ANAESTHETIC REQUIREMENTS IN PATIENTS WITH MEDICALLY REFRACTORY SEIZURES UNDERGOING NEUROSURGERY

Dissertation submitted for the partial fulfilment for the requirement of the degree of

DM Neuroanaesthesia

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DECLARATION

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ABBREVATIONS

ILAE : International League Against Epilepsy

AEDs: Anti-epileptic drugs

DNET: Dysembryoplastic neuroepithelial tumour

IV: Intravenous

GABA : Gamma-Aminobutyric acid

TIVA : Total intravenous anaesthesia

TCI : Target controlled infusion

BET regimen : Bolus elimination transfer regimen

Ce : effect site concentration

LBM : Lean body mass

BIS : Bi-spectral index

TLE : Temporal lobe epilepsy

HS : Hippocampal sclerosis

PI : Principle investigator

TOF : Train of four

ICU : Intensive care unit

SV2A : Synaptic vesicle protein 2A

AMPA : Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid

NMDA : N-methyl-D-aspartate

SLE : Systemic lupus erythematosus

ICP : Intracranial pressure

PONV : Postoperative nausea vomiting

CMRO2 : Cerebral metabolic rate of oxygen

CBF : Cerebral blood flow

CO2 : Carbon dioxide

EEG : Electroencephalogram

EMG : Electromyography

NSOT : Neurosurgical operation theatre

ASA : American society of anaesthesiology

BMI : Body mass index

CTRI : Clinical trials registry of India

NAP5 : 5^{TH} National audit project

MHD : Monohydroxy derivative

PaCO2 : Arterial partial pressure of carbon dioxide

EtCO2 : End tidal carbon dioxide

PEEP : Positive end expiratory pressures

ANOVA : Analysis of variance

MAP : Mean arterial pressure

mmHg : millimetres of mercury

HR : Heart rate

Bpm : Beats per minute

mg/kg/hr : Milligram per kilogram per hour

mg/kg : Milligram per kilogram

mcg/ml : Microgram per millilitre

Kg : Kilogram

% : Percentage

NSOT :Neurosurgery operation theatre

SD : standard deviation

CYP2B6 : Cytochrome P450 2B6

UGT1A9 **:** UDP-glucuronosyltransferase

ANI : Analgesia nociception index

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ABSTRACT

Background: In patients with medically refractory seizures (MRS), on multiple antiepileptic drugs (AEDs), intravenous (IV) anaesthetic agents require modifications in their dosages. However, data on requirement of anaesthetic agents in these patients during neurosurgeries is limited. This prospective observational study investigated the requirement of IV anaesthetic agents for general anaesthesia (GA), in MRS patients on multiple AEDs, undergoing neurosurgeries.

Materials and Methods: 40 ASA grade 1 and 2, MRS patients aged 18-60 years, undergoing elective neurosurgery; were recruited. In all patients GA was induced and maintained with total intravenous anaesthesia (TIVA) using propofol target controlled infusion (TCI). 20 patients on prophylactic levetiracetam were included as control group. Propofol dose required for induction, maintenance effect site concentration (Ce), total propofol required adjusted for the duration of surgery and the emergence parameters were compared between the MRS and control groups (group C). Multivariate analysis was conducted using logistic regression to effect of individual drugs on propofol requirement.

Results: The propofol required for induction in group MRS was significantly lower when compared with that in group C (1. 03 ± 0. 27 vs 1. 21± 0. 25 mg/kg) (p=0. 02). Ce of propofol required for maintenance in group was significantly lower when compared with that in group C MRS (2. 01±0. 38 vs 2. 92 ± 0. 45 mcg/ml) (p<0. 001). The total dose of propofol required in group MRS was significantly lower when compared with that in group C (4. 41 ±1. 07 vs 6. 17± 1. 08 mg/kg/hr) (p<0. 001) and this was more significant in patients on clobazam (4. 23±0. 75 vs 5. 91±0. 99) (p< 0. 001). The recovery from GA was faster in MRS group as compared to group C (p <0. 001). The time to extubation was significantly lower in patients on oxcarbazepine (p = 0. 03) and carbamazepine (p = 0. 03).

Conclusions- Propofol requirement for both induction and maintenance of GA is significantly lower in patients with MRS, on multiple AEDs, when compared with patients on prophylactic levetiracetam. MRS patients on Clobazam have reduced requirement of propofol when compared with patients on other AEDs. Patient's recovery from anaesthesia is significantly faster in MRS group of patients when compared with those on prophylactic levetiracetam.

Key words- Medically refractory seizures, Propofol, Antiepileptic drugs, Target controlled infusion, Anaesthetic requirements, Neurosurgery

INTRODUCTION

The drug resistant epilepsy is defined, by International League Against Epilepsy (ILAE), as a condition when a person has failed to become (and stay) seizure free with adequate trials of two antiepileptic drugs (AEDs); with appropriately chosen AEDs, for the person's seizure type. About 30 to 40% of people with epilepsy have seizures that are not controlled by medication. (1)

In patients with refractory epilepsy who do not respond to AEDs, surgery is one of the important therapeutic avenue; mainly in patients with distinct resectable lesions like glioma, hippocampal sclerosis, focal cortical dysplasia, Dysembryoplastic neuroepithelial tumour, etc. for which administration of general anaesthesia is required. (2)

General anaesthesia (GA) involves administration of multiple intravenous and inhalational anaesthetic agents. The pharmacokinetic and pharmacodynamic interactions between AEDs and commonly used anaesthesia drugs affect the efficacy and potency of anaesthetic agents.

There are multiple mechanisms by which AEDs interact with anaesthetic agents. Commonly used antiepileptics are eliminated via hepatic metabolism. Many of these drugs can be inducers or inhibitors of cytochrome enzymes which result in altered metabolism of anaesthetic agents. Hepatic enzyme inhibition, occurring due to competition at the enzyme site, decreases the rate of metabolism of the affected drug, which is associated with an increased plasma concentration of anaesthetic drugs. (3) (4)

Carbamazepine, phenytoin and phenobarbital, have potent enzyme-inducing properties. This leads to a decreased plasma concentration of anaesthetic agents and increase the dose required to maintain sufficient anaesthetic depth in these patients. Oxcarbazepine and eslicarbazepine are weaker inducers of hepatic microsomal

enzymes compared with carbamazepine, but the effects may be clinically significant. (5) Topiramate also induces hepatic microsomal enzymes in a dose-dependent manner. Valproate is an inhibitor of hepatic microsomal enzyme systems and may reduce the clearance of many concurrently administered medications, including other AEDs and anaesthetic agents, leading to increased plasma concentration of the anaesthetic drugs.

Other mechanism by which these AEDs can affect the action of the anaesthetic agent is by sharing the common site of action. Most of the anaesthetic agents and some of the AEDs act through the Gamma-Aminobutyric acid (GABA) receptor, which is the principle inhibitory transmitter. The reduction in the density of the GABA receptors is one of the cellular mechanisms leading to refractory epilepsy. (6) This loss of GABAergic receptor density is also the likely reason for the relative ineffectiveness of anaesthetic drugs that act on these receptors. Propofol exerts its action mainly via modulation of the GABA (A) receptor and thus the dose required in refractory epilepsy patients may be affected.

Total intravenous anaesthesia (TIVA) is an anaesthetic technique in which a hypnotic agent (propofol) is used in combination with an opioid for anaesthesia induction and maintenance. TIVA is commonly used in neurosurgery because of the fast onset of action, easy titratability and the ability to facilitate intraoperative neurophysiological monitoring techniques. (7)

In modern anaesthesia practice TIVA is commonly administered using target control infusion (TCI). TCI is a computer-controlled syringe driver, that replicates the principles of the BET (Bolus, elimination, transfer) regimen, electronically. It utilizes pharmacokinetic-pharmacodynamic models to continuously adjust the infusion rate to maintain the estimated plasma/effect site concentration and thereby provide a stable anaesthetic level of propofol. Marsh and Schnider are the two models used for

propofol TCI. Schnider's model of TCI is recommended for effect site targeting of propofol infusion. (8) The co-variates required in this model are total body weight, age, height, and lean body mass (LBM) (calculated from total weight, gender, and height).

Neither of these models account for the pharmacokinetic or pharmacodynamic properties of propofol being affected by other drugs used in anaesthesia or concomitant drugs the patients is already on. Of all the concomitant drugs used the AEDs have the maximum potential for affecting the pharmacodynamics of propofol because most of these drugs share the GABAminergic receptors for their action.

It is imperative to study about the requirements of IV anaesthetic agents in these patients so that under and or over dosage of anaesthetic agents can be avoided. The use of reduced anaesthetic doses have been implicated as an important cause for intraoperative awareness, (9) whereas overdosing leads to hemodynamic disturbances, delays awakening and increases the cost of the procedure.

According to pharmacokinetic effects, the dose of propofol required in patients on enzyme inducer AEDs will be higher whereas as the dose of propofol in patients on enzyme inhibiting AEDs will be reduced, when compared with patients who are not on any AED. We hypothesise that, patients with multiple AEDs, receiving combination of these drugs, may show similar results.

Our institute being a tertiary referral hospital for neurology and neurosurgery, caters to a large number of patients with MRS, who are on multiple AEDs, coming for neurosurgery and other diagnostic procedures requiring anaesthesia.

In this observational study, we intend to assess the effect site concentration (Ce) and propofol requirement during GA for neurosurgery in these unique group of patients

with MRS on multiple AEDs, which has not been studied previously to the best of our knowledge.

REVIEW OF LITERATURE

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1. MEDICALLY REFRACTORY SEIZURES

Introduction

Drug resistant epilepsy is defined as "failure of trials of two tolerated, appropriately chosen and used AED schedules, to achieve sustained freedom from seizures. " About 25% of all patients with epilepsy present with drug-resistant epilepsy. (10) MRS is associated with increased morbidity, mortality, psychosocial and cognitive problems, and reduced quality of life (11)

Rational polytherapy is initiated in these group of patients, with the aim of finding AED combinations that increase efficacy (supra-additive effect) and minimise adverse effects (infra-additive effect). Combining AEDs with different mechanisms of action can achieve a broad action spectrum which covers all types of epilepsy syndromes experienced by the patient.

Mechanisms by which general anaesthetic agents and multiple AEDs interact-

The mechanism (s) of refractory epilepsy are multifactorial, and can be genetic, environmental, or disease and drug-related factors. Drug-related factors can be pharmacokinetic or pharmacodynamic. Since anaesthetic agents and AED share a common receptors and common mode of metabolism, the factors that affect the refractoriness of AEDs can also affect the action and metabolism of anaesthetic agents. Important hypothesis and most cited theories of AED resistance are-

1. The pharmacokinetic hypothesis-

   The pharmacokinetic hypothesis proposes that overexpression of efflux transporters is found in the cerebral capillary endothelium of epileptic brain tissues. Efflux transporters are transmembrane molecules that function as active pumps to drive the substrates against the concentration gradient, and thus reduce the accumulation of

substrates within the cell. These pumps are increasingly expressed in cerebral capillary endothelium, astrocytes and neurons, in patients with intractable epilepsy and thus decrease AED levels at the target site.

2. The Pharmacodynamic hypothesis - As anaesthetic agents and AEDs share a common effect site, any mechanism which can modulate the effect site, can affect the anaesthetic agent requirement. There are different mechanisms which explain the pharmacodynamics effects –

a. Neural network hypothesis- which states that seizure induced degeneration and remodelling of the neural network suppress the endogenous anti-seizure system and inhibit AEDs from accessing neuronal targets. The development of abnormal neural networks and eventually AED resistance could be contributed by neurogenesis and astrogliosis in temporal lobe epilepsy.

b. Intrinsic severity hypothesis- The intrinsic severity hypothesis states that common neurobiological factors contribute to both epilepsy severity and pharmacoresistance. Pharmacoresistance is thus inherent to the disease severity, which might exist on a continuum ranging from mild to severe. (12)

c. The gene variant hypothesis-The gene variant hypothesis states that variations in genes associated with AED pharmacokinetics and pharmacodynamics cause inherent pharmacoresistance. Specifically, variations in genes that encode enzymes that metabolize AEDs or ion channels and neurotransmitter receptors targeted by AEDs can potentially affect AED response and there by effect of anaesthetics. (13)

d. The target hypothesis-The target hypothesis of refractory epilepsy postulates that alterations in the properties of AED targets, such as compositional changes in voltage-gated ion channels and neurotransmitter receptors, result in decreased drug sensitivity and thus lead to refractoriness. (14)

Management of medically refractory seizures -

Patients with refractory epilepsy carry a great burden of epilepsy treatment.

With regard to pharmacotherapy, clinical evidence shows that patients who do not respond to two AEDs have only a small chance to control their seizures with any additional administered AED. (15)

Management strategies of refractory epilepsy fall into three main categories (16) :

- Pharmacotherapy
- Epilepsy surgery
- Alternative treatment strategies like –
    - -Neurostimulation
    - -ketogenic diet
    - -lifestyle changes

In patients with refractory epilepsy who do not respond to AEDs, other therapeutic avenues are pursued including surgery. In this regard, patients with refractory epilepsy caused by distinct resectable lesions, such as hippocampal sclerosis (HS), are potential candidates for neurosurgical removal of the lesion. Epilepsy surgery has been shown to be superior to the continued use of AEDs, but the supporting clinical evidence from randomized controlled trials is limited to temporal lobe epilepsy (TLE) (16) .

An alternative treatment approach is neurostimulation such as vagus nerve stimulation and responsive neurostimulation. Vagus nerve stimulation can reduce the frequency and/or severity of seizures.

Other therapeutic options are ketogenic diet, an approach that is more commonly used in children with refractory epilepsy and lifestyle changes.

2. ANTI-EPILEPTIC DRUGS

Classification –

Table 1- Classification of antiepileptic drugs

CATEGORY	TARGET SITE	ANTIEPILEPTIC DRUG
Ion channel modulators (reduce neuronal excitability)	Sodium ion channel Potassium ion channel Calcium ion channel	Carbamazepine Eslicarbazepine Lacosamide Lamotrigine oxcarbazepine Retigabine Ethosuximide Gabapentine pregabaline
Enhancers of GABAergic inhibitory transmission	$GABA_A$ GABA Transporter GABA transaminase	Clobazam Clonazepam Diazepam Phenobarbital Tiagabin vigabatrine
Presynaptic modulators	SV2A	Levetiracitam
Postsynaptic inhibitors of excitatory neurotransmission	AMPA receptor	Perampanel
Multiple mechanisms of action		Felbamate Topiramate Valproate

Clobazam -

Clobazam is a GABA receptor partial agonist which binds allosterically to the GABA receptor to increase the opening frequency of the chloride channel, increasing the permeability to chloride ions. Its oral bioavailability is about 90% with plasma protein binding of 83%. Brain concentrations are proportional to the unbound fraction of the drug.

It is metabolized by oxidation in the liver to nor clobazam (*N* –desmethylclobazam) which has a long half-life (i. e. 50 h), but lower affinity for the benzodiazepine receptor. It has no significant clinical interactions with other AEDs. Development of tolerance is the major clinical problem with clobazam; sedation tolerance is more evident than antiepileptic tolerance.

It is a potent anticonvulsant for partial epilepsy and is also effective in a wide range of epilepsies and is considered as adjunctive therapy. Oral dose is 10-20 mg/d, taken at night or twice daily. No parenteral preparations are available.

Sedation is the most common adverse effects of clobazam. It is known to enhance the anaesthetic effect of propofol and is also an independent predictor of delayed emergence from general anaesthesia. (17) Other adverse effects include dizziness, depression, muscle fatigue, weakness, ataxia, blurred vision and diplopia.

Carbamazepine -

Carbamazepine has a membrane stabilizing effect by changing the ionic conductance to sodium. It is used in the treatment of convulsive and non-convulsive partial epilepsy, trigeminal and glossopharyngeal nerves neuralgia, bipolar disorders and alcohol withdrawal syndrome.

Its side effects are sedation, diplopia, dizziness, neutropenia, nausea, drowsiness, diarrhoea, jaundice, oliguria, hypertension, cardiac arrhythmias, hyponatremia, agranulocytosis, aplastic anaemia, allergic dermatitis, Stevens-Johnson syndrome and systemic lupus erythematosus (SLE). (18) Carbamazepine exacerbates hepatic oxidation and conjugation of other liposoluble drugs and also accelerates its own metabolism. Drugs like cimetidine, propoxyphene, diltiazem, verapamil, erythromycin and isoniazid inhibit the metabolism of carbamazepine and may increase its toxicity.

Carbamazepine has a potent enzyme inducer action, which reduces the plasma concentrations of thiopental, propofol, midazolam, opioids and nondepolarizing neuromuscular blockers. There is risk of hepatotoxicity after anaesthesia with halothane, enflurane, and possibly with sevoflurane. (19)

Oxcarbazepine-

Oxcarbazepine with its active metabolite, monohydroxy derivative (MHD), exert effects on sodium channels and possibly potassium and calcium channels. Neither oxcarbazepine nor its metabolite has an effect at binding sites for GABA or other neurotransmitter receptors. It is generally better tolerated than carbamazepine. The most common adverse effects are sedation, dizziness, headache, amnesia, ataxia, diplopia, depression, insomnia, anxiety and nausea. It do not induce the metabolism of other antiepileptic drugs and shows less pharmacokinetic changes.

Phenytoin-

Phenytoin is effective in the treatment of partial and generalized epilepsies. It has a high therapeutic index. It regulates neuronal excitability and thus the spread of seizure

activity from the seizure focus by blocking voltage dependent sodium channels, possibly in the transport of calcium through the neuronal membrane. Its cell membrane stabilizing effect is selective for the cerebral cortex, but also extends to peripheral nerves. It also has effect on the ion flow. Phenytoin acts on the second messenger systems as calmodulin and cyclic nucleotides.

Side effects of phenytoin include nystagmus, diplopia, dizziness (vestibular cerebellar dysfunction), ataxia, nausea and vomiting, gingival hyperplasia, depression, megaloblastic anaemia, drowsiness, agranulocytosis, aplastic anaemia, hepatotoxicity, pancreatitis, acne, rough skin, allergic dermatitis, Stevens-Johnson syndrome, hyperglycaemia, hirsutism and teratogenicity.

Phenytoin can induce the oxidative metabolism of several liposoluble drugs like as carbamazepine, valproic acid, ethosuximide, anticoagulants and corticosteroids. It also decreases the plasma concentrations of thiopental, propofol, midazolam, opioids and neuromuscular non depolarizing blockers. (19)

Valproic acid-

Valproic acid is a carboxylic acid (2-propylpentanoic acid) effective in all generalized primary epilepsy and other convulsive epilepsies. It is less effective in the treatment of partial non convulsive epilepsy. It is a weak inhibitor of two enzymatic systems that inactivate GABA: the GABA transaminase and succinate semialdehyde dehydrogenase. Some evidence indicates that the drug may potentiate GABA action, postsynaptically. It also works by sustained limiting the neuronal discharge through voltage-dependent sodium channels.

Drug adverse effects include tremors, weight gain, dyspepsia, nausea and vomiting,

anorexia, alopecia, edema, encephalopathy (due to increased levels of ammonia), teratogenicity, agranulocytosis, aplastic anaemia, allergic dermatitis, Stevens-Johnson syndrome, hepatotoxicity, pancreatitis and platelet changes that can lead to abnormal bleeding.

Chronic use of valproic acid, can cause inhibition of liver microsome enzyme and thus can increase the plasma concentration of phenobarbital by approximately 50%. It reduces the dose of propofol required for anaesthesia and lower doses of propofol should be used to induce anaesthesia for patients under valproate treatment. (20)

Levetiracetam-

Levetiracetam is a newer agent used in the treatment of partial seizures as adjunctive or monotherapy. It is generally well tolerated. The mechanism of action of the drug has not been determined, although recent studies show clearly that the drug binds to synaptic vesicle protein 2A (SV2A), related to the release of glutamate in the synaptic vesicle. Common side effects include drowsiness, weakness, dizziness, ataxia, amnesia, depression, anxiety, anorexia, diarrhoea, dyspepsia, skin changes and pancytopenia. It presents little risk of drug interactions. (18)

Thus the AEDs can act by multiple mechanisms and affect the anaesthetic requirements.

3. TOTAL INTRAVENOUS ANAESTHESIA IN NEUROSURGERY

Total Intravenous Anaesthesia uses a combination of agents given exclusively by the IV route. The increasing use of TIVA in neuroanaesthesia is mainly due to following reasons— first, drugs like propofol and opioids (remifentanil) are faster and short acting, and thus provide optimal conditions for maintaining the adequate plane of anaesthesia in neurosurgery. Second, the availability of computer based models of TCI, helps achieve the desired plasma/effect site concentration of the drug easily. Third, propofol in TIVA offers several advantages over inhalational techniques that include a reduction in intracranial pressure (ICP), hemodynamic stability, and reduced incidence of postoperative nausea vomiting (PONV). (21)

Propofol TIVA-

Propofol, an alkylphenol derivative, is used for intravenous induction of sedation and hypnosis during anaesthesia. It facilitates inhibitory neurotransmission by inhibition of presynaptic and postsynaptic chloride channels mediated by GABA. It has a short half-life with a duration of action of 2 to 10 minutes.

It is one of the commonest agents used in neurosurgical anaesthesia because of its properties such as the reduction in cerebral metabolic rate of oxygen (CMRO2), cerebral blood flow (CBF) reduction, maintenance of flow–metabolism coupling, reduction in ICP, inhibition of glutamate release, GABA-A receptor activation, cerebral autoregulation, carbon dioxide (CO2) responsiveness, and neuroprotection. (22) Other properties specific to neurosurgery include shorter and faster acting to facilitate rapid recovery, reduced incidence of PONV, and anticonvulsant action. It

causes the least interference with neurophysiologic monitoring and has better recovery profile as compared to inhalational anaesthetics. (23) However, it lacks analgesic property, so it is frequently administered with other short-acting opioids such as remifentanil or fentanyl.

Propofol has anticonvulsant effect and is considered a safe drug for sedation, induction and maintenance of general anaesthesia in children and adults. Propofol can cause abnormal movements like opisthotonus and myoclonia in both epileptic and healthy patients, though these changes do not seem to relate to epileptogenic activity. (24) Propofol is an effective alternative in the treatment of refractory epileptic seizures to usual antiepileptic drugs and in cases of status epilepticus. (25)

4. TARGET CONTROLLED INFUSIONS-

Target-controlled infusion (TCI) aims to achieve a predetermined drug concentration targeted by the user. This technique has been developed to meet the anaesthetic goals such as smooth induction, reliable and titratable maintenance, and rapid emergence. It is identified as a standard technique to administer IV anaesthetic drugs. The first TCI system “Diprifusor” was made commercially available in 1998 for use with propofol. (26)

TCI pump incorporates a computer based technology where the patient information such as height, weight, age, and gender is entered, and the anaesthetist sets the desired plasma concentration of drug that needs to be attained in a particular tissue or compartment. The computer uses the pharmacokinetic and pharmacodynamic properties of the drug, then it calculates the infusion rate to attain user defined plasma concentration in the specific tissue. TCI pumps display the plasma and effect site concentration of the drug, thereby allowing the anaesthetist to alter the desired drug

concentration, if required, depending upon the stages of surgery.

The fifth National Audit Project (NAP5) reported awareness during anaesthesia when manual infusion of the drugs was used to administer TIVA. (27) The availability of TCI to administer TIVA helps adjust the drug concentration in a desirable user friendly way that enables to maintain adequate and stable depth of anaesthesia. (28)

5. PROPOFOL TARGET CONTROLLED INFUSION MODELS

Propofol (2, 6-diisopropylphenol) is a commonly used hypnotic agent in TIVA due to its desirable pharmacodynamics and pharmacokinetic profile. For the propofol TCI systems the most commonly used pharmacokinetic models are Marsh and Schnider.

The Marsh model-

It has been incorporated into the first commercially available TCI system. It assumes that the central compartment volume is directly proportional to weight.

The Schnider model –

It is incorporated into the 'newer generation' TCI pumps. It is a 3 compartment model for propofol where age, height and weight, gender are entered into the system. The lean body mass of a patient is calculated and this is used to calculate doses and infusion rates. The central compartment is fixed i. e. same for every patient.

One major difference between these models is the size of the central compartment. A fixed central compartment volume used in Schnider's model, is smaller (4. 27L in a 70kg patient) than that used in Marsh model (15. 9L). Because of this difference, the estimated concentrations after a bolus vary markedly. The biggest difference in infusion rates occurs during the first few minutes after an increase in target

concentrations, with time the significance of these differences in infusion rates decreases. (8)

Choice of propofol TCI model is determined mainly by the programming of commercial infusion devices, and the patient's age. Currently, all the models have proved reliable in clinical practice and there is no evidence to support the use of one model in preference to another. They have similar limitations in terms of the accuracy and stability of predicted plasma and effect-site concentrations. Most anaesthetists have experience of using Marsh plasma-targeted infusions and are re-assured when embarking on TIVA that a larger amount of drug is administered in this model, for any given numeric target. Use of Schnider or modified Marsh effect-targeted models occurs as confidence and experience accrue. (29)

When inducing a patient with a plasma targeted TCI using Marsh model, initial target concentration and the dose of drug required are higher when compared to Schinider's model, whereas both the models have comparable doses during maintenance of anaesthesia. (8) So we used Schnider's effect site targeting for induction and maintenance of anaesthesia.

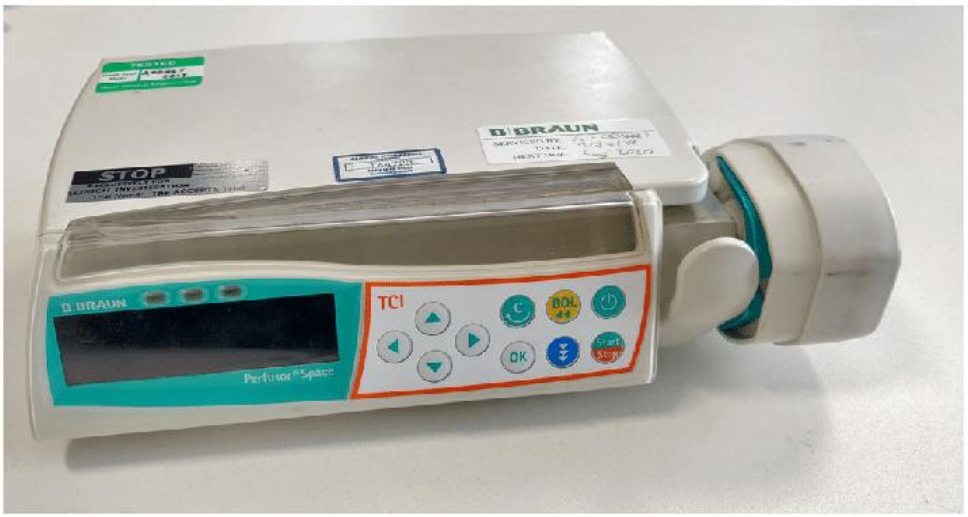

Figure 1 – Target controlled infusion (TCI) pump

6. DEPTH OF ANAESTHESIA MONITORS

Depth of anaesthesia monitoring is essential during TIVA for titration of anaesthetic drugs. It can be used as a guide to titrate the depth of anaesthesia without increasing the risk of intra-operative awareness. Processed electroencephalogram (EEG) is most commonly used for the same. All depth of anaesthesia monitors use processed EEG to obtain a dimensionless digital number which is easier to interpret. Raw EEG information is obtained mostly from the frontal region. The EEG signal is then filtered and amplified, digitised and sent to the device for mathematical processing. The raw EEG is usually divided into time segments/epochs and processed as segments. Of the different depth of anaesthesia monitors bispectral index (BIS) is the most commonly used modality.

BiSpectral Index (BIS)

BIS uses a frontal montage sensor and picks up the raw EEG signals from the frontal region and converts it into a number between 0 (isoelectric EEG) to 100 (fully awake). Its calculation algorithm involves power spectrum, bispectrum, relative activity in the beta frequency range, synchronised fast slow activity and burst suppression activity. Apart from the BIS value it also displays the signal quality index, burst suppression ratio, EEG and EMG (electromyogram). A value between 40 and 60 indicates adequate depth of anaesthesia. (30)

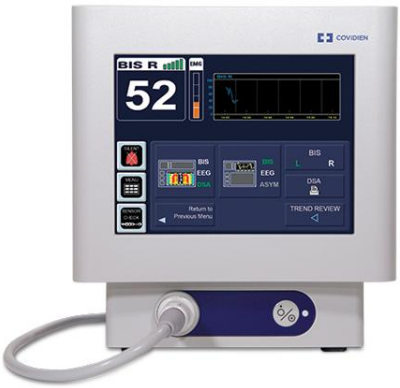

Figure 2- BiSpectral Index (BIS) monitor

7. MONITORING PATIENT DURING TIVA-

Monitoring of the patient during TIVA is done in accordance with the Association of Anaesthetists recommendations for standards of monitoring during anaesthesia and recovery. (31) Use of a processed EEG monitor is recommended when TIVA with neuromuscular blocking drug is used. The large majority of cases of self-reported awareness that were identified in 5thNational Audit Programme (NAP5) occurred in patients who had received a neuromuscular blocking drug. About half of the reports of awareness in NAP5 occurred around the time of induction of anaesthesia and transfer from the anaesthetic room to the operating theatre. Processed EEG monitoring should commence before administration of the neuromuscular blocking drug.

Monitoring of the effect of the anaesthetic drug on the cerebral cortex with a processed EEG (pEEG) monitor can reduce the likelihood of awareness. (32)

Processed EEG monitors provide much more information to the anaesthetist than just a derived index value. For example, the EEG waveform may be displayed together with measures of the EEG signal quality, EMG activity and degree of burst

suppression. Optimal use of a pEEG monitor involves using all the information it provides together with the information from other patient monitors, clinical judgement and experience.

RATIONALE OF THE STUDY

Our institute being a tertiary referral hospital for neurology and neurosurgery, caters to a large number of patients with refractory epilepsy, who are on multiple AEDs, coming for neurosurgery and other diagnostic procedures requiring anaesthesia.

The patients for neurosurgeries require general anaesthesia, which involves administration of multiple IV and inhalational anaesthetic agents. There are important pharmacokinetic and pharmacodynamic interactions between AEDs and drugs commonly used in anaesthesia which affect the drug efficacy and potency of anaesthetic agents.

Literature mentions that, the dose of propofol required in patients on enzyme inducer AEDs is increased whereas, the dose of Propofol in patients on enzyme inhibiting AEDs is reduced, when compared with patients who are not on any AED. We hypothesise that, patients with multiple AEDs, receiving combination of these drugs, may show similar results.

It is imperative to study about the requirements of IV anaesthetic agents in these patients so that under and or over dosage of anaesthetic agents can be avoided. The use of reduced anaesthetic doses have been implicated as an important cause for intraoperative awareness, whereas overdosing leads to hemodynamic disturbances and delays emergence from anaesthesia thereby increasing the cost of the procedure. (9) In our study we used Bi-spectral index (BIS) to monitor the depth of anaesthesia in these patients so that the dose of propofol can be titrated.

We assessed the Propofol requirement for induction and maintenance of anaesthesia in this unique group of patients with MRS on multiple AEDs, which has not been studied previously to the best of our knowledge.

HYPOTHESIS

NULL HYPOTHESIS-

Anaesthetic requirement in patients with medically refractory seizures on multiple AEDs, is comparable with that of patients on prophylactic AED.

ALTERNATIVE HYPOTHESIS-

Anaesthetic requirement in patients with medically refractory seizures on multiple AEDs, is higher than that of patients on prophylactic AED.

AIMS AND OBJECTIVES

Our **primary objectives** are–

1. To evaluate the hypothesis that anaesthetic requirement in patients with MRS on multiple AEDs, is comparable to that of patients on prophylactic AED, irrespective of the type of AEDs.
2. To compare the dose of Propofol required for induction and maintenance of anaesthesia, in patients with MRS on multiple AED regimen to that of patients on prophylactic AED.

Our **secondary objectives** were–

1. To compare the recovery parameters from general anaesthesia in patients with MRS on multiple AED regimen to that of patients on prophylactic AED
2. To compare the effect of different AED regimens on dose of propofol required for induction and effect site concentration of Propofol required for maintenance of anaesthesia, in patients with MRS.
3. To compare intraoperative hemodynamic parameters in patients with MRS to that on patients on prophylactic AED.

MATERIAL AND METHODS

SETTING AND RECRUITMENT OF PATIENTS -

This study was conducted in the neurosurgical operation theatre (NSOT) of Sree Chitra Thirunal Institute of Medical Sciences and Technology, Trivandrum, which is a specialized tertiary referral centre and a university level hospital.

Non-pregnant, non-lactating adult (>=18 years) patients with MRS disorder coming for elective neurosurgery in our hospital were the broad inclusion criteria that were required to be met prior to detailed scrutiny for recruitment. Minor, person incompetent to give informed consent, prisoner, normal/healthy volunteer, student, staff of the institute were not included in the study.

INCLUSION CRITERIA FOR Group- MRS -

1. Consenting adult patients of either sex, with age 18 years to 60 years with MRS disorder coming for elective neurosurgery in NSOT in our hospital
2. Belonging to ASA grade I or II

INCLUSION CRITERIA FOR CONTROL GROUP (Group- C) -

1. Consenting adult patients of either sex, within 18-60 years of age, coming for elective neurosurgery in NSOT in our hospital, on preoperative prophylactic levetiracetam
2. ASA grade 1 or 2 patients

EXCLUSION CRITERIA -

1. Refusal by the patient or patient relatives
2. Patients of age <18 or >60 years
3. Pregnant and nursing mothers

4. Mentally retarded
5. Coronary artery disease
6. Renal dysfunction
7. ASA grade 3 and above
8. Patients on anti-tubercular treatment
9. Hepatic dysfunction
10. Patients with hypoalbuminemia
11. Obese patients with BMI > 30
12. Allergy to anaesthetic drugs

STUDY DESIGN -

Prospective observational study

STUDY PROCEDURE–

After getting approval from the technical advisory committee and institutional ethics committee of SCTIMST and Clinical Trial Registry of India (CTRI/2019/04/018411) the study recruited cases from April 2019.

When a patient meeting broad inclusion criteria was admitted, the principal investigator (PI) was informed by the admitting team. PI explained the study procedures and screened patients for inclusion and exclusion criteria. When the participant was found eligible for inclusion, written informed consent was obtained.

Type of AED and the duration of treatment were noted on the case report form. Patients coming for elective neurosurgery on levetiracetam prophylaxis for more than two weeks were recruited as control group (group C).

Preoperative sedatives or analgesics were avoided in both groups. The morning dose

of AEDs were taken by all patients on the day of surgery.

All ASA standard monitors (IntelliVue MX700, Philips Medizin system, Germany) were connected after patient entered NSOT. Bispectral index (Coviden Ireland Ltd.) was used as the depth of anaesthesia monitor and was monitored using an electrode placed on the opposite side of the incision side. Baseline hemodynamic parameters were noted. Patients were induced with inj. fentanyl 2 mcg/kg (Verve human care laboratories, Delhi) and a bolus dose of inj. propofol (Troikaa pharmaceuticals Ltd. Uttarakhand, India) using TCI Schnider's protocol (B- braun perfusor space, Germany). Schnider, s protocol was initiated by entering patient's age, weight, height and gender. Induction was done by keeping the Ce of propofol as 2. 5 mcg/ml and was then increased by 0. 5 increments till the loss of verbal response and the dose of propofol and Ce attained was noted. Inj. vecuronium (Neon laboratories limited, Palaghar) 0. 1 mg/kg was given for muscle relaxation, and patients were intubated after 3 minutes. BIS was maintained at 40 during intubation. Patients were connected to anaesthesia machine and were ventilated with air and oxygen at the ratio 1:1, with the ventilator settings of tidal volume of 8 ml/kg body weight, respiratory rate targeting end tidal carbon dioxide (EtCO2) of 30 to 35 mmHg (titrated to PaCO2 levels of 35-40 mmHg), and positive end expiratory pressures (PEEP) of 5 mmHg.

The induction Ce was continued and was further titrated by increments or decrements of 0. 2 to target the BIS value of 45-55 throughout the procedure. The Ce was noted at predefined intervals.

Infusion fentanyl at 1 mcg/kg/hr and atracurium (Gland pharma limited, Telangana, India) at 4mcg/kg/min were used as maintenance using an infusion pump (Injectomat Agilia, Fresenius-Kabi India Pvt. Ltd). A bolus fentanyl of 2mcg/kg was

given 2 mins before the patient's head was positioned on a Mayfield clamp. Intraoperatively any increase in heart rate more than 20% from the baseline was taken as an episode of tachycardia and an increase in blood pressure by more than 20% of the baseline was considered as hypertension and was treated initially with bolus of 1mcg/kg of fentanyl.

Intraoperatively, any decrease in blood pressure by more than 20% of the baseline was considered as hypotension and was managed by fluid boluses and mephentermine boluses (Neon) or blood transfusion depending on the cause of hypotension. Any change in BIS, intraoperatively to more than 55 or less than 45 was adjusted with increase or decrease of Ce by 0. 2 respectively.

Post operatively all patients were planned for extubation, unless otherwise indicated by the intraoperative course of events. Fentanyl and atracurium infusions were stopped after the bone flap placement and Propofol infusion was stopped at declamping.

Muscle relaxation was reversed by inj. neostigmine 0. 05mg/kg and inj. glycopyrrolate 0. 008 mg/kg and trachea was extubated when patient obeyed simple verbal commands.

Emergence parameters were noted as time to achieve the following parameters from the time of discontinuation of propofol

1. Spontaneous eye opening
2. Obeying commands
3. Extubation of trachea

Ce at emergence was noted. Total dose of propofol administered adjusted for duration

of surgery was calculated at the end of the surgery using the formula-

Total dose= Propofol (mg) /patient's body weight (kg) /administration time (h).

Postoperatively, on postoperative day one, Brice questionnaire was used to assess intraoperative awareness.

STATISTICAL ANALYSIS

SAMPLE SIZE -

The study needed to recruit 34 subjects to detect with 80% power and at 5% probability of type I error, a clinically significant difference of 0. 2 in the Propofol requirement (Ce effect site concentration) for maintenance of anaesthesia in patients on multiple AEDs assuming a standard deviation of 0. 4. We recruited 43 patients with MRS and 23 non-MRS patients (control) in our study.

STATISTICAL METHODS –

The demographic data was analysed using the Student's T test (continuous variables) or the chi square test (qualitative variables).

For comparing the induction dose, maintenance Ce and emergence parameters, students t-test was used between the two groups.

One way Analysis of variance (ANOVA) with post hoc analysis of multiple comparison Tukey HSD was used to compare between different drug groups in patients having MRS.

To study independent variables affecting the outcome, possible predictive variables i. e. AEDs were selected with stepwise regression, for which the cut off was a P value. 20, it was followed by a multiple regression analysis. A 'p' value of <0. 05 is considered as significant.

For comparing the hemodynamic parameters like heart rate (HR) and mean arterial pressure (MAP) within a group at different time points, repeated measures ANOVA with post hoc analysis and Bonferroni correction was used.

To compare the values of the HR and MAP between the groups at different time points student T test was used.

The software used for statistical analysis was IBM®SPSS statistics (version 26. 0) software.

RESULTS AND OBSERVATIONS

We screened 70 patients fulfilling the inclusion criteria for the study. Of the 66 patients enrolled, 43 patients had MRS (group MRS) and 23 patients were on levetiracetam prophylaxis (group C). Amongst the patients in group MRS, 22 patients were on oxcarbazepine and clobazam combination (oxcarbazepine and clobazam group) and 21 were on mixed combination of drugs (mixed group). Total 60 patients completed the study. Four patients were excluded because of inability to obtain BIS values due to BIS sensor failure and were then maintained with inhalational anaesthesia. Two patients were excluded because the trial for early postoperative extubation could not be given due to intraoperative surgical complications and requirement of postoperative imaging and assessment. The recruitment is detailed in the Strobe diagram as follows

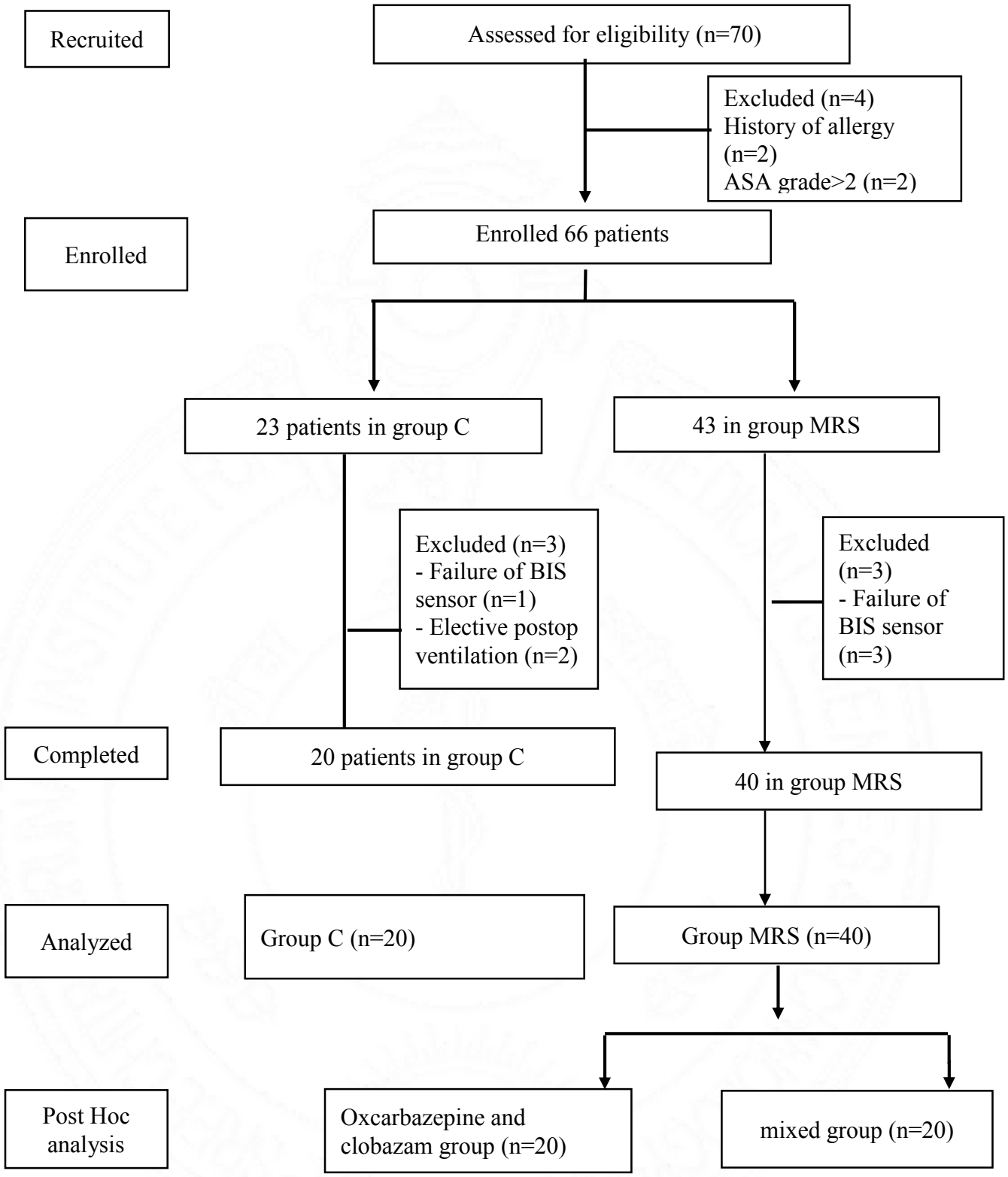

Figure 3 -Strobe Diagram

Demographic data

Table 2 – Table comparing the demographic data between the two groups

Demographic characteristics	Group MRS (n=40)	Group C (n=20)	p
Age (years)	28. 28 (8. 12)	30. 45 (4. 44)	0. 78
Gender [male: female (%)]	24:16 (60:40)	12:80 (60:40)	1. 00
Weight (kg)	65. 75 (10. 30)	64. 45 (11. 30)	0. 65
Height (cm)	163. 15 (8. 01)	164. 70 (9. 87)	0. 51
BMI	24. 51 (2. 75)	23. 54 (2. 44)	0. 18
ASAgrade 1 (%)	38 (95)	19 (95)	1. 00
ASAgrade2 (%)	2 (5)	1 (5)	
Duration of treatment (months)	19. 08 (5. 45)	1. 53 (0. 73)	**<0. 001***
Duration of anaesthesia (hrs)	4. 51 (0. 74)	4. 85 (1. 50)	0. 24

*p value < 0. 05. Data represented as mean (± SD) and numbers (percentages). MRS- medically refractory seizures, BMI- body mass index, ASA- American society of anesthesiologists

There was a significant difference between the duration of treatment with AEDs, among group MRS and group C (p<0. 001).

The mean values of other demographic data were comparable between both the groups. (table 2)

Hemodynamic parameters

Table 3 – Table comparing the mean arterial pressures between the two groups

MAP (mmHg)	Group MRS (n=40)	Group C (n=20)	p
Baseline	109. 5 (9. 07)	110. 3 (6. 1)	0. 72
Induction	104. 4 (10. 4)	106. 5 (11. 5)	0. 47
Intubation	111. 7 (7. 5)	113. 9 (6. 7)	0. 27
Pinning	111. 7 (7. 5)	114. 2 (6. 8)	0. 21
Skin incision	102. 2 (12. 4)	108. 0 (10. 8)	0. 08
Opening of Duramater	106. 3 (13. 1)	111. 1 (14. 2)	0. 19
Closure	106. 4 (12. 3)	108. 7 (14. 3)	0. 52
Extubation	109. 5 (9. 9)	110. 3 (6. 1)	0. 74

Data represented as mean (± SD) MAP- mean arterial pressure, MRS- medically refractory seizures, mmHg- millimetres of mercury

The mean values of MAP at different time points were comparable between both the groups. (Table 3, Figure 4)

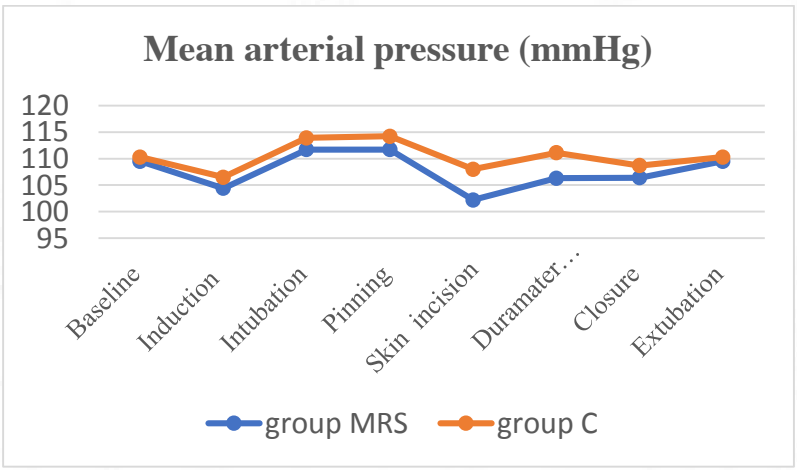

Figure 4- Graph showing comparison of mean arterial pressure at different time points, between the two groups

Table 4– Table comparing the heart rate at different time points between two groups

Heart rate (beats per min)	Group MRS (n=40)	Group C (n=20)	p
Baseline	78. 3 (9. 5)	81. 0 (7. 0)	0. 26
Induction	75. 5 (9. 6)	78. 6 (7. 5)	0. 21
Intubation	80. 8 (8. 6)	84. 1 (7. 2)	0. 14
Pinning	77. 8 (9. 9)	81. 7 (9. 0)	0. 14
Skin incision	75. 4 (8. 6)	79. 3 (7. 7)	0. 09
Opening of Duramater	75. 4 (8. 9)	79. 1 (8. 2)	0. 12
Closure	75. 8 (8. 5)	79. 9 (8. 4)	0. 08
Extubation	82. 0 (8. 7)	85. 8 (7. 2)	0. 09

Data represented as mean ± SD, MRS- medically refractory seizures

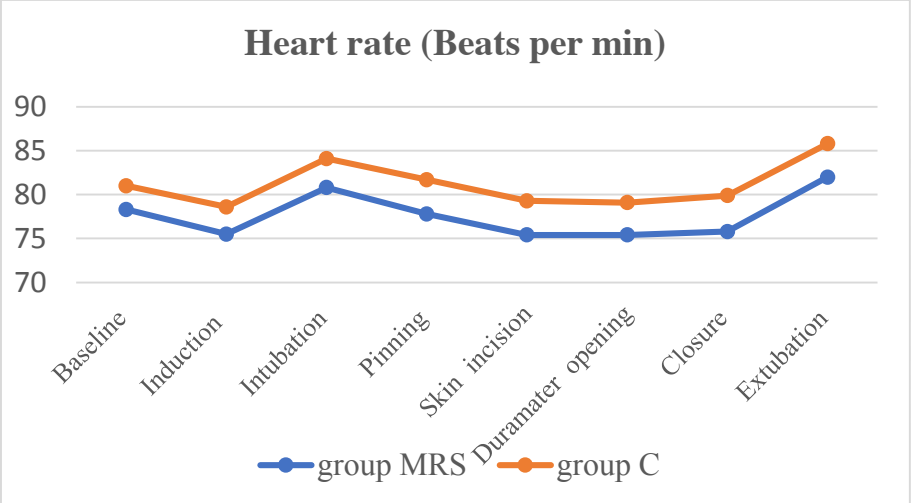

Figure 5- Graph showing comparison of heart rate at different time points, between the groups

The mean values of heart rate at different time points were comparable between both the groups. (Table 4, Figure 5)

Table 5 – Table comparing the BIS values at different time points between two groups

BIS VALUE	Group MRS (n=40)	Group C (n=20)	p
Baseline	97. 1 (1. 25)	97 (1. 4)	0. 78
Induction	47. 2 (1. 98)	47. 55 (2. 1)	0. 52
Intubation	39. 85 (1. 26)	39. 85 (1. 2)	1. 00
Pinning	47. 2 (1. 9)	47. 55 (2. 1)	0. 51
Skin incision	47. 2 (1. 9)	48. 55 (2. 1)	0. 51
Opening of Duramater	47. 20 (1. 9)	48. 55 (2. 0)	0. 51
Closure	48. 65 (2. 3)	47. 55 (2. 1)	0. 07
Extubation	93. 30 (1. 5)	93. 50 (1. 3)	0. 61

Data represented as mean (± SD), MRS- medically refractory seizures, BIS-bispectral index

The mean values of BIS values at different time points were comparable between both the groups. (Table 5, Figure 6)

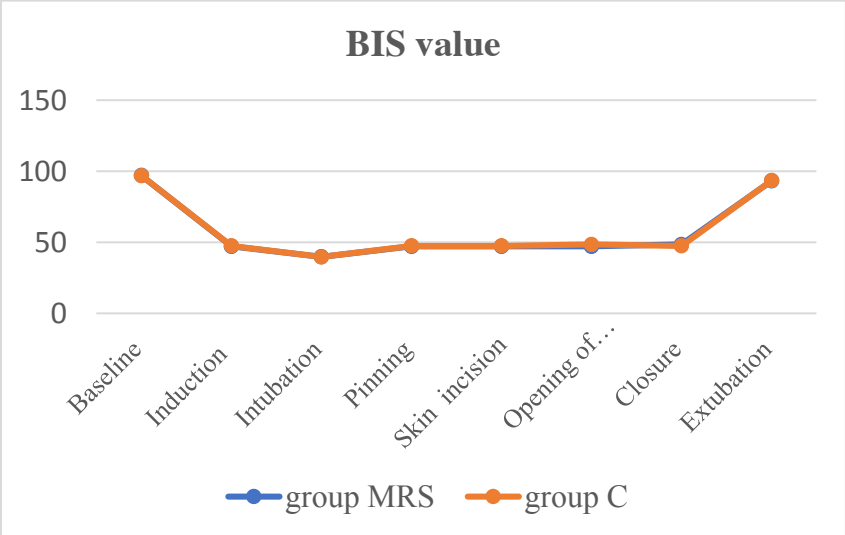

Figure 6- Graph showing comparison of BIS value at different time points, between the groups

Anaesthetic requirements

Table 6 – Table comparing the induction dose of propofol required between the groups

Group	Induction dose of propofol (mg / kg)	p
Group MRS (n=40)	1. 03 (0. 27)	**0. 02***
Group C (n=20)	1. 21 (0. 25)	

* (P<0. 05). Data represented as mean (± SD) MRS-medically refractory seizures

There was a significant difference in the propofol dose required for induction between both the groups. The propofol required for induction ingroup MRS (1. 03 ± 0. 27mg/kg) was significantly lower when compared with that in group C (1. 21± 0. 25 mg/kg) (p=0. 022). (Table 6, fig 7)

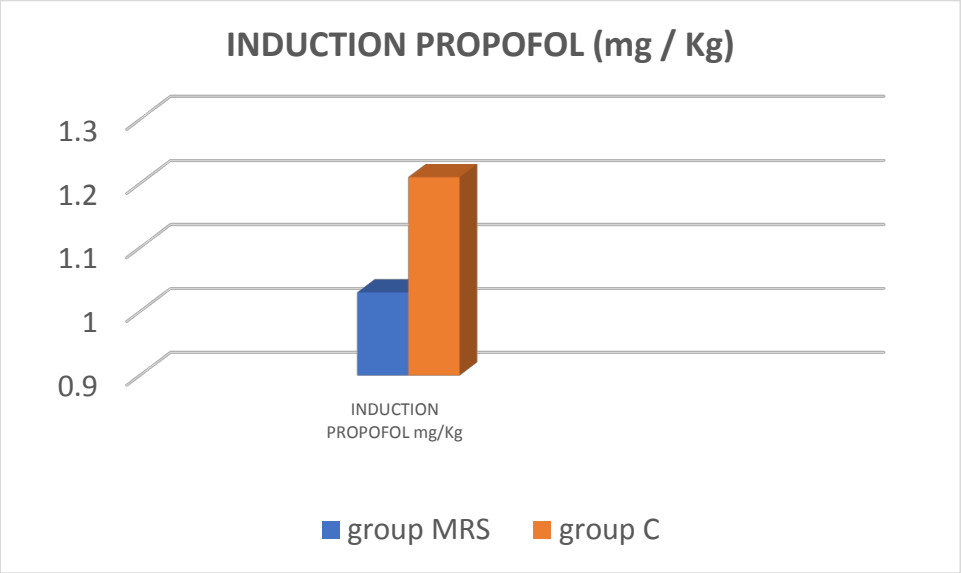

Figure 7- Graph showing comparison of induction dose of propofol required between the groups

Table 7 – Table comparing the maintenance effect site concentration (Ce) of propofol between the two groups

Group	Maintenance Ce (mcg/ml)	p
Group MRS (n=40)	2. 01 (0. 38)	**<0. 001***
Group C (n=20)	2. 92 (0. 45)	

* (P<0. 05). Data represented as mean (± SD) MRS- medically refractory seizures, Ce- effect site concentration

There was a significant difference in the Ce of propofol required for maintenance of anaesthesia between both the groups. Ce of propofol required for maintenance in group MRS (2. 01±0. 38 mcg/ml) was significantly lower when compared with that in group C (2. 92 ± 0. 45 mcg/ml). (Table 7, Figure 8)

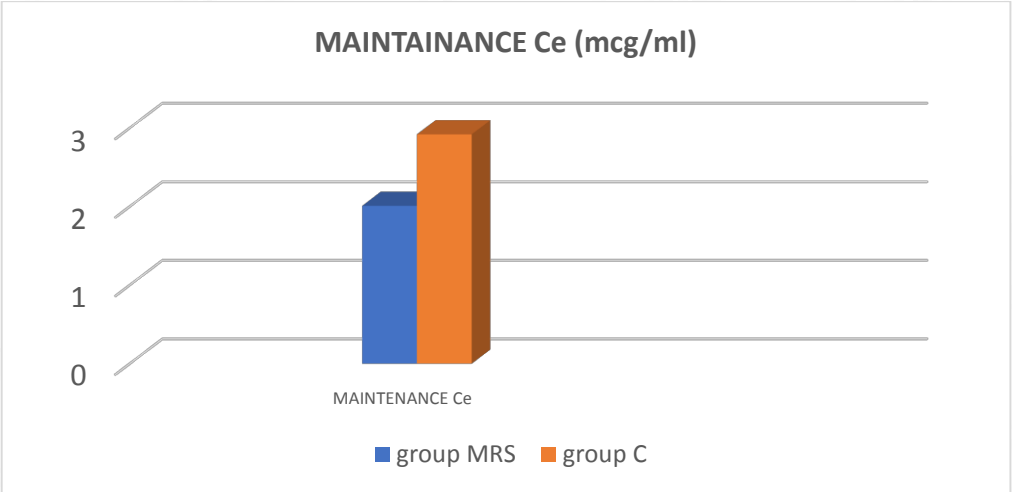

Figure 8- Graph showing comparison of the maintenance Ce of propofol between the two groups

Table 8 – Table comparing the total dose of propofol required between the two groups

Group	Total dose of Propofol required (mg/kg/hr)	p
Group MRS (n=40)	4. 41 (1. 07)	**<0. 001***
Group C (n=20)	6. 17 (1. 08)	

* (P<0. 05). Data represented as mean (± SD), MRS- medically refractory seizures.

There was a significant difference in the total dose of propofol required (adjusted for duration) between both the groups. The total dose of propofol required (adjusted for duration) in group MRS (4. 41 ±1. 07mg/kg/hr) was significantly lower when compared with that in group C (6. 17± 1. 08 mg/kg/hr). (Table 8, fig 9)

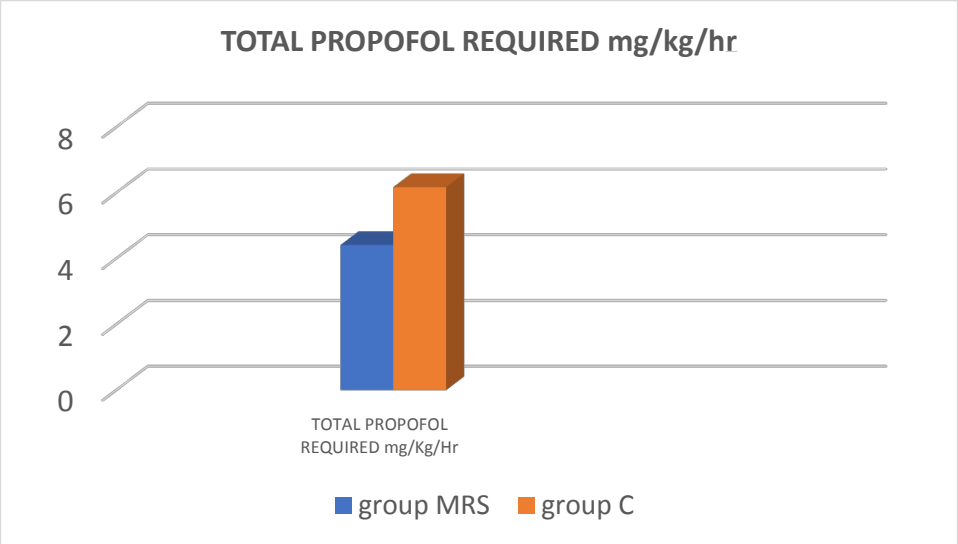

Figure 9- Graph showing comparison of the total dose of propofol required between the two groups

Table 9 – Table comparing the total amount of fentanyl required between the two groups

Group	Total fentanyl required (mcg/kg/hr)	p
Group MRS (n=40)	1. 90 (0. 36)	0. 16
Group C (n=20)	2. 02 (0. 16)	

Data represented as mean (± SD), MRS medically refractory seizures

The total dose of fentanyl required (adjusted for duration) was comparable between both the groups. (Table 9, Figure 10)

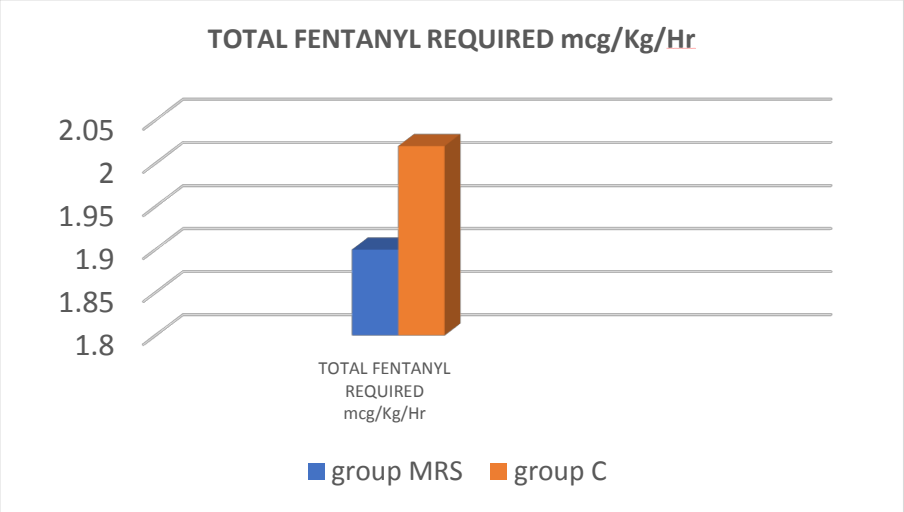

Figure 10- Graph showing comparison of the total dose of Fentanyl required between the two groups

Table 10 – Table comparing the total amount of Atracurium required between the two groups

Group	Total dose of Atracurium required (mg/kg/hr)	p
Group MRS (n=40)	0. 16 (0. 16)	0. 92
Group C (n=20)	0. 15 (0. 05)	

Data represented as mean (± SD), MRS- medically refractory seizures

The total dose of atracurium required (adjusted for duration) was comparable between both the groups. (Table 10, figure 11)

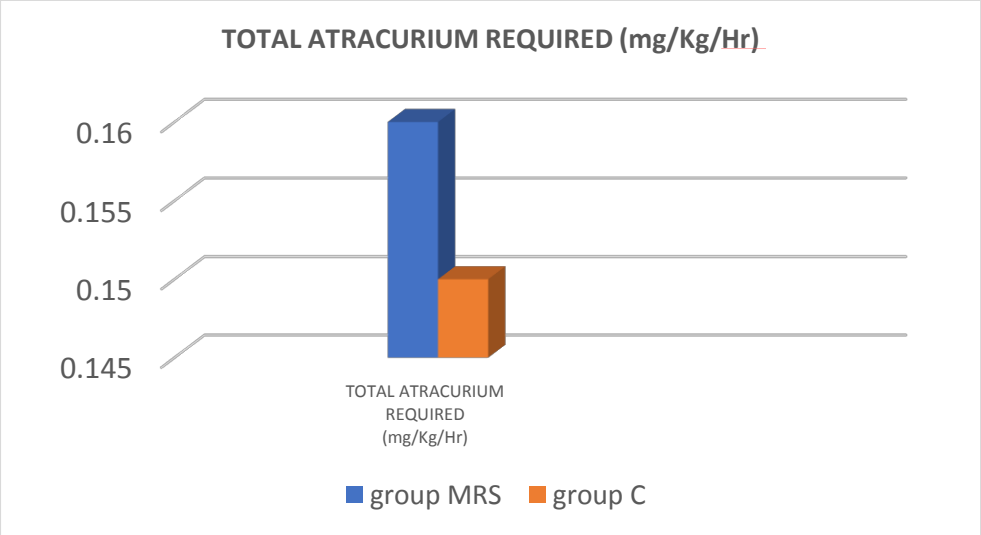

Figure 11- Graph showing comparison of the total dose of Atracurium required between the two groups

Table 11 – Table comparing the recovery parameters between the two groups

TIME (minutes)	Group MRS (n=40)	Group C (n=20)	p
T0	5. 51 (2. 9)	11. 6 (4. 1)	**<0. 001***
T1	6. 15 (3. 10)	12. 4 (4. 12)	**<0. 001***
T2	6. 88 (3. 28)	13. 50 (4. 20)	**<0. 001***

* (P<0. 05). Data represented as mean (± SD), MRS-medically refractory seizures, T0- time taken for eye opening, T1-time taken to obey commands, T2- and time for extubation

There was a significant difference in the recovery parameters between both the groups. The mean time taken for eye opening (T0), time taken to obey commands (T1) and time for extubation (T2), in MRS group was significantly lower than the corresponding recovery time in C group (p <0. 001). (Table 11, Figure 12)

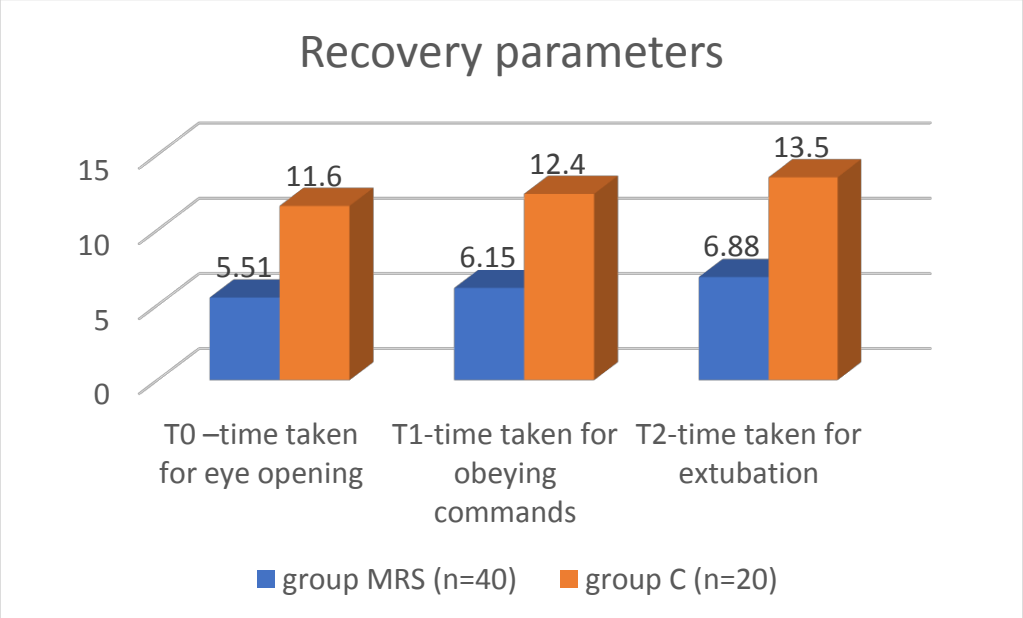

Figure 12- Graph showing comparison of recovery parameters between the two groups

Table 12- Table showing number of patients receiving each kind of antiepileptic drugs

AEDs	Number of patients (n=60)
Oxcarbazepine	24 (40%)
Clobazam	34 (56. 6%)
Carbamazepine	11 (18. 3%)
Levetiracetam	30 (50%)
Valproate	4 (6%)
Lacosamide	3 (5%)
Phenytoin	2 (3. 3%)
Lamotrigine	2 (3. 3%)

Data represented as numbers (percentage), AEDs-anti epileptic drugs

We performed a post hoc analysis of the requirement of Propofol in the patients with different drug regime within the group MRS.

Table 13 – Table comparing the total amount of propofol required between the MRS patients with clobazam and MRS patients without clobazam

Within the group MRS	Total dose of Propofol required mg/kg/hr	p
Clobazam (n=34)	4. 23 (0. 75)	**0. 001***
Non clobazam (n=06)	5. 91 (0. 99)	

Data represented as mean (± SD), MRS- medically refractory seizures* (P<0. 05).

On univariate analysis, within the group of patients with MRS, patients on clobazam (4. 23±0. 75mg/kg/hr) were found to have significantly lower total propofol requirement (adjusted for duration), when compared with the MRS patients not on clobazam (5. 91±0. 99mg/kg/hr) p= 0. 001. (Table 13, Figure 13)

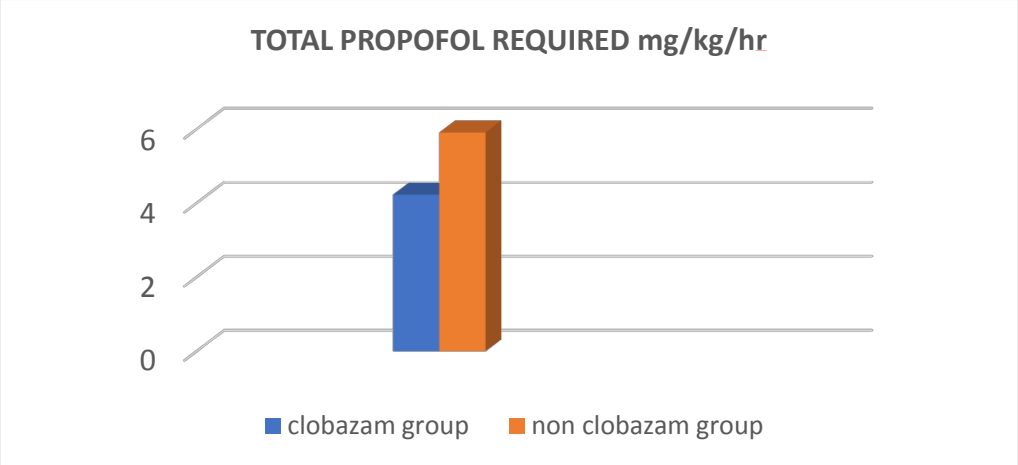

Figure 13- Graph showing comparison of the total dose of propofol required between the MRS patients with clobazam and MRS patients without clobazam

We did a stepwise logistic regression model to find the effect of individual AED on the Propofol requirement.

Table 14 – Stepwise Logistic Regression Model for dose of propofol required for induction (mg/kg) for different AEDs

INDUCTION PROPOFOL (mg /kg)					
AED	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	P value
(Constant)	1. 162	. 131		8. 837	. 00
Levietiracetam (n=30)	. 032	. 118	. 058	. 271	. 78
Oxcarbazepine (n=24)	-. 028	. 111	-. 050	-. 250	. 80
Clobazam (n=34)	-. 075	. 114	-. 136	-. 660	. 51
Carbamazepine (n=11)	-. 106	. 133	-. 149	-. 797	. 42
Valproate (n=4)	-. 193	. 145	-. 175	-1. 327	. 19

AED- antiepileptic drugs

The dose of propofol required for induction of anaesthesia, was not significantly different between patients for any given specific antiepileptic agent. (Table 14)

Table15 – Stepwise Logistic Regression Model for maintenance Ce of propofol for different AEDs

Maintenance Ce (mcg/ml)					
AEDs	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	P value
(Constant)	2. 687	. 213		12. 593	. 00
levetiracetam	. 120	. 192	. 103	. 626	. 53
oxcarbazepine	-. 310	. 181	-. 260	-1. 711	. 09
clobazam	-. 495	. 185	-. 421	-2. 671	**. 01***
carbamazepine	-. 230	. 216	-. 153	-1. 064	. 29
valproate	. 136	. 235	. 058	. 578	. 56

* (P<0. 05). Ce-effect site concentration, AEDs- antiepileptic drugs

The effect site concentration of Propofol required for maintenance was significantly lower in patients on clobazam when compared to other AEDs (**p=0. 01**) (Table 15)

Table 16– Stepwise Logistic Regression Model for total propofol required (mg/kg/hr) for different AEDs

Total Propofol mg/kg/hr					
AEDs	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
(Constant)	5. 542	. 459		12. 077	. 00
levetiracetam	. 529	. 412	. 197	1. 285	. 20
oxcarbazepine	. 446	. 389	. 163	1. 146	. 25
clobazam	-1. 854	. 399	-. 684	-4. 651	**<. 001***
carbamazepine	. 269	. 464	. 077	. 579	. 56
valproate	. 194	. 506	. 036	. 384	. 70

* (P<0. 05). Ce-effect site concentration, AEDs- antiepileptic drugs

In patients who received Clobazam, total Propofol required (mg/kg/hr) was significantly lower than in patients not on clobazam (**p<0. 001**). Total propofol required was not significantly different between patients given a specific antiepileptic agent and those not given the agent for all other AEDs. (Table 16)

Table 17– Stepwise Logistic Regression Model for time to extubation for different AEDs

TIME TO EXTUBATION (minutes)					
AEDs	Unstandardized Coefficients		Standardized Coefficients	t	P value
	B	Std. Error	Beta		
(Constant)	13. 910	1. 947		7. 146	. 00
levetiracetam	-1. 320	1. 747	-. 140	-. 756	. 45
oxcarbazepine	-3. 558	1. 650	-. 369	-2. 156	**. 03***
clobazam	-3. 376	1. 691	-. 354	-1. 997	. 05
carbamazepine	-4. 210	1. 968	-. 345	-2. 139	**. 03***
valproate	-. 880	2. 148	-. 046	-. 410	. 68

* (P<0. 05). AEDs- antiepileptic drugs

The time to extubation after general anaesthesia was significantly lower in patients on oxcarbazepine (**p = 0. 03**) and carbamazepine (**p = 0. 03**). (Table 17)

DISCUSSION

Patients with MRS on multiple AEDs may require surgeries under general anaesthesia which involves administration of multiple IV and inhalational anaesthetic agents. Presence of MRS and multiple AEDs can have complex pharmacokinetic and pharmacodynamic implications that require modifications in dosage of anaesthetic agents, to avoid side effects of either inadequate or very deep plane of anaesthesia.

Presently, there are few reports on the propofol requirement for sedation, and induction of anaesthesia in patients on AEDs, but we found no study assessing the propofol requirement for induction and maintenance of GA and assessing the emergence from GA in patients with MRS on multiple drug combinations coming for neurosurgery.

In our study we found that both the induction and maintenance dose of propofol is reduced in MRS group when compared with group C (control) patients, on levetiracetam. We used patients on levetiracetam as our control group, as the patients coming for neurosurgery in our institute were started on short term prophylactic levetiracetam. Also levetiracetam is known to have least potential for interaction with other AEDs and anaesthetic agents. (33)

Choi et al studied 19 epilepsy patients receiving long-term AED therapy and 20 non-epilepsy patients, to determine Ce of propofol required for achieving loss of consciousness. They found lower requirement of propofol for induction, by about by 10% to 15%, in epilepsy patients compared to non-epilepsy patients, (34) which was similar to our results.

The requirement of propofol dose for induction of anaesthesia, for electroconvulsive therapy, was found to be less in patients on valproate in a study by Hizli Sayar et al.

(20) Valproate is reported to inhibit cytochrome P450 2C9 which has a role in the metabolism of propofol, which might lead to reduced requirement of propofol in these patients. In our study we did not find any statistically significant reduction in propofol requirement, for induction or maintenance of GA, between patients with or without valproate. Our study had only 4 patients on valproate and hence was underpowered to estimate the effect of valproate, which might have affected our results.

In our study we also found that the maintenance Ce for propofol and the total dose of propofol required (adjusted for the duration of anaesthesia) during the surgery was significantly lower in MRS patients as compared to group C patients. Amongst the different AEDs, clobazam was found to be associated with maximum and significant reduction in maintenance Ce, as compared to other AEDs. The Ce for maintenance in MRS was lower than that in the Indian population undergoing general anaesthesia (2. 37±0. 35 mcg/ml). (35) In our search for literature, we did not find any study which primarily assessed the maintenance Ce of propofol required in MRS patients.

Maeda et al, in their retrospective cohort study, evaluated the variables that could affect the emergence from anaesthesia in MRS patients. Along with the primary findings, they also found that propofol rate was significantly decreased in patients taking clobazam and clonazepam as one of the AEDs. (17) In our study we found similar results.

We also evaluated the effect of individual AED, on the propofol requirement. We found that the total dose of propofol required (adjusted to duration of anaesthesia) was significantly lower in patients on clobazam when compared with the patients who did not have clobazam in their AED regimen. This result can be explained by the fact that daily medication with benzodiazepine enhances the clinical pharmacological effect

of propofol, as its mechanism is mainly mediated via activation of GABA, (36) which is the same mechanism of action for benzodiazepine. (37)

In our study we found that the emergence parameters like time taken for spontaneous eye opening, time taken to follow verbal commands and time to extubation, were significantly lower in MRS group when compared with group C patients. We have used BIS and TCI to titrate the dosage of propofol. We also evaluated the effect of individual AEDs on the emergence parameters and found that long term treatment with oxcarbazepine and carbamazepine were independent factors associated with early recovery and extubation. We also found that use of clobazam showed a trend towards early recovery when compared with other AEDs, though the results were not statistically significant.

Ouchi et al studied 224 patients with a neurological disorder, with or without an antiepileptic, who underwent dental treatment under intravenous general anaesthesia. They found that the time to emerge from anaesthesia in patients on antiepileptic was significantly longer than in patients not on any antiepileptic. (38) They found that despite a lower propofol rate, clobazam was still an independent predictor of delayed emergence. This could be explained by the fact that clobazam enhances the anaesthetic effect of propofol. In our study, we found a trend towards early emergence, though not statistically significant, among the patients on clobazam. This can be explained by the fact that, majority of our patients had clobazam as a combination drug with oxcarbazepine and carbamazepine, which have shown statistically significant early recovery among the MRS group patients. These drugs might have influenced the results and emergence for clobazam.

In our study, we relied on BIS, which would denote the degree of anaesthetic depth, to obtain the lower set dosage in TCI. This close titration would have contributed to the reduced time of emergence, as seen in our study. The duration of anaesthesia was comparable in both the groups, so this can be attributed to the finding that the total dose of propofol required in MRS group was much lower as compared to group C. The Ce for maintenance in group C was higher than that in the Indian population undergoing general anaesthesia (2. 37 ±0. 35 mcg/ml). (35) Higher total propofol dose can explain longer emergence time. (39) Though levetiracetam is not known to have serious drug interactions it is known to cause somnolence and drowsiness, (40) which might have contributed to the delay in emergence seen in these patients. As such, the effect of levetiracetam on emergence from anaesthesia has not been studied.

The statistical difference and comparatively lower dose of propofol required for induction and maintenance of GA in MRS group can be explained by several mechanisms. Patients with medically refractory seizures may show enhanced response to propofol due to reduced neuronal mass pertaining to their long duration disease state. In an experimental study on a pilocarpine model of temporal lobe epilepsy, the authors have found an enhanced response to general anaesthetic agents due to neuronal loss (41) . However it is not possible to study the effect of MRS alone on human beings, on multiple AEDs, as the results can be confounded by the effect of AEDs.

Another possible mechanism is that AEDs such as carbamazepine, phenytoin, zonisamide, phenobarbital, and valproate contribute to the competitive inhibition of hepatic CYP2B6 and CYP2C9, are responsible for propofol metabolism. Valproate inhibits CYP2C9 in vitro (42) . Also, phenytoin, phenobarbital, and valproate inhibit

UGT 1A9 in vitro, which thus affects the main metabolic pathway of propofol, reducing propofol metabolism and hence also the requirement of its maintenance dose. (43) In our study, patients in group MRS had all these AEDs in one or the other combinations, which would explain our findings.

Also AEDs may synergistically or additively affect propofol Ce for loss of consciousness because the AEDs and propofol share the target sites. Valproate and carbamazepine or phenobarbital are also known to have synergistic activity. (44) (45)

The requirement of fentanyl during anaesthesia, in patients on long duration AEDs is known to be higher than other patients. (33) In our study we did not find the statistically significant difference between fentanyl requirement between group MRS and group C. Though we did not use any objective analgesia monitor like Analgesia nociception index (ANI), we kept a strict vigilance for monitoring intraoperative pain, using hemodynamic parameters and BIS.

The BIS values at all the time points were comparable between both the groups in our study. Also none of our patients had any awareness intraoperatively which was evaluated by the modified Brice questionnaire.

STRENGTHS OF OUR STUDY

1. Our study is a first of its kind to detect effect of MRS on multiple AEDS, undergoing GA for neurosurgery, on anaesthetic requirement for induction, maintenance and on recovery parameters.

2. Our study was conducted on a homogenous adult population, without mental retardation, other cognitive disorders or comorbid conditions, which are known to alter the anaesthetic requirements and which if present, could have been a confounding factor by influencing the results of the study.

3. We used BIS along with Propofol TIVA using TCI, which facilitated better titration of depth of anaesthesia and ensured hemodynamic stability.

LIMITATIONS

1. Our patients were on multiple AEDs and we did not measure the plasma site concentrations of individual AEDs, and hence the effect of pharmacokinetic interactions between AEDs and propofol could not be assessed. However, many of the patients were on drugs whose blood levels cannot be assessed with the current facilities.
2. The study sample of MRS patients was heterogeneous in terms of AEDs, with different combinations, thus the effect of individual drug or combination on propofol requirement could not be assessed. However our study intended to evaluate the effect of MRS on anaesthetic requirements, and it was inevitable that these patients will be on multiple AEDs and hence it cannot be standardised.

3. Our study sample had very few patients on AEDs like valproate or newer generation AEDs, and hence it was underpowered to detect the effect of these individual drugs on the propofol requirement in patients with MRS. Since valproate alter the coagulation profile, it was not preferred by our neurosurgeons.

4. Our study had control group with prophylactic levetiracetam as our patients presented for neurosurgery and were started on short term prophylactic levetiracetam. However, levetiracetam is not known to cause clinically significant interactions with anaesthetic drugs and hence our results might not have been influenced by its presence in control group.

5. The study was done only in 40 MRS patients with limited drug combinations. A larger sample size or multicentric trials are required to estimate the effect of individual newer AEDs on propofol requirements and to better understand its clinical applications.

6. We did not use any objective analgesia monitor like ANI, however we kept a strict vigilance for monitoring intraoperative pain, using hemodynamic parameters and BIS.

CONCLUSIONS

In patients with refractory epilepsy, IV and inhalational anaesthetic agents require modifications in their dosages to avoid side effects of either inadequate or very deep plane of anaesthesia. In our study we compared and analysed the requirements of propofol in MRS patients and those on prophylactic levetiracetam. We conclude that,

1. Propofol requirement for both induction and maintenance of general anaesthesia is significantly lower in patients with MRS, on multiple AEDs, when compared with patients on prophylactic levetiracetam.
2. MRS patients on Clobazam have reduced requirement of propofol when compared with patients on other AEDs.
3. Patient's recovery from anaesthesia is significantly faster in MRS group of patients when compared with those on prophylactic levetiracetam.

Further studies with larger sample size of patients might be helpful in determining the role of individual antiepileptic agents in requirement of propofol in MRS group of patients.

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ANNEXURES

ANNEXURE 1

PROFORMA

Age-			Sex-
Weight-			Height-
Diagnosis-			BMI-
Surgery planned-			Known allergies-
Comorbid illness-			Baseline-
ASA grade-			Heart rate- Blood pressure-
Anti-epileptic medications-			
Duration of treatment-			

	yes	no
Informed consent		
Coronary artery disease		
Renal dysfunction		
Hepatic dysfunction		
Alcohol use (if yes specify duration)		
Allergy to anaesthetic agents		
Hypertension (duration)		
Patient on anti-tubercular treatment		
Pregnant or lactating mother		

TIME OF INDUCTION-
INDUCTION DRUGS-

DRUGS	DOSE (per Kg)	TOTAL DOSE
Inj. Fentanyl (mcg) -		
Inj. Vecuronium (mg) -		

SURGERY STARTING TIME-

Preoperative and intraoperative hemodynamic and other parameter-

TIME	Heart rate	BP SBP/DBP (MAP)	PROPOFOL Infusion rate ml/hr	Ce (effect site concentration)	Fentanyl	Atracurium	TOF ratio	BIS	Bolus drugs
Induction									
Intubation									
pinning									
Skin incision									
Opening of duramater									
Closure -									
. Duramater									
. bone									
. Subcutaneous layer									
. skin									
Declamping									
Extubation									

DURATION OF SURGERY-

RECOVERY CHARACHTERISTICS-

Events	Ce (effect site concentration)	BIS	TOF Ratio	Time (minutes)
Discontinuation of Fentanyl/ Atracurium				(T'0)
Discontinuation of TCI				(T0)
Time of emergence				
Spontaneous movement of limbs				
extubation				

INTRAOPERATIVE ADMINISTRATION OF FLUID AND BLOOD-

Total I. V. fluids used (in ml)	
Blood loss (ml)	
Blood transfused (ml)	
Urine output	

INTRAOPERATIVE ADMINISTRATION OF DRUGS-

DRUGS	TOTAL DOSE	Dose administered Drug/kg/hr
Propofol		
Fentanyl		
Atracurium		
Anti-epileptic drugs		
Mephentermine		

ANNEXURE 2

MODIFIED BRICE QUESTIONNAIRE

Were you expecting to be completely asleep for this operation (please circle) ? YES / NO

1. What is the last thing you remember before going to sleep (please tick one box) ?

-Being in the pre-op area ☐ -Being with family ☐ -Feeling mask on face ☐ -Burning or stinging in the IV line ☐

-Seeing the operating room ☐ -Hearing voices ☐ -Smell of gas ☐ -Other [Please write below]:

2. What is the first thing you remember after waking up (please tick one box) ?

-Hearing voices -Feeling mask on face -Seeing the operating room -Being with family -Nothing

☐ -Feeling breathing tube ☐☐ -Feeling pain ☐☐ -Being in the recovery room ☐☐ -Being in ICU ☐☐ -Other [Please write below]:

3. Do you remember anything between going to sleep and waking up (please tick box) ? -No ☐

-Yes: -Hearing voices ☐ -Unable to move or breathe ☐ -Feeling pain ☐ -Feeling surgery without pain ☐

-Hearing events of the surgery ☐ -Anxiety/stress ☐ -Sensation of

breathing tube ☐ -Other [Please write below]

4. Did you dream during your procedure (please tick box) ?

-No☐ -Yes☐ -What about [Please write below]:

5. Were your dreams disturbing to you (please tick box) ?

-No☐ -Yes☐

6. What was the worst thing about your operation (please tick box) ?

-Anxiety ☐ -Recovery process ☐ -Awareness ☐

-Pain ☐ -Unable to carry out usual activities ☐ -Other [Please write below]:

ANNEXURE 3

CONSENT FORM

Participant's name: **Date of Birth / Age (in years)** :

I_____,
son/daughter/husband/wife/relative (specify relation) of _____ (name of patient) hereby declare that (Please tick boxes)

- I have read the above information provided to me regarding the study - **"Anaesthetic requirements in patients with medically refractory seizures undergoing neurosurgery"** [ ]
- I have clarified any doubts that I had. [ ]
- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]
- I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
- I understand that my identity will not be revealed in any information released to third parties or published [ ]
- I voluntarily agree to take part in this study [ ]
- I have been provided with the contact numbers of the principal investigator, in case I want to know more about the study and participants rights [ ].
- I received a copy of this signed consent form [ ]

Name Signature/thumb impression of patient/legally acceptable representative:
Date:

Name and signature of witness:
Relation to participant: Date:

Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him or her in non-technical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Name and signature with date:

<u>കാര്യബോധത്തോടെയുള്ള സമ്മതപത്രം</u>

പ്രഖ്യാപനം

പങ്കെടുക്കുന്നയാളുടെ പേര് ജനനതിയതി, വയസ്സ് (വർഷത്തിൽ)
ഞാൻ,

_____,മകൻ/മകൾ/ഭർത്താവ്/ഭാര്യ/ബന്ധു

(കൃത്യമായ ബന്ധം) , ... (രോഗിയുടെ പേര്)

ന്യൂറോ ശസ്ത്രക്രിയക്ക് വിധേയരാകുന്ന, മരുന്ന് കഴിച്ചാലും ആവർത്തിക്കുന്ന അപസ്മാരമുള്ള രോഗികളെ മയക്കുന്നതിന് ആവശ്യമായവ എന്ന പഠനസംബന്ധമായി എനിക്ക് നൽകിയ വിവരങ്ങൾ വായിച്ചു എന്ന് പ്രസ്താവിക്കുന്നു.
(ദയവായി കോളങ്ങളിൽ ടിക് ചെയ്യുക)

- എനിക്കുണ്ടായ സംശയങ്ങൾ പരിഹരിച്ചു [ ]
- എന്റെ ഈ പഠനത്തിലുള്ള പങ്കാളിത്തം സ്വമേധയായുള്ളതാണെന്നും, എനിക്ക് ഒരു കാരണവും കൂടാതെ ഏതുസമയത്തും, എനിക്കുള്ള വൈദ്യശുശ്രൂഷയെയോ നിയമപരമായ അവകാശങ്ങളെയോ ബാധിക്കാതെ പിൻവാങ്ങാമെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]
- ഈ പഠനത്തിന്റെ ഗവേഷകർ, നൈതീക കമ്മിറ്റി, നിയന്ത്രണാധികാരികൾ എന്നിവർക്ക് എന്റെ ആരോഗ്യവിവരങ്ങൾ ഞാൻ പഠനത്തിൽനിന്നും പിൻവാങ്ങിയാലും പരിശോധിക്കാൻ എന്റെ സമ്മതം അവശ്യമില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. ഇതിനു ഞാൻ സമ്മതിക്കുന്നു, [ ]
- എനിക്ക് പഠനത്തെപ്പറ്റി കൂടുതലറിയാനോ, പങ്കെടുക്കുന്നയാളുടെ അവകാശങ്ങളെപ്പറ്റി അറിയേണ്ടതെങ്കിലോ വന്നാൽ വൈദ്യശാസ്ത്രപരമായ ഗവേഷണങ്ങളുടെ ബന്ധപ്പെടാനുള്ള നമ്പർ എനിക്ക് നൽകിയിട്ടുണ്ട് [ ]
- ഞാനിതിലെ ഏതെങ്കിലും കക്ഷികൾക്കോ പ്രോസിക്യൂഷനോ നൽകുന്നോൾ പ്പെന്റെ വ്യക്തിവിവരങ്ങൾ വെളിപ്പെടുത്തുകയില്ലെന്നും ഞാൻ മനസ്സിലാക്കുന്നു. [ ]

- സ്വമേധയാ പഠനത്തിൽ പങ്കെടുക്കാൻ ഞാൻ സമ്മതിക്കുന്നു. [ ]
- സമ്മതപത്രത്തിന്റെ ഒപ്പിട്ട ഒരു പ്രതി എനിക്ക് കിട്ടി. [ ]

പേര് സാക്ഷിയുടെ പേര്

ഒപ്പ്/ രോഗിയുടെ വിരലടയാളം/ ഒപ്പ്

നിയമപരമായ പ്രതിനിധി തീയതി

തീയതി

രോഗിയുമായുള്ള ബന്ധം

(സമ്മതം വാങ്ങുന്നയാൾ)

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണപദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകടസാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെ ചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതപത്രം വാങ്ങുന്ന ആളുടെ പേരും ഒപ്പും

ഡോ. നഗ്മോതി ശിൽപ്പ വികാസ്റാവു,

കാർഡിയോതൊറാസിക് ആന്റ് വാസ്ക്കുലാർ അനസ്തീഷ്യേ സീനിയർ റസിഡന്റ്

ഫോൺ: 9970850732, ഇമെയിൽ. shilpanagmoti@gmail.com

പഠനവുമായി ബന്ധമില്ലാത്ത വ്യക്തിയെ ബന്ധപ്പെടുന്നതിന് ദയവായി സ്ഥാപനത്തിലെ നൈതീക കമ്മിറ്റി മെംമ്പർ സെക്രട്ടറി ഡോ. മാല രാമനാഥനെ ബന്ധപ്പെടാം. ഫോൺ 0471 2524234, email: iec.mem.sec@sctimst.ac.in

ANNEXURE 4

PATIENT INFORMATION SHEET

Title of the study:

"Anaesthetic requirements in patients with medically refractory seizures undergoing neurosurgery"

Name of the Investigators:

Dr. Nagmoti Shilpa Vikasrao, Dr. Smita. V, Dr. Ajay Prasasd Hrishi, Dr. George C. Vilanilam

You are scheduled to undergo a major surgical procedure which will require general anaesthesia during surgery. The anti-epileptic drugs you have been taking may have an effect on the dose of anaesthesia drugs that are used for giving general anaesthesia. In our study we want to observe if these anti-epileptic drugs have any effect on the requirement of anaesthetic agents for your surgery.

During surgery, general anaesthesia can be given and maintained using inhalational anaesthetic agents (given through breathing tube) or intravenous anaesthetic agents. Intravenous anaesthesia technique involves use of target controlled infusion (TCI) pump for the administration of anaesthetic agent. We intend to use intravenous technique of general anaesthesia which is commonly used for neurosurgeries.

You are being requested to participate in this study which assesses the anaesthetic agent requirement in patients who have been taking two or more than two anti-epileptic medications for seizure disorder. In this study Total intravenous anaesthesia (TIVA) will be used, which will be given using a Target controlled infusion device (TCI). This study will require observation of hemodynamic parameters and depth of anaesthesia, which are routinely monitored in patients under general anaesthesia in neurosurgeries, in this hospital and worldwide. We have planned to include about 35 patients from this hospital in this study.

What is Total intravenous anaesthesia?

During surgery, general anaesthesia is maintained using inhalational anaesthetic agents or intravenous anaesthetic agents. If only injectable or intravenous anaesthetic drugs are used to maintain anaesthesia, then this technique is known as TIVA or total intravenous anaesthesia. It is commonly used technique in anaesthesia practice worldwide and in this institute for neurosurgeries. Intravenous anaesthesia technique involves use of target controlled infusion (TCI) pump for the administration of anaesthetic agent.

Who will be included in this study?

We are planning to include 35 patients from our hospital. Patients undergoing neurosurgery and requiring general anaesthesia. We are planning to include patients within age group of 18 to 60 years. We are not including patients with uncontrolled hypertension, patients with renal or liver disease, morbidly obese patients, or patients for emergency surgery. We are not including pregnant and breast feeding patients. We are also not including patients who participated in another study in this institution in the preceding one month.

If you take part what will you have to do?

On the day of surgery you will be taken inside the operation theatre. Monitors to check your heart rate, blood pressure and oxygen saturation level will be attached. A venous cannula will be inserted under local anesthesia in the hand for fluid and drug administration. BIS monitor will be attached. General Anaesthesia will be induced as per the routine anesthesia protocol in the hospital. After you have become unconscious and paralysed, you will be connected to the ventilator, and anaesthesia will be maintained with infusion drugs as routinely done in neurosurgeries. After this the parameters to be studied will be observed and recorded. Surgery will be started as planned by the surgical team.

No additional intravenous fluids or drugs, apart from what you receive as per routine anaesthesia protocol of this hospital irrespective of your participation in this study, will be used for the purpose of the study. We will be taking recordings from BIS monitor which will be otherwise used in your surgery; irrespective of your participation in this study.

Does TCI of Propofol method of anaesthesia have any side effect?

TIVA or total intravenous anaesthesia is a commonly used technique in anaesthesia practice worldwide. Intravenous anaesthesia technique involves use of target controlled infusion (TCI) pump for the administration of anaesthetic agent called Propofol. It has no specific side effects apart from those of routine general anaesthesia and anaesthsia drugs. Side effects of Propofol are allergy reaction, hypotension, bradycardia, ect. if allergy to the drug develops, the drug will be discontinued and hypotension ad bradycardia will be managed by your anaesthetist.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any

way. In addition, if you experience any side effects, the study will be stopped and you will be given additional treatment.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you on account of your participation in this study as the anaesthesia technique and monitoring tools would be same even if you were not part of the study. But if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will you have to pay for the cost of using the monitoring devices?

Our routine anaesthesia protocol will be used for your surgery. You will not be required to pay any extra charges for participation in this study.

What happens after the study is over?

The recordings for the study will be taken throughout the length of the surgery. After surgery is over, patient's anaesthesia will be reversed and the patient will be shifted to intensive care unit as per our institutional protocol.

Will your personal details be kept confidential?

The results of this study will be used for thesis submission as a part of academic research and will be submitted to a medical journal for publication, but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr. Nagmoti Shilpa Vikasrao (Principal investigator) Mobile number: 9970850732. email: shilpanagmoti@gmail. com

Dr Smita. V, Associate Professor, Anaesthesiology, SCTIMST, Trivandrum – 11; 09447699245, smita_vimala@sctimst. ac. in

For any further clarifications and concerns regarding the study's ethics clearance, please contact: The Member Secretary, Institutional Ethics Committee, SCTIMST, Trivandrum – 11. Phone: 0471-2524234, email: iec. mem. sec@sctimst. ac. in

രോഗിക്കുള്ള കാര്യവിവരണപത്രം

പഠനശീർഷകം:

ന്യൂറോ ശസ്ത്രക്രിയക്ക് വിധേയരാകുന്ന, മരുന്ന് കഴിച്ചാലും ആവർത്തിക്കുന്ന അപസ്മാരമുള്ള രോഗികളെ മയക്കുന്നതിന് ആവശ്യമായവ.

ഗവേഷകരുടെ പേര്:

ഡോ. നഗ്മോതി ശിൽപ്പ വികാസ്റാവു, ഡോ. സ്മിത വി, ഡോ. അജയ് പ്രസാദ് ഹൃഷി, ഡോ ജോർജ് സി വിളനിലം

ശസ്ത്രക്രിയക്കവേണ്ടി പൊതുവായ മയക്കൽ ആവശ്യമായ പ്രധാനപ്പെട്ട ഒരു ശസ്ത്രിക്രിയാ നടപടിക്ക് താങ്കൾ വിധേയമാകാൻ പോകുകയാണല്ലോ. താങ്കളുടെ ശസ്ത്രക്രിയക്കു വേണ്ടിയുള്ള പൊതുവായ മയക്കലിന് നൽകുന്ന മരുന്നുകളുടെ അളവിൽ താങ്കൾ കഴിക്കുന്ന അപസ്മാരത്തിനെതിരേ കഴിക്കുന്ന മരുന്നുകളുടെ പ്രഭാവമുണ്ടായേക്കാം. ഈ അപസ്മാരത്തിനെതിരേയുള്ള മരുന്നുകൾക്ക് മയക്കാൻ നൽകുന്ന മരുന്നുകളിൽ എന്തെങ്കിലും സ്വാധീനമുണ്ടാകുമോ എന്ന് ഞങ്ങളുടെ പഠനത്തിൽ നിരീക്ഷിക്കാൻ താത്പര്യപ്പെടുന്നു.

ശസ്ത്രക്രിയാസമയത്ത് പൊതുവായ മയക്കൽ നടത്തുകയും നിലനിർത്തുകയും ചെയ്യാൻ ശ്വസിക്കാനുള്ള (ശ്വസന കുഴലിലൂടെ നൽകുന്നത്) അനസ്തീഷ്യ മരുന്നുകളോ ഞരമ്പിലൂടെയുള്ള അനസ്തീഷ്യ മരുന്നുകളോ നൽകാം. കുത്തിവയ്പ്പിലൂടെയുള്ള മയക്കൽ സങ്കേതത്തിൽ നിയന്ത്രിതമായ ലക്ഷ്യത്തോടെ മരുന്ന് നൽകാനുള്ള (റ്റിസിഐ) പമ്പ് ഉപയോഗിക്കുന്നു. ന്യൂറോ ശസ്ത്രക്രിയക്ക് സാധാരണയായുപയോഗിക്കുന്ന ഞരമ്പിലൂടെയുള്ള പൊതുമയക്കൽ സംവിധാനം ഉപയോഗിക്കാൻ ഞങ്ങളുദ്ദേശിക്കുന്നു.

അപസ്മാര രോഗത്തിന് രണ്ടോ അതിലധികമോ അപസ്മാരത്തിനെതിരേയുള്ള മരുന്നുപയോഗിക്കുന്ന രോഗികളുടെ മയക്കലിനുള്ള മരുന്നുകളുടെ ആവശ്യകതകൾ വിലയിരുത്തുന്ന ഒരു പഠനത്തിൽ പങ്കാളിയാകാൻ താങ്കളോട് ഞങ്ങളഭ്യർത്ഥിക്കുന്നു. ഈ പഠനത്തിൽ നിയന്ത്രിതമായ ലക്ഷ്യത്തിൽ ലഭ്യമാകത്തക്കവിധമുള്ള ഉപകരണമുപയോഗിച്ച് (റ്റിസിഐ) പൂർണ്ണമായി ഞരമ്പിലൂടെയുള്ള മയക്കലാണ് ഉപയോഗിക്കുക (റ്റിഐവിഎ). ഈ ആശുപത്രിയിലും ലോകമെമ്പാടും പൊതുവായ മയക്കലിനു വിധയമാകുന്ന ന്യൂറോ ശസ്ത്രക്രിയാ രോഗികളിൽ പതിവായി നിരീക്ഷിക്കപ്പെടുന്ന രക്തചംക്രമണ വ്യവസ്ഥയുടെ മാനദണ്ഡങ്ങളും മയക്കലിന്റെ ആഴവും ഈ പഠനത്തിൽ നിരീക്ഷിക്കും. ഈ ആശുപത്രിയിൽനിന്നും 35 രോഗികളെ ഉൾപ്പെടുത്താൻ ഞങ്ങൾ ആസൂത്രണം ചെയ്യുന്നു.

കുത്തിവയ്പ്പിലൂടെയുള്ള പൂർണ്ണമായ മയക്കലെന്നാലെന്താണ്?

ശസ്ത്രക്രിയാസമയത്ത് പൊതുവായ മയക്കൽ നിലനിർത്തുന്നത് ശ്വസനത്തിലൂടെ മയക്കാനുള്ള മരുന്നുകളോ കുത്തിവയ്പ്പിലൂടെ മയക്കാനുള്ള മരുന്നുകളോ ഉപയോഗിച്ചാണ്. കുത്തിവയ്പ്പിലൂടെയോ ഞരമ്പിലൂടെയോ മാത്രം മയക്കൽ നിലനിർത്താനുള്ള മരുന്നുകൾ ഉപയോഗിച്ചാൽ, ഈ സങ്കേതത്തെ റ്റിഐവിഎ എന്നോ പൂർണ്ണമായി ഞരമ്പിലൂടെയുള്ള മയക്കൽ എന്നോ അറിയപ്പെടുന്നു. ന്യൂറോ ശസ്ത്രക്രിയക്കായി ഈ ആശുപത്രിയിലും ലോകമെമ്പാടും സാധാരണയായി ഈ സങ്കേതം ഉപയോഗിക്കുന്നു. ഞരമ്പിലൂടെയുള്ള മയക്കൽ സങ്കേതത്തിൽ നിയന്ത്രിതമായ ലക്ഷ്യത്തോടെ മരുന്ന് പ്രവഹിപ്പിക്കുന്ന പമ്പ് മയക്കാനുള്ള മരുന്ന് നൽകാൻ ഉപയോഗിക്കുന്നു.

ഈ പഠനത്തിൽ ആരെയൊക്കെ ഉൾപ്പെടുത്തും **?**

പൊതുവായ മയക്കലിന് വിധേയമായിന്യൂറോ സർജറിചെയ്യുന്ന 35 രോഗികളെ നമ്മുടെ ആശു പത്രിയിൽനിന്നും ഉൾപ്പെടുത്താൻ ഞങ്ങൾ ആസൂത്രണം ചെയ്യുന്നു. 18 വയസ്സുമുതൽ 60 വയ സ്സുവരെയുള്ളവരെയാണ് ഉൾപ്പെടുത്താൻ ഞങ്ങൾ ആസൂത്രണം ചെയ്യുന്നത്. അനിയന്ത്രിത മായ രക്തസമ്മർദ്ദമുള്ളവർ, വൃക്ക, കരൾ രോഗങ്ങളുള്ളവർ, ഗുരുതരമായ അമിതവണ്ണമുള്ള വർ, അടിയന്തിര ശസ്ത്രക്കിയക്കുവിധേയമാകുന്നവർ തുടങ്ങിയ രോഗികളെ പഠനത്തിലുൾപ്പെ ടുത്തില്ല. ഗർഭിണികളോ മുലയൂട്ടുന്നവരോ ആയ രോഗികളെ ഞങ്ങളുൾപ്പെടുത്തില്ല. കഴിഞ്ഞ ഒരു മാസത്തിനുള്ളിൽ ഈ ആശുപത്രിയിൽ മറ്റേതെങ്കിലും പഠനത്തിൽ പങ്കെടുത്ത രോഗിക ളെയും ഞങ്ങൾ ഉൾപ്പെടുത്തില്ല.

പങ്കെടുക്കുകയാണെങ്കിൽ താങ്കൾ എന്തുചെയ്യണം **?**
ശസ്ത്രക്രിയാ ദിവസം താങ്കളെ ശസ്ത്രക്രിയാമുറിയിൽ പ്രവേശിപ്പിക്കും. താങ്കളുടെ ഹൃദയമിടി പ്പ്, രക്തസമ്മർദ്ദം,പ്രണവായുവിന്റെ നിലവാരം എന്നിവ പരിശോധിക്കാനുള്ള ഉപകരണങ്ങൾ ഘടിപ്പിക്കും. പ്രാദേശീകമായ മയക്കലിന് വിധേയമാക്കി ദ്രാവകങ്ങളും മരുന്നും നൽകാനാ യുള്ള ഒരു കുഴൽ കൈയിലെ രക്തക്കുഴലിൽ കടത്തും. ബഐഎസ് നിരീക്ഷണ ഉപകരണം ഘടിപ്പിക്കും. ആശുപത്രിയിലെ പതിവ് നടപടിക്രമമനുസരിച്ച് പൊതുവായ മയക്കലിനുള്ള മരുന്ന് നൽകും. താങ്കൾ ബോധരഹിവും നിശ്ചലവുമായശേഷം താങ്കളെ കൃത്രിമ ശ്വസനയന്ത്ര വുമായി ബന്ധിക്കുകയും മരുന്ന് നൽകിക്കൊണ്ട് ന്യൂറോ ശസ്ത്രക്രിയയിൽ പതിവായി ചെയ്യു ന്നതുപോലെ മയക്കം നിലനിർത്തുകയും ചെയ്യും. ഇതിനുശേഷം പഠനവിഷയമായ മനദണ്ഡ ങ്ങൾ നിരീക്ഷിക്കുകയും രേഖപ്പെടുത്തുകയും ചെയ്യും. ശസ്ത്രക്രിയാ സംഘം ആസൂത്രണം ചെയ്തതുപോലെ ശസ്ത്രക്രിയ തുടങ്ങും.
താങ്കൾ പഠനത്തിൽ പങ്കെടുത്താലുമില്ലെങ്കിലും ഈ ആശുപത്രിയിലെ പതിവ് മയക്കൽ നടപടി ക്രമങ്ങൾ പ്രകാരം താങ്കൾക്കു നൽകുന്നതിൽ അധികമായി ദ്രാവകങ്ങളോ മരുന്നുകളോ പഠനാ വശ്യത്തിനായി ഉപയോഗിക്കില്ല. താങ്കൾ പഠനത്തിൽ പങ്കെടുത്താലുമില്ലെങ്കിലും താങ്കളുടെ ശസ്ത്രക്രിയക്കുപയോഗിക്കുന്ന ബിഐഎസ് മോണിറ്ററിൽനിന്നുള്ള വിവരങ്ങൾ, താങ്കൾ പഠന ത്തിൽ പങ്കെടുക്കുന്നുണ്ടെങ്കിൽ ഞങ്ങൾ ശേഖരിക്കും.

റ്റിസിഐ രീതിയിൽ മയക്കലിനുള്ള പ്രൊപ്പഫോൾ നൽകുന്നതിന് എന്തെങ്കിലും പാർശ്വഫലങ്ങ ളുണ്ടോ**?**

റ്റിഐവിഎ ആല്ലെങ്കിൽ പൂർണ്ണമായി ഞരമ്പിലൂടെ മയക്കൽമരുന്നുനൽകുന്നത് മയക്കലിന് ലോകമെമ്പാടും ഉപയോഗിക്കുന്ന സങ്കേതമാണ്. പൂർണ്ണമായി ഞരമ്പിലൂടെയുള്ള മയക്കലിന് (റ്റിഐവിഎ), നിയന്ത്രിതമായ ലക്ഷ്യത്തിൽ ലഭ്യമാകത്തക്കവിധമുള്ള ഉപകരണമാണ് (റ്റിസി ഐ) ഉപയോഗിക്കുക (റ്റിഐവിഎ). പതിവായുള്ള പൊതുമയക്കലിനും മയക്കൽ മരുന്നിനുമു ള്ളതിലധികമായി ഇതിന് പ്രത്യേകിച്ച് പാർശ്വഫലങ്ങളൊന്നുമില്ല. അലർജി, കുറഞ്ഞ രക്തസ മ്മർദ്ദം, ബ്രാഡികാർഡിയ എന്നിവയാണ് പ്രൊപ്പഫോളിന്റെ പാർശ്വഫലങ്ങൾ. ഇവയിലെന്തെ ങ്കിലും ഉണ്ടായാൽ മരുന്ന് ഉപയോഗിക്കുന്നത് സ്ഥാപനത്തിലെ നടപടിക്രമമനുസരിച്ച് നിർത്തും.

പഠനമാരംഭിച്ചശേഷം താങ്കൾക്ക് പിൻമാറാമോ?

താങ്കളുടെ പഠനത്തിലുള്ള പങ്കാളിത്തം തികച്ചും സ്വമേധയായാണ്, പഠനത്തിലെ പങ്കാളിത്ത ത്തിൽ നിന്നും പിൻമാറാൻ തീരുമാനമെടുക്കാൻ താങ്കൾക്ക് സ്വാതന്ത്ര്യമുണ്ട്. താങ്കളങ്ങിനെ ചെയ്താലും താങ്കളുടെ ഈ ആശുപത്രിയിലെ പതിവ് ചികിത്സയെ ഒരുവിധത്തിലും ബാധിക്കി ല്ല.

പഠനവുമായി ബന്ധപ്പെട്ട് താങ്കൾക്ക് എന്തെങ്കിലും പരുക്കുണ്ടായാലെന്ത് സംഭവിക്കും ?

താങ്കൾ പഠനത്തിൽ പങ്കെടുത്തില്ലെങ്കിലും ഉപയോഗിക്കുന്ന മയക്കൽ സങ്കേതങ്ങളും നിരീക്ഷണ ഉപകരണങ്ങളും ഒന്നുതന്നെയാകയാൽ ഞങ്ങളുടെ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് താങ്കൾക്ക് പരുക്കുണ്ടാകുമെന്ന് ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നില്ല. പക്ഷേ പഠനവുമായി ബന്ധപ്പെട്ട് താങ്കൾക്കെന്തെങ്കിലും പാർശ്വഫലളങ്ങളോ പ്രശ്നങ്ങളോ ഉണ്ടായാൽ താങ്കൾക്ക് ചിലവുണ്ടാകാതെ ചികിത്സിക്കും. എന്നിരുന്നാലും സാമ്പത്തികമായ നഷ്ടപരിഹാരം നൽകാനാവില്ല.

നിരീക്ഷണത്തിനായി ഉപോയോഗിക്കുന്ന ഉപകരണങ്ങൾക്ക് താങ്കൾ പണം ചിലവാക്കണോ?

നമ്മുടെ പതിവ് മയക്കൽ നടപടിക്രമമാണ് താങ്കളുടെ ശസ്ത്രക്രിയക്ക് ഉപയോഗിക്കുന്നത്. ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് താങ്കൾ അധികം പണം നൽകേണ്ടിവരില്ല.

പഠനം കഴിഞ്ഞശേഷം എന്തു സംഭവിക്കും**?**

ശസ്ത്രക്രിയയിലുടനീളം വിവരങ്ങൾ ശേഖരിക്കും ശസ്ത്രക്രിയ കഴിഞ്ഞ് രോഗിയുടെ മയക്കം മാറ്റുകയും രോഗിയെ തീവ്രപരിചരണവിഭാഗത്തിലേക്ക് മാറ്റുകയും ചെയ്യും.

താങ്കളുടെ വ്യക്തിവിവരങ്ങൾ രഹസ്യമായിരിക്കുമോ?

പഠനഫലങ്ങൾ പഠനഗവേഷണത്തിന്റെ ഭാഗമായുള്ള തീസിസിൽ ഉപയോഗിക്കുകയും ഒരു വൈദ്യശാസ്ത്ര ജേർണലിൽ പ്രസിദ്ധീകരണത്തിന് നൽകുകയും ചെയ്യുമെങ്കിലും താങ്കളെ വ്യക്തിപരമായി തിരിച്ചറിയാനിടയാക്കുന്നതൊന്നും പ്രസിദ്ധീകരണത്തിലോ, പഠനഫലങ്ങളുടെ പ്രദർശനത്തിലോ ഉണ്ടാവില്ല. എന്നിരുന്നാലും താങ്കൾ പങ്കെടുക്കുകയാണെങ്കിൽ താങ്കളുടെ ചികിത്സാ വിവരങ്ങൾ പഠനവുമായി ബന്ധപ്പെട്ടവർ താങ്കളുടെ അധികമായ സമ്മതമില്ലാതെ പരിശോധിച്ചേക്കാം.

താങ്കൾക്ക് കൂടുതൽ എന്തെങ്കിലും ചോദ്യങ്ങൾ ഉണ്ടെങ്കിൽ ദയവായി ഡോ. നഗ്മോതി ശിൽപ്പ വികാസ്റാവു, കാർഡിയോതൊറാസിക് ആന്റ് വാസ്ക്കുലാർ അനസ്തീഷ്യേ സീനിയർ റസിഡന്റിനോട് ചോദിക്കുക (ഫോൺ: 9970850732). ഇമെയിൽ. shilpanagmoti@gmail.com

പ്രധാന ഗവേഷകയുടെ പേര്. ഡോ. നഗ്മോതി ശിൽപ്പ വികാസ്റാവു,

ഡോ. സ്മിത വി, അസോസിയേറ്റ് പ്രൊഫസർ അനസ്തീഷ്യോളജി, SCTIMST, Trivandrum 11; 09447699245, smita_vimala@sctimst.ac.in

പഠനവുമായി ബന്ധമില്ലാത്ത വ്യക്തിയെ ബന്ധപ്പെടുന്നതിന് ദയവായി സ്ഥാപനത്തിലെ നൈതീക കമ്മിറ്റി മെംമ്പർ സെക്രട്ടറി ഡോ. മാല രാമനാഥനെ ബന്ധപ്പെടാം. ഫോൺ 0471 2524234, email: iec.mem.sec@sctimst.ac.in

ANNEXURE 5

TECHNICAL ADVISORY COMMITEE (Clinical Studies)
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
TRIVANDRUM,INDIA

7164/1/2018 Date : 07-May-2018

Project title : Anaesthetic requirements in patients with medically refractory seizures

Principal Investigator :		
Name	Address	Degree
Dr. Nagmoti Shilpa Vikasrao	Dept. of Anaesthesiology, SCTIMST	MBBS, MD, DNB, PDCC
Co-Principal Investigator(s) :		
Name	Address	Degree
Dr. Smita V.	Dept. of Anaesthesiology SCTIMST	MBBS, MD, DM (Neuroanaesthesia)
Dr Ajay Prasad Hrishi	Dept. of Anaesthesiology SCTIMST	MBBS, MD, DM (Neuroanaesthesia)
Dr George	Dept of Neurosurgery SCTIMST	MBBS, MS, Mch Neurosurgery

Specific Source of funding - Name of External/Intra mural/ Others: NO

Does this study involve Investigations/ Imaging protocols/Follow up visits that are not routinely mandated in these subjects ? : NO

Recommendation of HOD whether Investigations/Imaging protocols/Follow up visits are routinely mandated in these subjects : NO

Signature of HOD : (Dr) S. Manikanda

Signature of Dean
(Associate Dean R and P Cell in the absence of Dean) :

Signature of PI : Dr. Shilpa

ANNEXURE 6

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee
(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1236/AUGUST-2018

28.08.2018

Dr. Nagmoti Shilpa Vikasrao
Resident
Department of Anaesthesiology
SCTIMST, Thiruvananthapuram

Dear Dr.Nagmoti Shilpa Vikasrao,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "ANAESTHETIC REQUIREMENTS IN PATIENTS WITH MEDICALLY REFRACTORY SEIZURES UNDERGOING NEUROSURGERY (IEC/1236)" on 17th August, 2018.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 19.07.2018 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Forwarding Letter from the HOD*
6. *Proforma*
7. *Patient Information Sheet and Consent Form in English and Malayalam*
8. *List of abbreviations*
9. *CV of Principal Investigator and Co- Principal Investigators*

Revised submission

1. *Covering letter addressed to the Member Secretary, IEC, SCTIMST dated 21.08.2018 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *List of abbreviations*
8. *CV of Principal Investigator and Co- Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 17th August, 2018 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. V. Raman Kutty	M D, M Phil, M P H	Male	Health Sciences Expert/Clinician	Yes
3.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	Yes
4.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
5.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

ANNEXURE 7
PLIGARISM REPORT

URKUND

Document Information

Analyzed document	thesis 24_8.docx (D78156452)
Submitted	8/25/2020 2:31:00 PM
Submitted by	kanmanisethu
Submitter email	kanmanis@sctimst.ac.in
Similarity	6%
Analysis address	kanmanis.sctims@analysis.urkund.com

Sources included in the report

W	URL: https://bmcanesthesiol.biomedcentral.com/articles/10.1186/s12871-015-0006-z Fetched: 8/25/2020 2:33:00 PM	3
W	URL: https://academic.oup.com/bja/article/108/4/562/257975 Fetched: 8/25/2020 2:33:00 PM	3
SA	**UzmaKhan_Final thesis_1.pdf** Document UzmaKhan_Final thesis_1.pdf (D40544694)	1
W	URL: https://www.scielo.br/pdf/rba/v61n2/en_v61n2a13.pdf Fetched: 8/25/2020 2:33:00 PM	16

1/35

ANNEXURE 8

MASTER CHART

Group C								
SR.NO	**DATE**	**AGE (yrs)**	**SEX**	**WEIGHT (kg)**	**HEIGHT (cms)**	**BMI (kg/m2)**	**DIAGNOSIS**	**SURGERY**
1	4-Sep	28	M	67	168	23.7	Lt temporal lesion	craniotomy and excision
2	20-Aug	25	M	56	169	19.6	Rt temporal cavernoma	craniotomy and excision
3	15-Oct	30	F	65	155	27	Rt frontal lesion	craniotomy and excision
4	6-Aug	35	F	50	153	22.2	Lt insular lesion	craniotomy and excision
5	24-Sep	36	F	44	152	19	Lt insular lesion	Craniotomy and excision
6	11-Oct	34	F	44	144	21	rt. Temporal lesion	craniotomy and excision
7	7-Feb	37	M	72	171	24	Lt frontal lesion	craniotomy and excision
8	16-Oct	30	M	78	168	27.6	rt cingulate gyrus lesion	craniotomy and excision
9	31-Oct	32	M	72	171	24.9	colloid cyst	craniotomy and excision
10	5-Nov	25	M	60	160	23.4	Rt temporal cavernoma	Craniotomy and excision
11	4-Nov	29	M	78	176	25.1	Left parietal lesion	craniotomy and excision
12	18-Nov	25	M	45	146	21.1	RT temporal lesion	craniotomy and excision
13	29-Nov	28	M	70	170	24.2	Rt frontal glioma	craniotomy and excision
14	21-Dec	26	M	68	177	21.7	left frontal lesion	craniotomy and excision
15	13-Jan	25	M	60	170	20.7	Left parietal lesion	craniotomy and excision
16	6-Feb	26	F	66	160	25.7	Pineal region tumour	craniotomy and excision
17	11-Feb	30	M	72	170	24.4	Rt temporoparietal lesion	craniotomy and excision
18	14-Feb	32	M	77	169	26.9	left frontal lesion	craniotomy and excision
19	18-Feb	36	M	70	170	24.2	Left parietal lesion	craniotomy and excision
20	19-Feb	28	M	75	175	24.4	Rt frontal glioma	Craniotomy and excision

Group C									
ASA GRADE	**Antiepileptics**	**DURATION OF TREATMENT (months)**	**INDUCTION PROPOFOL (mg/kg)**	**MAINTAINANCE Ce(mcg/ml)**	**DURATION OF ANAESTHESIA (hours)**	**T0- time taken for eyeopening (minutes)**	**T1- time taken to obey commands (minutes)**	**T0 - EXTUBATION TIME (minutes)**	**TOTAL PROPOFOL REQUIRED (mg/kg/hr)**
I	Levipil	3	1.11	4	4.5	13	14	15	8.55
I	Levipil	2	1.42	2.5	3	13	14	15	5.23
I	Levipil	2	1	2.5	6.5	17	19	20	5.4
I	Levipil	2	1.8	2.5	6	14	14	15	6
I	Levipil	1	1.34	3.5	6	8	9	10	6.81
I	Levipil	3	1.36	2.4	5	13	14	15	7.27
I	Levipil	0.5	0.8	2.8	2.5	6	7	8	5.39
I	Levipil	2	1.28	2.8	7.5	18	18	20	5.61
I	levipil	1	1.35	2.9	4	6	7	8	7.2
1	Levipil	1	1.08	2.9	3.5	8	9	10	6.95
1	levipil	1	1.53	2.8	6.5	16	17	18	5.12
1	levipil	1	1.11	3	6	13	14	15	5.3
1	levipil	2	1.12	2.8	4	8	9	10	5.2
1	levipil	1.5	1.34	3.5	6	9	9	10	6.81
1	levipil	1	1.36	2.4	5	14	14	15	7.27
1	levipil	2	1.1	3.8	5	13	14	15	8
1	levipil	0.5	0.8	2.8	2.5	6	7	8	5.39
1	levipil	1	1.2	2.8	6	13	14	15	5.61
1	levipil	1	0.8	2.6	2.5	6	7	8	5.28
1	Levipil	2	1.22	3	5	18	19	20	5

Group C											
TOTAL FENTANYL REQUIRED (mcg/kg/hr)	**TOTAL ATRACURIUM REQUIRED(mg/Kg/hr)**	**NO. OF FENTANYL BOLUSES**	**NO OF MEPHENTERMINE BOLUSES**	**SYSTOLIC BLOOD PRESSURE (mmHg)**							
				baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
2	0.11	3	1	130	124	136	136	149	121	118	130
2	0.14	2	1	120	114	124	124	118	106	106	120
2.2	0.12	2	1	130	68	136	136	147	151	147	130
2.17	0.14	2	0	120	130	130	130	113	130	140	120
1.96	0.3	2	0	120	147	122	122	145	132	136	120
2	0.18	2	1	120	123	124	124	132	125	124	120
1.98	0.13	2	1	140	124	136	136	130	156	138	140
2	0.13	1	1	117	120	113	113	98	114	118	117
2	0.14	2	0	126	117	127	127	125	125	128	126
2.3	0.13	2	1	110	110	120	120	108	118	108	110
1.8	0.14	1	0	134	122	136	136	114	110	108	134
2.3	0.13	2	0	138	122	136	136	124	120	118	138
2.3	0.14	2	1	110	124	129	129	111	132	132	110
1.96	0.3	2	0	130	118	128	128	108	106	108	130
1.9	0.18	2	1	120	124	132	132	114	118	110	120
1.9	0.11	3	1	130	124	136	136	149	121	118	130
1.98	0.13	2	1	120	114	130	130	118	106	106	120
1.8	0.13	1	1	130	68	138	138	147	151	147	130
1.8	0.13	2	1	116	121	148	148	150	141	153	116
2.1	0.13	1	1	140	138	136	136	140	130	110	140

Group C							
DIASTOLIC BLOOD PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
80	82	84	84	99	80	68	80
85	70	88	88	68	66	62	85
80	115	82	82	99	103	99	80
80	90	82	82	77	80	88	80
88	116	84	84	100	92	96	88
78	88	76	76	90	91	84	78
80	86	82	82	80	92	84	80
76	80	79	79	70	76	84	76
78	77	79	79	90	86	90	78
86	88	82	82	84	86	78	86
84	80	80	80	64	60	62	84
82	78	80	80	80	76	76	82
78	80	80	80	74	95	88	78
80	76	78	78	68	64	60	80
78	78	88	88	70	70	72	78
88	82	84	84	99	80	68	88
76	70	82	82	68	66	62	76
80	115	88	88	99	103	99	80
97	71	98	98	93	110	97	97
80	90	80	80	100	90	78	80

Group C							
MEAN ARTERIAL PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
113	110	118	118	132	107	101	113
108	99	112	112	101	92	91	108
113	83	118	118	131	135	131	113
106	116	114	114	101	113	122	106
109	136	109	109	130	118	122	109
106	111	108	108	118	113	110	106
120	111	118	118	113	134	120	120
103	106	101	101	88	101	106	103
110	103	111	111	113	112	115	110
102	102	10	10	100	107	98	102
117	108	117	117	97	93	92	117
119	107	117	117	109	105	104	119
99	109	112	112	98	119	117	99
113	104	111	111	94	92	92	113
106	108	117	117	99	102	97	106
116	110	118	118	132	107	101	116
105	99	114	114	101	92	91	105
113	83	121	121	131	135	131	113
109	104	131	131	131	130	134	109
120	122	117	117	126	116	99	120

Group C							
HEART RATE (per minute)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
84	82	82	88	80	80	81	88
90	88	94	92	90	91	92	95
90	88	94	92	90	91	92	95
80	78	85	80	78	77	78	85
90	88	94	92	90	91	92	95
70	66	75	66	68	67	68	75
90	88	94	92	90	91	92	95
80	78	85	80	78	77	78	85
79	75	80	78	78	76	76	84
82	82	82	88	80	80	81	88
79	75	80	78	78	76	76	84
76	70	75	77	70	72	72	78
90	88	94	92	90	91	92	95
70	66	75	66	68	67	68	75
80	78	85	80	78	77	78	85
84	82	82	88	80	80	81	88
80	78	85	80	78	77	78	85
80	78	85	80	78	77	78	85
66	65	70	64	65	66	66	70
80	78	85	80	78	77	78	85

Group C							
BIS VALUE							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
95	44	40	44	44	50	44	92
98	45	38	45	45	51	45	91
99	44	38	44	44	52	44	95
96	52	40	52	52	52	52	94
95	46	41	46	46	46	46	95
95	47	39	47	47	47	47	92
96	48	39	48	48	48	48	93
98	46	40	46	46	46	46	94
99	47	41	47	47	47	47	93
99	48	39	48	48	48	48	95
96	46	39	46	46	46	46	94
97	47	42	47	47	47	47	92
95	48	41	48	48	48	48	93
97	49	40	49	49	49	49	93
98	50	42	50	50	50	50	92
97	52	42	52	52	52	52	94
98	49	39	49	49	49	49	95
98	48	39	48	48	48	48	96
98	47	39	47	47	47	47	93
96	48	39	48	48	48	48	94

Group MRS								
SR.NO	**DATE**	**AGE (yrs)**	**SEX**	**WEIGHT (kg)**	**HEIGHT (cms)**	**BMI (kg/m2)**	**DIAGNOSIS**	**SURGERY**
1	3-Oct	35	M	75	170	25.9	rt. Temporoparital lesion	craniotomy and excision
2	29-Aug	24	M	70	168	24.8	RT MTS	RT. ATL-AH
3	14-Feb	19	M	62	165	22.7	left MTS	LT ATL-AH
4	7-Aug	37	M	82	176	26.4	RT MTS	RT. ATL-AH
5	10-Oct	37	F	72	168	25	left MTS	LT ATL-AH
6	6-Feb	29	M	65	162	24.76	Lt frontal lesion	craniotomy and excision
7	10-Jul	37	F	72	166	26.1	left MTS	LT ATL-AH
8	17-Dec	24	F	65	164	23.7	left MTS	LT ATL-AH
9	28-Nov	25	F	52	154	21.9	Left parital gliosis	craniotomy and excision
10	19-Sep	41	M	70	170	24.2	RT MTS	RT. ATL-AH
11	17-Jul	22	M	80	170	27.6	left MTS	LT ATL-AH
12	17-0ct	25	F	43	140	21	left MTS	lT ATL-AH
13	3-Jul	22	M	45	160	18	left MTS	LT ATL-AH
14	11-Apr	43	M	80	170	27.6	Rt frontal FCD	Craniotomy and excision
15	20-Jan	19	M	60	169	21	rt temporal DNET	Craniotomy and excision
16	27-Nov	21	F	60	156	24.7	Lt temporal DNET	Craniotomy and excision
17	27-Nov	21	F	60	156	24.7	Lt temporal DNET	Craniotomy and excision
18	24-Jul	25	F	56	160	21.8	Lt MTS	LT ATL-AH
19	13-Feb	21	M	77	181	23.7	Lt frontal lesion	Craniotomy and excision
20	7-Mar	54	M	82	170	28.3	RT MTS	RT. ATL-AH

Group MRS								
ASA GRADE	**Antiepileptics**				**DURATION OF TREATMENT (months)**	**INDUCTION PROPOFOL (mg/kg)**	**MAINTAINANCE Ce(mcg/ml)**	**DURATION OF ANAESTHESIA (hours)**
II	oxcarbazepine		valproate	clobazam	22	0.8	2.5	4.5
I	Oxcarbazepine		Valproate	Clobazam	12	0.85	2.2	4.5
I	Oxcarbazepine		Valproate	Clobazam	13	1.04	1.8	4.5
I	Oxcarbazepine	levipil		Clobazam	20	1.7	2.8	4
I	Carbamazepine	levipil		Clobazam	23	0.77	2.2	4
I		Levipil	phenytoin	Clobazam	13	1.18	2	4.5
I	Oxcarbazepine	Levipil		Clobazam	13	0.77	1.8	4
I		Levipil	lacosamide	clobazam	20	0.92	1.5	5
I	Oxcarbazepine	Levipil		Clobazam	12	0.73	1.3	4.5
I			lamotrigine	clobazam	13	0.92	2	5.5
I	Oxcarbazepine		Topiramate	clobazam	14	1	1.8	4
I	Oxcarbazepine		Topiramate	Clobazam	12	1.16	1.2	4
I			lamotrigine	Clobazam	12	1.24	1.8	5
I	Carbamazepine		Lacosamide	Clobazam	12	0.76	2.4	5
I		levipil	valproate		24	0.91	2.5	4
I	Oxcarbazepine	levipil			23	1.4	2.2	4
I	Oxcarbazepine	levipil			24	1.4	2.2	4
I	oxcarbazepine	levipil			23	1	2.5	5
I	Carbamazepine		Lacosamide		23	1.03	1.8	4.5
I	Carbamazepine	Phenobarbitone	Phenytoin		23	0.63	2	4.5

Group MRS							
T0- time taken for eyeopening (minutes)	**T1- time taken to obey commands (minutes)**	**T0 - EXTUBATION TIME (minutes)**	**TOTAL PROPOFOL REQUIRED (mg/kg/hr)**	**TOTAL FENTANYL REQUIRED (mcg/kg/hr)**	**TOTAL ATRACURIUM REQUIRED(mg/Kg/hr)**	**NO. OF FENTANYL BOLUSES**	**NO OF MEPHENTERMINE BOLUSES**
13	14	15	5.33	1.78	0.11	2	1
3	4	5	4.44	1.65	0.11	1	1
3	4	5	4.08	2.07	0.15	2	0
13	14	15	5.54	2.19	0.12	2	2
4	4	5	3.61	1.8	0.12	1	1
4	4	5	3.55	1.92	1.12	2	0
2	3	3	4.68	2	0.17	1	2
3	3	3	3.84	1.63	0.13	1	0
3	3	3	4.4	2.3	0.17	2	2
8	9	10	2.66	1.4	0.11	1	0
4	4	5	4.37	1.9	0.1	1	1
4	4	5	4.4	2.1	0.13	2	2
8	9	10	4.66	1.8	0.15	1	0
9	9	10	3.65	1.6	0.11	1	1
4	4	5	5.4	2.1	0.12	2	1
4	5	6	6.12	1.8	0.15	1	1
5	5	6	6.12	1.8	0.15	1	1
8	9	10	7.5	3.21	0.14	3	1
9	9	10	5.84	2.14	0.12	2	0
3	3	3	4.49	1.62	0.14	2	0

Group MRS							
SYSTOLIC BLOOD PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
130	128	136	136	104	104	106	130
130	115	140	140	150	154	156	130
100	120	120	120	124	120	110	100
110	124	124	124	131	124	118	110
124	110	128	128	120	128	124	124
126	140	128	128	111	124	120	126
108	90	120	120	100	115	113	108
128	116	130	130	118	115	110	128
131	110	122	122	106	112	120	131
120	130	130	130	113	130	140	120
120	147	122	122	145	132	136	120
120	123	124	124	132	125	124	120
140	124	136	136	130	156	138	140
117	120	128	128	98	114	118	117
126	117	127	127	125	125	128	126
110	110	120	120	108	118	108	110
134	122	136	136	114	110	108	134
138	122	136	136	124	120	118	138
110	124	130	130	111	132	132	110
130	118	128	128	108	106	108	130

Group MRS															
DIASTOLIC BLOOD PRESSURE (mmHg)								MEAN ARTERIAL PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**	**baseline**	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
80	88	77	77	71	70	59	80	113	114	116	116	93	92	90	113
80	87	98	98	90	110	110	80	113	105	126	126	130	139	140	113
80	60	70	70	78	70	80	80	93	100	103	103	108	103	100	93
72	68	88	88	78	87	74	72	97	105	112	112	113	111	103	97
84	72	86	86	78	86	80	84	110	97	114	114	106	114	109	110
84	92	88	88	95	87	81	84	112	124	114	114	105	111	107	112
70	70	60	60	62	85	78	70	95	83	100	100	87	105	101	95
78	72	80	80	76	72	68	78	111	101	113	113	104	100	96	111
80	70	74	74	69	74	81	80	114	96	106	106	93	99	107	114
84	90	72	72	77	80	88	84	108	116	110	110	101	113	122	108
70	116	74	74	100	92	96	70	103	136	106	106	130	118	122	103
78	88	76	76	90	91	84	78	106	111	108	108	118	113	110	106
80	86	82	82	80	92	84	80	120	111	118	118	113	134	120	120
76	80	79	79	70	76	84	76	103	106	111	111	88	101	106	103
78	77	79	79	90	86	90	78	110	103	111	111	113	112	115	110
84	88	74	74	84	86	78	84	101	102	104	104	100	107	98	101
84	80	80	80	64	60	82	84	117	108	117	117	97	93	99	117
82	78	80	80	80	76	76	82	119	107	117	117	109	105	104	119
84	80	68	68	74	95	88	84	101	109	109	109	98	119	117	101
80	76	78	78	68	64	88	80	113	104	111	111	94	92	101	113

Group MRS							
HEART RATE (per minute)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
78	70	75	77	70	72	72	78
63	63	68	64	64	62	63	68
95	95	98	88	89	89	88	98
84	82	82	88	80	80	81	88
80	78	85	80	78	77	78	85
90	88	94	92	90	91	92	95
70	66	75	66	68	67	68	75
72	66	75	66	68	67	68	75
71	66	75	66	68	67	68	75
65	63	68	64	64	62	63	68
84	82	82	88	80	80	81	88
80	78	85	80	78	77	78	85
90	88	94	92	90	91	92	95
65	65	70	64	65	66	66	70
79	75	80	78	78	76	76	84
82	82	82	88	80	80	81	88
79	70	75	77	70	72	72	78
76	70	75	77	70	72	72	78
60	65	70	64	65	66	66	70
70	66	75	66	68	67	68	75

Group MRS							
BIS VALUE							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
95	44	40	44	44	50	44	92
98	45	38	45	45	50	45	91
99	44	38	44	44	50	44	95
96	45	40	45	45	45	45	94
95	46	41	46	46	46	46	95
95	47	39	47	47	47	47	92
96	48	39	48	48	48	48	93
98	46	40	46	46	46	46	94
99	52	41	52	52	52	52	93
99	48	39	48	48	48	48	95
96	46	39	46	46	46	46	94
97	47	42	47	47	47	47	92
95	48	41	48	48	48	48	93
97	49	40	49	49	49	49	93
98	50	42	50	50	50	50	92
97	52	42	52	52	52	52	94
98	49	39	49	49	49	49	95
98	48	39	48	48	48	48	96
98	47	39	47	47	47	47	93
96	48	39	48	48	48	48	94

Group MRS								
SR.NO	**DATE**	**AGE (yrs)**	**SEX**	**WEIGHT (kg)**	**HEIGHT (cms)**	**BMI (kg/m2)**	**DIAGNOSIS**	**SURGERY**
21	10-Oct	20	M	58	165	21	Lt frontal FCD	Craniotomy and excision
22	26-Sep	18	M	85	165	31	Lt frontal FCD	Craniotomy and excision
23	22-Aug	18	F	68	165	24	Rt frontal FCD	Craniotomy and excision
24	16-May	34	F	57	148	26	Lt insular lesion	Craniotomy and excision
25	13-Jun	29	M	70	160	27.3	RT MTS	RT. ATL-AH
26	20-Mar	26	M	77	165	28	RT MTS	RT. ATL-AH
27	8-May	21	M	60	165	22	Rt temporal cavernoma	Craniotomy and excision
28	19-Dec	32	M	57	170	19	RT MTS	RT. ATL-AH
29	22-Nov	32	F	72	162	27.4	Rt frontal FCD	craniotomy and excision
30	4-Sep	27	F	46	155	20.4	left MTS	LT ATL-AH
31	1-Aug	34	M	58	158	23	Lt MTS	Lt ATL-AH
32	17-May	34	F	60	145	28	Lt insular lesion	Craniotomy and excision
33	14-Jun	30	M	70	160	27.3	RT MTS	RT. ATL-AH
34	17-Oct	22	F	67	165	24.6	RT MTS	rT. ATL-AH
35	8-Dec	23	M	68	160	26.5	Left frontal FCD	craniotomy and excision
36	5-Feb	37	M	72	170	24.9	Lt perisylvian gliosis	craniotomy and electrode placement
37	6-Feb	29	M	68	168	24	left MTS	LT ATL-AH
38	17-Feb	28	F	62	160	24.21	Lt temporal glioma	Craniotomy and excision
39	19-Feb	37	M	72	170	24.9	Lt perisylvian gliosis	LT ATL-AH
40	20-Feb	19	F	55	155	23	Rt temporal FCD	RT. ATL-AH

Group MRS								
ASA GRADE	**Antiepileptics**		**DURATION OF TREATMENT (months)**	**INDUCTION PROPOFOL (mg/kg)**	**MAINTAINANCE Ce(mcg/ml)**	**DURATION OF ANAESTHESIA (hours)**	**T0- time taken for eyeopening (minutes)**	**T1- time taken to obey commands (minutes)**
I	Oxcarbazepine	Clobazam	22	1.03	1.4	2.5	3	4
I	Oxcarbazepine	Clobazam	24	0.72	2.1	5.5	8	9
I	Oxcarbazepine	Clobazam	26	0.9	2.2	5	8	9
I	Carbamazepine	Clobazam	26	0.91	2.5	4.5	4	4
I	Carbamazepine	Clobazam	2	1.4	2	5	10	11
I	Carbamazepine	Clobazam	18	1.2	1.8	5	4	4
I	Oxcarbazepine	Clobazam	18	2	2.2	4.5	3	4
I	Carbamazepine	Clobazam	19	1.06	1.5	3.5	3	3
I	Escicarbazepine	clobazam	23	0.7	1.5	4	4	4
I	carbamazepine	clobazam	23	1.08	2	6	4	4
I	Oxcarbazepine	Clobazam	22	0.94	1.6	3.5	8	9
I	Carbamazepine	Clobazam	24	0.9	2.5	4	4	4
I	Carbamazepine	Clobazam	19	1.23	2	5	11	11
I	Oxcarbazepine	Clobazam	29	1.04	2.3	4	3	4
1	oxcarbazepine	clobazam	22	0.8	1.8	3.5	3	4
1	oxcarbazepine	clobazam	18	1.1	1.8	4	4	5
1	Oxcarbazepine	Clobazam	19	1.21	2	6	8	9
1	oxcarbazepine	clobazam	20	0.91	2.3	6	7	7
1	Oxcarbazepine	Clobazam	18	1.1	1.8	5	5	6
1	Oxcarbazepine	Clobazam	20	0.95	2.5	5	5	6

Group MRS					
T2 - EXTUBATION TIME (minutes)	**TOTAL PROPOFOL REQUIRED (mg/kg/hr)**	**TOTAL FENTANYL REQUIRED (mcg/kg/hr)**	**TOTAL ATRACURIUM REQUIRED(mg/Kg/hr)**	**NO. OF FENTANYL BOLUSES**	**NO OF MEPHENTERMINE BOLUSES**
4	4.05	2.5	0.18	2	0
10	3.74	1.36	0.1	1	0
10	3.5	1.6	0.11	2	0
5	4.4	1.7	0.11	1	1
12	3.14	1.62	0.17	1	0
5	4.8	1.87	0.1	2	0
5	5.1	2	0.12	1	1
3	3.73	2.6	0.17	2	0
5	3.95	1.63	0.1	1	0
5	6.7	1.59	0.14	2	0
10	2.51	2.6	0.13	1	0
5	4.3	1.7	0.11	1	1
12	3.1	1.62	0.17	1	0
5	2.9	2.2	0.15	2	0
4	4	2	0.14	1	0
5	4.8	1.87	0.1	1	0
10	3.5	1.62	0.17	1	0
8	4.4	1.7	0.11	1	1
6	4.7	1.8	0.1	1	0
7	4.4	1.7	0.11	1	1

Group MRS							
SYSTOLIC BLOOD PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
116	105	110	110	104	102	103	116
124	104	114	114	116	123	128	124
131	110	122	122	106	112	120	131
130	128	136	136	104	104	106	130
160	114	150	150	118	122	124	160
140	117	138	138	121	115	126	140
124	106	125	125	106	99	100	124
124	121	120	120	90	112	122	124
150	123	150	150	126	147	136	150
130	128	136	136	104	104	106	130
130	115	140	140	150	154	156	130
100	120	120	120	124	120	110	100
110	124	124	124	131	124	118	110
124	110	128	128	120	128	124	124
126	140	128	128	111	124	120	126
108	90	120	120	100	115	113	108
128	116	130	130	118	115	110	128
128	116	126	126	118	114	130	128
124	106	125	125	106	99	100	124
124	121	120	120	90	112	122	124

Group MRS							
DIASTOLIC BLOOD PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
78	69	79	79	63	71	67	78
84	68	81	81	85	85	92	84
80	70	74	74	69	74	81	80
80	88	77	77	71	70	59	80
80	78	90	90	61	82	80	80
100	78	90	90	86	84	80	100
84	59	75	75	66	58	60	84
80	83	80	80	55	69	78	80
90	82	84	84	84	96	88	90
80	88	77	77	71	70	59	80
80	87	98	98	90	110	110	80
80	60	70	70	78	70	80	80
72	68	88	88	78	87	74	72
84	72	86	86	78	86	80	84
84	92	88	88	95	87	81	84
70	70	60	60	62	85	78	70
78	72	80	80	76	72	68	78
84	82	84	84	72	76	84	84
84	59	75	75	66	58	60	84
80	83	80	80	55	69	78	80

Group MRS							
MEAN ARTERIAL PRESSURE (mmHg)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
103	93	99	99	90	91	91	103
110	92	103	103	105	110	116	110
114	96	106	106	93	99	107	114
113	114	116	116	93	92	90	113
133	102	130	130	99	108	109	133
126	104	122	122	109	104	110	126
110	90	108	108	92	85	86	110
109	108	106	106	78	97	107	109
130	109	128	128	112	130	120	130
113	114	116	116	93	92	90	113
113	105	126	126	130	139	140	113
93	100	103	103	108	103	100	93
97	105	112	112	113	111	103	97
110	97	114	114	106	114	109	110
112	124	114	114	105	111	107	112
95	83	100	100	87	105	101	95
111	101	113	113	104	100	96	111
113	104	112	112	102	101	114	13
110	90	108	108	92	85	86	110
109	108	106	106	78	97	107	109

Group MRS							
HEART RATE (per minute)							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
89	88	94	92	88	88	84	92
81	84	82	88	81	80	80	85
101	94	92	95	94	92	90	92
78	72	77	78	70	70	71	77
84	82	82	88	80	80	81	88
82	78	85	82	78	78	82	88
68	67	72	73	70	70	72	75
78	72	77	78	70	70	71	77
81	80	88	85	80	80	82	86
78	70	75	77	70	72	72	78
63	63	68	64	64	62	63	68
95	95	98	88	89	89	88	98
84	80	88	78	78	79	78	88
80	80	88	78	78	79	78	88
90	88	94	92	90	91	92	95
70	66	75	66	68	67	68	75
72	66	75	66	68	67	68	75
82	80	88	78	78	79	78	88
65	66	75	66	68	67	68	75
78	70	75	77	70	72	72	78

Group MRS							
BIS VALUE							
baseline	**induction**	**intubation**	**pinning**	**skin incision**	**duramater opening**	**closure**	**extubation**
95	44	40	44	44	44	50	90
98	45	38	45	45	45	45	92
99	44	38	44	44	44	54	91
96	45	40	45	45	45	52	95
95	46	41	46	46	46	52	94
97	47	39	47	47	47	47	95
98	48	39	48	48	48	48	92
99	46	40	46	46	46	46	93
97	47	41	47	47	47	47	94
98	48	39	48	48	48	48	93
96	46	39	46	46	46	46	95
97	47	42	47	47	47	47	94
95	48	41	48	48	48	48	92
97	49	40	49	49	49	49	93
98	50	42	50	50	50	50	93
97	52	42	52	52	52	52	92
98	49	39	49	49	49	49	94
98	48	39	48	48	48	48	95
98	47	39	47	47	47	47	96
96	48	39	48	48	48	48	93