PERIOPERATIVE COURSE OF PATIENTS WITH PRE-EXISTING NEUROLOGICAL DISORDER UNDERGOING ANAESTHESIA FOR NON-NEUROLOGICAL SURGERY: A PROSPECTIVE OBSERVATIONAL STUDY

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfilment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

ANAESTHESIOLOGY AND CRITICAL CARE

JULY, 2020 **DR ATHUL V**

AIIMS, JODHPUR

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DECLARATION

I hereby declare that the thesis titled **"PERIOPERATIVE COURSE OF PATIENTS WITH PRE-EXISTING NEUROLOGICAL DISORDER UNDERGOING ANAESTHESIA FOR NON-NEUROLOGICAL SURGERY: A PROSPECTIVE OBSERVATIONAL STUDY"** embodies the original work carried out by the undersigned at All India Institute of Medical Sciences, Jodhpur.

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All India Institute of Medical Sciences, Jodhpur

All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

Certified that the submitted thesis titled **"PERIOPERATIVE COURSE OF PATIENTS WITH PRE-EXISTING NEUROLOGICAL DISORDER UNDERGOING ANAESTHESIA FOR NON-NEUROLOGICAL SURGERY: A PROSPECTIVE OBSERVATIONAL STUDY"** is a record of the research work undertaken by Dr ATHUL V under our guidance and supervision in the Department of Anaesthesiology and Critical Care at All India Institute of Medical Sciences, Jodhpur.

DR PRADEEP BHATIA
Professor and Head
Department of Anesthesiology and Critical Care
All India Institute of Medical Sciences, Jodhpur

CERTIFICATE

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As I am near the completion of one of the most difficult academic pursuits, the MD thesis, I'd be negligent if I didn't convey my gratitude to everyone who helped me to get there. This massive project could not have been finished without the blessings of God, the unbelievable support of my family, the guidance and help of professors, seniors and friends.

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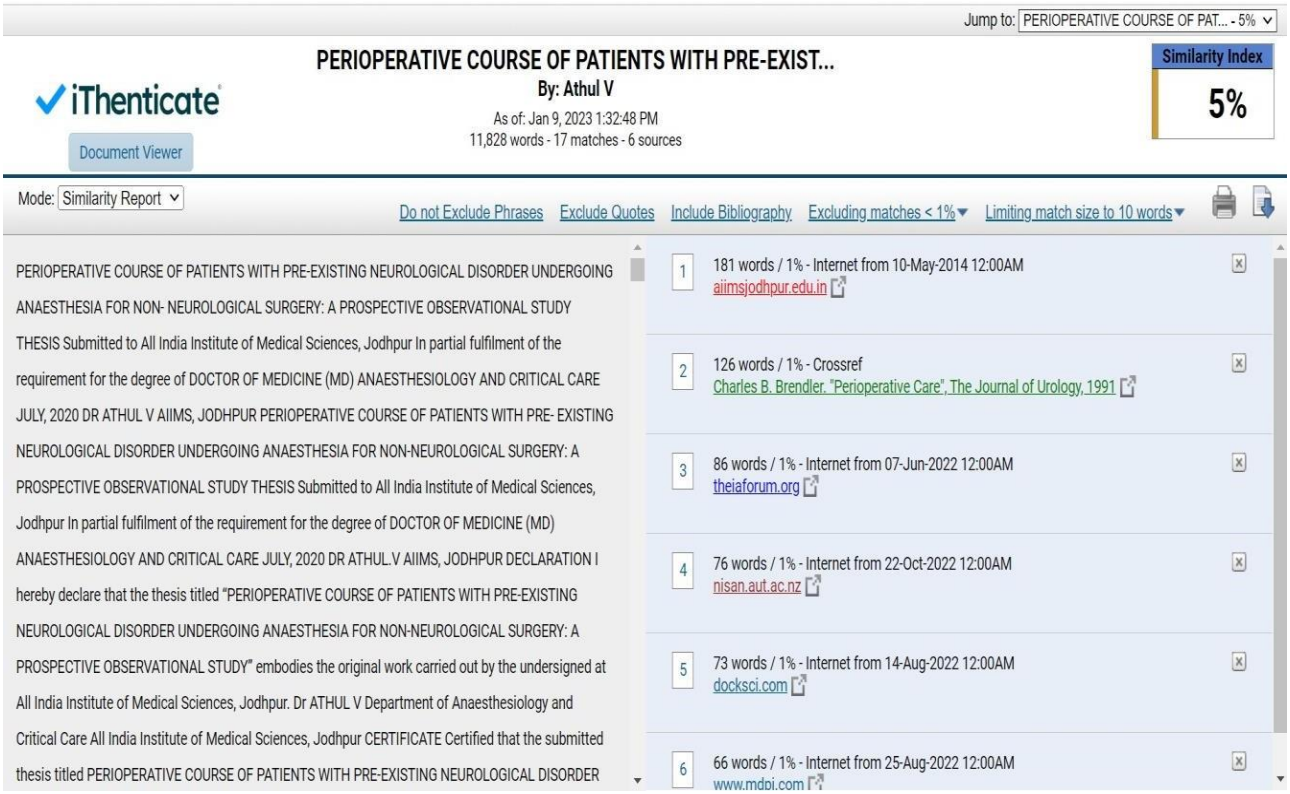
PLAGIARISM REPORT



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LIST OF ABBREVIATIONS

ABBREVIATION	EXPANSION
ABPM	Ambulatory Blood Pressure Monitoring
AED	Anti-Epileptic Drug
AOR	Adjusted Odds Ratio
AVM	Arteriovenous Malformation
BIS	Bispectral index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclooxygenase
DAPT	Dual Antiplatelets
DKA	Interquartile range
DM	Diabetes Mellitus
GA	General Anaesthesia
GI	Gastrointestinal
GTCS	Generalized Tonic Clonic Seizure
HR	Heart rate

HRV	Heart Rate Variation
IV	Intravenous
MAO	Monoamine oxidase
MCA	Middle Cerebral Artery
MDCT	Multidetector Coronary Computed Tomography
MMGA	Multimodal General Anesthesia
PAC	Preanesthesia check up
RA	Regional Anesthesia
RCRI	Revised Cardiac Risk Index
SANAD	Standard And New Antiepileptic Drug
TIA	Transient Ischemic Attack
TOF	Train Of Four
VT	Ventricular Tachycardia
WHO	World Health Organisation

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SUMMARY

Background: Patients with diseases affecting the central nervous system may need to undergo surgery to treat the neurological condition or surgery unrelated to neurological disorder. It is very important to have knowledge of the underlying neurological disorder, anaesthetic techniques, drugs and monitoring modalities. The neurological disorder's perioperative course is influenced by the condition itself, medication management, the anaesthetic method, comorbidities etc. The choice of medications and perioperative management of anaesthesia may be affected by a variety of neurological conditions, including stroke, epilepsy, and Parkinson disease. Knowledge about the perioperative course of patients with pre-existing neurological diseases is important to reduce morbidity and mortality.

Objectives: The study's objective was to ascertain the postoperative outcomes of adult patients with pre-existing neurological diseases scheduled for non-neurological surgery. The patient characteristics, comorbidities, medication management, intraoperative events, postoperative events up to 30 days were noted to determine the perioperative course of these patients.

Methods: Patients of either gender aged more than 18 years scheduled to undergo surgical/diagnostic procedure under general anaesthesia were included in the study. These patients' medical history were recorded in the preoperative clinic. Complete information about neurological disorders was recorded, including medical history, comorbidities like diabetes mellitus and hypertension were identified. Preoperative medication management was recorded. According to the patient's record form, both intraoperative events and postoperative problems were recorded. Any important intraoperative occurrence, such as an arrhythmia, changes in the hemodynamic parameters, or the escalation of a neurological illness, was noted. Any new development of weakness, an exacerbation of the underlying neurological condition, or any other medical complications in the postoperative period were reported as postoperative occurrences. Patients were telephonically and physically followed up after surgery up until the 30^{th} postoperative day.

Results: Fifty five patients were included in the study, of which, 39 had history of stroke, 8 had history of epilepsy, 4 had Parkinson disease, two patients had history of

both stroke and epilepsy and two patients had history of both stroke and Parkinson disease. Thus, we studied the perioperative course of 59 neurological diseases. Most of the patients were elderly with an overall mean ± SD age of 57.6±17.2 years. 60.5% of stroke patients and 33.3% of patients with Parkinson disease were hypertensive. 14% of the stroke patients had a history of coronary artery disease while none of the patients with epilepsy or Parkinson disease had such history. 78% cases were done under GA and 22% cases in regional anaesthesia.

We found that 34.9% of stroke patients had residual paralysis and 37.2% patients were not taking DAPT. Among stroke patients 55.8% patients had an uneventful intraoperative period while 34.9% had hypotension and 9.3% had hypertensive episodes. Among patients having hypotension, 16.3% had post induction hypotension and 18.6% patients were on vasopressor support. Postoperative period was uneventful for 79% while delirium was present in 9.3% patients. Out of 43, 3 patients died in the postoperative hospital stay while one died at home within 30 postoperative days.

Among the 10 patients with epilepsy, 80% patients were taking antiepileptic medication and 20% patients were not taking any medications. Intraoperative period was uneventful in 80% patients and 20% had hypotension. Post operative period was uneventful in 70% patients while one of the patients had generalised seizures within 30 postoperative days.

Among the 6 patients with Parkinson disease, all patients were taking syndopa. Intraoperative period was uneventful in 50% patients and 50% patients had hypotension. One of the patients died during the postoperative hospital stay.

Conclusion: Patients with pre-existing neurological disease undergoing anaesthesia for non-neurological surgeries are having an unpredictable perioperative course, which may be due to the brain insult itself or may be due to associated comorbidities. Preoperative neurologist consultation will be useful for modification of the medications before surgery especially in patients with parkinson disease. Modalities which can reduce the exposure of anaesthetic drugs can also help to improve the perioperative outcome.

INTRODUCTION

Neurological diseases are common in the general population and patients with neurological diseases frequently present for non-neurosurgical procedures. Collectively, these diseases include a wide range of disorders which have different pathophysiology, age of presentation, management strategies etc. Common neurological diseases which are seen in the perioperative period are cerebrovascular diseases e.g. stroke, epilepsy, Parkinson disease, neuromuscular disorders, dementia etc.[1] Additionally, the patients might present for elective or emergency diagnostic or therapeutic procedures. Nevertheless, irrespective of the type of pre-existing neurological disease, it is imperative to know the underlying pathophysiology of a particular disease and considerations arising out of a particular surgical scenario. Perioperative risks are higher with certain non-neurosurgical procedures than others.[2,3,4]

The goal of anaesthesia management of patients with pre-existing neurological diseases involves planning the most appropriate anaesthesia technique which minimises the chances of neurological decompensation while preventing intraoperative and postoperative adverse events.[1,2] The management of the medications being used for the neurological disease and evaluating new neurological changes in the perioperative period are of paramount importance.

Changes in the cerebral metabolic rate and cerebral blood flow during anesthesia and surgery are known to result in new onset neurological events intraoperatively or postoperatively. Hence, it is logical to mention that pre-existing neurological disease might get exacerbated in the perioperative period. The role of anesthetics and anesthesia techniques has been explored and so has been the role of altered hemodynamics in the perioperative period.

Perioperative stroke is defined as a stroke occurring within 30 postoperative days.[5] The stroke could be clinically recognisable or unrecognisable with a reported incidence of 0.1-0.8% and 7% respectively. The patient-related factors are older age, co-existing cardiovascular disease, history of stroke, renal disease, diabetes, COPD, female gender, tobacco use, non-cardioselective beta blocker therapy etc. The surgical factors include cardiac surgery, neurosurgery, major vascular surgery, transplant

surgery, shoulder surgery in beach chair position, head and neck surgery etc.[3,6] Prior history of stroke is not only a risk for perioperative stroke but also for cardiovascular morbidity and mortality.[7] Available literature suggests that risk of recurrent stroke within 30 postoperative days might be 4 to 16 times greater in patients with a history of stroke than without.[8] The perioperative stroke is more commonly ischaemic in nature than the haemorrhagic type.[9,10] The underlying mechanism could be embolic, thrombotic, haemodynamic or a combination of these. Various intraoperative parameters and events (hypotension, hypocarbia, hypercarbia) have been studied but direct causal relationships have not been established.[2]

Epilepsy is a neurological disorder characterized by recurrent seizures (two or more) with brief episodes of involuntary movement that may involve a part of the body (partial/focal) or the entire body (generalized) and may be accompanied by loss of consciousness and bowel/bladder incontinence.[11] Absence seizures do not present with involuntary movement but just transient loss of consciousness. Irrespective of the type of seizures, the patients with epilepsy are prone to injuries resulting from seizures and might present for surgery for injury related causes or otherwise. Surgical patients with epilepsy are more prone to postoperative complications than those without. Breakthrough seizures in the perioperative period have been observed in 3.4% patients with epilepsy.[12] The risk factors include poor preoperative seizure control, frequency of seizures and the most recent seizure. The intravenous anaesthetics have both pro and anti-convulsant effects, though the incidence of general anesthetic-induced seizures is not known. Additionally, acid-base imbalance, perioperative alcohol or drug withdrawal, perioperative stroke can cause seizures in the perioperative period [11,12]

Parkinson disease is a neurodegenerative disease with slow progression. It can manifest with motor and non-motor symptoms.[13] The cardinal motor symptoms start to appear when at least 80% of the dopaminergic cells are lost in the nigro-striatal system.[14] Bradykinesia, muscle rigidity, resting tremors, postural instability are common clinical features for diagnosis which is confirmed by unilateral onset and persistent asymmetry of symptoms. There is a good response to medication i.e levodopa. Additionally, autonomic dysfunction is an important manifestation and is characterised by orthostatic hypotension, thermal dysregulation, abnormal sweating,

and sialorrhea. The main perioperative considerations in the surgical patients with Parkinson disease are the need for assessment of pulmonary, swallowing, volume status and medication management. These patients are susceptible to cognitive impairment in the postoperative period.[15]

Pre-existing neurological diseases have important anaesthetic considerations and the perioperative course of the patients also depends on patient-, disease- and surgery-specific factors. We performed an observational study to determine the perioperative course of pre-existing neurological disease in patients undergoing non-neurological surgery at our institute.

AIMS AND OBJECTIVES

The aim of the study was to determine the perioperative course of adult patients who have pre-existing neurological disorders and are scheduled to undergo non-neurological surgery. The objective was to record the associated comorbidities, medication management, intraoperative events, postoperative complications (up to 30 days) in these patients.

The pre-existing neurological disorders will include but will not be limited to:

- Cerebrovascular Disease
- Epilepsy and Seizures
- Headache
- Neuromuscular Disease and Muscular Dystrophy
- Demyelinating Diseases
- Dementia

REVIEW OF LITERATURE

In spite of all the advances in anaesthesia we clearly don't know the exact neuroscience behind anaesthesia and how anaesthetic causes loss of consciousness in a normal brain. The effect of anaesthetic agents and techniques in patients with neurological diseases is less studied. Some of the common neurological diseases are stroke, epilepsy, and Parkinson disease. The lifetime prevalence of neurological diseases is 6%.[16] Stroke is one of the common neurological diseases that affects 13.7 million people and kills around 5.5 million people annually. Epilepsy is the second most common neurological disease with 70 million people suffering from it worldwide of which 90% of the patients are from developing nations.[17] Parkinson disease affects one million people of age 60.[18] About 1% of people over 60 have Parkinson disease and it's one of the most prevalent neurological conditions that causes disability.

STROKE

The burden of stroke has increased considerably over the past 30 years and is now the second greatest cause of death and disability worldwide. Earlier WHO defined stroke as rapidly developing clinical evidence of focal or global disturbance of cerebral function, lasting >24 hours or leading to death, with no evident cause other than that of vascular origin and transient ischaemic attack (TIA) as sudden onset of a focal neurological symptom and sign lasting 24 hours and caused by reversible cerebral ischemia.[19] In the past, stroke was referred to as a circulatory system disorder. However, the definition has altered, and the involvement of brain tissue has been added as well, making stroke a brain disease rather than a circulatory system disease.

The time-based components noted in the traditional WHO definition have been eliminated, and the new American Heart Association/American Stroke Association definition of stroke now includes silent or subclinical tissue-based strokes that can only be detected with more sensitive brain imaging and the most recent epidemiological studies. Acute focal neurological impairment brought on by focal infarction at one or more places in the brain is known as a cerebral ischemic stroke. Neuroimaging or another approach in the clinically pertinent area of the brain may show evidence of

acute infarction if symptoms persist for more than 24 hours or the duration of symptoms is >24 hours.[16,19]

It is important to have a basic knowledge about the blood supply of the brain before studying stroke. Left MCA artery is the most common artery involved in stroke.Anterior cerebral artery stroke are rare with an incidence of 0.3 to 4.4%.Two internal carotids located anteriorly and two vertebral arteries located posteriorly which form the circle of Willis control the blood flow to the brain.The anterior and middle cerebral arteries, two significant cerebral arteries, are created by the internal carotid arteries branching. The midline basilar artery is formed when the right and left vertebral arteries confluence at the level of the pons on the ventral portion of the brainstem. Other arteries include posterior cerebral arteries,anterior and posterior communicating arteries.[27]

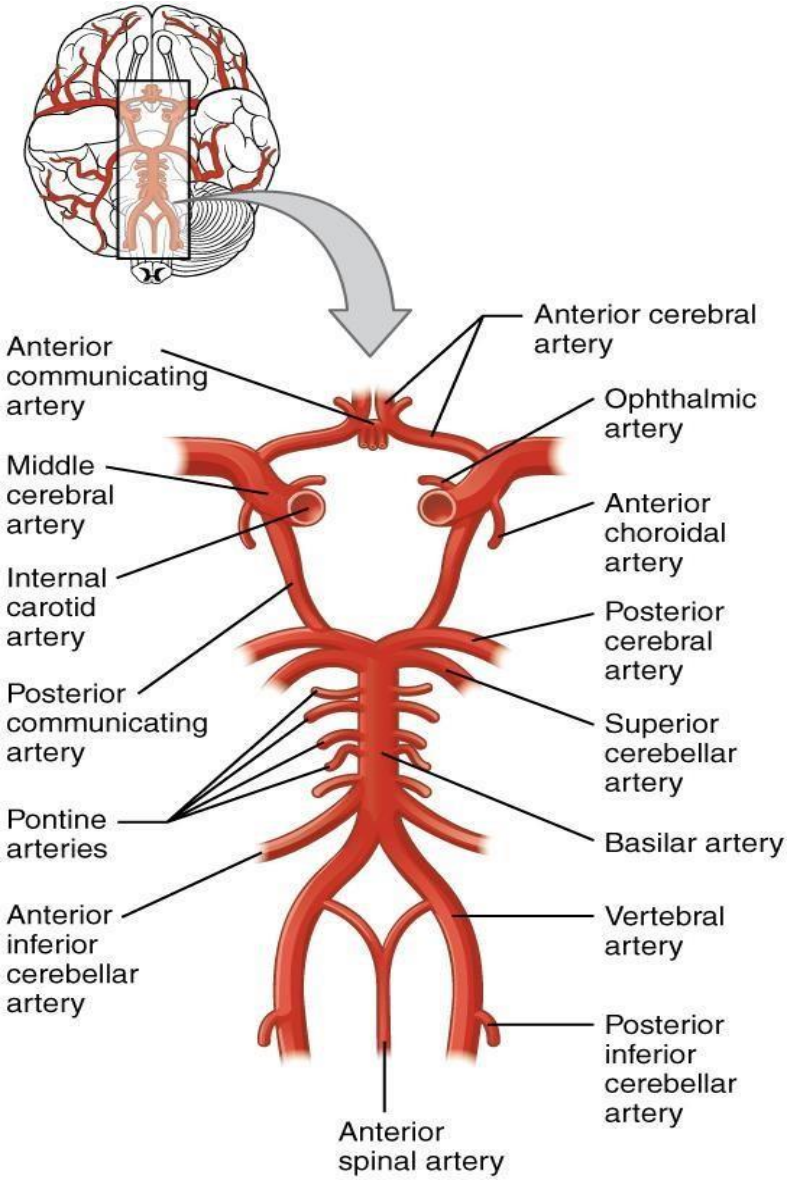

Figure 1: Blood supply of the brain; the circle of Willis

The middle cerebral artery (MCA) is the most commonly involved artery in acute strokes. It has four main branches, designated M1, M2, M3, and M4, and it splits off immediately from the internal carotid artery. Parts of the frontal, temporal, and parietal lobes of the brain as well as deeper brain structures including the caudate, internal capsule, and thalamus receive blood supply from MCA.[26]

Plaque accumulation in the cerebral arteries eventually causes the vascular chamber to narrow and clot, leading to thrombotic stroke. In an embolic stroke, an embolus reduces blood flow to the affected area of the brain. Reduced blood supply to the brain results in extreme stress and premature cell death and necrosis. After necrosis, the plasma

membrane is disrupted, organelles enlarge and leak cellular contents into extracellular space and neuronal function is lost.[20] Inflammation, energy failure, loss of homeostasis, acidosis, elevated intracellular calcium levels, excitotoxicity, free radical-mediated toxicity, cytokine-mediated cytotoxicity, complement activation, impairment of the blood-brain barrier, activation of glial cells, and oxidative stress are additional important events that contribute to stroke pathology.[21]

Risk factors

The risk factors for stroke could be modifiable and non-modifiable. (Table 1) One of the main risk factors for stroke is hypertension.[22] Blood pressure (BP) levels above 115/75 mm Hg, increases the risk of stroke. Nearly two thirds of stroke burden worldwide is related to non-optimal BP. Two thirds of this burden affects people in their middle years (45 to 69 years)[23] After age 55, the incidence of stroke doubles. Stroke incidence rises with age. However, an alarming trend shows that between 1990 and 2016, the percentage of stroke cases worldwide among adults aged 20 to 54 rose from 12.9% to 18.6%.[24]

Diabetes mellitus (DM) results in a 20% higher death rate and increases the risk of having an ischemic stroke. Additionally, people with DM have a worse prognosis than non-diabetic patients after a stroke, including higher rates of severe impairment and delayed recovery.[25]

Table 1: Risk factors for stroke

Non modifiable risk factors	**Modifiable risk factors**
Age	Hypertension
Sex	Diabetes mellitus
Race	Smoking
	Alcohol abuse
	Physical inactivity
	Hyperlipidaemia
	Atrial fibrillation

Perioperative stroke

In patients undergoing non cardiac and non-neurological surgeries incidence of perioperative stroke is 0.1 to 1%.[5,22] The majority of postoperative strokes are ischemic. Patients having significant vascular, neurologic, or cardiac surgery are most at risk. After a stroke, elective surgery should be postponed for up to 9 months to allow for the recovery of cerebral autoregulation and the elimination of risk factors.[22] When compared to patients who do not experience a stroke, those who experience a perioperative stroke have an eightfold greater risk of passing away within 30 days of surgery. [28]

Table 2: Risk factors for perioperative stroke

Patient related factors	**Surgery related factors**
Age	Vascular surgeries
Hypertension	Abdominal exploration
MI within 6 months	Small bowel resection
Renal dysfunction	Amputation
COPD	Perioperative metoprolol use
TIA	
Smoking	
Atrial Fibrillation	

Landercasper J et al studied 173 consecutive patients with a history of previous cerebrovascular accidents during an 8-year period, and underwent general anesthesia for surgery. Five patients (2.9%) had documented postoperative cerebrovascular accidents from 3 to 21 days (mean, 12.2 days) after surgery. The risk of postoperative cerebrovascular accident did not correlate with age, sex, history of multiple cerebrovascular accidents, poststroke transient ischemic attacks, American society for anaesthesia physical status, aspirin use, coronary artery disease, peripheral vascular disease, intraoperative blood pressure, time since previous cerebrovascular accident, or cause of previous cerebrovascular accident. Postoperative stroke was more common in patients given preoperative heparin sodium. They concluded that the risk of perioperative stroke is low (2.9%) but not easily predicted and that the risk continues

beyond the first week of convalescence. Unlike myocardial infarction, cerebral reinfarction risk does not seem to depend on time since previous infarct.[29]

Autonomic instability in stroke

The circulatory, respiratory, and sudomotor systems show autonomic dysfunction after a stroke. Although the exact mechanism is not fully known, numerous studies suggest an anatomical asymmetry between the right and left cerebral hemispheres in the modulation of autonomic nervous system activity of the central nervous system. Autonomic dysfunction is a common complication of cerebrovascular disorders but is not limited to cardiovascular manifestations. Autonomic dysfunction secondary to stroke extends to sudomotor, vasomotor, impotence, and urinary dysfunction.[30]

Korpelainen JT et al studied 31 patients with hemispheric brain infarction on the middle cerebral artery area, underwent HRV(Heart Rate Variation) analysis during the acute phase as well as at 1 and 6 months following the initial event. None of the participants in the study had any signs of primary cardiovascular illness, and none of them were taking any drugs that would have affected autonomic function. It was discovered that decreased HRV was related to the magnitude and severity of the infarct rather than its location. This difference persisted one and six months after the acute stroke began.[31]

Stroke and cardiac diseases

Sobiczewski W et al in a prospective study investigated the association between Coronary artery disease and Stroke in 1,183 participants who were recommended for diagnostic coronary angiography with no history of stroke. The COX proportional hazard regression model was used to investigate the correlation between stroke and coronary artery disease. 50 strokes took place during the follow-up period (mean 6.7 years). Multi-vessel coronary artery disease was more common in the group who had suffered strokes (62 vs. 46%, p 0.01) Multivessel CAD and the stroke hazard ratio (HR) of 1.8 were both strongly correlated in the COX proportional hazard regression model (CI 1.03–3.43).[32]

Stroke is one of the six clinical risk predictors updated Goldman's cardiac risk index; Lee et al. created the Revised Cardiac Risk Index (RCRI) in 1999. Each of the six clinical risk predictors used by the RCRI is given equal weightage.[33]

Table 3: Revised Cardiac Risk Index

Risk factors	**Points**
History of ischemic heart disease	1
High risk type of surgery	1
History of congestive heart failure	1
History of cerebrovascular disease	1
Preoperative treatment with insulin	1
Pre operative creatinine > 2.0mg/dl	1

Total Points	**RCRI Class**	**Risk of major adverse cardiac event**
0	I	0.40%
1	II	0.90%
2	III	6.60%
3 or more	IV	11%

Kim YD et al conducted a retrospective investigation in a prospective cohort of patients who had successive ischemic strokes. From the 3117 patients registered 1842 patients (MDCT (+) group) (Multidetector Coronary Computed Tomography) and 1275 patients (non MDCT group). The group's rates of fatalities, cardiovascular incidents, and recurrent strokes were compared. During follow-up, acute stroke patients who received MDCT had fewer fatalities, cardiovascular incidents, and recurrent strokes.[34] This study indirectly showed that ischemic stroke patients are at risk of developing cardiovascular events.

Stroke and delirium

Postoperative delirium is described as the sudden onset of confusion, disorientation, emotional dysregulation, perceptual problems, and sleep disruptions within a specific time frame.[35] Decreased risk of cognitive impairment is observed with TIVA, dexmedetomidine, ketamine, and EEG-guided anaesthesia[36].

Shankar A et al did study on perioperative multimodal general anaesthesia focusing on specific CNS targets (THE PATHFINDER TRIAL). In this non-randomized

prospective observational feasibility experiment, they developed MMGA exclusively for cardiac procedures. Twenty patients aged 60 or older undergoing on-pump coronary artery bypass graft (CABG) surgery or combined CABG/valve surgery were enrolled. Remifentanil, ketamine, dexmedetomidine, magnesium, were delivered intravenously in combination with a pecto-intercostal fascia block to produce antinociception. Propofol was administered while being monitored by an electroencephalogram and was used to induce unconsciousness. Postoperative delirium and intraoperative EEG suppression episodes were reported to be uncommon.[37]

EPILEPSY

In the general population, there is a 3% probability of developing a chronic seizure disease and an 8% to 10% lifetime risk of having a single seizure.[38] Epilepsy affects almost 50 million people globally. According to estimates, 60 to 70% of epileptics will experience a seizure-free period.[39] According to the THAI incidents study of perioperative convulsion, the incidence of perioperative convulsion was 3.1 per 10,000 surgeries.[40]

Causes of seizures in perioperative period

According to Akavipet et al, anaesthesia was a minor contributor to perioperative seizure. Medication error and human mistakes were the common risk factors. Some of the other common causes of perioperative seizures are given below.

1) Breakthrough seizures

A person who is having epilepsy under good, consistent control as shown in the medical records and subsequently experiences another seizure is said to be experiencing a breakthrough seizure.[12] Bonnet et al analysed the standard vs new antiepileptic drug in SANAD study. 34% of those recruited into SANAD went on to experience their first breakthrough seizure. The probability of a first breakthrough seizure was higher in patients with neurological damage, frequency of tonic-clonic seizures,and time to reach the initial phase of 12-month remission. 63% of subjects who experienced their initial breakthrough seizure afterwards experienced another seizure.[41]

2) Anaesthetic agent

IV anaesthetic agents - It appears that some anaesthetics have both proconvulsant and anticonvulsant effects. Inherent pharmacodynamic heterogeneity in the response of inhibitory and excitatory target tissues in the CNS is one potential contributing factor. iv agents like propofol, etomidate, benzodiazepines, thiopentone have antiepileptic activity. In epileptic population etomidate, ketamine, methohexital, benzodiazepine has a proconvulsant effect.In both individuals with and without a history of seizure disease, local anaesthetics are well-known convulsants.[42]

Inhalational agents- Enflurane is epileptogenic. Isoflurane and sevoflurane have both anticonvulsant and proconvulsant properties. On comparison sevoflurane have more epileptogenic property than isoflurane.[43]

3) Previous history of stroke - The leading cause of epilepsy in the aged population is cerebrovascular illness.[44]After ischemic strokes, there are a number of reasons why early onset seizures occur. Hypoxia, metabolic dysfunction, global hypoperfusion injury, increased intracellular Ca2+ and Na+ with a resulting lower threshold for depolarization, glutamate excitotoxicity, and hyperperfusion injury (especially after carotid endarterectomy) have all been proposed as putative neurofunctional etiologies. It is believed that seizures following hemorrhagic strokes are induced by irritation from blood metabolic by products.[45]

Niesen AD et al retrospectively examined the medical records of all patients who had received anaesthesia and who had a history of seizures. Demographic information on the patient, the kind of seizure disorder, specifics of the surgical treatment, andclinically evident seizure activity within three days of the anaesthesia were all noted. 641 individuals with a history of seizures were admitted for at least 24 hours following anaesthesia over the course of the six-year study period. 22 patients had seizures after surgery, for a total frequency of 3.4% (95% confidence interval, 2.2%-5.2%). The chance of having a perioperative seizure was found to be substantially correlated with both the frequency of preoperative seizures and the timing of the most recent seizure. The frequency of perioperative seizures in this patient population was unaffected by the kind of surgery or anaesthesia used (general anaesthesia, regional anaesthesia, or managed anaesthesia care).[46]

Akavipat P et al did an incidence study on perioperative convulsions. The Thai Anesthesia Episodes Study (THAI Study) database was mined for information on postoperative convulsion incidents, including demographic information, event details, outcomes, contributing factors related to anaesthesia, and corrective measures. From all 172,592 anaesthetics, the incidence of perioperative convulsion was 3.1 per 10,000. 73.59% of patients fully healed within 24 hours. Anesthesia was only a modest risk factor (30.19%), with the bulk of risk variables being associated with surgery (67.92%) and patient factors (54.72%). Medication error (43.75%) and human error (poor care, inadequate knowledge, and inadequate communication) (43.75%) were the contributing causes in anaesthesia. Medication mistakes and human error were the main risk factors.[40]

Schneider F et al studied the incidence epileptic seizures and epileptic discharges in epilepsy patients anaesthetised with propofol. A study was conducted on 33 partial epileptic patients who were chosen for video electrocorticography monitoring. 23 of them underwent epilepsy surgery and underwent at least one year of follow-up. Subdural electrodes were surgically removed while being sedated with propofol. There were no seizures found. In 8 of the 33 patients (24.2%), spike-burst-suppression patterns were present. Three (60%) of those five patients who underwent epilepsy surgery recovered from their seizures.[47]

Benish SM et al conducted a retrospective evaluation of all patients with seizure disorders who underwent general anaesthesia between 1995 and 2005. Six of the 297 incidents (2%) were linked to clinical seizure activity: one occurred during intubation and the other five occurred during the surgery but before coming out of general anaesthesia. With a mean age of 8 years, five of the six patients were children, five of whom had intractable seizure disorders and were taking multiple AEDs. Acute benzodiazepine medication was necessary for one of the six individuals to stop seizure activity. One out of every 122 adult procedures (0.8%) and five out of every 174 paediatric procedures (3.3%) resulted in anaesthesia-related seizures. There were no seizures in any of the 11 individuals who also had spinal or local anaesthetic.[48]

PARKINSON DISEASE

It is a clinical syndrome that includes resting tremors, bradykinesia, rigidity, postural instability, shuffling gaits, flexed postures, masked faces, and micrographia and a favourable response to levodopa.[49] Dysautonomia, sleep issues, depression, and dementia are further symptoms.[50] Parkinson's disease affect men more than women and it affects about 1% of people over 60.[51,52]

The single biggest risk factor for the onset of this disease is growing older. As a result of the characteristic loss of dopaminergic fibres that are typically seen in the basal ganglia, regional dopamine concentrations are diminished. Dopamine is thought to slow down the neurons that govern the extrapyramidal motor system's firing rate.[28]

Preoperative consideration

The majority of those affected are over 65 and present with geriatric issues such prostate surgery, accidental general surgical operations, cataract, gynaecological surgeries, etc.[53]Patients with long-term parkinsonism take a number of medications, some of which may interfere with agents used during anaesthesia.

1) Upper airway obstruction - Hypophonia is the most typical symptom of upper airway involvement in Parkinson disease patients. Approximately 70% of Parkinson disease patients have this symptom.The thyroarytenoid muscles' stiffness and fatigability during vocalisation cause hypophonia. Along with this sialorrhea, gastric dysmotility and dysphagia are also present which can contribute to a difficult airway during intubation. It may also lead to aspiration. Patients with Parkinson disease may require intubation more frequently than those without these symptoms when sedated.[54]

2) Medications - Many adverse reactions to levodopa have been reported, including dyskinesias and psychological problems. Increased amounts of circulating dopamine produced when levodopa is converted may be the cause of the elevated myocardial contractility and heart rate observed in treated patients. In treated patients, orthostatic hypotension may be apparent. Levodopa therapy gastro-intestinal side effects include nausea and vomiting.[28]

A sudden reduction or withdrawal of dopaminergic medications, notably levodopa, can be fatal and result in parkinsonism hyperpyrexia syndrome. These symptoms, which include altered mental status, stiffness, tremors, fevers, and autonomic dysfunction, are similar to those of neuroleptic malignant syndrome. Mortality is reported to be 4% in treated individuals and 20% in untreated patients, with an overall incidence of 4%.[55]

It is advised to stop taking monoamine oxidase-B inhibitors, such as rasagiline or selegiline, one to two weeks before surgery. These drugs interact with opioids, raising the risk of serotonin syndrome and contributing to labile blood pressure.[56,57]

3) Orthostatic hypotension- Neurogenic orthostatic hypotension is due to failure of the autonomic nervous system to regulate blood pressure in response to postural changes due to an inadequate release of norepinephrine, leading to orthostatic hypotension and supine hypertension.[58] MAO inhibitors are advised to stop 2 weeks before surgery.

4) Pulmonary functions - Patients with Parkinson disease are more likely to experience postoperative pulmonary problems due to the rigidity and bradykinesia of their respiratory muscles. The restrictive dysfunction may become even more exacerbated by kyphosis, pharyngeal dysfunction, and sialorrhea.[59] Although they are not frequently done before high-risk surgery, preoperative pulmonary function tests and arterial blood gas measurements can be acquired in order to create a baseline or help with surgical risk assessment. Incentive spirometry, percussion, early mobilisation are advised for post operative care. [55]

Mueller MC et al studied the perioperative risk profile for individuals with Parkinson disease undergoing surgery. Retrospective matched-pair analysis was used to compare 51 Parkinson disease patients treated in the general, visceral, thoracic, vascular, and trauma surgery departments during a 13-year period with 51 healthy controls. Parkinson disease patients undergoing surgery had a higher risk of morbidity. Falls following surgery happened more frequently (across the board, $p = 0.03$). Postoperative falls (p 0.04), postoperative stay (p 0.03), and overall treatment duration (p 0.02) were all considerably longer in Parkinson disease patients treated in the trauma surgery department than in patients without Parkinson disease.[60]

MATERIAL AND METHODS

Study setting

The observational study was conducted in the Department of Anaesthesiology and Critical Care at AIIMS Jodhpur after approval from the Institutional Ethics Committee (vide letter no. AIIMS/IEC/2021/3322 dated March 12, 2021). Registration with the clinical trials registry of India was done prior to the recruitment of patients (CTRI/2021/04/042612) on 22/04/2021.

Study participants

Adult patients (age > 18 years; ASA physical status 1 to 4), with pre-existing neurological diseases scheduled to undergo elective/ emergency non-neurological surgery were included in the study. Pregnant patients and the patients who do not consent to participate were excluded from the study.

Methodology

All adult patients having pre-existing neurological disorders posted for elective or emergency surgery were included in the study. Pre-operative history of these patients was noted in the proforma in the PAC clinic. Complete history pertaining to neurological disorders was noted including medical history, and whether recent neurologist consultation has been sought or any specific investigation pertaining to neurological disorders has been done. Comorbidities like hypertension, diabetes mellitus were noted. Preoperative advice regarding medication management was noted. The choice of anaesthetic technique was left to the discretion of the anaesthesiologist in charge. Intraoperative events and the postoperative complications were noted as per patient's record form. Any significant intraoperative event like greater than 20% increase or decrease in hemodynamic parameters, aggravation of underlying neurological disorder or any other significant events like arrhythmias etc was noted. Post operative events like aggravation of underlying neurological disorder, any new onset of weakness or any other medical complication in the post op period were noted. Postoperatively patients were followed up physically till discharge and till 30th postoperative day telephonically.

Statistical analysis

Data collected were tabulated in the MS Excel spreadsheet. Categorical data was presented as number or ratio. Continuous data was expressed as mean ± standard deviation/error while ordinal data as median and interquartile range.

RESULTS

A total of 55 patients were included in the study. Of these, 39 had history of stroke, 8 had history of epilepsy, 4 had Parkinson disease, two patients had history of both stroke and epilepsy and two patients had history of both stroke and Parkinson disease. Thus, we studied the perioperative course of 59 neurological diseases. Among the 59 neurological diseases, 43 were stroke, 10 epilepsy and 6 Parkinson disease. All the patients were assessed throughout the perioperative period. Preoperatively a thorough history was taken including the course of disease, medication history along with routine anaesthetic check-up. Patient's demography, comorbidities, medication history, type of surgery, intraoperative and postoperative events were noted. Among the 43 stroke patients, three patients died in the postoperative period and remaining 40 patients were followed up for 30 days of which 4 were lost to follow up. Among the 10 epilepsy cases, all patients were followed up for 30 days postoperatively. One patient died in the postoperative period. Among the 6 Parkinson disease cases, one patient died in the postoperative period.

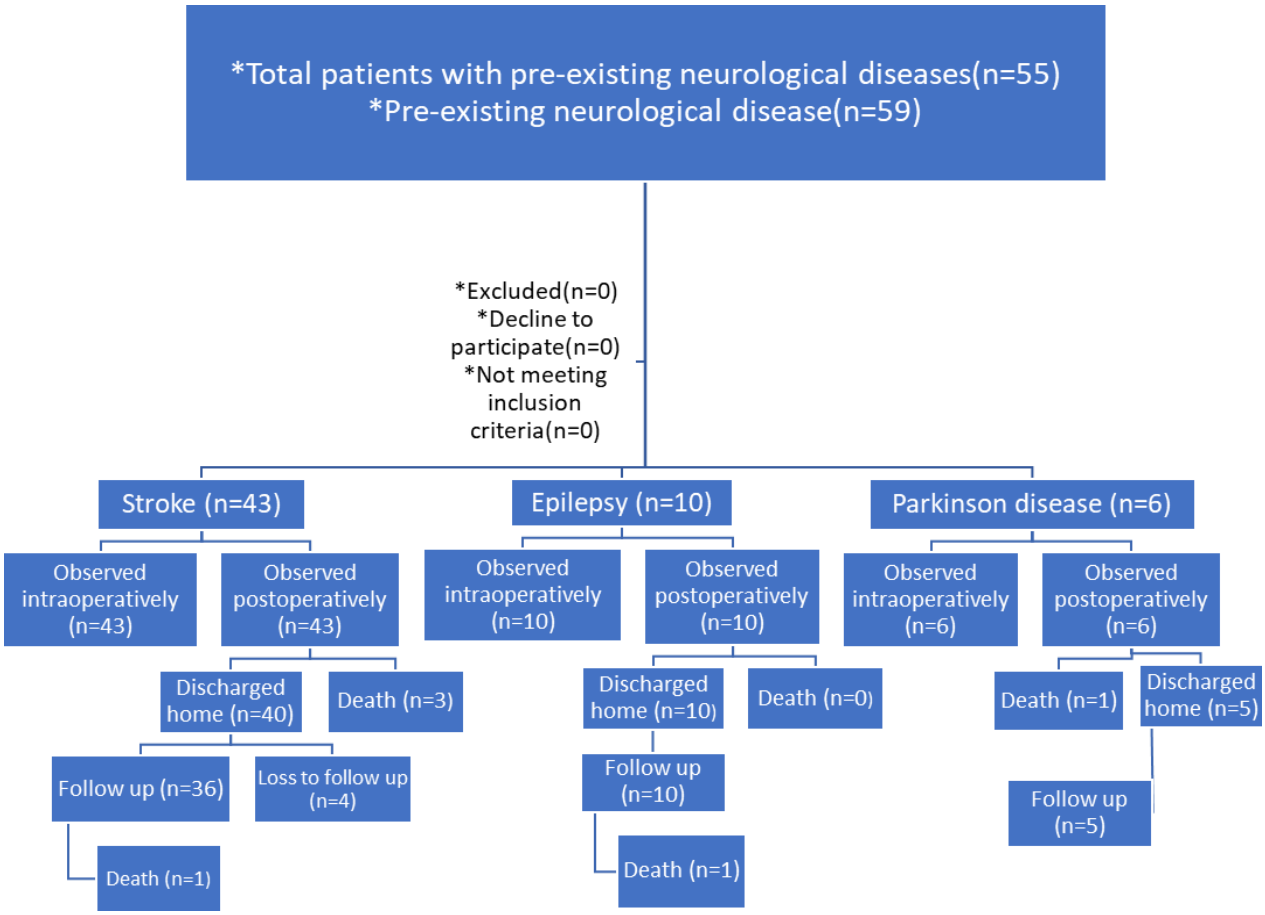

Figure 2: Flow chart

Table 4: Distribution of patients with pre-existing neurological diseases

Neurological Disease	**No. of Patients**
Stroke	43 (72.9%)
Epilepsy	10 (16.9%)
Parkinson disease	6 (10.2%)

The above table shows distribution of patients with pre-existing neurological disease posted for non neurological surgeries. Majority of the patients had a history of stroke (79.9%), followed by epilepsy (16.9%) and Parkinson disease patients (10.2%).

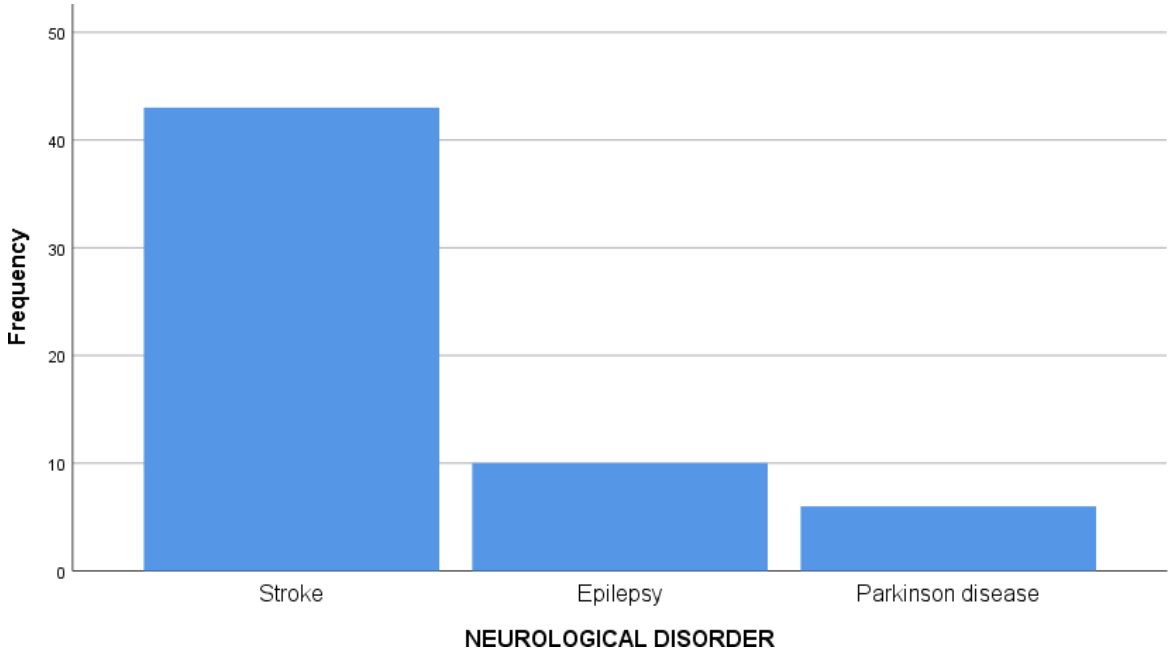

Figure 3: Distribution of patients with pre-existing neurological diseases posted for non neurological surgery

Table 5: Distribution of patients in different age groups between patients with stroke, epilepsy and Parkinson disease

Neurological Disease	Number of patients in the age group; n (%)			Mean Age ± SD (years)
	18-39 years	40-59 years	60 years or above	
All Patients	12 (20.1%)	16 (27%)	31 (52.9%)	57.6 ±17.2
Stroke	5 (11.6%)	13 (29.6%)	25 (58.8%)	61.4 ± 14.8
Epilepsy	8 (80%)	2 (20%)	0	35.6 ± 11.4
Parkinson disease	0	2 (16.7%)	4 (83.3%)	67.6 ± 12.5

The above table shows the distribution of patients in different ages having pre-existing neurological diseases. The overall mean ± SD age was 57.6±17.2 years. The mean ± SD age for patients with stroke was 61.4 ±14.8. The mean ± SD of age in patients having epilepsy and Parkinson disease was 35.6 ±11.4.

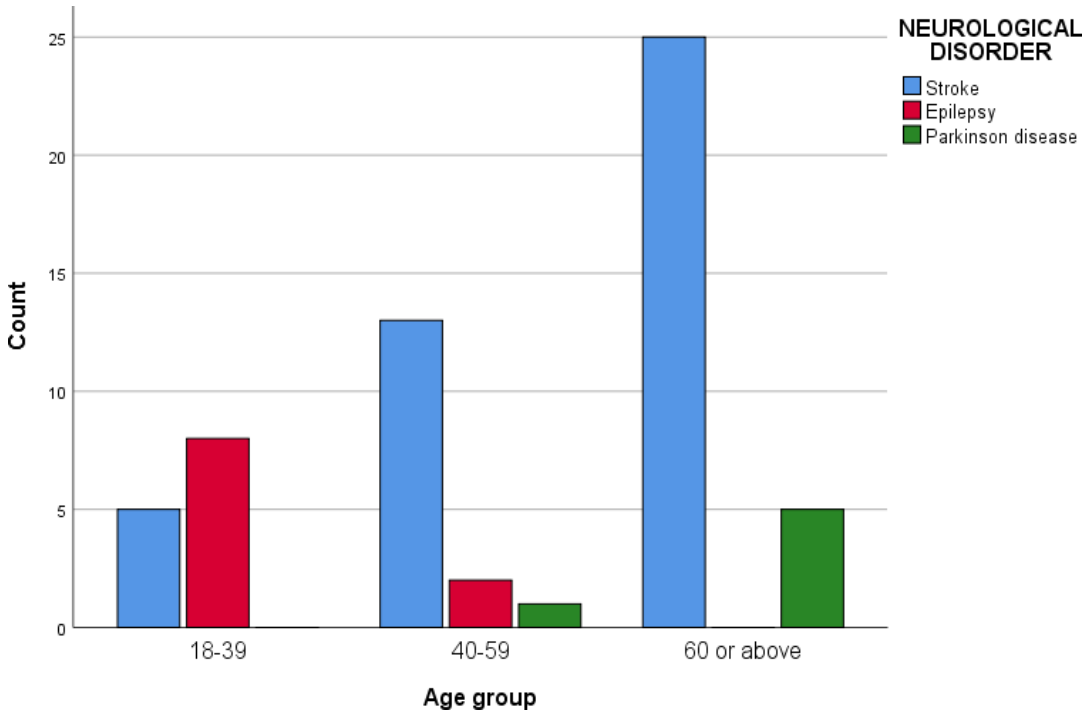

Figure 4: Distribution of patients in different age groups of patients with Stroke, Epilepsy and Parkinson Disease

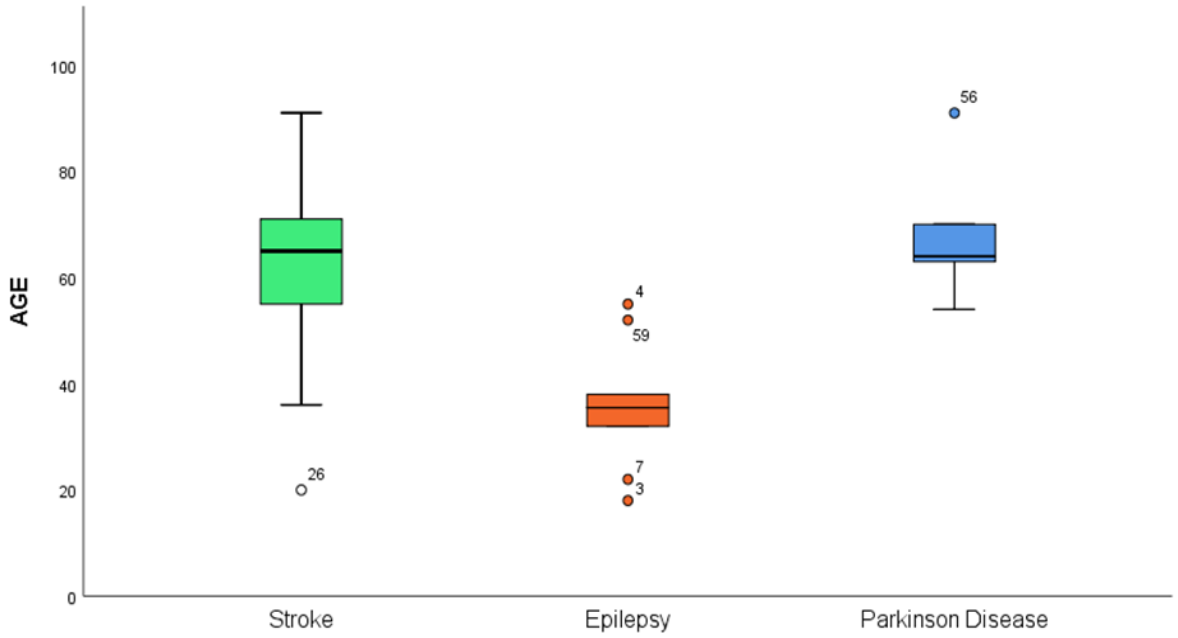

Figure 5: Boxplot showing distribution of patients in different age groups in patients with pre-existing neurological diseases

Table 6: Gender distribution in patients with pre-existing neurological disease

Neurological Disease	**Female**	**Male**
Stroke	31 (72.1%)	12 (27.9%)
Epilepsy	7 (70%)	3 (30%)
Parkinson disease	3 (50%)	3 (50%)

The above table shows the gender distribution of patients with pre-existing neurological diseases. Among the 43 stroke patients, 31 were female while 12 were male. Among the 10 patients with epilepsy, 7 were female and 3 were male. Among the 6 patients with Parkinson disease, female and male patients were equally distributed.

Table 7: Distribution of hypertension among patients with pre-existing neurological diseases.

Neurological Disease	Hypertension	
	Yes	No
Stroke	26 (60.5%)	17 (39.5%)
Epilepsy	0	10 (100%)
Parkinson Disease	2 (33.3%)	4 (66.7%)

The above table shows the distribution of hypertensives among patients with pre-existing neurological diseases. Among the 43 stroke patients, 60.5% were hypertensives. There were no hypertensives amongst the patients with epilepsy. Among the 6 patients with Parkinson disease, 2 were hypertensives.

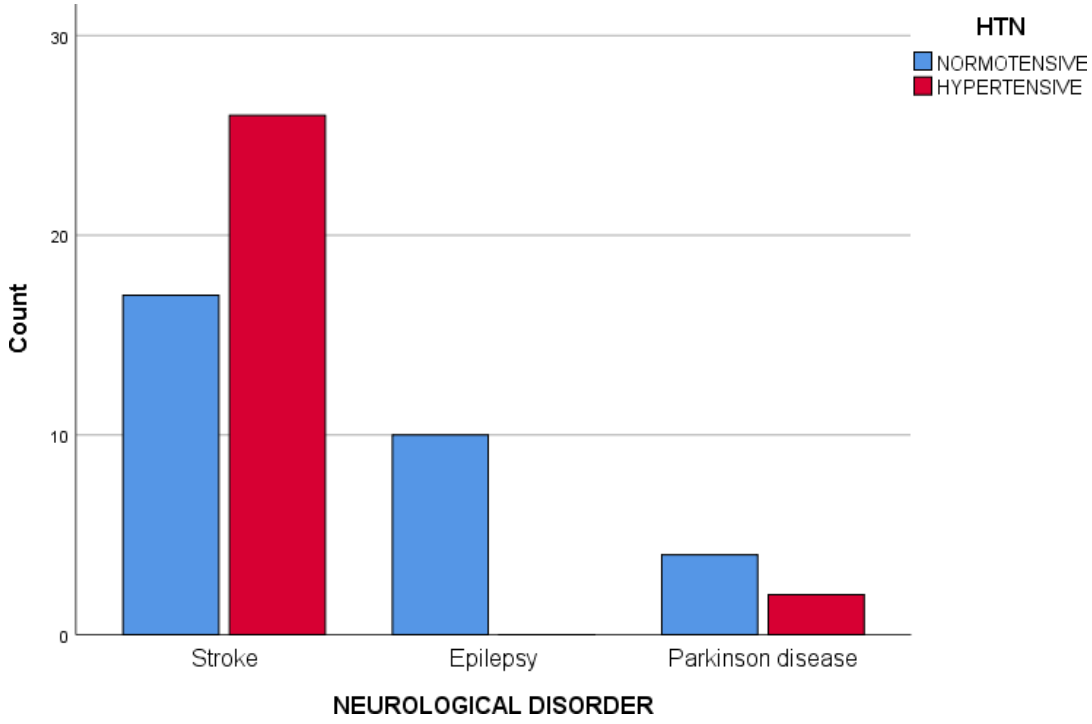

Figure 6: Distribution of Hypertensives among patients with pre-existing neurological diseases

Table 8: Distribution of diabetes mellitus among patients with pre-existing neurological diseases.

Neurological Disease	Diabetes Mellitus	
	Yes	No
Stroke	10 (23.3%)	33 (76.7)
Epilepsy	1 (10%)	9 (90%)
Parkinson disease	0	6 (100%)

The above table shows the distribution of diabetes mellitus among patients with pre-existing neurological diseases. Among the 43 stroke patients, 23.3% had diabetes. Among the 10 patients with epilepsy, only one patient had diabetes mellitus while none of the patients with Parkinson disease was diabetic.

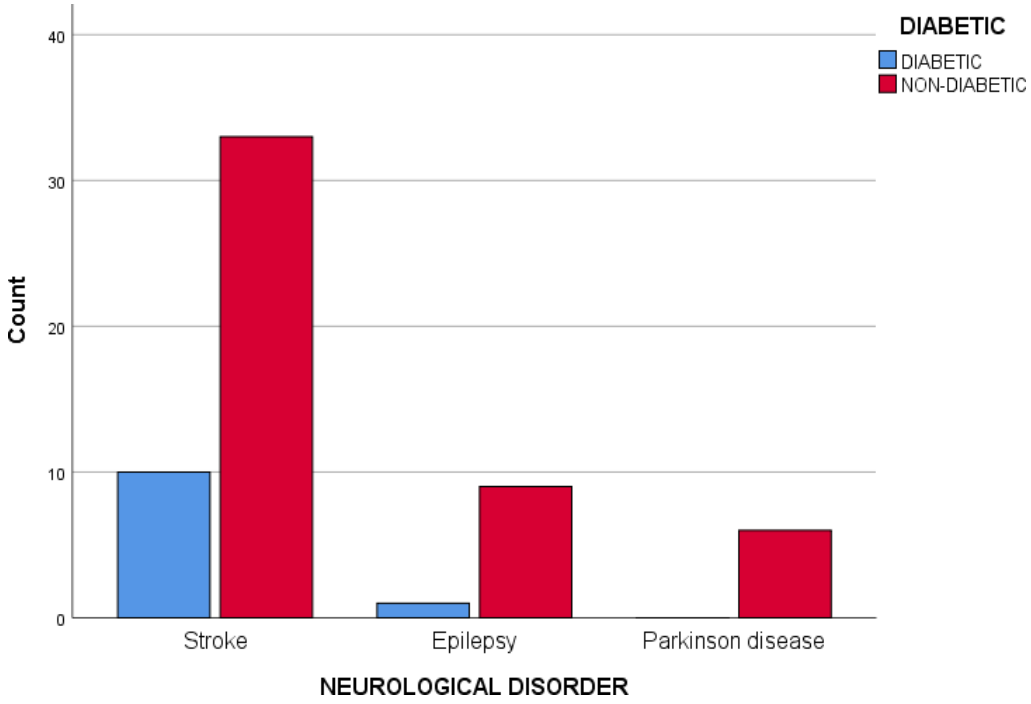

Figure 7: Distribution of diabetes mellitus among patients with pre-existing neurological diseases

Table 9: Distribution of coronary artery disease among patients with pre-existing neurological diseases

Neurological Disease	**Coronary Artery Disease n(%)**	
	Yes	**No**
Stroke	6 (14%)	37 (86%)
Epilepsy	0	10
Parkinson disease	0	6

The above table shows the distribution of coronary artery disease among patients with pre-existing neurological diseases. Fourteen percent of the stroke patients had a history of coronary artery disease while none of the patients with epilepsy or Parkinson disease had such history.

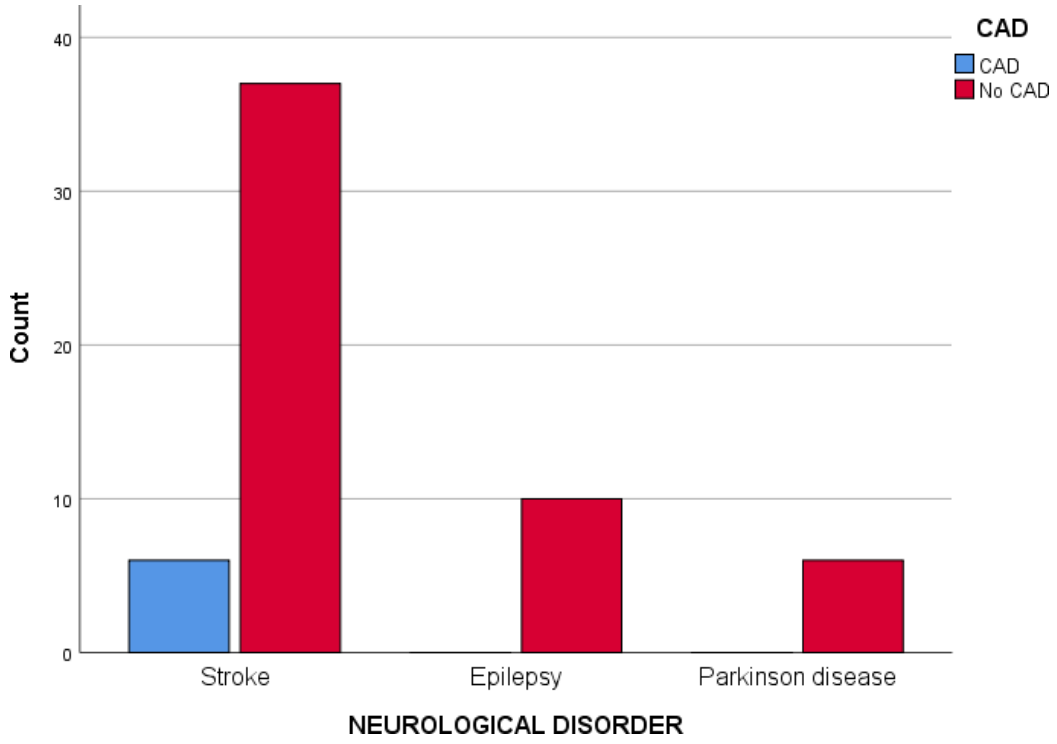

Figure 8: Distribution of coronary artery disease among patients with pre-existing neurological diseases

Table 10: Distribution of patients according to the nature of surgery (trauma vs non trauma) among patients with pre-existing neurological diseases

Neurological Disease	Trauma Surgeries	Non-trauma Surgeries
Stroke	11 (25.6%)	32 (74.4%)
Epilepsy	2 (20%)	8 (80%)
Parkinson disease	4 (66.7%)	2 (33.3%)

The above table shows the distribution of patients according to the nature of surgery (trauma vs non trauma) among patients with pre-existing neurological diseases. Among the 43 stroke patients, 11
were posted for trauma surgeries while 32 were posted for non-trauma surgeries. Among the 10 patients with epilepsy, two patients were posted for trauma surgeries and 8 were posted for non trauma surgeries. Among the 6 Parkinson disease patients, 4 were posted for trauma surgeries and 2 were posted for non trauma surgeries.

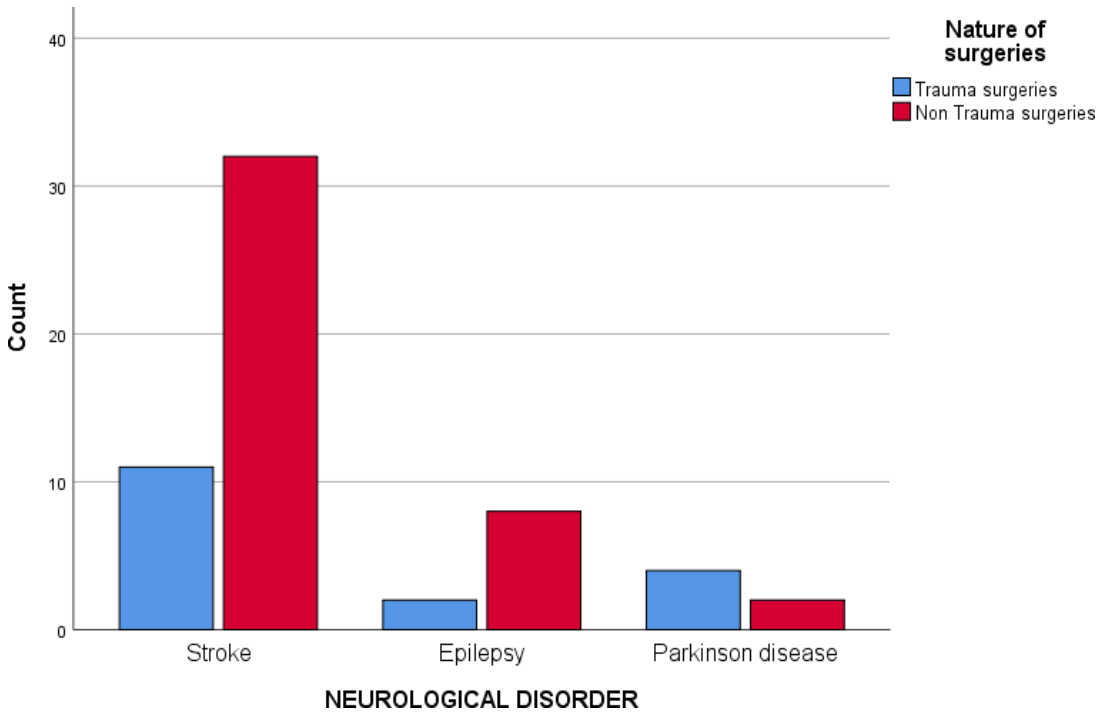

Figure 9: Distribution of patients with trauma surgeries and non trauma surgeries among patients with pre-existing neurological diseases

Table 11: Distribution of patients according to the surgical specialty

Type of Surgery	**Number of patients n (%)**
Cardiothoracic and vascular surgery	1 (1.7%)
General Surgery	13 (22%)
GI Surgery	1 (1.7%)
Gynaecology	2 (3.4%)
Oral Maxillofacial surgery	6 (10.2%)
Orthopaedics	20 (33.9%)
Otorhinolaryngology	4 (6.8%)
Plastic Surgery	2 (3.4%)
Surgical Oncology	7 (11.9%)
Urology	3 (5.1%)

The above table shows the distribution of patients according to the surgical specialty.

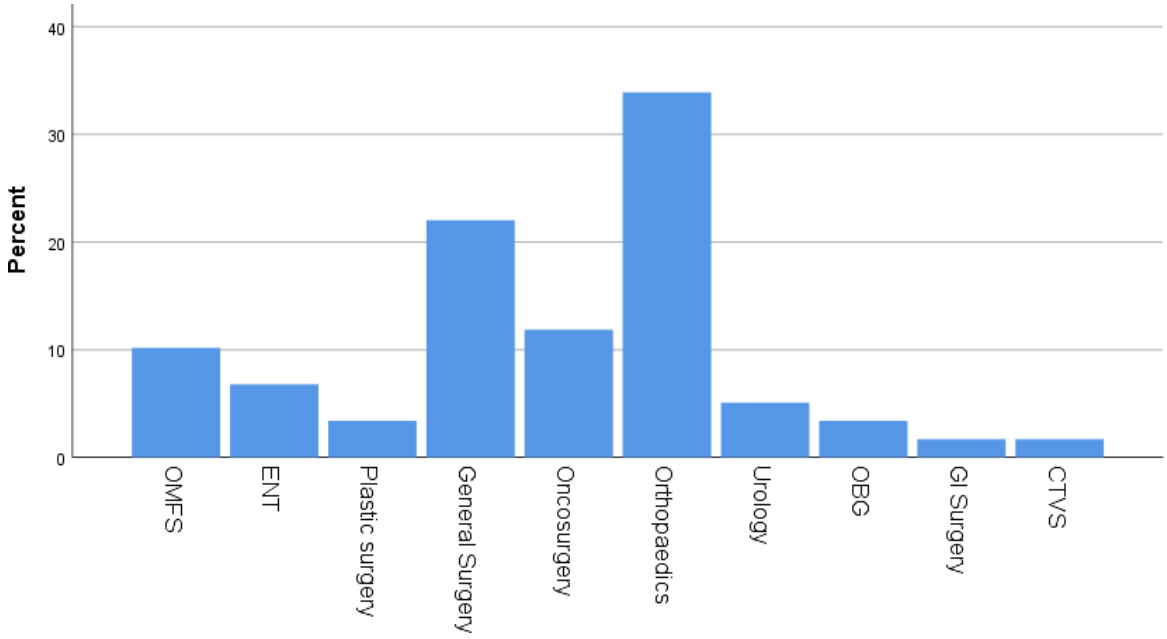

Figure 10: Distribution of patients according to the surgical specialty

Table 12: Distribution of patients according to the anaesthetic technique

Neurological Disease	Anaesthetic technique	
	General Anaesthesia	Regional Anaesthesia
Stroke	33 (76.7%)	10 (23.3%)
Epilepsy	8 (80%)	2 (20%)
Parkinson disease	5 (83.3%)	1(16.7%)

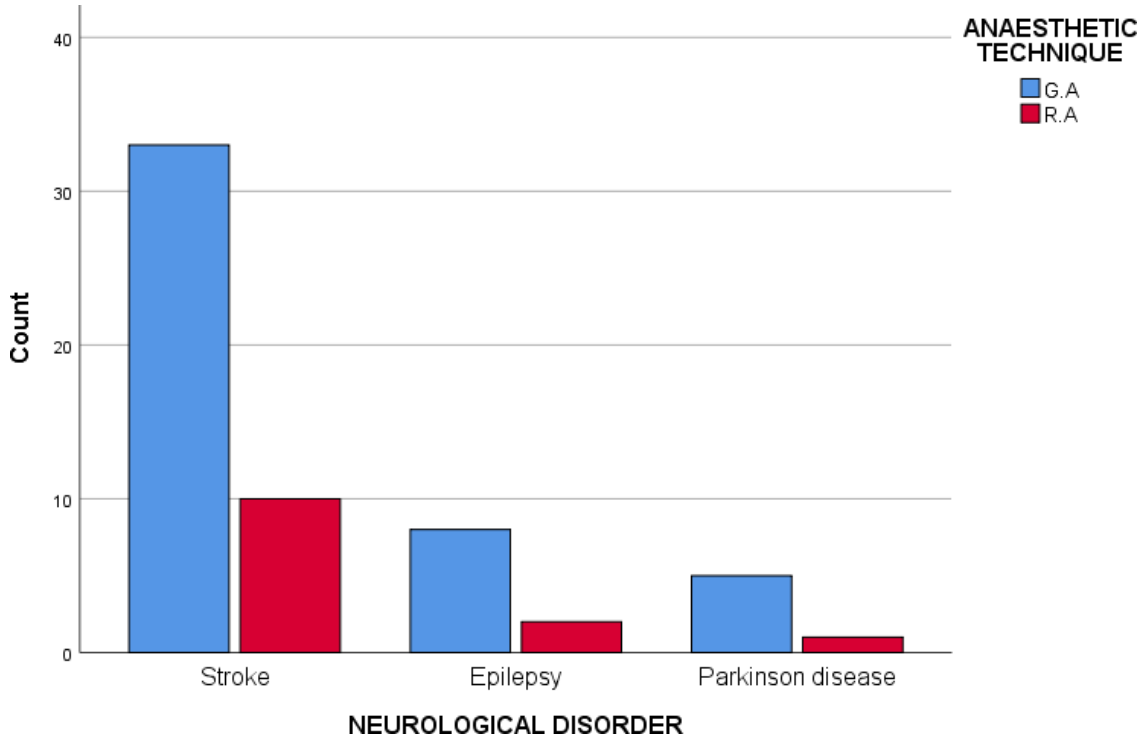

Figure 11: Distribution of patients according to the anaesthetic technique

Table 13: Patients with history of stroke (n=43) having residual paralysis or on DAPT

Patients with history of stroke			
Residual Paralysis		**On DAPT**	
YES	**NO**	**YES**	**NO**
15 (34.9%)	28 (65.1%)	27 (62.8%)	16 (37.2%)

The above table shows the distribution of patients with a history of stroke having residual paralysis or on DAPT. Among the 43 patients with a history of stroke, 34.9% had residual paralysis and 62.8% were on DAPT.

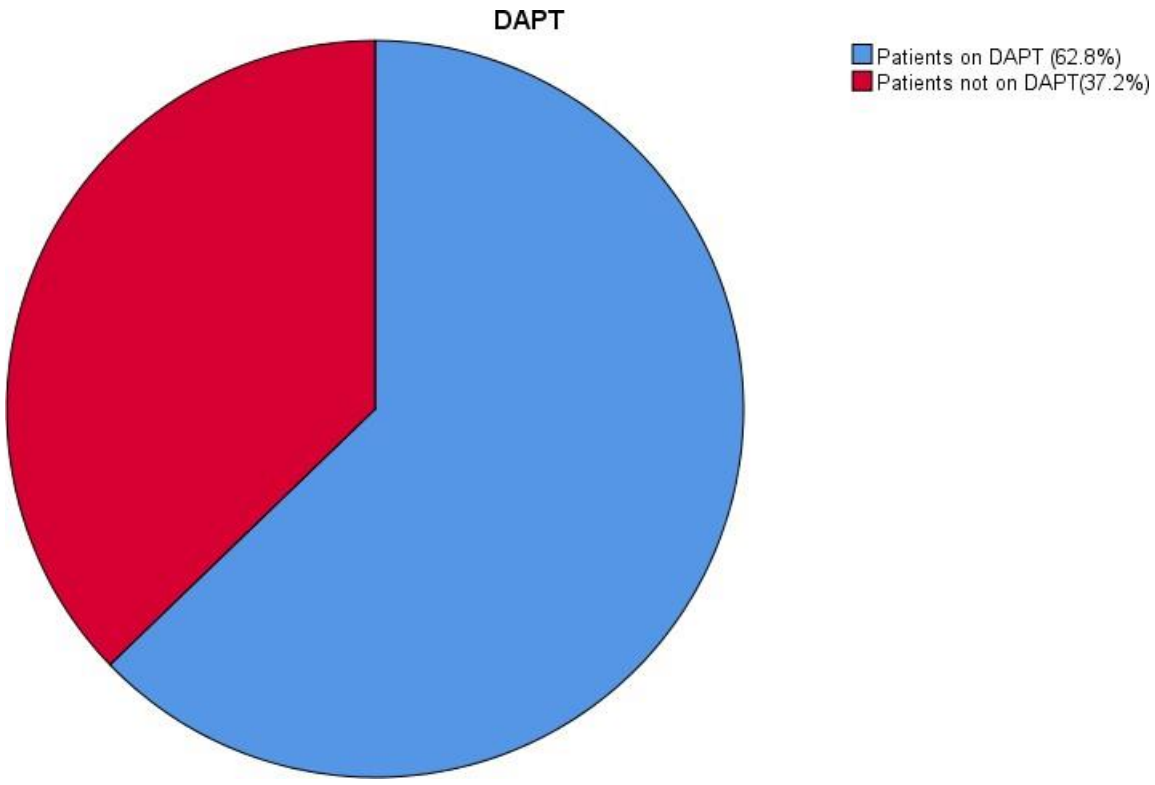

Figure 12: Distribution of patients with stroke on DAPT (dual antiplatelet therapy)

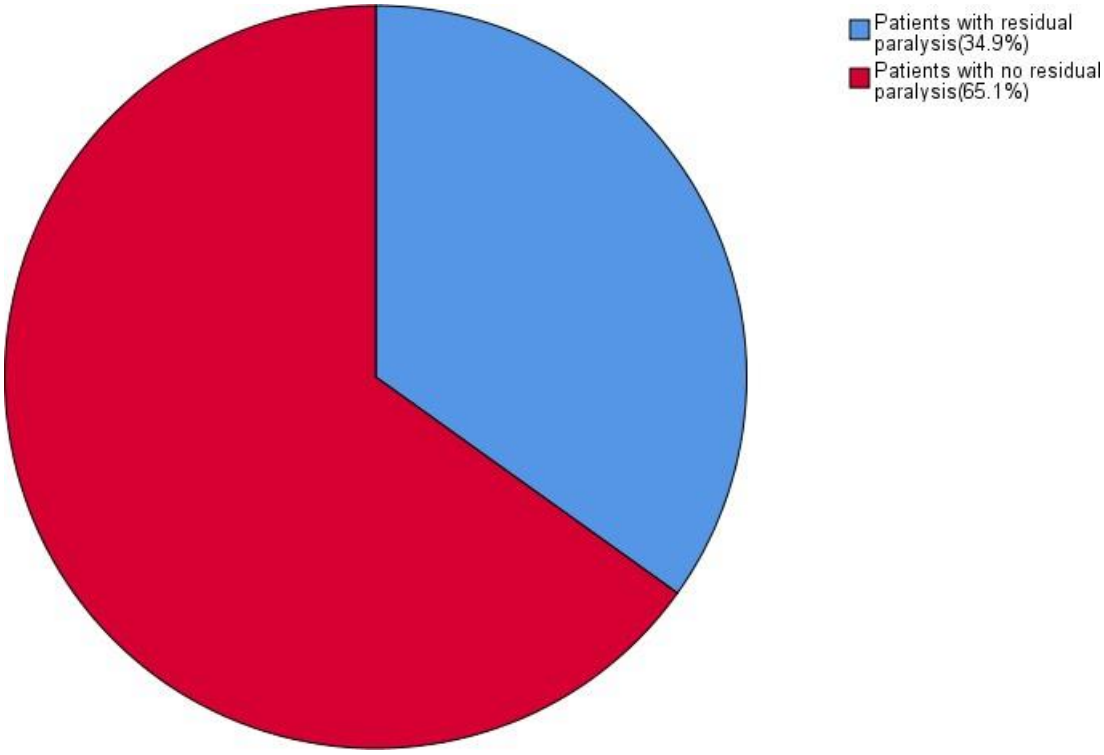

Figure 13: Distribution of patients with residual paralysis among stroke patients

Table 14: Distribution of intraoperative haemodynamic events among the patients with history of stroke (n=43)

Events		**Number of patients; n (%)**
Uneventful		24 (55.8%)
Hypotension	Post Induction hypotension	7 (16.3%)
	Hypotension requiring vasopressor infusion	8 (18.6%)
Hypertension		4 (9.3%)

The above table shows distribution of intraoperative haemodynamic events among the patients with a history of stroke. Among the 43 patients, 55.8% had an hemodynamically uneventful intraoperative course. 34.9% of the patients had intraoperative hypotension while 9.3% had hypertensive episodes.

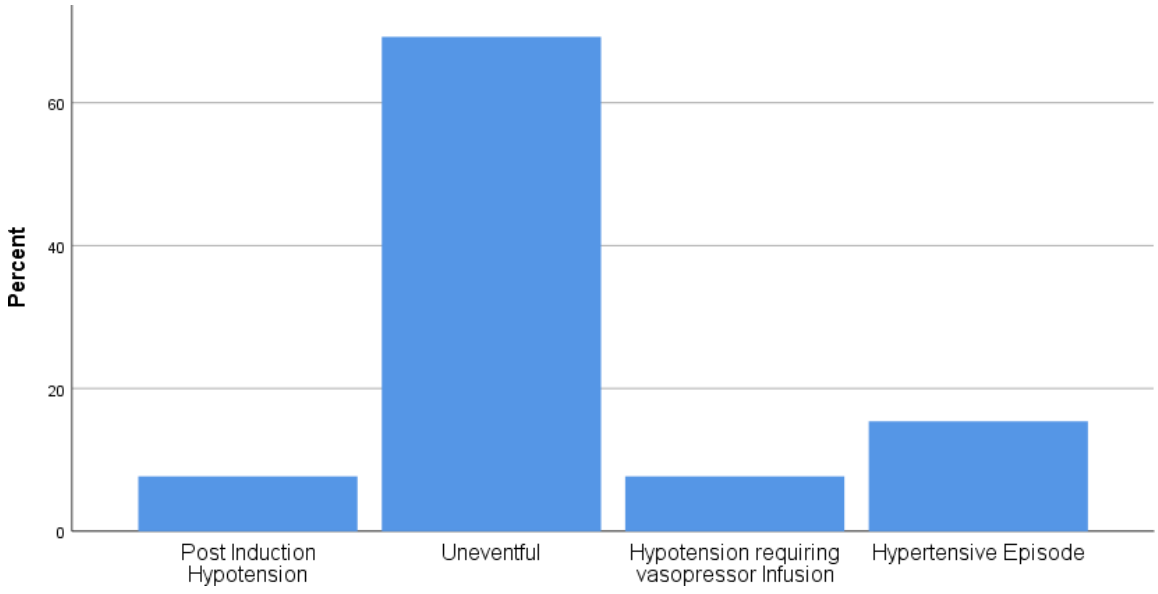

Figure 14: Distribution of intraoperative haemodynamic events among the patients with history of stroke

Table 15: Distribution of postoperative events among the patients with history of stroke (n=43) till discharge from the hospital

Events	**Number of patients n (%)**
Uneventful	34 (79%)
Hypotension	4 (9.3%)
Refractory VT	1 (2.3%)
Hypertensive Episode	1 (2.3%)
Delirium	4 (9.3%)
Death	3 (6.9%)

The above table shows distribution of postoperative events till discharge from the hospital. Among the 43 patients with a history of stroke, 79% had an uneventful postoperative course. which was of total patients with stroke. 4 patients had hypotension which was managed with vasopressor infusion. 4 patients had delirium which was 9.3% of total stroke patients. 3 of the patients died during the postoperative hospital stay. The cause of death in these 3 patients was refractory hypotension in 2 and refractory VT in the third.

Table 16: Distribution of events among the patients with a history of stroke from discharge till postoperative day 30. (n=40)

Events	**Number of patients n (%)**
Uneventful	33 (82.5%)
Delirium	2 (5%)
Lost to follow up	4(10%)
Death	1 (2.5%)

The above table shows distribution of events among the patients with a history of stroke from discharge till postoperative day 30. Among the 40 patients, 33 patients (82.5%) had an uneventful postoperative course at home. 2 patients had delirium and one patient died postoperative day 20 (15 days after discharge). 4 of the patients were lost to follow up after their discharge from hospital.

Table 17: Distribution of total number of antiepileptic drugs taken among patients having epilepsy

Number Of Antiepileptic	No of patients n (%)
0	2 (20%)
1	5 (50%)
2	2 (20%)
3	0
4	1 (10%)

The above table shows the distribution of the total number of antiepileptic drugs taken among patients having epilepsy. Among 10 patients two patients were not taking any antiepileptic drugs. One patient was taking Levetiracetam alone. Two patients were taking valproate and Levetiracetam. One patient was taking Levetiracetam, Sodium Valproate, Phenytoin and Phenobarbitone.

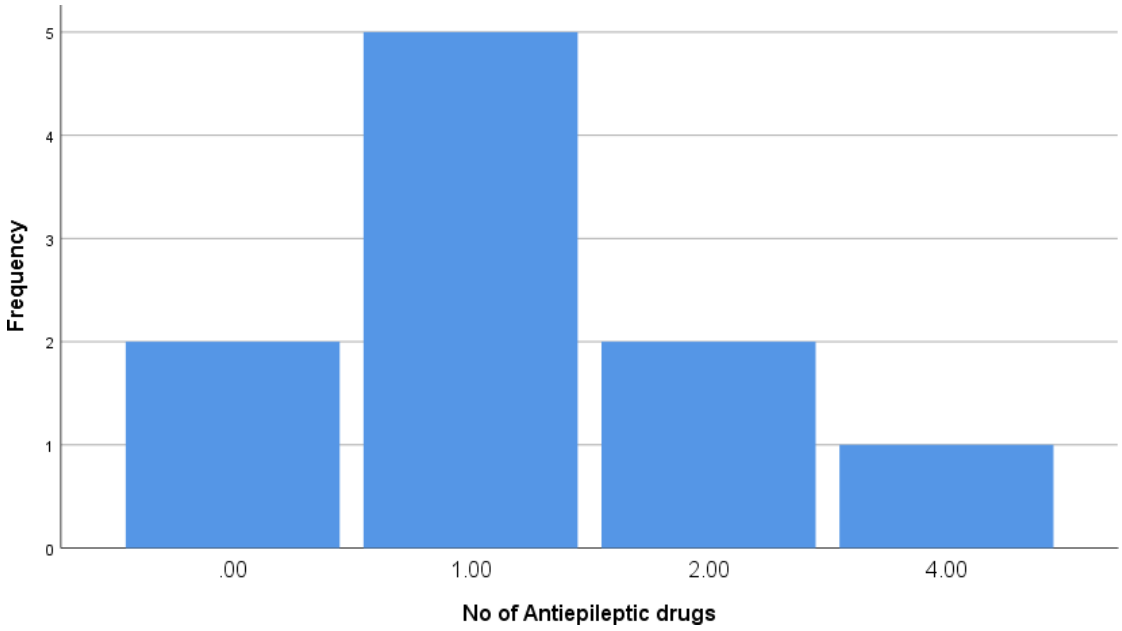

Figure 15: Distribution of total number of antiepileptic drugs taken among patients having epilepsy.

Table 18: Distribution of intraoperative hemodynamic events among the patients having epilepsy (n=10)

Intraoperative Events	Number Of Patients n (%)
Uneventful	8 (80%)
Hypotension	2 (20%)

The above table shows the distribution of intraoperative hemodynamic events among patients having epilepsy. Among the 10 patients, 80% had an uneventful intraoperative period while the remaining had intraoperative hypotension.

Table 19: Distribution of postoperative events among the patients with epilepsy till discharge from the hospital (n =10)

Post Operative Events	Number of patients n (%)
Uneventful	7 (70%)
Hypotension	1 (10%)
Tremors	1 (10%)
GTCS	1 (10%)

GTCS : Generalized Tonic Clonic Seizure

The above table shows the distribution of postoperative events among the patients with epilepsy. Among the 10 patients, 7 had an uneventful postoperative period. One patient had postoperative hypotension postoperatively, managed with vasopressor infusion. One patient each had involuntary tremors on bilateral lower limbs and GTCS.

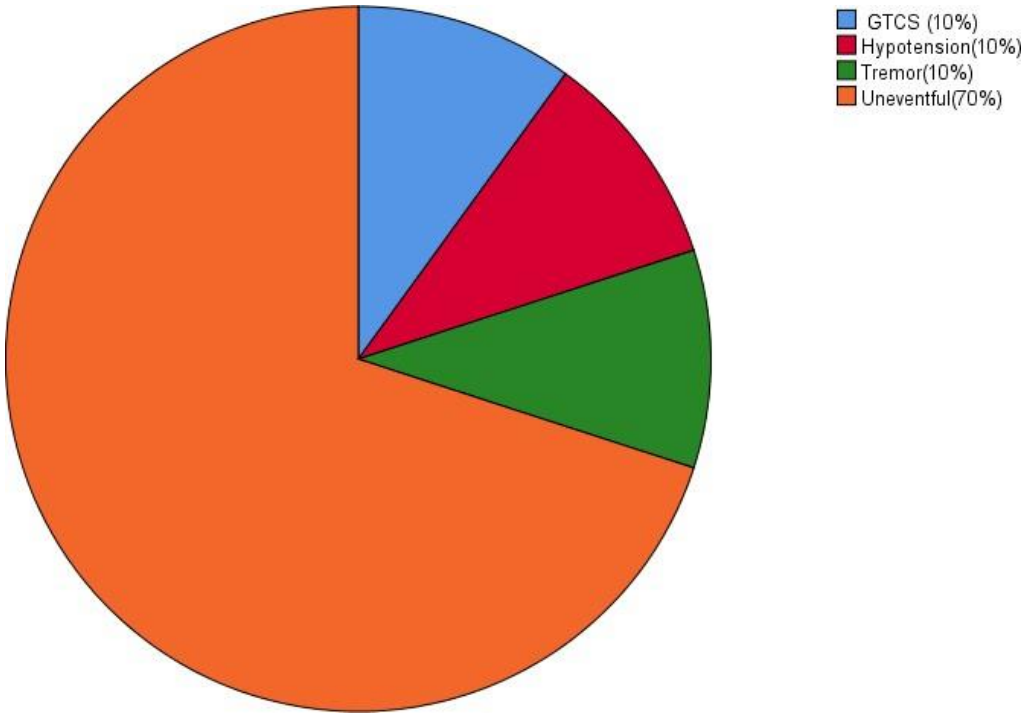

Figure 16: Distribution of postoperative events among patients having epilepsy

Table 20: Distribution of postoperative events among the patients with epilepsy from discharge till postoperative day 30 (n=10)

Events	Number of patients n (%)
Uneventful	8 (80%)
Tremor	1 (10%)
Death	1 (10%)

The above table shows the distribution of postoperative events among the patients with epilepsy from discharge till postoperative day 30. Among the 10 patients, 8 patients had an uneventful course at home. One patient had continued intermittent tremors in bilateral lower limbs post discharge. One patient died on postoperative day 20.

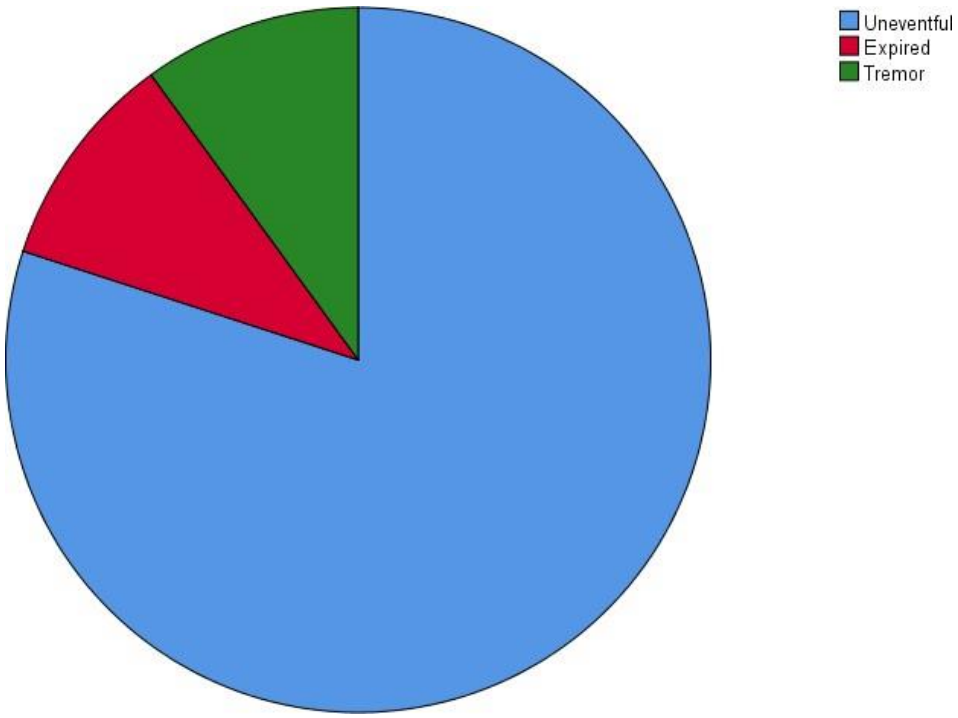

Figure 17: Distribution of postoperative events among the patients with epilepsy from discharge till postoperative day 30

Table 21: Distribution of anti -Parkinson medication among patients with Parkinson disease.(n=6)

Anti Parkinson Medications	**Number of patients n (%)**
Syndopa	3 (50%)
Syndopa +Melatonin+Amantadine	1 (26.7%)
Syndopa +Donepezil+Amantadine	2 (33.3%)

The above table shows the distribution of patients taking anti-Parkinson medications. Among a total 6 patients, 3 patients were taking Syndopa alone. One patient was taking Syndopa alongwith Melatonin and Amantadine. Two patients were taking Syndopa along with Donepizil and Amantadine.

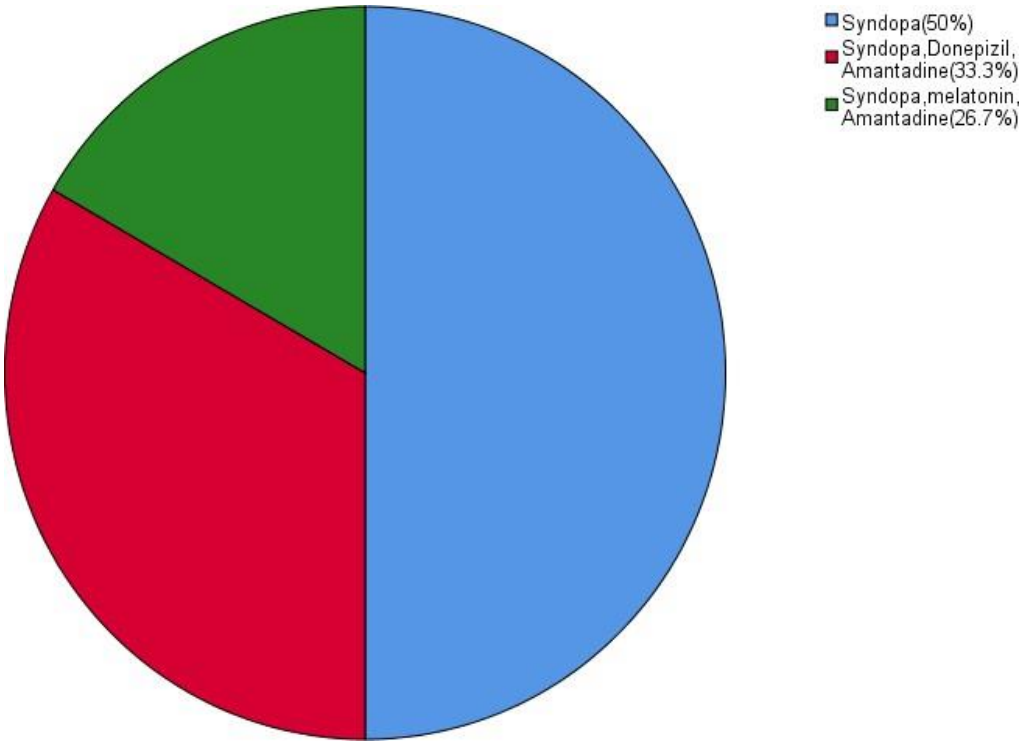

Figure 18: Distribution of anti -Parkinson medication among patients with Parkinson disease

Table 22: Distribution of intraoperative events among patients with Parkinson disease (n = 6)

Events	Number of patients n (%)
Uneventful	3 (50%)
Hypotension on vasopressor infusion	3 (50%)

The above table shows the distribution of intraoperative events among patients with Parkinson disease. Among the 6 patients, 3 had an uneventful intraoperative period. 3 patients had intraoperative hypotension intraoperatively which was managed with vasopressor infusion.

Table 23: Distribution of postoperative events among patients with Parkinson disease till discharge from the hospital (n=6)

Post Operative Events	Number of patients n (%)
Uneventful	4 (66.7%)
Delirium	1 (16.7%)
Death	1 (16.7%)

The above table shows the distribution of postoperative events among patients with Parkinson disease till discharge from the hospital. Among a total of 6 patients, the postoperative period was uneventful in 4 patients. One patient had delirium in the postoperative period while one of the patients died due to refractory VT.

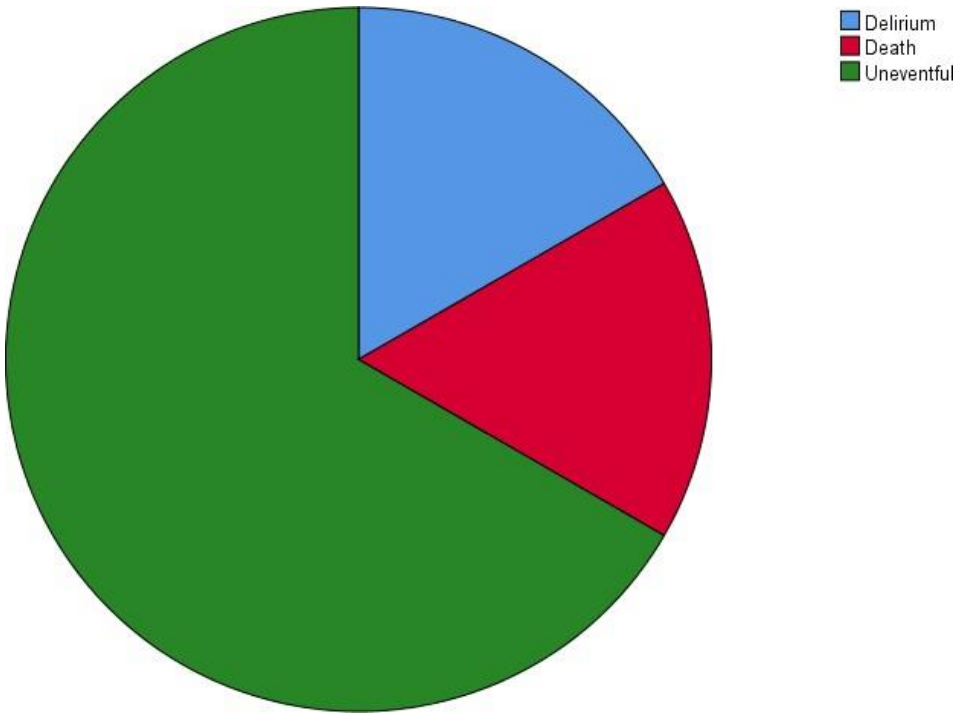

Figure 19: Distribution of postoperative events among patients with Parkinson disease till discharge from the hospital

Table 24: Distribution of post operative events among patients with Parkinson disease from discharge to postoperative day 30 (n=5)

Events	**Number of patients n (%)**
Uneventful	4 (66.6%)
Delirium	1 (17.2%)

The above table shows the distribution of postoperative events among patients with parkinson disease from discharge to postoperative day 30. This period was uneventful in 4 patients while one had delirium.

DISCUSSION

Perioperative care of patients with neurological diseases needs a thorough understanding about the pathophysiology, course of the disease, physiological changes that can occur after anaesthesia to reduce intraoperative and postoperative events. There is ample literature about postoperative neurological complications, not much literature is available about the perioperative course of patients with pre-existing neurological disorders undergoing non-neurological surgeries. Perioperative complication includes intraoperative hemodynamic changes, interaction of preoperative medication with anaesthetic agent, postoperative cognitive dysfunction and recurrence of the neurological disease. Stroke, delirium, and neurocognitive impairment are frequent perioperative consequences that increase morbidity and death.[61]

Pre anaesthetic check-up of patients with neurological diseases mainly focuses on the medication used and the course of disease. There is no standardised method for assessing cerebrovascular physiology prior to surgery. High-intensity transcranial Doppler signals have been used to find cerebral micro embolism.[62]

Drugs given during anaesthesia may also alter the physiology of a pathological brain. Patients with prior brain diseases have recurrences of earlier localised neurological impairments after receiving sedatives and opioid analgesics.[63]

We conducted a study to observe the perioperative course of patients with pre-existing neurological diseases such as stroke, epilepsy, Parkinson disease posted for non-neurological surgeries. The study included preoperative, intraoperative and postoperative (till day 30) periods .

Demographic profile

Age: In our study the mean age group of patients (in years) was 57.6 ± 17.2. In patients with stroke the mean age was 61.4 ± 14.8. In patients with epilepsy the mean age was 35.6 ±11.4 and in Parkinson's disease patients the mean age was 67.6 ±12.5. The risk of stroke is most strongly influenced by ageing, which doubles every 10 years after age 55. Strokes affect those under 65 years old in about 75 percent of cases.[64]

Dahl Hansen et al in a cross-sectional investigation assessed 1771 individuals with active epilepsy. The causes of epilepsy were mapped out for each of the distinct age groups of this group of people with current epilepsy. Age groups 5 to 19 were represented by 27% (unknown aetiology) and age groups 10 to 19 years by 41%. Stroke was the most frequent cause of epilepsy in the group of individuals with epilepsy under 60 years old (44%).[65]

Parkinson's disease normally appears between the ages of 55 and 65, affects 1% to 2% of persons over 60, and increases to 3.5% of people between the ages of 85 and 89.[66]

Gender: In our study among a total of 59 patient's female patients were 41 and male patients were 18. Among the 43 stroke patients, 31 were female and 12 were male. Females are more prone to stroke than male due to female specific risk factors which include use of OCP, late menarche, and early menopause. Death and disability from strokes affect women disproportionately[67]. Preterm birth, gestational hypertension, preeclampsia, and foetal growth restriction are all adverse pregnancy outcomes that have been repeatedly linked to an elevated risk of stroke and other long-term cardiovascular conditions in the mother.[68]

Among total 10 seizure patients 7 were female and 3 were male. Among 6 patients with Parkinson disease male and female patients were equally distributed. Males are slightly more likely to have epilepsy than females, and the condition tends to peak in the elderly. Both in kids and adults, focal seizures are more frequent than generalised seizures which have male predominance. Men are twice as likely to acquire Parkinson disease when compared to women, but women die from the disease more frequently and it advances more quickly in women. Additionally, there are differences between men and women in terms of disease risk factors, treatment response, and motor and nonmotor symptoms.[69]

Comorbidities: In our study among 59 patients 28 patients were hypertensives. Among 43 stroke patients 26 patients were hypertensive which is 60.5% of total stroke patients. Among 10 epilepsy patients none of the patients were hypertensive and among 6 patients with Parkinson disease 2 were hypertensives.

Ishitsuka et al conducted a study in 1874 patients with their first-ever acute ischemic stroke (within 24 hours of onset) were prospectively enrolled. The average values

throughout the first 48 hours following onset were used to establish the post stroke BP levels. The higher post stroke BP values were substantially related with a reduced likelihood of a satisfactory neurological recovery and elevated chances of neurological deterioration and a poor functional outcome.[70]

Even in the early stages of Parkinson disease, abnormalities in blood pressure (BP) caused by autonomic dysfunction can occur, frequently before the onset of the condition's characteristic motor symptoms. Parkinson disease patients also exhibit nocturnal and supine hypertension in addition to orthostatic and postprandial hypotension, which shows that BP regulation is compromised in these patients [71].

According to Tsukamoto et al up to 64.9% of Parkinson disease patients had nocturnal hypertension. A total of 44 patients with other diseases and 37 patients with Parkinson disease patients who were all in patients had their blood pressure checked every 30 minutes by 24-hour ambulatory blood pressure monitoring (ABPM). There was no difference between the two groups in terms of the average systolic blood pressure or the number of patients who displayed postprandial hypotension. However, the Parkinson disease patients were substantially more likely to experience nocturnal hypertension, BP fluctuations of over 100 mmHg per day, and BP of over 200 mmHg than patients having other diseases.[72]

In our study among 59 patients 11 patients were having diabetes mellitus. Among 43 stroke patients 10 patients were having diabetes mellitus which is 23.3% of total stroke patients. Among 10 epilepsy patients one patient was having diabetes mellitus and among 6 patients with Parkinson disease none of the patients had diabetes.

Diabetes results in a variety of microvascular and macrovascular alterations that frequently lead to serious clinical problems, one of which is stroke. Despite the fact that the burden of stroke has decreased over the past 20 years, recent increases in diabetes rates pose a threat to undo these achievements. People with diabetes frequently have greater risk, which is linked to worse clinical outcome , particularly after ischemic stroke.[73]

In order to monitor the incidence of stroke in diabetic patients Janghorbhani et al followed 116,316 women aged 30-55. 3,463 incident strokes occurred over 2.87 million person-years of follow-up. Compared to non-diabetic women, incidence of total stroke

was four times higher in type 1 diabetic women and twice as high in type 2 diabetic women. In type 1 diabetes and type 2 diabetes, the multivariate RR of ischemic stroke was increased sixfold (6.3 [4.0-9.8]) and twice (2.3 [2.0-2.6] respectively. The risk of haemorrhagic stroke was also substantially correlated with type 1 diabetes (3.8 [1.2-11.8]), but not type 2 diabetes (1.0 [0.7-1.4]).[74]

Different kinds of seizures are experienced by about 25% of diabetes mellitus patients. Additionally, diabetic patients with DKA episodes also experience seizures more frequently. The majority of people with non-ketosis diabetes who have partial epilepsy are resistant to commonly used antiepileptic medications. Seizures due to ketoacidosis should be managed with correction of electrolyte abnormality and dehydration.[75]

In our study among 59 patients 6 patients were having a history of CAD. All of these patients were stroke patients. There were no patients with epilepsy and Parkinson disease having a history of CAD. Kim et al. conducted a retrospective investigation in a prospective cohort of patients who had successive ischemic strokes. From the 3117 patients registered 1842 patients (MDCT (+) group) (Multidetector Coronary Computed Tomography) and 1275 patients (non MDCT group). The group's rates of fatalities, cardiovascular incidents, and recurrent strokes were compared. During follow-up, acute stroke patients who received MDCT had fewer fatalities, cardiovascular incidents, and recurrent strokes.[34] This study shows an association with stroke and CAD. In our study all patients with CAD had a stroke history.

Type of surgery: In our study among 59 patients most of the patients were posted for orthopaedics surgery which was 33.9% of total cases followed by general surgery (22%) and oncosurgery(11.9%). According to Teasel et al in a retrospective cohort study to find out the incidence of fall among stroke patients. Among 238 patients, 88 (37%) fell at least once, and nearly half of these fell at least twice.[76] These findings were similar to our study. Most of the patients in our study had a history of fall and were posted for orthopaedics surgery. Bloem et al in prospective study found that the incidence of fall was high among patients with Parkinson disease.[77] In our study also most of the patients were admitted for orthopaedics surgery with history of fall or othertrauma.

Type of anaesthesia: In our study among 59 patients, 46 patients received GA and 13 patients received RA. Among stroke patients 33 patients received GA and 10 patients received RA. Among 10 patients with epilepsy 8 received GA and 2 received RA. Out of 46 patients receiving GA, 26 patients had an intraoperative period that was uneventful, 18 patients had hypotension, 2 patients had hypertensive episodes. Out of 13 patients who received RA, 8 patients had an uneventful intraoperative period, 2 patients had intraoperative hypotension and 2 patients had intraoperative hypertensive episodes.

After vascular brain injury, autonomic and cardiac dysfunction may arise without any signs of underlying heart disease. The circulatory, respiratory, sudomotor, and sexual systems may be affected by autonomic dysfunction following a stroke, but the precise process is not well understood.[3] The dysfunctional autonomic nervous system may be the reason for hemodynamic changes in the intraoperative period.

Among 43 patients with a history of stroke 15 patients had residual paralysis and 27 patients were receiving DAPT. Out of 15 patients with residual paralysis,13 patients were taking DAPT. In our study we didn't find any association with residual paralysis and discontinuing DAPT. Within 24 hours after the onset of symptoms, aspirin is advised for patients with an acute ischemic stroke. Patients who have had a small stroke or transient ischemic attack may benefit from receiving dual antiplatelet medication with clopidogrel and aspirin for early secondary prevention.[78]

In our study among 43 stroke patients, 24 patients had an uneventful intraoperative period , 15 patients had hypotension out of 7 patients had post induction hypotension,8 patients were on noradrenaline infusion intraoperatively and 4 patients had hypertensive episodes. Postoperative period was uneventful in 34 patients. 4 patients had intraoperative hypotension, out of which 1 patient expired. One patient had refractory VT and expired on POD 2. One patient had hypertensive episode in the postoperative period. This patient went into refractory hypotension after giving labetalol. Delirium was present in 4 patients, out of which haloperidol was started after psychiatry reference in post operative period. Shankar et al adopted an MMGA strategy in the PATHFINDER (Perioperative multimodal general anesTHesia FocusINg on particular CNS targets in patients undergoing carDiac surgERies) pilot research EEG-guided MMGA anaesthesia was given to patients undergoing cardiac surgeries

hemodynamic stability was better and Postoperative delirium and intraoperative EEG suppression episodes were reported to be uncommon.[37] This strategy may be tried in stroke patients so that there will be lesser exposure of anaesthetic drug to the already affected brain. This might help to improve the perioperative outcome.

Among 43 stroke patients there was no exacerbation of the pre-existing neurological disease, 3 patients expired during the hospital stay and one patient expired after discharge before postoperative day 30. According to Landscaper et al the risk of perioperative stroke cannot be predicted and persists through the first week of recovery with a risk of 2%. He studied perioperative risk of 173 stroke patients undergoing GA, only patients had perioperative stroke within 30 days of surgery.[29] Benesch et al in population-based studies found acute ischemia episodes with silent brain infarctions, often known as covert strokes, do not manifest clinically. These infarcts, which are often detected by brain imaging, have been linked to cognitive decline, dementia, an increased risk of stroke, and an increased mortality rate.[79,80] Patients undergoing vascular or cardiac surgery are probably more likely to experience perioperative silent brain infarctions than other types of patients.[22]

Glance et al studied the risk of recurrence of stroke in older patients posted for non-cardiac and non-neurological surgeries on 54,033 patients who had previous history of stroke. Patients who underwent surgery within 30 days of a previous stroke had higher adjusted odds of 30-day all-cause mortality than patients without a history of stroke (AOR, 2.51; 95% CI, 1.99-3.16; P .001), and the AOR decreased to 1.49 (95% CI, 1.15-1.92; P .001) at 61 to 90 days from the previous stroke to surgery but did not change significantly after a gap of 360 days or more.[26]

Among 40 stroke patients 37 patients had no events after hospital discharge till postoperative day 30. One patient expired and 2 patients had delirium for which they were on psychiatric evaluation.

Among 10 patients with epilepsy 2 patients were not taking any AED, one patient was on single AED, two patients were on dual antiplatelets and one patient was on four antiepileptics. Two patients had a history of GTCS within the last 1 year, one patient had a history of GTCS 3 years before. Most of the patients were taking Levetiracetam, phenytoin. Other than this some patients were taking clobazam and phenobarbitone.

Acutely administered antiepileptic medications can amplify the neuromuscular effects of NDMBs due to their direct pre- and post-junctional effects, even though antiepileptic therapy alone only has minor neuromuscular effects. During long-term antiepileptic therapy, resistance to NDMBs is caused by a number of independent or cooperative mechanisms, including activation of hepatic drug metabolism, enhanced NDMB protein binding, and overexpression of cholinergic receptors.[81] So patients taking AED may need NDMBs at frequent intervals for adequate relaxation when compared to normal patients. This is one of the challenges faced in neurosurgical patients like AVM where movement of patients may be disastrous. TOF monitoring will be helpful in such patients.

Among 10 patients with a history of epilepsy intraoperative period of 8 patients were uneventful, two patients had intraoperative hypotension. The postoperative period was uneventful in 7 patients, one patient had hypotension and was on noradrenalineinfusion, one patient had tremor and one patient had GTCS, which was managed with IV antiepileptic drug.Anaesthetic drugs have both anticonvulsive and proconvulsive effect. It is challenging to identify any intraoperative seizure. Serum prolactin can be checked to confirm the diagnosis of intraoperative seizures. The normal range is 5–12 ng/ml. According to Fabregas et al bilateral BIS monitoring was not able to detect seizure activity in awake patients.[82] According to Sreenivas et al from two case reports,patients may have high BIS values during intraoperative seizures. In his study he foundBIS value coming to normal range after giving phenytoin to patient.[83] Identifying seizure activity during intraoperative period is challenging. Benisch et al suggested, general anaesthesia may potentially raise the risk of side effects or perioperative seizures in patients with epilepsy. In his population-based study Only 6 of 297 (2%) anaesthetic procedures resulted in seizures, and only one patient needed intravenous medication.[49] In our study one patient was having postoperative GTCS which was managed with IV Levetiracetam and phenytoin. The anticonvulsant and proconvulsant effects of anaesthetic drugs are debatable.

According to Niesen et al the incidence of perioperative seizures among patients with epilepsy is unclear. He studied 641 individuals with a history of seizures who received anaesthesia over the course of the six-year study period. 22 individuals had perioperative seizure activity, with a 3.4% overall frequency. He concluded that the

majority of perioperative seizures in patients with a history of seizure disorders are probably connected to the underlying illness. The kind of anaesthesia or technique has no effect on the frequency of seizures. Patients who had numerous baseline seizures are more likely to have a seizure during surgery.[47]

Among the 10 epilepsy patients, 8 patients had an uneventful course, one patient had tremor of bilateral lower limb for which he was on neurological evaluation and one patient expired after discharge from hospital till postoperative day 30.

Among 6 patients with Parkinson disease, all patients were taking syndopa, 2 patients were taking donepezil and amantadine along with syndopa and one patient was taking melatonin and amantadine along with syndopa. Abrupt drug withdrawal can frequently result in a very quick return or even worsening of symptoms, and in some cases, even death. Neuroleptic malignant syndrome, which can be extremely deadly, can occur in some circumstances. Levodopa has a half-life of 1-3 hours; thus interruptions should be kept to a minimum and therapeutic administration should be continued on the day of surgery.[54]

Among 6 patients with Parkinson disease intraoperative period was uneventful among 3 patients and 3 patients had intraoperative hypotension which was managed by norepinephrine infusion. Post operative period was uneventful in 4 patients, one patient had delirium and one patient expired due to refractory VT. Huang et al Patients in an extensive countrywide population-based study with Parkinson disease who underwent non-neurological surgery showed increased 30-day in hospital mortality compared to those without Parkinson disease. Pulmonary embolism, pneumonia, stroke, urinary tract infection, and septicaemia had higher rates of surgical complications in Parkinson disease patients.[84]

Study Limitations

1. Due to the observational nature of our study, the inherent bias in trial design could not be entirely excluded.
2. The outcomes of this study cannot be generalised because it was only conducted at one centre.
3. The fact that the anaesthetic management was left up to the anesthesiologist in charge, which could differ from person to person, was a drawback of this study.
4. The anaesthetic technique chosen by the attending anaesthesiologist could have been based on personal preference, type of surgery rather than just the nature of pre-existing neurological disease.
5. The sample size may be small because this was a time-limited study. To replicate our findings, similar studies with a large enough sample size are required.

CONCLUSION

The perioperative course of patients with pre-existing neurological disease receiving anaesthesia for non-neurological procedures is unpredictable, which may be caused by the brain injury itself or by related comorbidities. Further studies may be needed to pinpoint the exact cause. We found that there is much variation in the hemodynamics of patients with pre-existing neurological diseases in the perioperative period when compared to other patients. There is ample literature about postoperative neurological complications, not much literature is available about the perioperative course of patients with pre-existing neurological disorders undergoing non-neurological surgeries. To lower morbidity and mortality, understanding the perioperative course of patients with pre-existing neurological disorders is crucial.

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ANNEXURES

I. IEC certificate

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/3487 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3322**

Project title: **"Perioperative course of patients with pre-existing neurological disorder undergoing anaesthesia for non-neurological surgery: A prospective observational study"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Athul V**
Guide:	**Dr. Swati Chhabra**
Co-Guide:	**Dr. Sadik Mohammed, Dr. Pradeep Bhatia, Dr. Samhita Panda & Dr. Bharat Paliwal**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary

Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

II. Consent Form

All India Institute of Medical Sciences

Jodhpur, Rajasthan

Informed Consent Form

Title of the project Perioperative **course of patients with pre-existing neurological disorder undergoing anaesthesia for non-neurological surgery: A prospective observational study**

Name of the Principal Investigator : DrAthul v

Patient/Volunteer Identification No. : _____

I,_____S/o or D/o_____R/o _____ give my full, free, voluntary consent to be a part of the study **:** An observational study to know the incidence and perioperative course of neurological disorders in adults undergoing non-neurological surgery**.** The procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason.

I understand that the information collected about me and any of my medical records may be looked at by responsible individuals from **AIIMS Jodhpur** (Company Name) or from regulatory authorities. I give permission for these individuals to have access to my records.

Date : _____ _____

Place :_____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date : _____ _____

Place :_____ Signature of Principal Investigator

1. Witness 1 2.Witness2

_____ _____

Signature Signature

Name:_____ Name:_____

Address : _____ Address : _____

All India Institute of Medical Sciences

Jodhpur, Rajasthan

PARTICIPANT INFORMATION SHEET (PIS)

Title of the project: **Perioperative course of patients with pre-existing neurological disorder undergoing anaesthesia for non-neurological surgery: A prospective observational study**

Name of the Principal Investigator: Dr Athul V

Tel. No:7736012173

I have been explained in my own understanding language by the principal investigator that they are doing this observational study to know the incidence and perioperative course of neurological disorders in adults undergoing non-neurological surgery**.**

I have been informed that I can withdraw myself from study at any time.

The data obtained from me will be used for the purpose of the study only. All my records will be kept confidential.

Patient name and registration id:

Signature:

अखिल भारतीय चिकित्सा विज्ञान संस्थान जोधपुर, राजस्थानभाग

लेने के लिए सूचना पत्र (पीआईएस)

परियोजना का शीर्षक: **Perioperative course of patients with pre-existing neurological disorder undergoing anaesthesia for non-neurosurgical surgery: A prospective observational study**

प्रधान अन्वेषक का नाम: Dr Athul V

दूरभाष् नंबर: 7736012173

प्रस्तावित अन्वेषण द्वारा मुझे अपनी समझ भाषा में समझाया गया है कि **Perioperative course of patients with pre-existing neurological disorder undergoing anaesthesia for non- neurosurgical surgery: A prospective observational study** और इसके साथ जुड़े जोखिमों और लाभों को भी समझाया गया है।

मुझे सूचित किया गया है कि मैं किसी भी समय अध्ययन से अपना हटा सकता हूं।

मेरे द्वारा प्राप्त आंकड़ों का उपयोग केवल अध्ययन के उद्देश्य के लिए किया जाएगा। मेरे सभी रिकॉर्ड गोपनीय रखा जाएगा।

रोगी का

नामऔर

पंजीकरण आईडी:

हस्ताक्षर:

PROFORMA

PATIENT ID :

Phone No:

ASA physical Status- I/II/III/IV/E

Age/Sex: Weight: Height:

Diagnosis:

Procedure:

Neurological disorder:

Brief history:

Duration:

Medications:

Interventions:

Other comorbidities:

Brief history:

Previous record available: Yes/no

Neurologist opinion sought: Yes/no

Anaesthetic technique:

Intraoperative events:

Baseline Mean Arterial pressure:

Highest Mean arterial blood pressure:

Lowest Mean arterial blood pressure:

Other intra op events :

Postoperative events:

Any exacerbation of the underlying neurological disease till discharge:

Date of discharge:

At 30 days post op (date):

Supervisor