TO STUDY THE PREVALENCE OF HYPONATREMIA IN ACUTE CEREBROVASCULAR DISEASE AND ITS EFFECT ON FUCTIONAL OUTCOME

THESIS

Submitted to

All India Institute of Medical Sciences, Jodhpur

In partial fulfillment of the requirement for the degree of

DOCTOR OF MEDICINE (MD)

(GENERAL MEDICINE)

July, 2020 **Dr. Shilpi Goyal**

AIIMS, JODHPUR

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DECLARATION

I hereby declare that the thesis titled "**TO STUDY THE PREVALENCE OF HYPONATREMIA IN ACUTE CEREBROVASCULAR DISEASE AND ITS EFFECT ON FUCTIONAL OUTCOME**" embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled " **TO STUDY THE PREVALENCE OF HYPONATREMIA IN ACUTE CEREBROVASCULAR DISEASE AND ITS EFFECT ON FUCTIONAL OUTCOME**" is the bonafide work of Dr Shilpi Goyal carried out under our guidance and supervision, in the Department of General Medicine, All India Institute of Medical Sciences, Jodhpur.

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ACKNOWLEDGEMENT

"***Alone we can do so little; together we can do so much***"

-Helen Keller

Nothing worth achieving as ever been achieved without the guidance of our teachers and the support of family and friends. The immortal words of Helen Keller could not be more undeniable as I stand at the cusp of one of the most prestigious achievements of my life.

I would not be at this landmark moment without the trust and patient patronage of Dr Mahendra Kumar Garg, Head of Department of General Medicine, All India institute of Medical Sciences, Jodhpur. I am truly honored and grateful for the opportunity to learn under his tutelage.

I am also indebted to my Co-guides Dr Bharat Kumar Associate Professor, Department of General Medicine and Dr Samhita Panda Additional Professor and Head, Department of Neurology. All India institute of Medical Sciences, Jodhpur. Their step by step support and guidance has been instrumental in creating the environment of success and excellence needed for a dissertation from our esteemed institute.

I am also thankful to Dr Gopal Krishna Bohra, Additional professor , Dr Maya Gopalakrishnan, Dr Deepak kumar ,Dr Naresh Kumar Midha and Dr Satyendra Khichar (Associate Professors, Department of General Medicine) , Dr Amit Kumar , Dr Durga Shankar Meena (Assistant professors , Department of general medicine) who educated me about research and helped me whenever I needed.

Family is the backbone which has prevented me from ever faltering in the quest for excellence and knowledge. I cannot express in words my appreciation and love for my parents, Mr. Satish Goyal , Mrs. Santosh Goyal and my younger brother Mr. Prince Goyal for their immense support and understanding even when I was not worthy of it.

I acknowledge the nurturance I have received from my seniors Dr Karthikeyan and Dr Kamlesh, Dr Akhilesh, Dr Neeraja , Dr Saurabh , Dr Sonu , Dr Swapnil , Dr Prakrati, Dr Veena Surendran, Dr Kartikey, Dr Tejaswee , Dr Vishwanath , Dr Nakka Vihari, Dr Naveen, Dr Arjun of the Department of General Medicine. Without their help and reprimands, I would been clueless as to how to proceed with the work involved in this dissertation. I thank my batch mates Dr Pranav, Dr Naja, Dr Isha; Dr Ramanand, Dr Pankaj whose company always made the environment lighter and funny to work. I also thank my juniors Dr Venkat, Dr Mayur, Dr Ninad, Dr Sachin, Dr Sanjay, Dr Bijit, Dr Divya, Dr Manika , Dr Lochan, Dr Shubham, Dr Naveen, Dr Naman, Dr Pankaj, Dr Samarth ,Dr Shawon ,DrAkash,Dr Dipasha, Dr Pyrus, Dr Shekhar, Dr Manish who have stepped up in times of need to help balance the duties of a junior resident of our beloved department and the commitments to my thesis. I also thank my dear friend Dr Eram, Dr Harsh, Dr Dhanashri, Dr Bharti, Dr Falguni, Dr Chitra, Dr Ankita and many more who has persistently motivated me during this time.

All the faculties of the Department of General Medicine, All India institute of Medical Sciences, Jodhpur have been pillars of support and understanding and this would not have been possible without them.

Last but by far not the least, I express thanks to all my patients without whom this milestone was not possible.

Dr. Shilpi Goyal

Dedicated to
My Family

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LIST OF ABBREVIATIONS

S. No.	Abbreviations	Full forms
1.	ADH	Antidiuretic hormone
2.	AIIMS	All India Institude of Medical Sciences
3.	aSAH	Aneurysmal subarachnoid haemorrhage
4.	CKD	Chronic kidney disease
5.	CSWS	Cerebral salt-wasting syndrome
6.	CVA	Cerebrovascular accident
7.	ECF	Extracellular fluid
8.	GOS	Glasgow outcome scale
9.	HTN	Hyprtension
10.	ICF	Intracellular fluid
11.	ICU	Intensive care unit
12.	IQR	Interquartile range
13.	mBI	modified Barthel Index
14.	MRS	modified Rankin scale
15.	NIHSS	National Institutes of Health Stroke Scale
16.	SIADH	Syndrome of inappropriate secretion of antidiuretic hormone
17.	SD	Standard deviation

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ABSTRACT

Background: Cerebrovascular disease is the second most common cause of death and disabling life worldwide and hyponatremia is the most common dyselectrolytemia among CVA patients.

Aims and objectives: To study the prevalence of hyponatremia in acute cerebrovascular disease and its effect on functional outcome and mortality at 90 days.

Methods: In this study we observed the stroke patients from July 2021 to March 2022 at All India Institute of Medical Sciences (AIIMS), Jodhpur. Patients were assessed clinically with GCS ,mRS and NIHSS . Patients were tested for serum sodium levels and followed to reassess the mRS after 90 days.

Results: One hundred and fifty stroke patients were enrolled in the study. Mean age was 57.96±15.90 years, were 64% males and 36% females. Hyponatremia is prevalent in 53.3% of population under study .Baseline sodium is significantly associated with age groups, outcome of hospitalization and mortality at 90 days. But there is no association of hyponatremia with gender, mRS, NIHSS and GCS of the patient.

Conclusion: Hyponatremia is significantly associated with mortality at 90 days. By this we can conclude hyponatremia need to be treated soon to improve the outcome of the patients. Similarly severity of hyponatremia is helpful with the prediction of mortality at 90 days but not associated with overall functional outcome.

INTRODUCTION

INTRODUCTION

A cerebrovascular disease is a group of heterogeneous medical conditions that affects the blood vessels and blood supply of brain. It includes several types of vascular malformations, aneurysm and blood vessels stenosis, which can lead to transient ischemic attacks, hemorrhages and stroke. A different etiological subtype includes cardio embolic, atheroembolic, lacunars ischemic strokes, aneurysmal subarachnoid hemorrhage and other intracranial vascular disorders. Among the cerebrovascular diseases stroke is the most prevalent and life threatening.

A stroke, or cerebrovascular accident, is defined as an abrupt onset of a neurologic deficit that is attributable to a focal vascular cause [1]. It is of two types -Ischemic stroke and hemorrhagic stroke. It is the second most common cause of death worldwide. With 6.2 million dying from stroke in 2015,an increase of 830,000 since the year 2000. From the age of 25 onward, the lifetime global risk of stroke increased from 8.9% in 1990 to 25% in 2016 [1]. Stroke is the second most common cause of disabling condition in individual aged 50 or older worldwide [1]. The burden of stroke is increasing in India. Crude incidence of stroke ranged from 108 to 172/100,000 people per year, crude prevalence from 26 to 757/100,000 people per year, and one-month case fatality rates from 18% to 42% [2]. It is a complex disease that requires the efforts and skills of all members of the multidisciplinary team. A coordinated care of the stroke patient results in improved outcomes, decreased lengths of stay, and decreased costs [3].

Hyponatremia is defined as a plasma sodium concentration <135meq/L. It is the most common electrolyte disorder both in the in-hospital and the community

setting with a reported incidence up to 30 and 8%, respectively [4,5]. It is found that even mild hyponatremia has been associated with increased morbidity and mortality among the patients including gait disturbances, cognitive impairment, osteoporosis, falls and fractures etc. [4]. Two types of hyponatremia 'true' and 'pseudo' hyponatremia are known.

True hyponatremia will be further subdivided into three types on the basis of fluid level i.e -

- Hypovolumic hyponatremia- (renal losses, vomiting, diarrhoea , CSWS, diuretic excess)
- Hypervolumic hyponatremia-(nephritic syndrome, cirrhosis ,cardiac failure)
- Euvolumic hyponatremia – (SIADH , hypothyroidism, glucocorticoid deficiency)

European guidelines classify hyponatremia in adults according to serum sodium concentration, as follows [6].

Mild: 130-134mmol/L

Moderate: 125-129mmol/L

Profound: <125mmol/L

Pathogenesis of hyponatremia – The hypothalamus produces anti diuretic hormone (ADH), which is then stored in secretory granules of posterior pituitary until it is released in response to osmotic or no osmotic stimuli [7]. The main triggers for ADH secretion are serum hyperosmolality and effective circulation

volume depletion, although other factors can also affect it, such as nausea, stress (such as pain), or medications (such as oxcarbazepine, carbamazepine, and selective serotonin reuptake inhibitors) [7]. In the pathogenesis of hyponatremia, ADH promotes water reabsorption at the cortical and medullary collecting tubules [7]. Hyponatremia may result from water retention or through the loss of potassium and sodium salts in excess water [7]. In patients with primary polydipsia, where high water consumption (10–15 L per day) can exceed the normal renal excretory capacity, retention of water does not cause hyponatremia; rather, it only happens in the presence of diseases that inhibit renal excretion of water [7]. Considering the fact that the suppression of ADH secretion is essential for the excretion of water excess, the presence of inappropriately high serum concentrations of ADH in relation to low plasma osmolality should be considered as the prerequisite for the development and maintenance of hyponatremia [7]. The major of causes of hyponatremia with the exception of renal failure, primary polydipsia, beer potomania, and low dietary solute intake, are linked to an absolute or relative excess of ADH (despite the presence of hypo tonicity), primarily as a result of the syndrome of inappropriate ADH secretion (SIADH) or the depletion of effective circulating volume [7].

Prevalence of hyponatremia in stroke patient

Stroke patients frequently develop various electrolyte disturbances in their clinical course like hyponatremia , hypernatremia, hyperglycemia and hypokalemia etc. out of which hyponatremia is especially a trigger that exacerbates neurological symptoms. Its prevalence rate in stroke patients is approximately ≥10% compared

with 1–2% in generally hospitalized patients [8-11]. During admission (3.9-45.3%) of patients with stroke are found to have hyponatremia or (40-45%) develop while they are being treated in the hospital [12]. Other co-morbid illnesses become more severe when hyponatremia emerges during the course of those conditions.

Aneurysmal subarachnoid hemorrhage (aSAH), a fatal disorder caused by the abrupt rupture of an aneurysm of one of the intracranial arteries, is one of the most dangerous types of bleeding inside the brain [13,14] . Although aSAH only makes up around 5% of all strokes, it affects a younger population and results in the loss of as many productive years as all acute ischemic strokes combined [15]. There is a high acute mortality of up to 30% , but also a high morbidity in survivors [16].Some studies show an incidence of hyponatremia upto 50% following the SAH [17].

Etiology of hyponatremia in stroke patients- [12]

A) Stroke-related causes –

- CSW syndrome: inappropriate renal sodium wasting
- SIADH: increased hypothalamic production of ADH
- Secondary adrenal insufficiency: pituitary ischemia or hemorrhage

B) Nonstroke-related causes other causes and/or superimposed factors

- Poor solute intake –Infections (e.g., aspiration pneumonia)
- Co morbidities: diabetes mellitus, chronic renal failure, and heart failure

- Inappropriate administration of intravenous fluids (e.g., hypotonic solutions)

C) Drug-induced hyponatremia

- Mannitol
- Anxiolytics (benzodiazepines)
- Antipsychotics (phenothiazines, butyrophenones)
- Diuretics (thiazides, indapamide, loop and potassium sparing diuretics)
- Antidepressants (tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-nor epinephrine reuptake inhibitors)
- Anticonvulsants drugs (oxcarbazepine, carbamazepine, eslicarbazepine, sodium valproate, lamotrigine, levetiracetam, gabapentin, phenytoin, topiramate)
- Others: non-steroidal anti-inflammatory drugs, proton pump inhibitors, antibiotics (ciprofloxacin,co-trimoxazole),angiotensin-converting enzyme inhibitors, antiarrhythmics (amiodarone, lorcainide, propafenone), opioids.

Hyponatremia in stroke patients can lead to cerebral edema, seizures, and disturbance of consciousness [18,19]. .Additionally, it may also cause volume depletion leading to cerebral ischemia and cerebral infarction [20]. Moreover, an inappropriate correction rate of serum sodium can cause a demyelination of the pons known as central pontine myelinolysis [21,22]. This electrolyte abnormality has an unfavorable and sometimes fatal effect on stroke patients in their clinical course. Hyponatremia has been reported to negatively affect stroke outcomes

more so when caused by CSWS than SIADH [23]. Because of this, the neurologist's comprehension of these conditions is based on a number of crucial management concepts, including the control of osmolality, modifications to the body's fluid compartments, and the importance of early detection and effective treatment.

It has been found in few studies that hyponatremia can lead to reduced functionality and significantly lower quality of life. In Indian population, there are many studies on stroke, its associated conditions and their effects on stroke patient's outcome. But very few studies have explored the effects of serum sodium levels on clinical outcomes and its prognostic significance in CVA patients.

The objective of this study was to determine the prognostic significance of hyponatremia at presentation and its effect on functional outcomes in patients of acute cerebrovascular diseases.

This will be a prospective, analytical hospital based cross-sectional study with controls in the medical ward from All India Institute of Medical Sciences, Jodhpur from January 2021 to July 2022.

Need for study:

1. A Very few studies are available from India on hyponatremia in acute cerebrovascular disease despite it being a very common disorder.
2. Hyponatremia is one of the common causes of morbidity & mortality in stroke patients as we discussed earlier.
3. To prognosticate the outcome of patient at the time of admission.

REVIEW OF LITERATURE

REVIEW OF LITERA.TURE

Sodium plays a vital role in the maintenance of normal cellular homeostasis and in the regulation of fluid and electrolyte balance and blood pressure (BP). Due to its significant osmotic activity, it plays an essential role in maintaining ECF volume and is also necessary for the excitability of muscle and nerve cells, the transfer of nutrients and substrates through plasma membranes, and other processes. [24].

It is the major cation of extracellular fluid. The mean body content of sodium in the adult male is 92 g, half of which is located in the ECF at a concentration of 135–145 mmol /L, ∼11 g is found in the intracellular fluid at the concentration of ∼10 mmol/L, and ∼35 g is found in the skeleton [25]**.** Its concentration gradient between ECF and intracellular fluid is highly maintained by various mechanisms in our body. Different ways of insult can lead to disregulation of sodium level and can lead to development of hyponatremia or hypernatremia in our body. Hospitalized individuals, notably those who are young children and elderly frequently develop hyponatremia. Symptomatology depends more on the rate of development of the electrolyte abnormality than on its severity [1]. It is the most common electrolyte disturbance encountered in clinical practice [5] and also associated with increased morbidity and mortality among hospitalized patients.

Stroke is the second most common cause of death worldwide and 3rd leading cause of disability and its association with hyponatremia is very crucial. The two main causes of hyponatremia after stroke are cerebral salt-wasting syndrome, which is characterized by natriuresis and extracellular fluid depletion, and

syndrome of inappropriate antidiuretic hormone secretion, which causes hypoosmolar hyponatremia due to free water retention caused by excessive antidiuretic hormone secretion [26-29] .

In 2020 in Bangalore, a hospital-based, analytical prospective observational study was conducted among fifty individuals. The study population included patients aged 16 years or above of both genders admitted within 48 hours of onset and with a CT-Brain confirmation of stroke. Total serum sodium and potassium levels were determined. Patients were followed-up for two weeks during their stay and before discharge from the hospital using Glasgow outcome scale. Majority 52 % had ischemic stroke followed by 46 % had intracerebral hemorrhagic stroke and 2% had subarachnoid hemorrhagic stroke. Among patients with hemorrhagic stroke 66.6 % had dyselectrolytemia and 33.4 % had normal electrolytes and among patients with ischemic stroke 46.2 % had dyselectrolytemia and 53.8 % had normal electrolytes. They concluded by this, hyponatremia and hypokalemia are most common electrolyte imbalances in both ischemic and hemorrhagic stroke [30].

Kalita et al. (2017) in their study evaluate the cause for hyponatremia in CVA patients. One hundred patients with stroke were included: 47% had ischemic stroke and 53% had intracerebral hemorrhage. Forty-three percent of the patients had hyponatremia, 6% had hypernatremia, and 4% had both. Hyponatremia was due to CSW in 19 (44.2%), SIADH in 3 (7%), miscellaneous causes in 14 (32.6%), and indeterminate in 7 (16.3%) patients. Hyponatremia occurred in 43% of stroke patients. CSW was the most common cause of hyponatremia [31].

In 2014 in a study done in Srinagar's tertiary hospital, it was discovered that hyponatremia, a common electrolyte disorder in patients with neurological conditions like stroke, subarachnoid haemorrhage, and meningitis, is typically caused by either the SIADH or CSWS. Out of 1,000 patients, 353 patients had hyponatremia. Out of this 353 patients, 238 (67%) had SIADH and 115 (33%) had CSWS. SIADH was seen in 83 patients who had an ischemic stroke and 155 patients of hemorrhagic stroke. CSWS was found in 38 patients with ischemic stroke and 77 patients with hemorrhagic stroke. Out of 353 patients with hyponatremia with stroke, 197 survived and 156 died. Out of 647 patients without hyponatremia, 553 survived and 94 died. The P value for this was 0.00 which is statistically significant. In the SIADH group of patients (n = 238), 129 survived while 109 died, whereas in the CSWS group of patients (n = 115), 68 survived and 47 died. On statistical analysis, it was found that CSWS significantly affected the outcome of stroke [23].

There are many studies which show that hyponatremia in stroke patients as an independent factor in mortality and increased duration of stay and other complications.

Wang et al. (2021), in their prospective study of 10,299 patients observed the association of electrolytes with their functional outcome and death at 3 months and 1 year . Patients were classified into three groups according to tertiles and the normal range of each electrolyte (sodium, potassium and chloride). In the first tertile electrolytes were associated with increased risk of poor functional outcome (mRS score 3–6) at 1 year, the adjusted odds ratios (95% confidence intervals)

were 1.33 (1.14–1.55) for potassium, 1.41 (1.20–1.60) for sodium, 1.27 (1.08–1.48) for chloride, compared with the second tertile. Similar results were found when poor functional outcome was defined as mRS score 2–6 and all-cause death [32].

Swamy NYN et al. (2019) observed among the 150 patients admitted with acute ischemic stroke, 68% were males and 36% patients had hyponatremia. Hyponatremic patients had higher NIHSS score on admission, on day 5 and at discharge (p= =<0.001).Hyponatremic patients had a longer duration of ICU stay (p=<0.001) and in hospital stay (p=<0.001). Hyponatremia was associated with higher mortality in hospital (p=0.026).This Study demonstrates that hyponatremia at admission in acute ischemic stroke patients is associated with acute mortality, worse NIHSS score at admission and at discharge, and longer duration of ICU and hospital stay[33].

S.Shima et al. (2020) in their study of meta analysis of 835 studies, 15 studies met the inclusion criteria (n=10,745) .The prevalence rate of stroke patients with hyponatremia was 7.0- 59.2%. They had significantly higher 90 day mortality (OR- 1.73; 95% confidence interval (CI), 1.24- 2.42) and longer length of hospital stay (mean difference, 10.68 days; 95% CI,7.14-14.22) than patients without hyponatremia. Patients with hyponatremia had a higher tendency of in hospital mortality than those with no hyponatremia (OR, 1.61; 95% CI, 0.97- 2.69) 0- 5.03, for a shift to higher mRS. Hyponatremia could be a significant predictor of poor outcome after stroke [34].

Saha G et al (2020) in their study of 100 patients assessed the disability by mRS score. The patients were followed up at admission and at the time of discharge. Mean age of hyponatremia patients and eunatremia patients were 64.8 ± 12.3 years and 60.9 ± 13.1 years respectively. Mean Na+ level in hyponatremia patients was significantly lower than eunatremia patients (127.6 ± 5.7 mg/dl vs 139.3 ± 3.5 mg/dl). Even mortality rate was higher in hyponatremia group (12.0%) than that of eunatremia group (4.0%) the difference was not statistically significant ($p>0.05$). No significant difference was observed in disability rate between hyponatremia group and eunatremia group (81.8% vs. 72.9%). The mean mRS scores at the time of admission (4.16 ± 1.03 vs. 3.74 ± 0.75) and at the time of discharge (3.56 ± 1.21 vs 3.04 ± 0.98) were significantly higher in hyponatremia than eunatremia patients. This study result shows that mRS score is higher in hyponatremic stroke patients than that of eunatremic stroke patients. So, it can be concluded that outcome of ischemic stroke patients with hyponatremia is worse than ischemic stroke patients with eunatremia [35].

Sivakumar Karunanandham et al (2018) , conducted a cross-sectional study among 202 diagnosed stroke patients for presence of hyponatremia. Among the 202 CVA patients, 78 patients (38.61%) presented with hyponatremia. Among the 78 patients, 43 (21.28%) were ascertained as Syndrome of Inappropriate Secretion of Ant diuretic Hormone (SIADH), in which ischemic stroke and hemorrhagic stroke were diagnosed in 31 and 12 patients respectively. Fifteen patients (7.42%) had Cerebral Salt Wasting Syndrome (CSWS), in which 5 patients had ischemic stroke and 10 patients had hemorrhagic stroke. A total of 20 (9.90%) cases had

hyponatremia with unknown etiology. They concluded that hospital stay of patients with hyponatremic CVA was more than patients with normal serum sodium level [36].

Kr.B et al. (2016) observed in their study of 677 patients after first-time ischemic stroke. They divided the patients into two groups according to sodium concentration: ≤ 135 mmol/L and > 135 mmol/L. For patients with hyponatremia the median NIHSS score was 5 points, the median mRS was 4 points, and the mortality within 1 month of ischemic stroke was 10.5%. Patients with normal sodium level - NIHSS 3 points, mRS 2 points and mortality 1 month after ischemic stroke 3.4%. Mortality within 1 month of ischemic stroke in hyponatremic patients: women 16.4%, men 3.5% (p = 0.0194). Hence, after a first ischemic stroke, hyponatremia is linked to worsening health status in patients in the acute and sub acute phases as well as higher mortality within one month. in comparison to men ,women were found to have greater mortality after one month of ischemic stroke[37].

Soiza et al. in 2015 conducted a study among the patients admitted with acute stroke in Norfolk & Norwich University Hospital consecutively from January 2013 to June 2013 were included. Odds ratios or hazard ratios for death were constructed for various time points that is within 7 days, 8-30 days, within one year and overall full follow up. There were 8540 participants included in the study. Point prevalence of hypernatremia and hyponatremia were 3.3% and 13.8%, respectively. When stratified by age groups, outcomes were poorer in younger hyponatremic patients (aged <75 years). Hyponatremia was prevalent in

acute stroke admissions and was independently associated with higher mortality in patients <75 years [38].

Roy et al. (2014, Kolkata) found in their observational study that electrolyte disturbances are an important cause of mortality and morbidity in a cerebrovascular accident (CVA) and timely treatment is very effective and can decrease mortality significantly. They studied the blood and urine sodium and potassium levels in CVA patients. The measurements were done on days 1, 5, and 10 and the data were then analyzed for any correlation with mortality.

They had 50 patients in their study, with 76% having cerebral infarction. Maximum number of patients was in the 51 - 60 year age group (38%). They found hyponatremia in 80% of cases at presentation, and on Day 10, hyponatremia persisted in 46%. Urinary sodium excretion was also significantly high on Day1. Both hyponatremia and urinary sodium excretion was significantly linked to mortality by regression analysis. High urinary excretion of sodium on D10 has an odds ratio of 1.57 ($p < 0.05$) in predicting mortality. As a result, hyponatremia is a significant factor in CVA mortality and SIADH is the most important reason of hyponatremia in CVA patients [39].Treatment of this hyponatremia is essential to prevent further complications [40].

Rodrigues et al (2014) investigated both acute and chronic clinical outcomes after a stroke in hyponatremic patients. Out of 3585 patients with stroke hyponatremia was observed in 565 (16%) patients. Hyponatremic patients had higher NIHSS score on admission (P 5.032) and at discharge (P 5.02). Despite similar modified Barthel Index (mBI) preadmission, patients with hyponatremia

had worse mBI on admission (P 5.049). Hyponatremia was associated with higher mortality in hospital (P 5.039) and at 3-month (P 5.001) and 12-month follow-ups (P 5 .001). A poorer discharge disposition was seen in the hyponatremia group (P 5.004). Patients with hyponatremia had worse NIHSS and mBI values on admission, and their deficits worsened during their hospitalization [41].

Huang et al. (2012) in their study concluded that patients with acute first-ever ischemic stroke, hyponatremia can predict 3-year mortality independently of other clinical indicators of unfavorable prognosis. In their study of 925 patients presenting with acute first-ever ischemic stroke sodium levels were obtained on arrival at the emergency room within 3 days of acute stroke onset. Clinical presentation, stroke risk factors, associated medical disease, and outcome were recorded. All patients were followed for 3 years for survival analysis. At the end it was found that hyponatremia is an independent predictor of 3-year mortality in patients with acute first-ever ischemic stroke [42].

In a study of 1995 patients, 144 (7.2%) had hyponatremia on admission, 102 (70.8%) reached eunatremia and 42 (29.2%) remained hyponatremia at discharge. An increase of initial sodium was associated with better functional outcome at 3 months (odd ratio 0.94; 95% CI, 0.90 -0.99, for a shift to higher MRS per 1mmol/L sodium increase). Patient with hyponatremia at discharge had a worse functional outcome at 3 months [43].

There are studies which showed how treating hyponatremia on time will improve the outcome of patient.

Kieningeret.al. (2021) in their retrospective study in 180 patients with acute aneurysmal subarachnoid hemorrhage examined the course of serum sodium levels. According to the frequency, severity, and medicine used to treat hyponatremic episodes, each patient's file was examined. Out of 180 patients, 18 patients had hyponatremia and 4 patients had hypernatremia upon admission to the ICU. Out of 158 patients 88 patients with normal serum sodium levels developed at least one hyponatremic episode during ICU treatment. Patients with higher-grade and lower-grade aneurysmal SAH experienced about the same number of hyponatremic episodes (P = 0.848). Patients with and without hyponatremia experienced the same outcomes at the end of ICU care (45.5% vs. 54.3%, P = 0.270). However, at 6 months following SAH, patients with hyponatremia were more likely to have a favorable result (Glasgow outcome scale, GOS 4-5 (29.5% vs. 45.7%, P = 0.036). 75.4% of patients with mild hyponatremia (130-134 mmol/L) and 92.9% of patients with moderate hyponatremia (125-129 mmol/L) had started taking sodium chloride, fludrocortisones, or tolvaptan medications for the hyponatremia correction. Patients who got tolvaptan had a lower rate of poor outcome at 6 months following SAH than those who did not (7.1% vs. 33.8%, P = 0.045). Hyponatremia was treated as a result to prevent adverse outcomes in patients with acute aneurysmal SAH and hyponatremic episodes. This therapy appears to be a promising therapeutic strategy because the administration of tolvaptan quickly restored serum sodium levels [44].

Gala et al. conducted a retrospective study on 502 patients out of which 263 were women admitted to the hospital on stroke onset (440 ischemic stroke and 62 hemorrhagic stroke patients). The post-stroke mortality was defined as early if death occurred within 30 days. Hyponatremia was found in 18.4% of patients with Ischemic Stroke and 25.8% of patients with Hemorrhagic S. Hyponatremia is an independent prognostic factor of mortality in people with IS (p = 0.003). Na concentrations were lower in IS patients who died than in those who survived (134.8 4.99 vs. 136.6 3.01 mmol/L; p = 0.02) Patients with IS who had Na levels below 132 mmol/L and were under 75 years old had a higher mortality rate. Hyponatremia corresponds with NIHSS and the magnitude and site of the stroke in IS patients (p = 0.005, p = 0.002, respectively). Therefore, there is a need to control electrolyte levels at the onset of the stroke, especially in patients with co morbidities, irrespective of age [45].

However, **Maliha et al.** in their cross-sectional study, included 209 patients admitted with acute stroke (65 ischemic, age 61.5±13.3 years, M/F: 45/20; 144 hemorrhagic, age 59.2±13.1 years, M/F: 80/64).. Those having hyponatremia (serum sodium <135 mmol/L) on admission were evaluated by clinical features (history of vomiting or diarrhea, volume status, urine output) and laboratory parameters (urine osmolality, urine sodium, plasma osmolality, blood urea, hematocrit) to determine the types of hyponatremia. Out of 209, 36 (17.6%) had hyponatremia on admission. The frequency of hyponatremia was similar in ischemic and hemorrhagic stroke (17.2% vs. 17.7%, p=0.925).There was no significant difference of age, gender, NIHSS score and GCS score on admission as

well as in hospital stay and in-hospital mortality between patients with or without hyponatremia (p=ns for all) [46].

These studies have shown that sodium can be used for assessment of functional outcome of the patient. These studies showed that prevalence of lower levels of sodium are seen in CVA patients as compared to normal population. This study was done to evaluate role of sodium management in improvement in functional outcome of the patients.

METHODOLOGY

AIM

- To find out the sodium disturbances in acute stroke patients and its effect on the functional outcome of the patients.

OBJECTIVES

PRIMARY OBJECTIVES-

- To assess the prevalence of Hyponatremia in cases of acute cerebrovascular disease.

SECONDARY OBJECTIVES-

- To assess the effect of hyponatremia on the functional outcome and mortality among the acute CVA patients.
- To find the association between severity of hyponatremia and functional outcome.

Type of study:

- An observational, prospective hospital-based study.

Duration of study:

- The study period will be from January 2021 - July 2022.

Place of study:

- Department of Internal Medicine and Department of Neurology, AIIMS Jodhpur

Study population:

- All patients of 18 years and above presented with acute cerebrovascular disease.

Sample size:

Non-probability convenience sampling methods will be used for the selection of the study participants. Consecutive patients who agree to participate in study will be recruited. Sample size calculation done by utilizing data of resilience from previous study [47]. Sample size calculation formula for prospective cohort study will be used.

Sample size found out to be total of 150 participants.

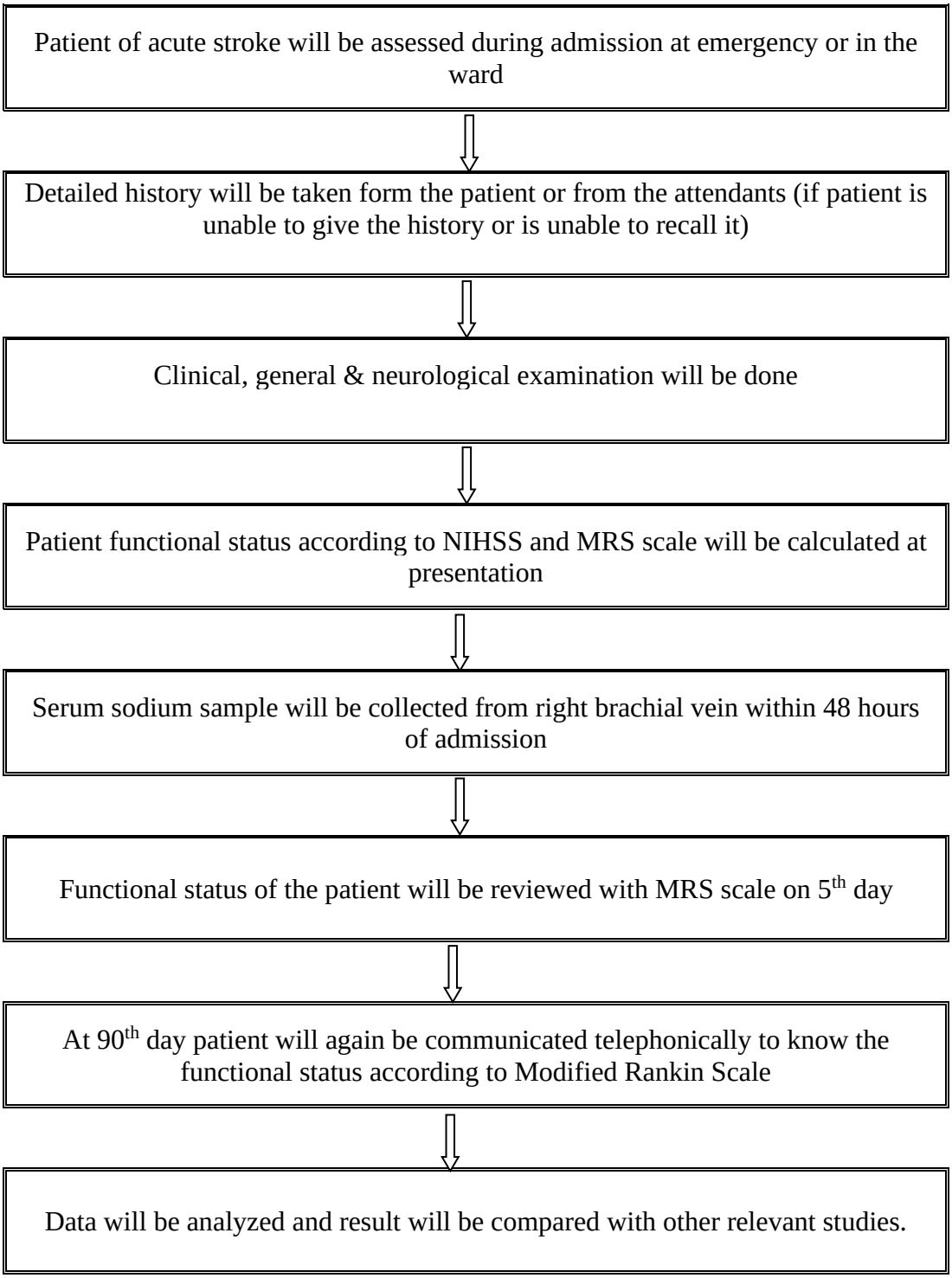
Inclusion Criteria

- All patients of 18 years and above, who presented with acute stroke and their sodium level was assessed within 48 hours of admission will be included in the study after taking informed written consent.

Exclusion Criteria

- Patient less than 18 years of age
- Patient not giving consent

Methodology:



STATISTICAL ANALYSIS

Statistical analysis was carried out using software program SPSS version 20.0. (SPSS Inc. Chicago, USA). All the continuous variables are expressed as mean ± SD and categorical variables as number (%). Chi-square test was used to calculate significance value for categorical variables. Unpaired t test was applied to find out significance for continuous variables. As variables were not normally distributed, hence nonparametric Krushkal Wallis test were used to calculate significances across the subgroups. Spearman correlation coefficient was used to assess relation between various continuous variables. A p value of <0.05 is considered as significant.

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RESULTS

&

DISCUSSION

Patient characteristics-

A total of 150 admitted patients of acute stroke who met the inclusion criteria were included in the study. Patients were excluded from the study if they did not give consent for study participation.

Table 1: Baseline characteristics of patient population

Total Patients = 150	**Frequency**	**Percentage**
Mean age ±SD	57.96±15.90	-
Gender Male Female	 96 54	 64% 36%
Types of stroke Ischemic Hemorrhagic	 118 32	 78.6% 21.3%
Co morbidities Diabetes HTN CKD	 42 60 8	 28% 40% 5.3%
GCS (median/ IQR)	14/4	-
MRS (median/ IQR)	5/1	-
NIHSS(median/ IQR)	10/5	-
Hyponatremia	80	53.3%

All stroke patients aged >18yrs were included and age ranged between 18-90 years. Patients were further sub grouped in different age groups, as mentioned in the table below.

Table-2: Age distribution

Age groups (in years)	Frequency	Percentage
<30 years	10	6.66%
31-40	9	6.00%
41-50	29	19.33%
51-60	35	23.33%
61-70	35	23.33%
71-80	26	17.33%
>80	6	4.00%
Total	150	100%

Distribution of patients as per gender and type of stroke they suffered are shown in Fig 1 and Fig 2.

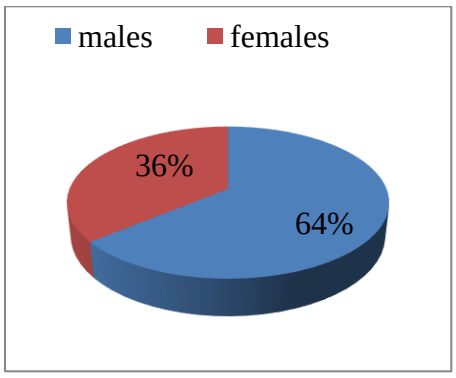

Fig 1: Sex distribution

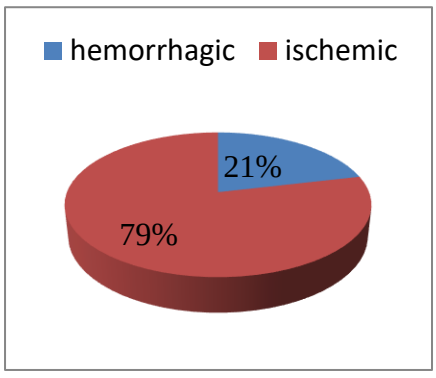

Fig 2: Types of stroke

Table 3: Characteristics of patients with and without hyponatremia

	Total	**Hyponatremia**	**No hyponatremia**	**p-value**
Age(Mean ±SD)	57.96±15.9	59.45±17.15	56.25±14.30	**0.004**
Gender				
Male (%)	96(64)	48(50)	48(50)	0.275
Female (%)	54(36)	32(59.8)	22(40.7)	
Types of stroke				
Ischemic (%)	118(78.6)	61(51.6)	57(48.3)	0.439
Hemorrhagic (%)	32(21.3)	19(59.3)	13(40.6)	
Co morbidities				
Diabetes (%)	42(28)	25(59.5)	17(40.5)	0.343
HTN (%)	60(40)	37(61.6)	23(38.4)	0.095
CKD (%)	8(5.3)	6(75)	2(25)	0.207
Outcome of hospitalisation				
Survived (%)	129(86)	61(47.2)	68(52.7)	**0.0002**
Died (%)	21(14)	19(90.4)	2(9.5)	
Mortality at 90 days (%)	44(29.3)	30(68.1)	14(31.8)	**0.0188**

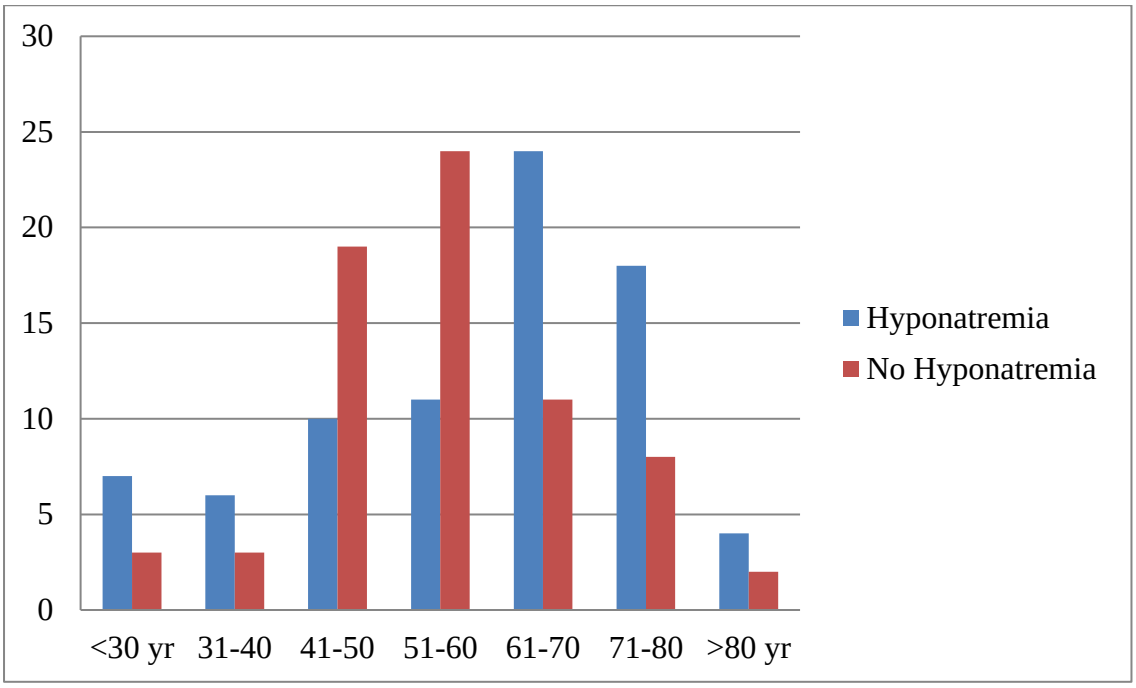

Fig 3: Distribution of hyponatremia among various age groups

Statistically significant differences were found in the age, hospitalization outcome and 90 day mortality between the patient groups. There were no statistically significant differences in sex and co morbidities between the groups.

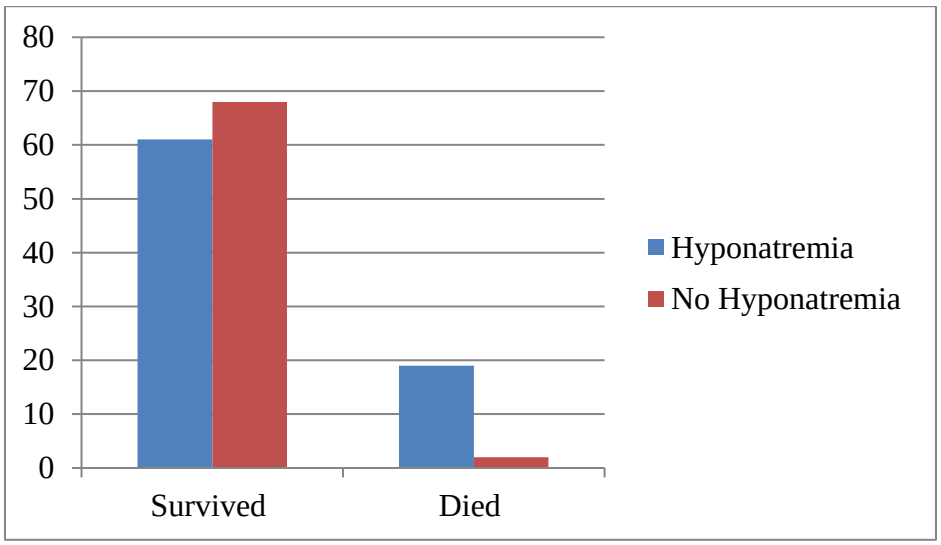

Fig 4: Distribution of hyponatremia with outcome of hospitalization

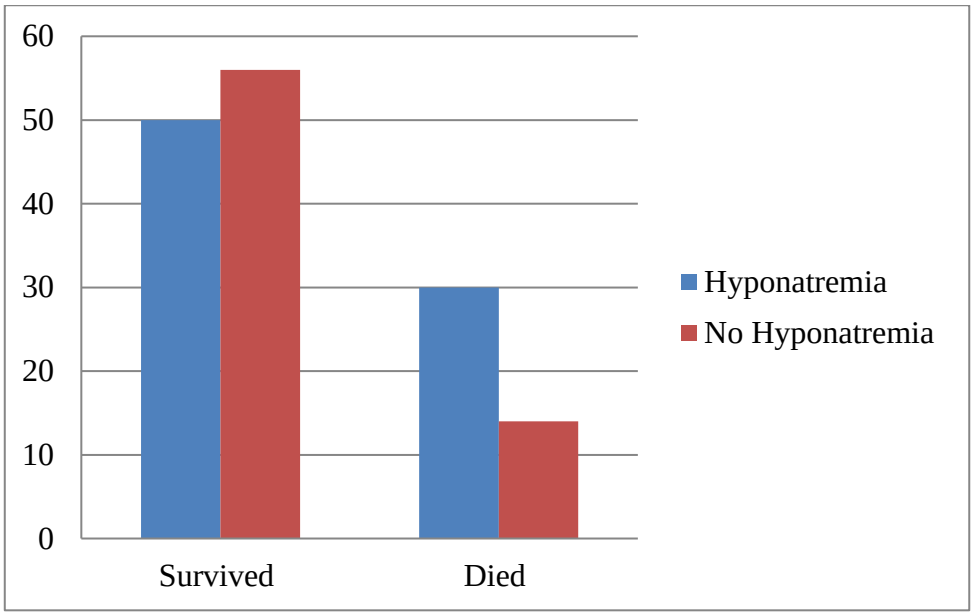

Fig 5: Distribution of hyponatremia with mortality at 90 days

Table 4: Correlation of Hyponatremia with various clinical parameters

Parameters	Correlation coefficient	P-value
GCS	-0.030	0.716
NIHSS	-0.079	0.336
MRS (day 0)	-0.079	0.336
MRS (day 5)	-0.052	0.527
MRS (day 90)	-0.086	0.294
Hospital stay (days)	-0.082	0.319

There was no statistically significant correlation between clinical parameters with sodium level at presentation.

Table 5: Distribution of patients according to the severity of sodium levels.

Sodium levels	Frequency	Percentage (%)
Mild	61	41
Moderate	17	11
Severe	2	1

- The outcome of hospitalization and mortality at 90 days is significantly associated with the categories of severity of hyponatremia (p= 0.003, 0.029).
- The distribution of NIHSS and GCS is significantly associated across the categories of severity of hyponatremia (p=0.033, 0.045 respectively).

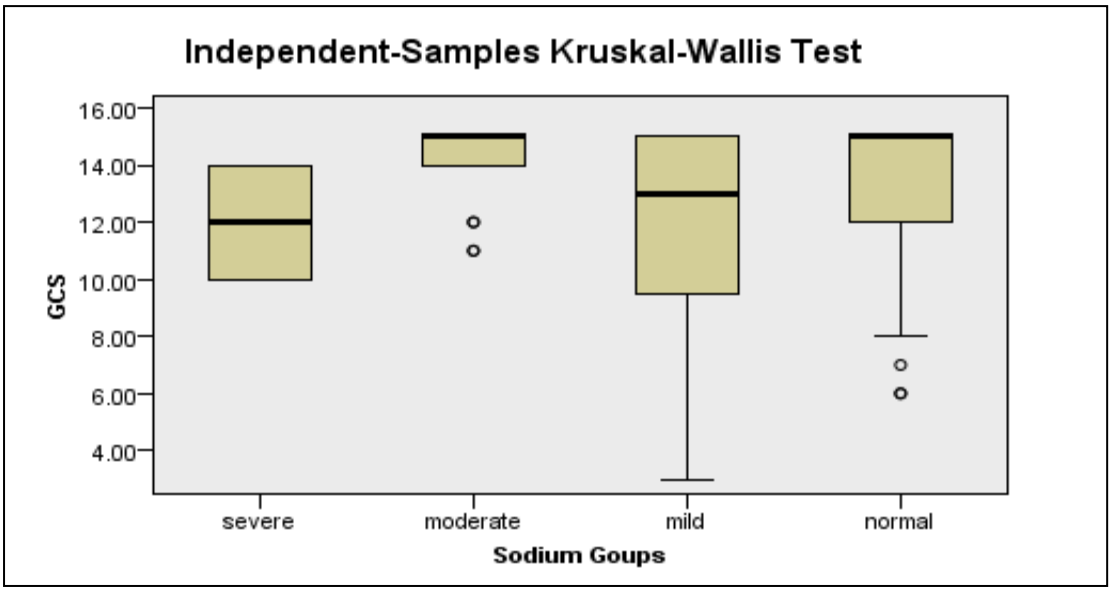

Fig 6: Distribution of GCS across the severity of hyponatremia

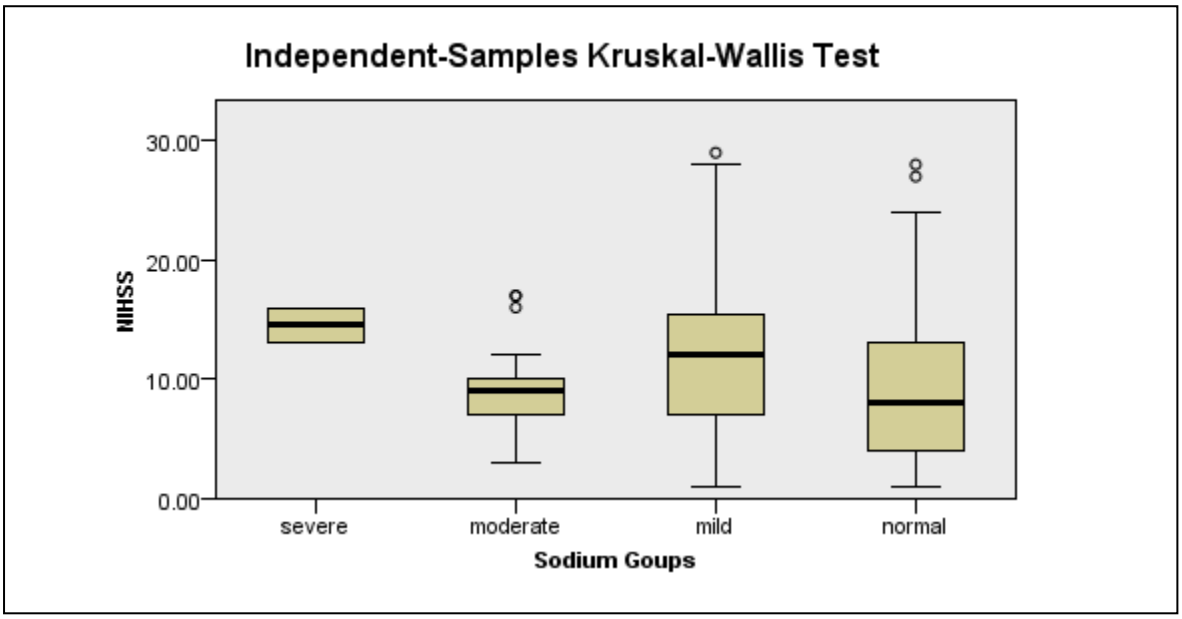

Fig 7: Distribution of NIHSS across the severity of hyponatremia

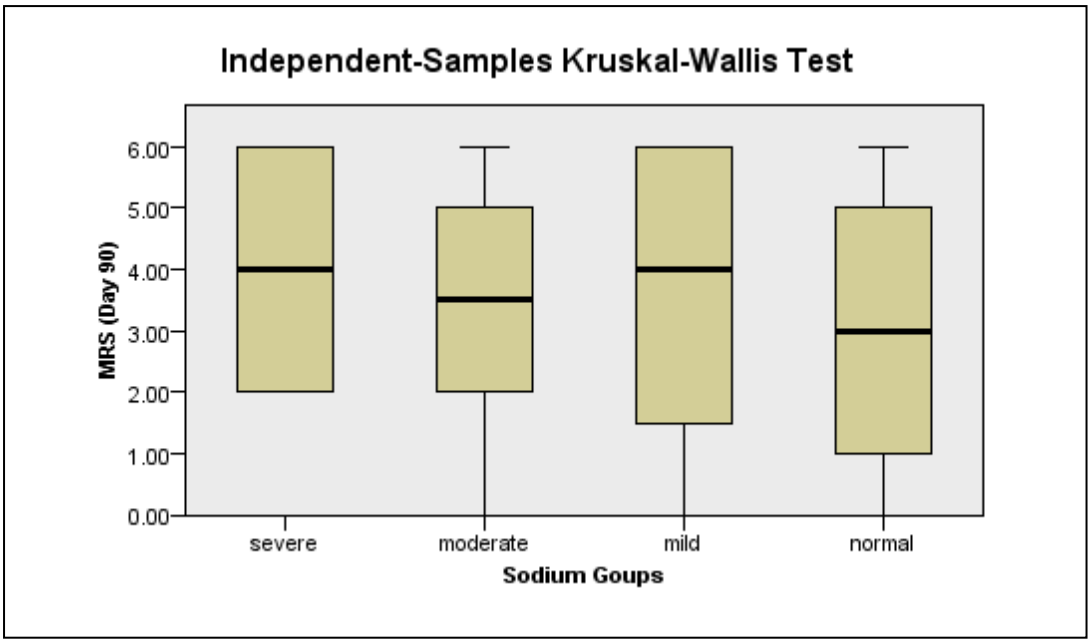

Fig 8: Distribution of mRS at 90 days across the severity of hyponatremia

- The distribution of age and mRS (Day 0, 5, 90) is not significantly associated across the categories of severity of hyponatremia (p=0.142, 0.165,0.277,0.161).

DISCUSSION

One hundred and fifty patients were enrolled in the study. The prevalence of hyponatremia among CVA patients in our study was 53.3 %. Previous studies had a wide range of prevalence, anywhere between 39% to 80%. [4, 31, 36, 40]

Age and sex distribution

Stroke is more common in the people above the age of 50 years. In this study as well, the majority of stroke patients (70%) were found to be above the age of 50. The mean age of patients with hyponatremia was 59.5 years and that without hyponatremia was 56 years. The results were similar from study done by Gray JR [49] et al in 2014 who reported mean ages of patients with and without hyponatremia as 59.41 and 58.6 respectively, Rodrigues [41] et.al did not report any significant differences between ages in patients with and without hyponatremia (71 years & 70.9 years in hyponatremic and normonatremic patients respectively). Also Huang WY [42] et al. did not find a difference in age between the two groups (69.4 years vs. 70.5 years in normonatremic and hyponatremic patients).

A statistically significant difference was observed in the distribution of hyponatremia with age (p=0.004). The results were comparable to study done by Sumit Mohan et al.[48] in 2013 who reported hyponatremia increases with age (4.52% in age group of >85 years) and also more common in age group of 65-84 years (3.11%). There was no statistically significant difference of hyponatremia between genders (p=0.275) similar to previous studies. [46]

Hyponatremia with type of stroke

Ischemic stroke was more prevalent than hemorrhagic stroke (78.6% and 21.3% respectively). Hyponatremia was more prevalent in hemorrhagic stroke (59.3%) than ischemic stroke (51.3 %). Mohan et al [30] and Gala et al [45] found similar higher prevalence of hyponatremia in hemorrhagic stroke.

Hyponatremia in stroke and co-morbidities

Sumit Mohan et al. [48] who reported that patients with co-morbidities are more prone to hyponatremia because of some medications like thiazide diuretics and ARBs/ACEIs. Similar results were shown by a study done by Huang WY [42] et al. in which DM (p-<0.001) and chronic renal insufficiency (p-0.002) were significant risk factor for hyponatremia. But our study reveals the no significant association of hyponatremia with the co-morbidities such as diabetes, hypertension and renal failure. Diabetes mellitus (p-0.343), HTN (0.095) and nephropathy (p-0.207) were statistically not a significant risk factor for hyponatremia.

Hyponatremia and outcome of hospitalization

In this study, we found a significant association between hyponatremia and outcome of hospitalization (p=0.002). 90% of the patients who expired were hyponatremic at presentation. Another Indian study[33] also found that hyponatremia was associated with higher mortality in hospital (p=0.026). The results were comparable to a study done by Huang WY[42] et al. in 2012; who reported a significant contribution of hyponatremia in outcome of stroke and

higher death rates in hyponatremic patients than in normonatremic patients i.e. 5.6% (6 out of 107) and 4.8% (39 out of 818) in patients with and without hyponatremia. Another study by Kuramatsu JB [8] et al. in 2014 concluded that hyponatremia is associated with increased in hospital and short term mortality. Rodrigues [41] et al also found similar association between hyponatremia and in hospital mortality .Study done by Sozia [38] et al. reported increased 7 day mortality in stroke patients with hyponatremia than without hyponatremia. It is still unknown what causes hyponatremia and how a stroke may manifest clinically. Hyponatremia in stroke patients may worsen osmotic cerebral edema through fluid shifts, according to one theory [50] (Chen et al., 2019). The cause of subsequent ionic edema in hyponatremia is the increased ionic gradient between the interstitial fluid and the vascular compartment[54] (Khanna et al., 2014) Furthermore, sodium is closely related to the interrupted Na+/K+-ATPase function, which can result in cytotoxic edema, as a quantitative marker of ischemia lesions and tissue healing[55] (Yin et al., 2020). Additionally, studies[51] (Chen et al., 2021) have shown that, under ischemic stroke settings, BBB malfunction can lead to an increase in paracellular permeability, which directly contributes to the extravasation of blood components into the brain and results in cerebral vasogenic edema. Hyponatremia can speed up this process by causing a chain reaction of ionic homeostasis disruptions. The absolute water content of the brain and brain swelling have both been found to fluctuate significantly in response to relatively slight changes in the brain's water content[53] (Keep et al., 2012). Therefore, cerebral edema brought on by hyponatremia can lead to significant cerebral swelling, which in turn causes an increase in intracranial

pressure, a quick decline in neurological function, and a rise in morbidity and mortality after an ischemic stroke (Chen et al., 2021)

Hyponatremia with short and long term mortality

There is significant 90 days mortality was observed in the patients (p=0.0188).Many studies have also reported long term mortality in cerebrovascular stroke patients with hyponatremia. Study done by Huang WY [42] et al. reported that hyponatremia is a predictor of 3-year mortality in ischemic stroke patients despite other factors. Another study done by Rodrigues [41] et al. reported higher mortality in hyponatremic patients at 3 months and 12 months. Similar results also reported by Sozia [38] et al. in their study at 1 month and 1 year. Wang [32] et al. (2021), in their prospective study of 10,299 patients observed the significant association of electrolytes with their functional outcome and death at 3 months and 1 year. Gala [45] et al. found hyponatremia is an independent prognostic factor of mortality in people with IS (p = 0.003). Na concentrations were lower in IS patients who died than in those who survived (134.8 4.99 vs. 136.6 3.01 mmol/L; p = 0.02). The present study could not assessed long term mortality due to time limitations.

Severity of hyponatremia and clinical parameters

Symptomatology depends more on the rate of development of the electrolyte abnormality than on its severity [1].In our study we find the significant association of outcome of hospitalization and mortality at 90 days (p=0.003, 0.029).but not significantly associated with overall functional outcome of the patients.

5 patients were found hypernatremic but it did not affect the overall outcome of study.

Strengths of this study

1. It compares the outcome between both types of stroke (ischemic and hemorrhagic).
2. It has low attrition rate.

Limitations of this study

1. Small study population was taken.
2. Only Asian populations were under study, cant applied to worldwide population.
3. Larger studies will be required.

SUMMARY

- The prevalence of hyponatremia is 53.3% in population study.
- There is statistically significant association was found between age and hyponatremia (p=0.004)
- There is statistically significant association was found between hospitalization outcome and 90 day mortality (p=0.0002, 0.0188).
- The distribution of GCS and NIHSS is significantly associated across the categories of severity of hyponatremia (p= 0.045, 0.033)
- The outcome of hospitalization and mortality at day 90 is significantly associated across the categories of severity of hyponatremia (p= 0.003, 0.029).
- There is statistically no association was found between hyponatremia with gender, GCS,NIHSS and mRS (0,5,90 day).(p>0.05)
- The distribution of gender, age and mRS (0,5 and 90 days) is not significantly associated across the categories of severity of hyponatremia (p >0.05)

CONCLUSION:

1. The prevalence of hyponatremia in stroke population is 53.3%
2. There was an association between baseline sodium levels with outcome of hospitalization and mortality at 90 days.
3. There was no association between severity of hyponatremia with the functional outcome of the patient.

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APPENDICES

APPENDIX-1
All India Institute of Medical Sciences
Jodhpur, Rajasthan
Informed Consent Form

Title of Thesis/Dissertation: To study the prevalence of hyponatremia in acute cerebrovascular disease and its effect on functional outcome

Name of PG Student: **Dr. Shilpi Goyal** Tel. No.**7206168172**
Patient Identification No : _____

I, _____ S/o or D/o _____
R/o_____
give my full, free, voluntary consent to be a part of the study "A comparative study of functional outcome of acute Cerebrovascular disease in relation to Hyponatremia", 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 I 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 individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.
Date: _____ _____
Place: _____ Signature/Left thumb impression

This is to certify that the above consent has been obtained in my presence.
Date: _____ _____
Place: _____ Signature of PG Student

1. Witness 1
Signature
Name: _____
Address: _____
_____

2. Witness 2
Signature
Name: _____
Address: _____
_____

APPENDIX-1

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर, राजस्थान

<u>सूचित सहमति पत्र</u>

थीसिस का शीर्षक**:** तीव्र सेरेब्रोवास्कुलर रोग में हाइपोनेट्रेमिया की व्यापकता और इसके संबंधी **कार्यात्मक** परिणाम का अध्ययन करना |

पीजी छात्रा का नाम: **डॉ.शिल्पी गोयल** दूरभाष।संख्या :**7206168172**

रोगी / स्वयं सेवी पहचान संख्या.: _____

मैं,_____पुत्र /पुत्री_____

निवासी_____मेरी पूर्ण, नि: शुल्क तथा स्वैच्छिक सहमति देता हु निम्नलिखित अध्ययन का हिस्सा बनने के लिए-

"हाइपोनैट्रीमियाके संबंध में तीव्र सेरेब्रोवास्कुलर रोग के कार्यात्मक परिणाम का एक तुलनात्मक अध्ययन",जिसकी प्रक्रिया और प्रकृति, मेरी पूरी संतुष्टि के लिए, मेरी अपनी भाषा में मुझे समझाया गया है। मैं पुष्टि करता हूं कि मेरे पास प्रश्न पूछने का अवसर था।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और किसी भी कारण के बिना ,किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं।

मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्र की गई जानकारी एम्स जोधपुर से या नियामक प्राधिकरणों से जिम्मेदार व्यक्ति द्वारा देखी जा सकती है । मैं इन व्यक्तियों के लिए अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

दिनांक: _____ _____

स्थान : _____ हस्ताक्षर/बाएं अंगूठे की छाप

यह प्रमाणित करने के लिए कि उपर्युक्त सहमति मेरी उपस्थिति में प्राप्त की गई है।

तारीख :_____ _____

स्थान: _____ हस्ताक्षर पीजी छात्र

साक्षी1 साक्षी2

हस्ताक्षर हस्ताक्षर

नाम: _____ नाम: _____

स्थान : _____ स्थान : _____

APPENDIX-2
PATIENT INFORMATION SHEET

Name of the patient: **Patient ID.:**

Study title- To study the prevalence of hyponatremia in acute cerebrovascular disease and its effect on fuctional outcome

Investigator- Dr. Shilpi Goyal

Contact number- 7206168172

Department of Internal Medicine

All India Institute of Medical Sciences, Jodhpur, Rajasthan

PURPOSEOFSTUDY-The purpose of this study is to assess the functional outcome of acute cerebrovascular disease in relation to Hyponatremia in a tertiary care hospital.

PROCEDURE OF STUDY- If you wish to participate in the study, you will be required to undergo complete physical, clinical, hematological examination and follow up after 90 days with telephonic conversation.

BENEFITS FROM THE RESEARCH- The diagnosis of Hyponatremia may help in better prognosis of the functional outcome of patient after the acute stroke event.

CONFIDENTIALITY- The personal data collected for the purpose of this study will be kept confidential.

FREEDOM TO PARTICIPATE AND WITHDRAW- The participation in the study is completely at your own will and you are free to withdraw yourself from the study at any point of time. At any time in course of study you wish to get any information, you are free to contact the investigator.

APPENDIX-2

रोगी सूचना पत्र

रोगी का नाम:

रोगी आईडी:

अध्ययन शीर्षक-" तीव्र सेरेब्रोवास्कुलर रोग में हाइपोनेट्रेमिया की व्यापकता और इसके संबंधी **कार्यात्मक** परिणाम का अध्ययन करना |

अन्वेषक- डॉ. शिल्पी गोयल संपर्क नंबर- 7206168172

आंतरिक चिकित्सा विभाग

अखिल भारतीय आयुर्विज्ञान संस्थानजोधपुर, राजस्थान

अध्ययन का उद्देश्य- इस अध्ययन का उद्देश्य तृतीयक देखभाल अस्पताल में हाइपोनेट्रेमिया के संबंध में तीव्र सेरेब्रोवास्कुलर रोग के कार्यात्मक परिणाम का आकलन करना है।

अध्ययन की प्रक्रिया- यदि आप अध्ययन में भाग लेना चाहते हैं, तो आपको पूरी शारीरिक, नैदानिक, चिकित्सीय परीक्षा से गुजरना होगा और 90 दिनों के बाद टेलीफोनिक बातचीत के बाद अनुवर्ती कार्रवाई करनी होगी।

अनुसंधान से लाभ - निश्चित निदान तीव्र स्ट्रोक घटना के बाद रोगी के कार्यात्मक परिणाम के निदान में मदद करेगा।

गोपनीयता- इस अध्ययन के उद्देश्य के लिए एकत्र किए गए व्यक्तिगत डेटा को गोपनीय रखा जाएगा।

स्वतंत्र रूप से भाग लेने और निकालना- अध्ययन में भागीदारी पूरी तरह से आपकी मर्जी पर है और आप किसी भी समय अपने आप को अध्ययन से दूर करने के लिए स्वतंत्र हैं। अध्ययन के दौरान किसी भी समय आप किसी भी जानकारी को प्राप्त करना चाहते हैं, आप अन्वेषक से संपर्क करने के लिए स्वतंत्र हैं

APPENDIX-3

CASE RECORD FORM

- **Patient id:**
- **Name of patient**
- **Age/Gender**
- **Address**
- **Contact number**
- **Complaints**
- **Diagnosis**
- **Co-morbid conditions**
- **GCS (Glasgow coma scale) at admission**
- **NIHSS at admission**
- **Baseline Na level**
- **Modified Rankin scale at admission**
- **Serum sodium at 5^{th} day**
- **Modified Rankin scale on 5^{th} day**
- **Duration of hospital stay**
- **Modified Rankin scale at 90 days**
- **Outcome of hospitalization**

APPENDIX-4

MODIFIED RANKIN SCALE

Patient Name: _____

Rater Name: _____

Date: _____

Score Description

0- No symptoms at all

1- No significant disability despite symptoms; able to carry out all usual duties and activities

2- Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3- Moderate disability; requiring some help, but able to walk without assistance

4- Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5- Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6 -Dead

APPENDIX-5

NATIONAL INSTITUTES OF HEALTH STROKE SCALE(NIHSS)

Interval: [] Baseline [] 2 hours post treatment [] 24 hours post symptoms±20minutes

[] 7-10 days [] 3 months [] Other_____Time:___:_____[] am []pm

Patient name-

1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, or tracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, or tracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	
1c. LOC Commands: The patient is asked to open and close the eyes andthen to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, thetas should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partialgaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation ortotal gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind	

if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item11.	including cortical blindness).	
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, or tracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: ____ **5a. Left Arm** **5b. Right Arm**	
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1=**Drift;** legfallsbytheendofthe5-secondperiodbutdoes not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: ____ **6a. Left Leg** **6b. Right Leg**	
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: ____	
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of	

hands], legs, trunk, face) as needed to accurately check for hemi sensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnor mality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	

PPENDIX-6
Glasgow Coma Scale

Domain	Response	Score
Eye opening	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best verbal response	Oriented	5
	Confused	4
	Inappropriate	3
	Incomprehensible	2
	None	1
Best motor response	Obeying	6
	Localizing	5
	Withdrawing	4
	Flexing	3
	Extending	2
	None	1
Total score	Deep coma and death	3
	Fully alert and oriented	15

APPENDIX-7
Ethical Clearance Certificate

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

No. AIIMS/IEC/2021/ 3509 Date: 12/03/2021

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3344**

Project title: **"To study the prevalence of hyponatremia in acute cerebrovascular disease and its effect on functional outcome"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Shilpi Goyal**
Guide:	**Dr. M.K.Garg**
Co-Guide:	**Dr. Bharat Kumar & Dr. Samhita Panda**

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

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com