jones et al., 1996	Propofol / Nitrous oxide	No	ADM and AH	95%
Kothbauer et al.,1998	Propofol / Nitrous oxide	No	APB and TA	100%
Calancie et al., 1998	Propofol / Nitrous oxide	No	APB, Quad, TA and AH	94%
Calancie et al., 2001	Propofol / Nitrous oxide	No	Thenar and Hypothenar, Quad, TA and AH	85%
Lyon et al., 2005	Propofol / Nitrous oxide / Succinyl Choline	No	TA, EHL, Flexor foot muscles	100%
Lo et al., 2006	Desflurane / Propofol / Fentanyl	No	TA and AH	100%
Sala et al., 2006	Propofol / Nitrous oxide / Fentanyl	No	APB and TA	100%
Chen et al., 2007	Propofol / Fentanyl	No	Thenar and TA	100%

Table-5.1. Clinical details and postoperative outcome in IM and IDEM tumour patients

Clinical Details	IM	EM
Pathology:		
Astrocytoma	4	---
Ependymoma	5	1
Lipoma	3	1
Glioma	3	---
Schwanomma	---	34
Meningioma	---	5
Neuroecto dermal tumour	---	2
Fibrous connective tissue	---	2
Arachnoid cystic mass	---	1
Dermoid	4	2
Haemengioparacytoma	---	1
Gliotic Nervous tissue	---	2
Syrinx	1	---
Neurofibroma	2	2
Surgical Plane:		
Good	12	50
Bad	10	3
Radicality of Tumour excision:		
Total	6	48
Sub total	12	5
Partial	4	---
Postoperative Clinical Outcome:		
Improvement	---	39
Deterioration	6	---
Same	16	14

Table -5.2 shows the proportion of the baseline iMEP could be recorded in IDEM and IM tumour patients

Muscle	Proportion with responses (%)		Total (n = 75)
	IDEM (n =53)	IM (n = 22)	
Tibialis anterior	68 / 106 (64%)	38 / 44 (86%)	106 / 150 (71%)
Soleus	54 / 106 (51%)	36 / 44 (82%)	90 / 150 (60%)
Quadriceps	41 / 106 (39%)	27 / 44 (61%)	68 / 150 (45%)
External Anal Sphincter	58 / 106 (55%)	36 / 44 (82%)	94 / 150 (63%)

Table 5.3 shows the iMEP changes and postoperative outcome in patients with intradural extramedullary tumours (IDEM) based on the tumour levels.

iMEP amplitude changes	No. of patients (%)	Postoperative Outcome
> 50% deterioration		
Cervical	4 (7.5%)	3, Improved; 1, Same
Thoracic	4 (7.5%)	2, Improved; 2, Same
Thoraco-lumbar	3 (6%)	2, Same; 1, Improved
Complete loss		
Cervical	3 (6%)	3, Same
Thoracic	1 (2%)	1, Same
Thoraco-lumbar	----	----
>50% improved		
Cervical	15 (28%)	15, Improved
Thoracic	18 (34%)	18, Improved
Thoraco-lumbar	5 (9%)	5, Improved

Figure. 5.1:

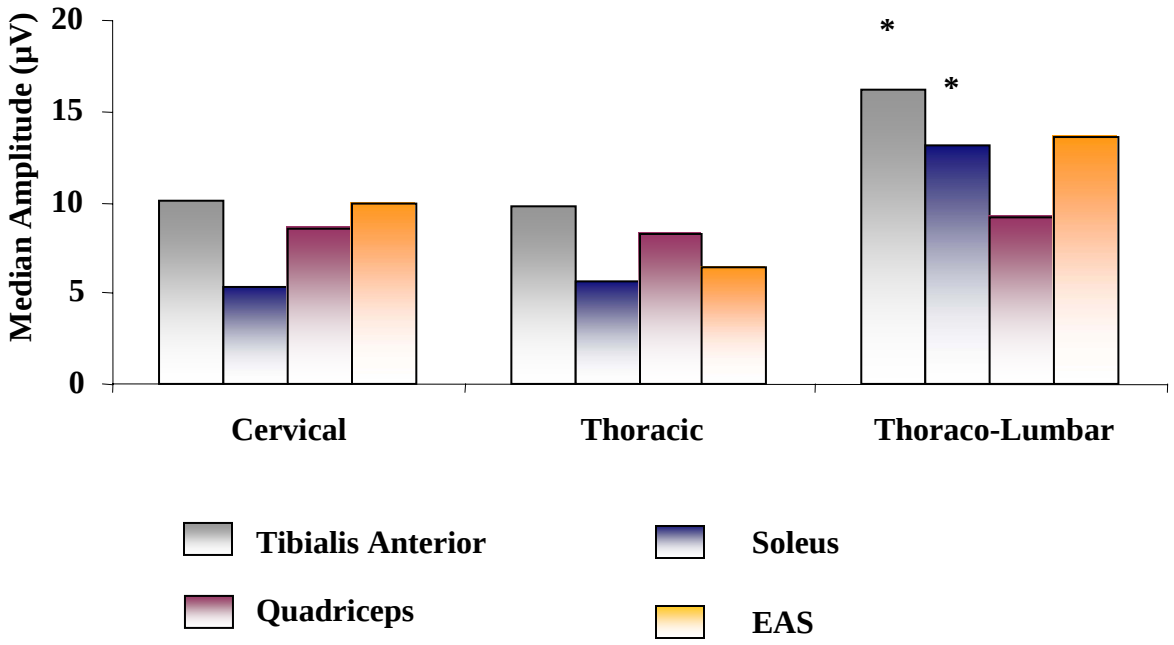


Figure 5.1 shows the location of tumours on x-axis and median iMEP amplitudes recorded from four groups of muscles. * = $p < 0.05$.

Figure. 5.2: Tibialis Anterior

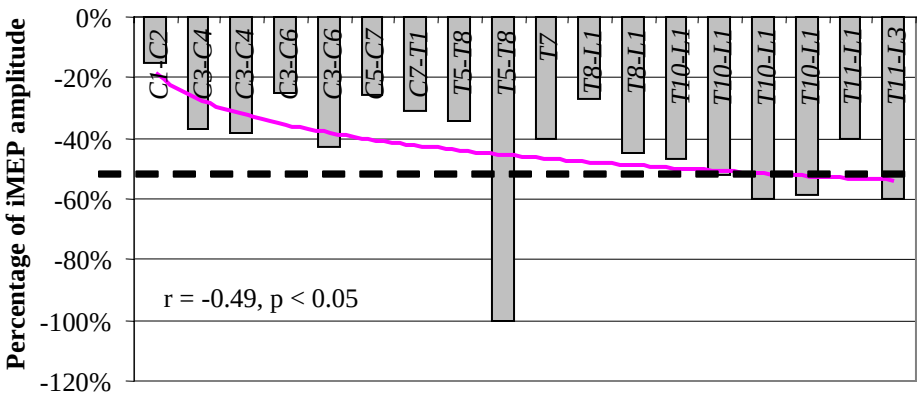


Figure. 5.3: Soleus

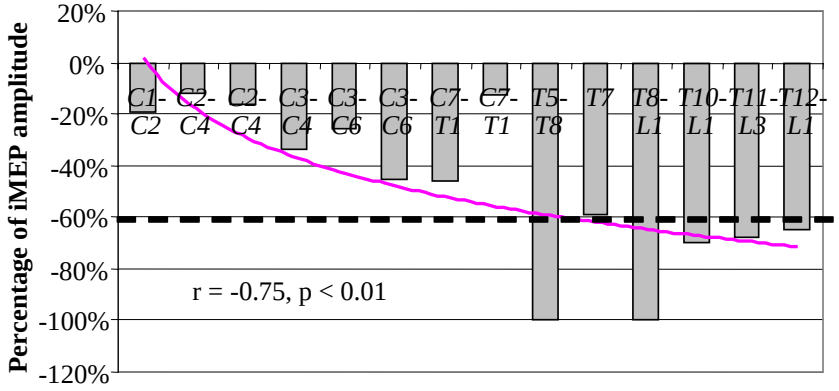


Figure. 5.4: Quadriceps

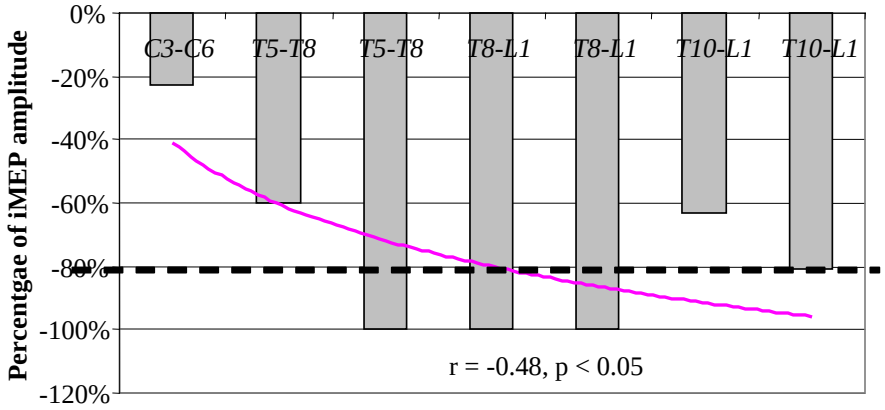


Figure. 5.5: EAS

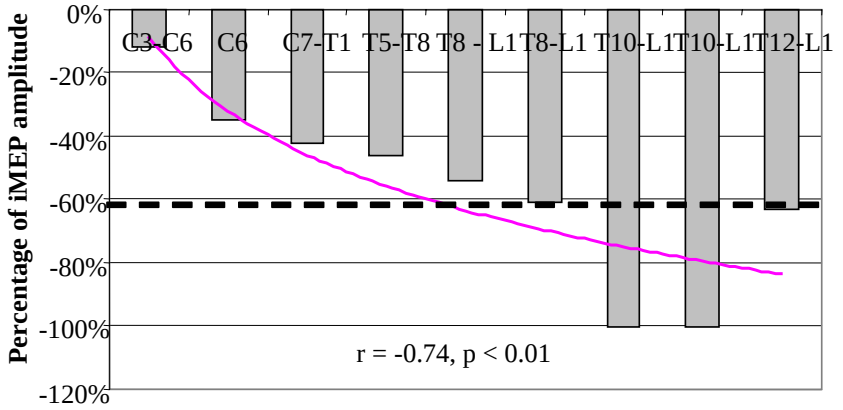


Figure-5.2-5.5 shows the percentage changes in iMEP amplitude in monitored muscles. The dotted line indicates the cut off point at which postoperative deficit occurred in intramedullary (IM) tumours.

Table-5.4:

Tumour location	True Positive	True Negative	False Positive	False Negative	Sensitivity	Specificity
IM and IDEM (n=75)	29	21	25	0	1	0.46
IM (n=22)	7	11	4	0	1	0.73
IDEM (n=53)	22	10	21	0	1	0.32

Table 5.4 shows the TES to sensitivity and specificity of iMEP changes in predicting postoperative outcome in both IM and IDEM tumours.

Table 5.5:

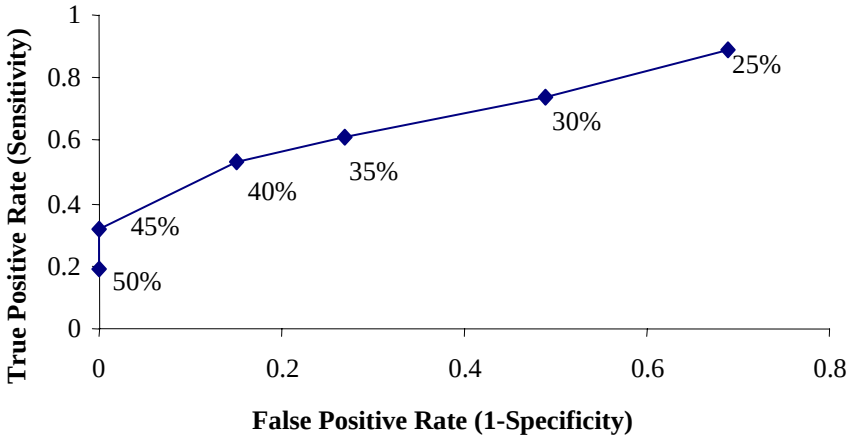
	LIKELIHOOD RATIO (Positive)	
TYPE OF SURGERY	**40% - 45% Amplitude Changes**	**45% - 50% Amplitude Changes**
Both IM and EM	1.90	2.75
IM Only	2.14	5.90
EM Only	1.25	1.67

Table 5.5 shows the TES to Likelihood ratio to iMEP changes in predicting postoperative outcome in both IM and IDEM tumours.

Table- 5.6.

Cut-Offs Analyzed	True Positives	False Positives
25%	0.89 %	0.69 %
30%	0.74 %	0.49 %
35%	0.61 %	0.27 %
40%	0.53 %	0.15 %
45%	0.32 %	0 %
50%	0.19 %	0 %

Figure 5.6:



The **table-5.6** and **Figure 5.6** shows the ROC cut-off point of iMEP amplitude changes in intramedullary patients to predict the postoperative deteriorated outcome.

Table.6.1.

Factors in H group	Significance (Regression analysis)
Preoperative	
Age	$p < 0.01$
Weight	$p < 0.01$
Intraoperative	
Pain (endtidal.Isoflurane)	$p < 0.01$
Blood Loss	$p < 0.01$
Duration of Anaesthesia	$p < 0.01$
Duration of Procedure	$p < 0.01$

Table.6.1 show the prediction based analysis of preoperative and intraoperative factors which affects intraoperative MAP. MAP = Mean arterial pressure.

Table.6.2.

	Normotensive	Hypertensive
et.Isoflurane (%)	0.71±0.1	1.2±0.1*
Fentanyl (µg/kg)	2.4±0.4	3.4±0.6*
Blood Loss (ml)	488±68	756±164*
Duration Of Surgery (mins)	201±39	284±39*
Duration Of Anaesthesia (mins)	273±46	334±48*
Extubation Time (mins)	16±4	36±5*
Emergence time (mins)	10±2	22±4*

Table.6.2 show the intraoperative anaesthesia and surgical factors differed significantly between normotensive (Group N) and hypertensive (Group H) patients.

Figure. 6.1A:

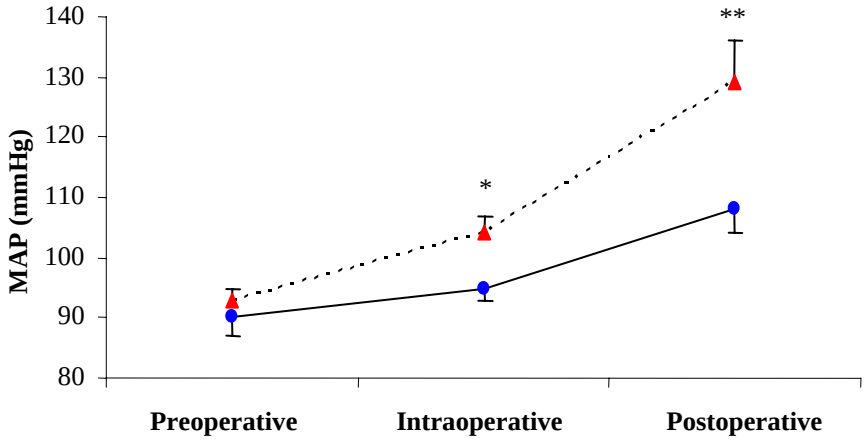
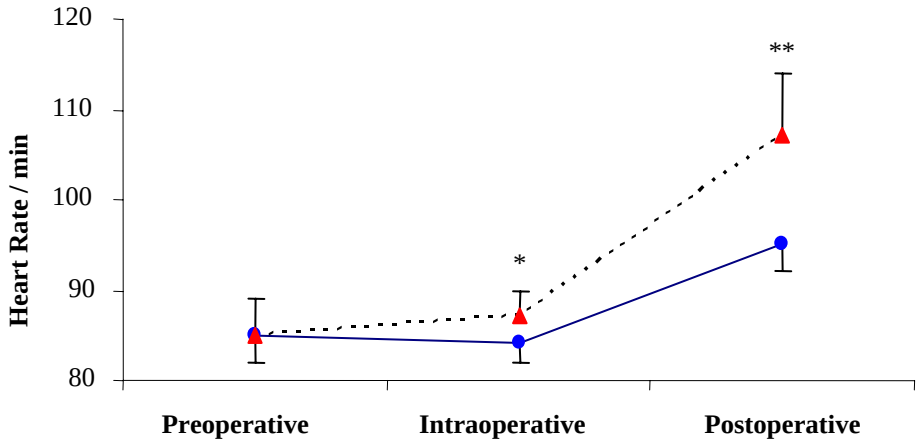


Figure. 6.1B:



MAP (**Figure.6.1A)** and heart rate **(Figure.6.1B)** variations during the course of surgery between normotensive (Group N) and hypertensive (Group H) patients. MAP = Mean arterial pressure. * = $p < 0.05$, ** = $p < 0.01$.

Table 6.3:

	Group	Preoperative	Intraoperative	Postoperative
Renin (ng/ml/hr)	N	6.43±3.2	8.62±5.1	7.34±3.9
	H	11.52±1.2	13.9±3.1	26.54±7.7
Aldosterone (pg/ml)	N	67.71±27	75.59±26	63.6±13.4
	H	99.2±32	117±40.9	203±90.7
Norepinephrine (ng/ml)	N	13.5±4.9	15±3	14.4±5
	H	9.89±3.9	15.4±5.2	34.06±11
Sodium (mmol/lit)	N	135±5.4	142±10	156±6
	H	140±8.5	135±4.4	125±7

Table.6.3 show the vasoactive modulators changes in preoperative, intraoperative and postoperative periods between normotensive (Group N) and hypertensive (Group H) patients.

Figure 6.2A:

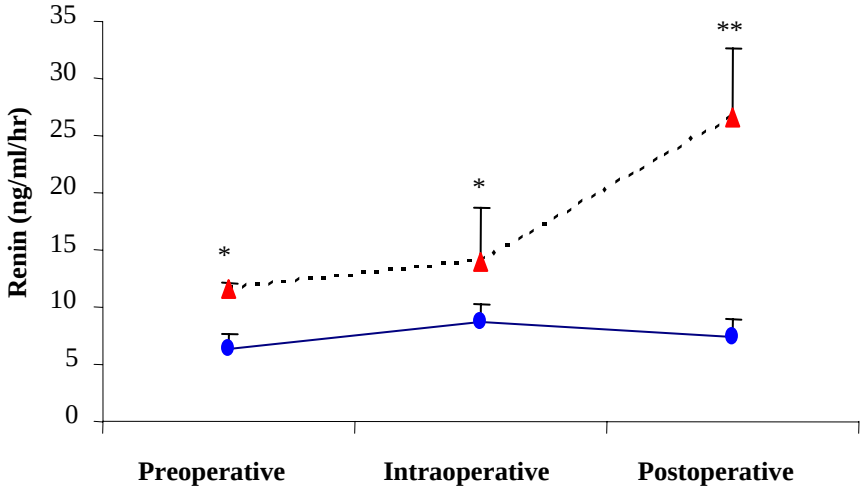
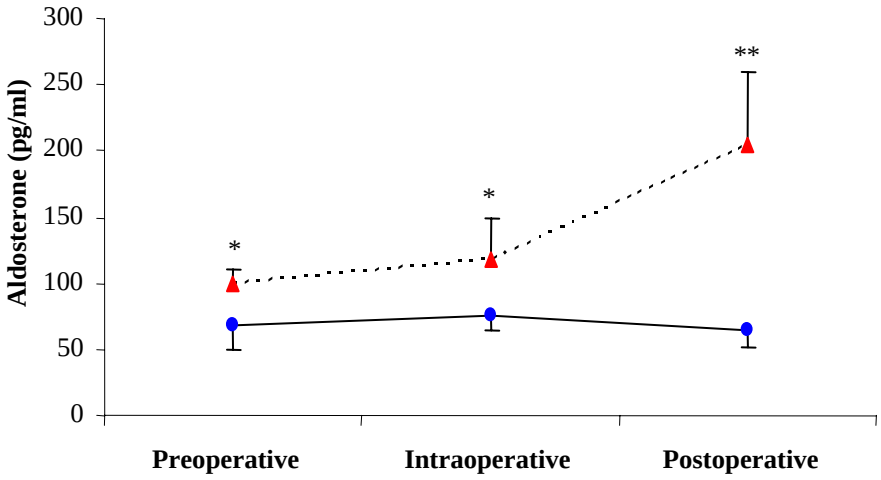


Figure 6.2B:



Renin (**Figure.6.2A)** and Aldosterone **(Figure.6.1B)** variations during the course of surgery between normotensive (Group N) and hypertensive (Group H) patients. * = $p < 0.05$, ** = $p < 0.01$.

Figure.6.3:

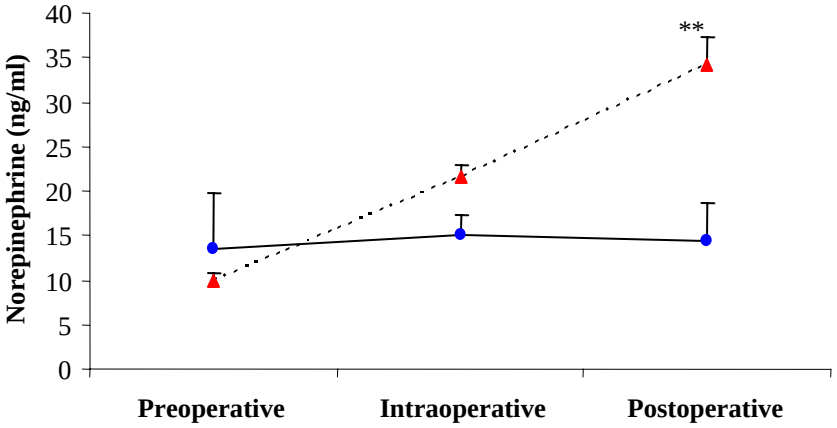
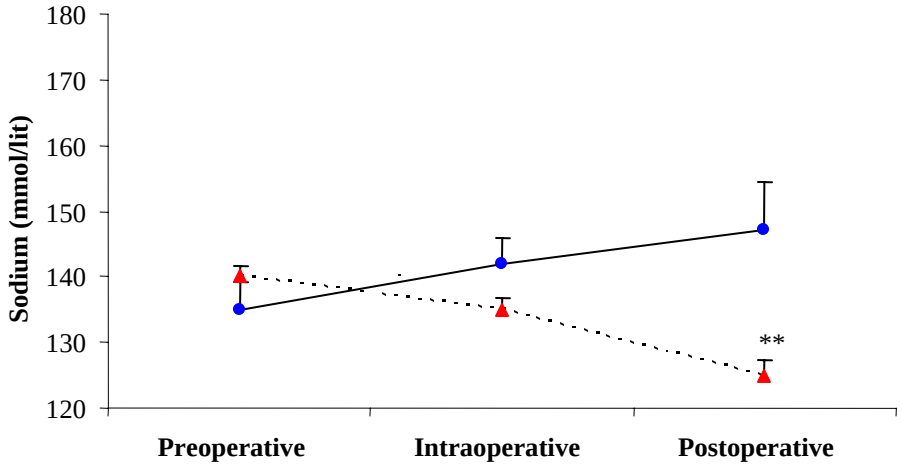


Figure.6.4:



Norepinephrine (**Figure.6.3)** and serum Sodium levels **(Figure.6.4)** variations during the course of surgery between normotensive (Group N) and hypertensive (Group H) patients. ** = $p < 0.01$.

Figure.6.5:

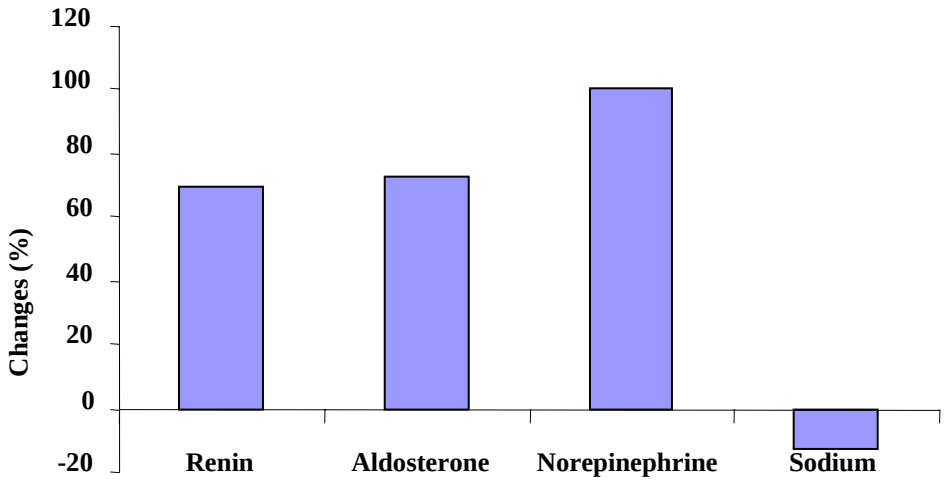


Figure6.5 show the percentage changes in vasoactive modulator levels in group H patients.

Figure 6.6A:

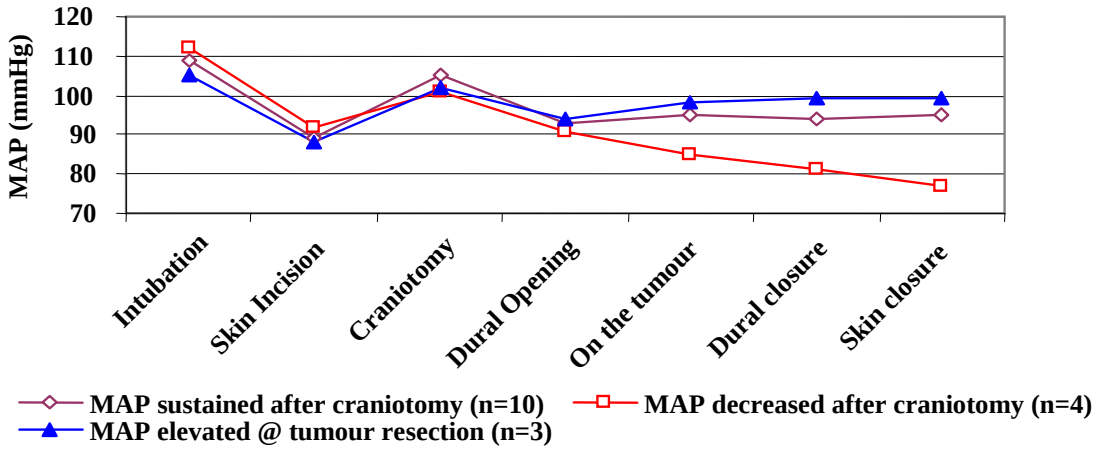


Figure 6.6A shows MAP variations after the craniotomy period (pain) in three subgroups in hypertensive (group H) patients.

Figure 6.6B:

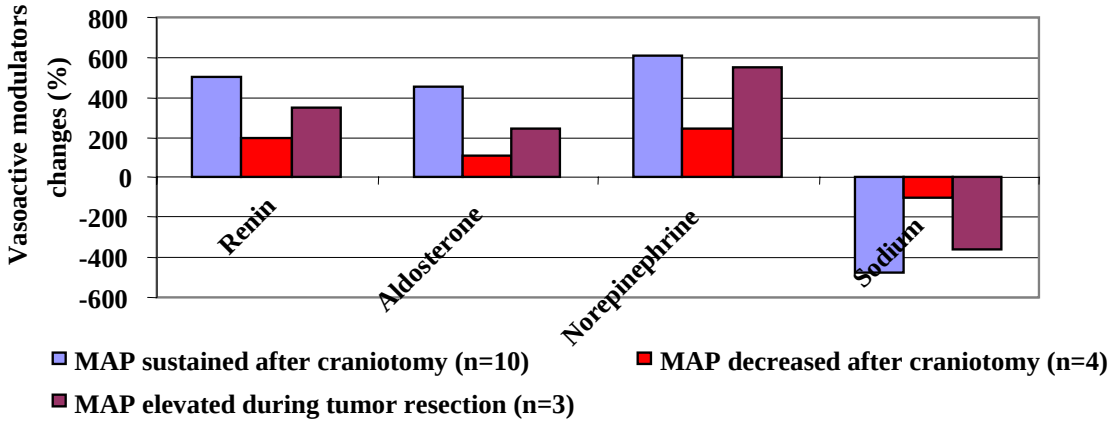


Figure6.6B show the percentage changes in vasoactive modulator levels in three subgroups of the group H patients.

Table.7.1A:

ATENOLOL	Group	Preoperative	Intraoperative	Postoperative
Renin (ng/ml/hr)	N	5.275±3	7.62±6	5.53±3.9
	H	7.8±1.5	8.621±3.5	8.58±9.2
Aldosterone (pg/ml)	N	45.69±36	63.02±39	112.03±135
	H	60.33±45	106.76±50.9	194.05±130.57
Norepinephrine (ng/ml)	N	14.22±6.9	13.9±6.3	13.0±10.3
	H	11.60±3.7	18.03±4.4	36.11±13.4
Sodium (mmol/Lit)	N	141±5.4	131±10	147±6
	H	140±8.5	134±4.4	127±8.6

Table.7.1B:

LISINOPRIL	Group	Preoperative	Intraoperative	Postoperative
Renin (ng/ml/hr)	N	5±3.1	8.1±4.98	10.23±8.1
Aldosterone (pg/ml)	N	64.4±44.6	45.1±38.5	31.9±26.9
Norepinephrine (ng/ml)	N	15.8±4.3	9.68±2.45	5.74±3.3
Sodium (mmol/Lit)	N	137±11.9	135±11	146±13

Table 7.1A showed the vasoactive modulators level after the treatment with atenolol in group N and H patients and **table-7.1B** after the treatment with lisinopril.

Figure.7.1A

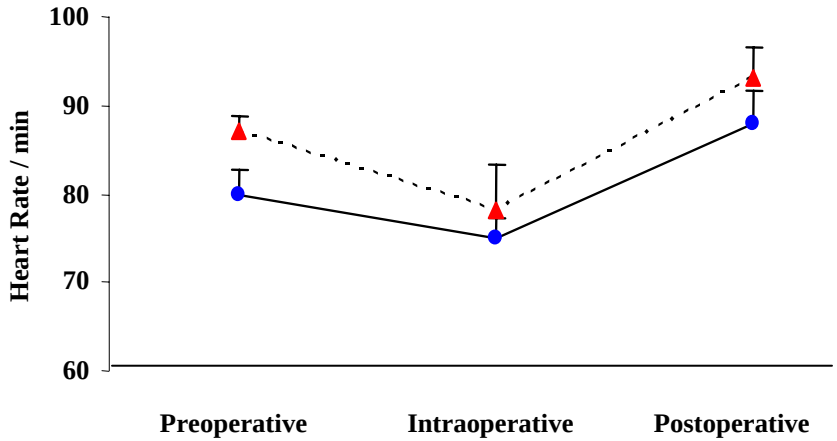


Figure.7.1B:

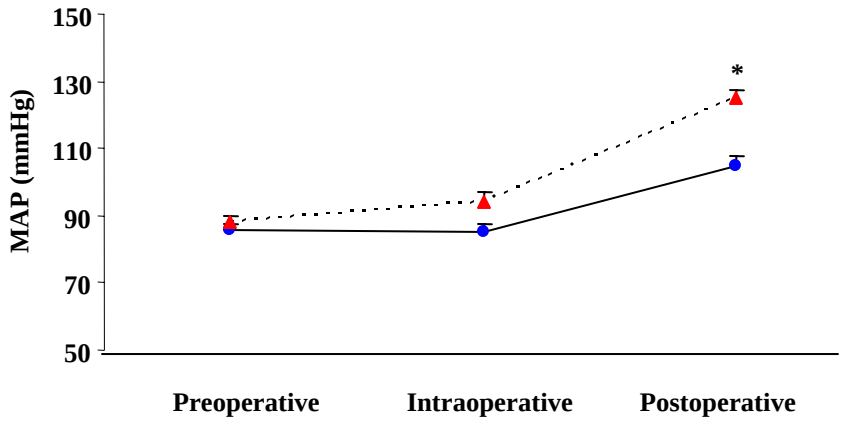


Figure.7.1A shows the heart rate and **Figure.7.1A** MAP between N and H groups in the atenolol administered patients. * = p < 0. 05

Figure 7.1C:

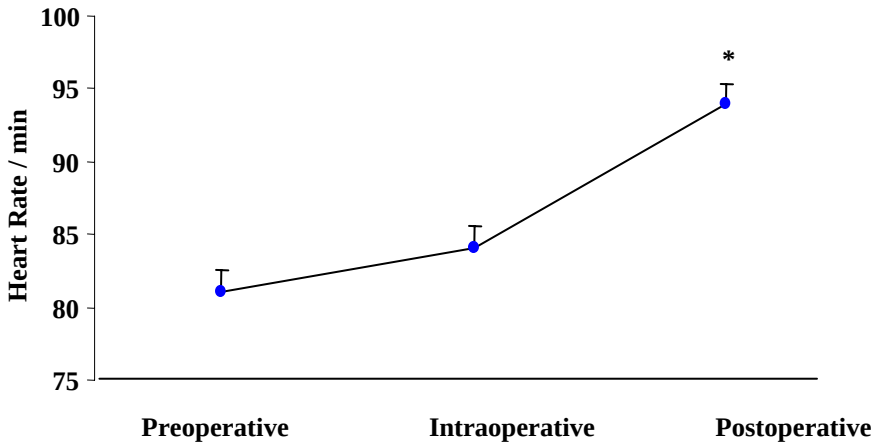
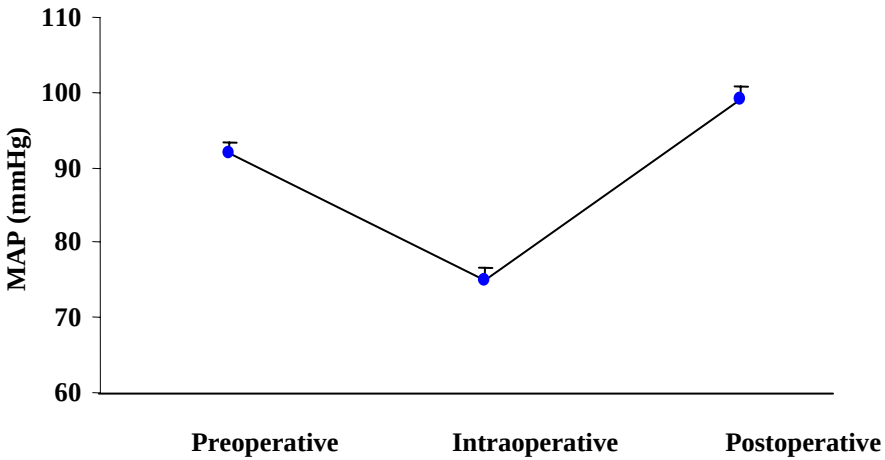


Figure 7.1D:



The above figure shows the heart rate **(Figure.7.1C)** and MAP **(Figure.7.1D)** in the lisinopril administered patients. * = $p<0.05$.

Figure.7.2A:

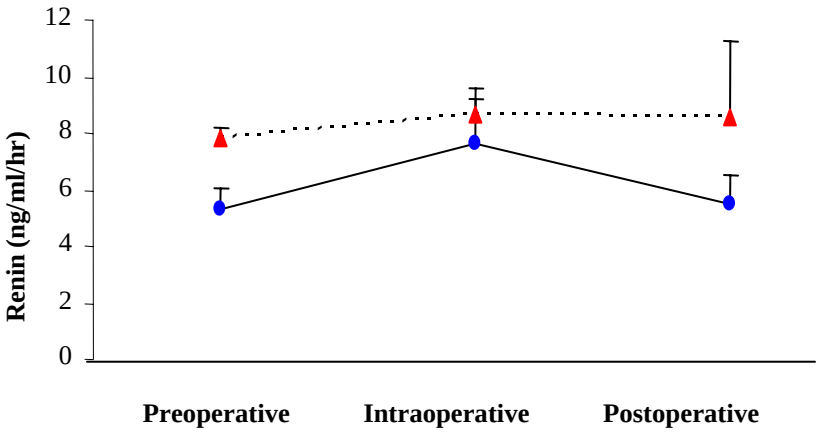


Figure.7.2B:

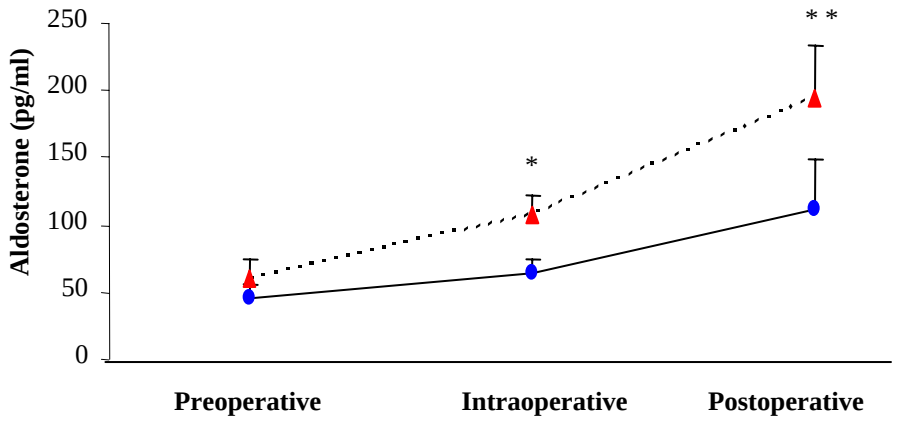


Figure.7.2A shows the renin and **Figure.7.2B** aldosterone levels in atenolol administered patients. * = $p<0.05$, ** = $p<0.01$.

Figure.7.2C:

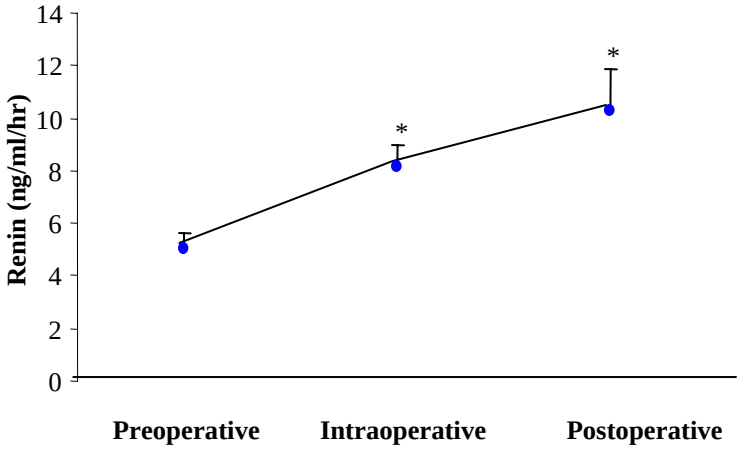


Figure.7.2D:

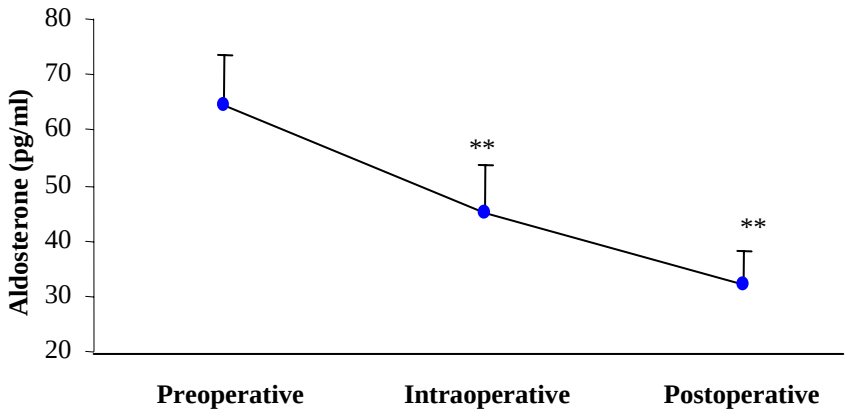


Figure 7.2C shows the renin levels and **Figure 7.2D** aldosterone levels in lisinopril administered patients. * = p<0.05, ** = p <0.01.

Figure.7.3A:

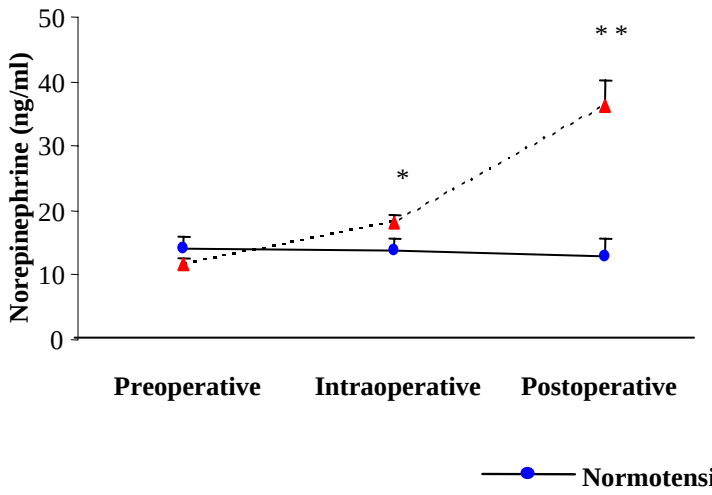


Figure.7.3B:

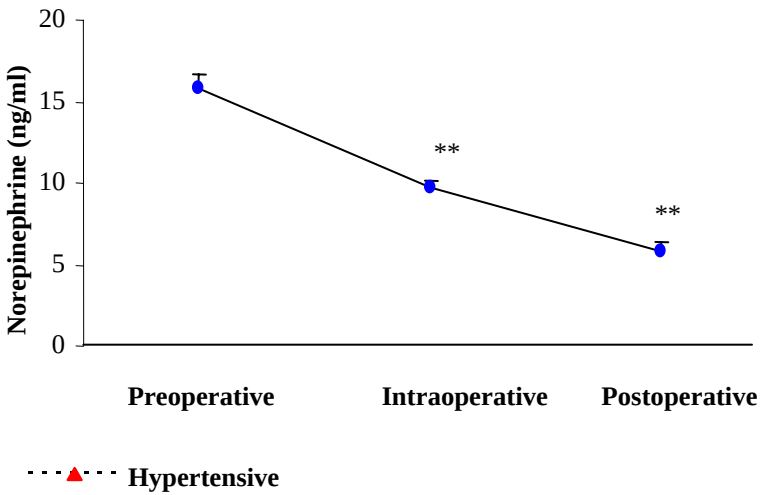


Figure7.3A shows the norepinephrine plasma spill over rate in atenolol administered patients and **Figure.7.3B** showed the blunted effect on norepinephrine after the lisinopril administered patients
* = $p<0.05$, ** = $p<0.01$.

Figure.7.3C:

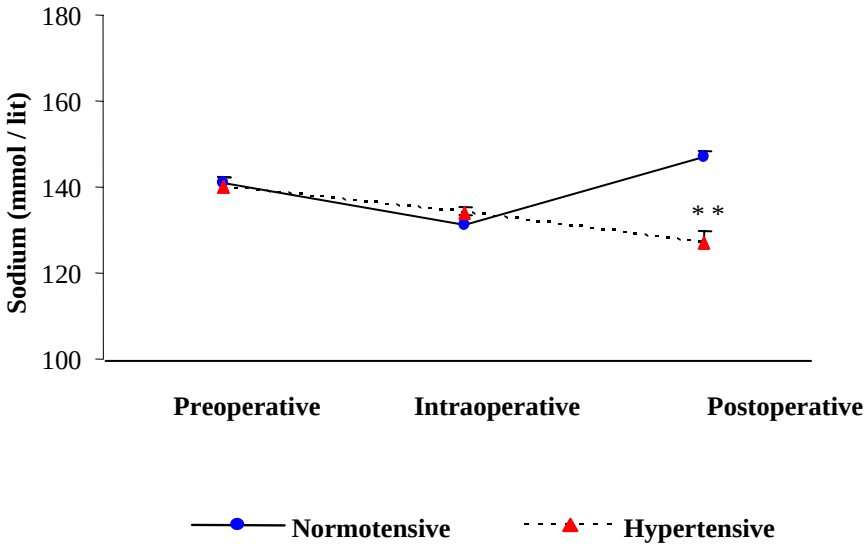


Figure.7.3D:

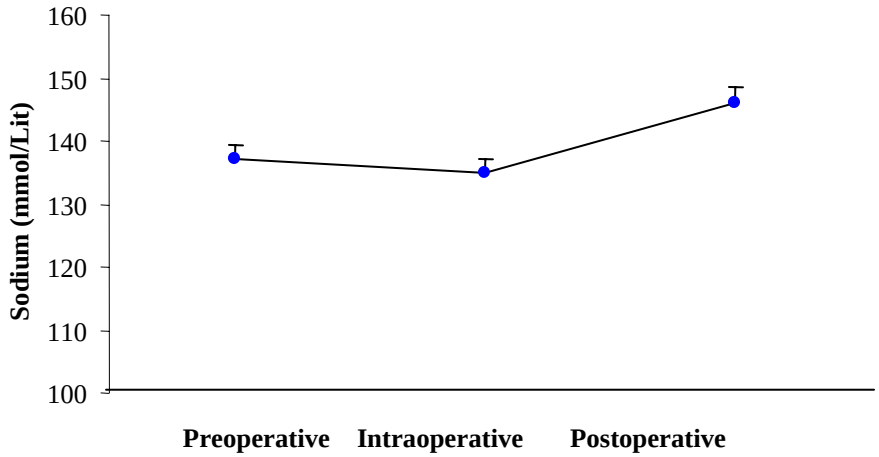


Figure7.3C shows the serum sodium in atenolol administered patients and **Figure.7.3D** showed after the administration of lisinopril to the patients. ** = p <0.01.

Figure.7.4A:

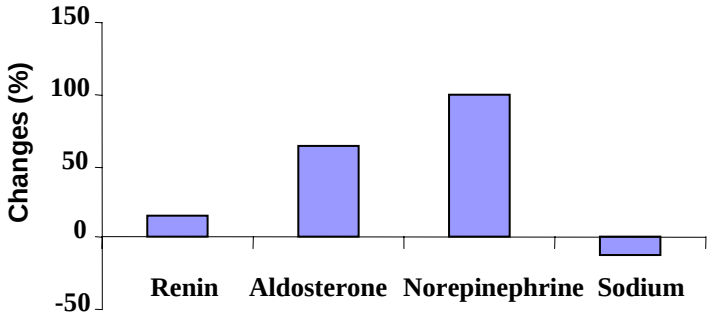


Figure.7.4B:

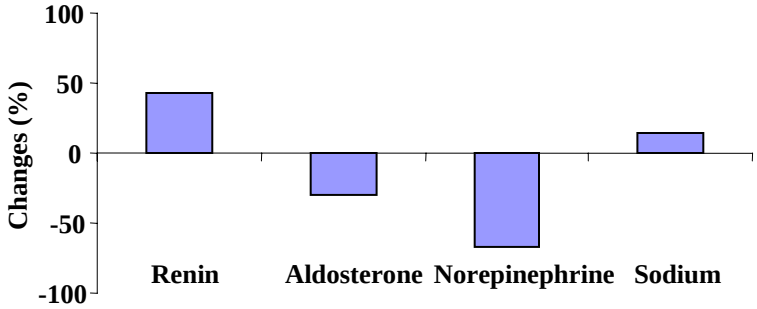


Figure7.4A show the percentage changes in vasoactive modulators level in atenolol administered patients and **Figure.7.3B** show the percentage changes in vasoactive modulators level after the administration of lisinopril to the patients.