IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 7 Ver. II (July. 2016), PP 00-00
www.iosrjournals.org

"Hyponatremia in Stroke: Cerebral Salt Wasting Versus Syndrome of Inappropriate Anti-Diuresis"

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Abstract: *Hyponatremia is the most common electrolyte imbalance in neurologic patients. The causes of hyponatremia are varied, but in neurologically ill patients, is most commonly attributed to Syndrome of Inappropriate Anti-diuresis and Cerebral Salt Wasting. Both these entities are cerebral in origin but have distinct pathophysiology, prognosis and treatment options. The importance of distinguishing both lies in the fact that the therapy indicated for one if used for the other, can be deleterious.*
SIADH is a subclinically volume expanded state due to inappropriate anti-diuresis.. In stroke SIADH occurs due to AVP secretion inappropriate to the osmotic threshold. It thus requires fluid restriction as the treatment. CSW, on the other hand, is essentially a volume depleted state, which occurs due to the combined effects of decreased sympathetic outflow and increased natriuretic peptides and needs rigorous volume repletion. Hyponatremia, especially Cerebral Salt Wasting, occurring in the setting of stroke has been shown to worsen the prognosis of stroke, increase morbidity, short and long term mortality, and cause a poorer discharge disposition.. The purpose of this study is to observe the occurrence of SIADH vs CSW in the setting of stroke and to study the short term mortality, morbidity and discharge disposition among the two entities.
This study is an observational descriptive study carried out to emphasise the importance of hyponatremia in the setting of a stroke and the impact it can have on the prognosis of the patient.
The prevalence of hyponatremia in stroke patients in our study is 20%. It was found that hyponatremia per se, and Cerebral Salt Wasting in stroke resulted in poorer discharge disposition and longer duration of in-hospital stay and significantly impacted on the short term in-hospital mortality.
The pathophysiology of the two conditions (SIADH and CSW) being entirely different need a completely differing treatment regime and hence the distinction between the two is of utmost importance
Keywords: *Hyponatremia in Stroke, SIADH- Syndrome of Inappropriate Anti-Diuresis, CSW- Cerebral Salt Wasting, Electrolyte imbalance in Stroke*

I. Introduction

Hyponatremia is the most common abnormality seen in hospitalised patients and is also the most common electrolyte imbalance seen in critically ill neurologic patients. It can significantly alter the morbidity and short and long term mortality of the underlying disease. The causes of hyponatremia are varied, but in neurologically ill patients, is most commonly attributed to Syndrome of Inappropriate Anti-diuresis and Cerebral Salt Wasting. Both these entities are cerebral in origin but have distinct ;;pathophysiology, prognosis and treatment options. The importance of distinguishing both lies in the fact that the therapy indicated for one if used for the other, can be deleterious.

Distinction between the two requires a battery of parameters since there is considerable overlap between the two conditions, and no single parameter can define either entity.

SIADH is a subclinically volume expanded state due to inappropriate anti-diuresis. This causes excessive volume overload over the body sodium content leading onto euvolemichyponatremia. In stroke SIADH occurs due to AVP secretion inappropriate to the osmotic threshold. The suppressed proximal renal tubular transport in this condition can lead on to bicarbonaturia and hypouricemia. The effective treatment is fluid restriction. Hypertonic saline therapy is reserved for cases of severe hyponatremia.

CSW, on the other hand, is essentially a volume depleted state, which occurs due to the combined effects of decreased sympathetic outflow and increased natriuretic peptides. This resultant natriuresis leads to volume depletion and an appropriate AVP response. So the treatment for CSW includes an aggressive volume replacement regimen with isotonic saline or in severe cases, hypertonic saline.

Thus most CSW patients meet the criteria for SIADH and have elevated AVP levels but worsen with the treatment protocol given for SIADH. This observation lead to the description of CSW as a separate entity and widespread studies were carried out to distinguish the two entities.

At present the two entities are differentiated using combined analysis of sodium levels, plasma osmolality, uric acid, effective arterial blood volume, urine sodium, serum potassium,haematocrit, BUN/creatinine ratio.
Hyponatremia, especially Cerebral Salt Wasting, occurring in the setting of stroke has been shown to worsen the prognosis of stroke, increase morbidity, short and long term mortality, and cause a poorer discharge disposition.

II. Material And Methods

(i) **Source Of Data :** Data consists of primary data collected by the principal investigator directly from the patients who are admitted in the Government Medical College and Hospital
(ii) **Study Area:** Coimbatore medical college hospital
(iii) **Design Of Study:** Observational prospective study
(iv) **Period Of Study:** One year, July 2014 - June 2015.
(v) **Sample Size:** Based on past records and previous evidence, it is expected that about fifty number of cases would be available during the period of study.

(vi) Definition Used In The Study

- STROKE

"Neurological deficit of cerebrovascular cause that persists beyond 24 hours"

- HYPONATREMIA

Hyponatremia is defined as sodium level < 130 meq/L
True hyponatremia is defined as those patients with a sodium level of 130meq/L and plasma osmolality less 275mosm/kg

- PLASMA OSMOLALITY

The plasma osmolality is calculated using the formula- 2(Na)+Glu/18+BUN/2.8

- SODIUM CORRECTION

Total body water (TBW) - 50% of body weight in females
60% of body weight in males
Free water deficit-$[(Na^+ - 140) / 140]$* TBW
Free water clearance- V * [1- $(U_{Na}+U_{K)} / P_{Na}$]
V- Urinary volume; U_{Na} - Urinary sodium, U_K- Urinary potassium, P_{Na}- Plasma Sodium

Normal Ranges Of Parameters Used In The Study

Plasma Osmolality - 275 – 295mosm/kg
Serum Potassium -3.5- 5 m Eq/L
Serum Albumin - 3.5-5 g/dl
Hematocrit - Male: 40.7-50%
Female: 36.1-44.3%
Serum Uric acid -Male: 3.4-7 mg/dl
Female: 2.4-6 mg/dl
BUN/ Creatinine – 10:1-20:1

Inclusion Criteria: Confirmed cases of stroke by history, neurologic and imaging modalities.
Exclusion Criteria: The following patients are excluded:
Patients with

- Head injury
- CNS tumor
- Pulmonary tuberculosis
- Bacterial pneumonia
- Bronchogenic carcinoma
- Hematologic malignancies
- Recent surgery
- Meningitis
- Encephalitis
- Drug usage-SSRI, TCA, narcotics, NSAIDs, Antipsychotics, Carbamazepine, Cyclophosphamide, Clofibrate, Chlorpropamide

About 50 stroke patients admitted to Coimbatore Medical College Hospital during the one year study period (July 2014 to July 2015) were studied.

The diagnosis was confirmed by imaging- CT scan or MRI.
The stroke type- ischemic or hemorrhagic, the side of the stroke and the involved vascular territory was confirmed using the imaging study.

After ruling out the exclusion criteria, serial serum sodium levels were done. In patients with hyponatremia, plasma osmolality was measured to differentiate between true and pseudo-hyponatremia. Cerebral causes of hyponatremia were identified and classified as SIADH/CSW and treated as per the standard protocol. The patient was put on in-patient follow-up till discharge/ death. The patients with prior/ admission diuretic usage are not taken into the study group as cases.

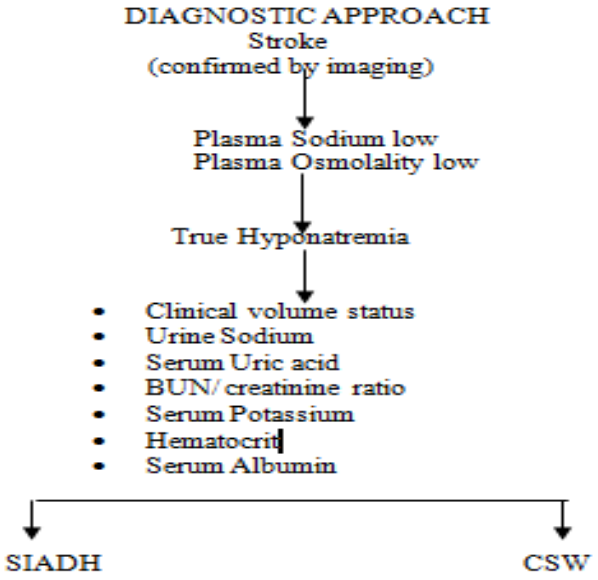
Day1 Clinical estimation of Extracellular fluid volume – estimated by Jugular venous pressure elevation, Peripheral edema, Negative/ positive fluid balance by input /output, Blood pressure levels On Day 1 of hyponatremia, levels of Serum Sodium Plasma osmolality Serum potassium Serum uric acid Hematocrit BUN/ Creatinine ratio Serum albumin Urine Sodium are measured. This helps in tentative differentiation between SIADH and CSW. Based on Day 1 values, Sodium correction is carried out using the standard protocols i.e., fluid restriction in case of SIADH and intravenous saline in case of suspected CSW; hypertonic saline where severe hyponatremia is encountered.

Serial Day 5 values Serum sodium, Serum uric acid, Hematocrit, Serum albumin were measured and confirmatory assessment of SIADH / CSW was made.

A short term follow up of the outcome of the patient till discharge/ death was done to see whether hyponatremia could affect the outcome of the patient significantly.

Investigations

- Chest X-ray
- CT scan brain/ MRI brain
- Plasma osmolality
- Urine sodium
- Plasma sodium
- Serum Potassium
- Hematocrit
- Serum Uric acid
- Serum Albumin
- BUN / Creatinine ratio
-



III. Statistical Analysis

The data are reported as the mean +/- SD or the median, depending on their distribution.

The differences in quantitative variables between groups were assessed by the unpaired t test.

Comparison between groups was made by the Non parameteric Mann - whitney test ANOVA was used to assess the quantative variables.

A Chi Square test was used to assess differences in categoric variables between groups.

Kaplan Meiyer was performed A p value of <0.05 using a two-tailed test was taken as being of significance for all statistical tests.

All data were analysed with the statistical software package.(SPSS, version 16.0 for windows)

IV. Figures And Tables

Table 1: Association Of Demographic Variables & Clinical Variables With Hyponatremia

Clinical	**HYPONATREMIA**				
Variables	**Without [n=37]**	**SIADH [n=6]**	**CSW [n=4]**	**Others[n=3]**	**Sig**
AGE					
21 -40	5	0	0	0	
%	14%	0%	0%	0%	
41 – 60	21	2	0	0	
%	57%	33%	0%	0%	<0.05
61 – 80	7	4	3	3	
%	19%	67%	75%	100%	
>80	4	0	1	0	
%	11%	0%	25%	0%	
GENDER					
Male	30	4	3	1	
%	81%	67%	75%	33%	
Female	7	2	1	2	
%	19%	33%	25%	67%	>0.05
Types of Stroke					
Ischemic	30	5	2	3	
%	81.10%	83.30%	50.00%	100.00%	
Hemorrhagic	7	1	0	0	
%	18.90%	16.70%	0.00%	0.00%	<0.001
Ischemic+Hemorrhagic	0	0	2	0	
%	0.00%	0.00%	50.00%	0.00%	
TERRITORY					
ACA	4	0	0	0	
%	10.80%	0.00%	0.00%	0.00%	
MCA	20	2	3	3	
%	54.10%	33.30%	75.00%	100.00%	>0.05
PCA	13	4	1	0	
%	35.10%	66.70%	25.00%	0.00%	
SIDE					
RIGHT	20	4	3	0	
%	54.10%	66.70%	75.00%	0.00%	
LEFT	12	1	0	1	
%	32.40%	16.70%	0.00%	33.30%	>0.05
BILATERAL	5	1	1	2	
%	13.50%	16.70%	25.00%	66.70%	

TABLE 2 ASSOCIATION OF BIO CHEMICAL PROPERTIES WITH HYPONATREMIA

BIO CHEMICAL PROPERTIES					
Clinical	**HYPONATREMIA**				
Variables		**SIADH [n=6]**	**CSW [n=4]**	**Others[n=3]**	**Sig**
Volume Status					
Increased		3	0	0	
%		50.00%	0.00%	0.00%	
Decreased		0	4	0	
%		0.00%	100.00%	0.00%	<0.05
Normal		3	0	0	
%		50.00%	0.00%	0.00%	
Uric Acid -day5					
Decreased		0	3	0	
%		0.00%	75.00%	0.00%	<0.05
Normal		5	0	0	
%		100.00%	0.00%	0.00%	
BUN/ Creatinine					
Increased		0	4	1	
%		0.00%	100.00%	33.30%	
Decreased		5	0	0	
%		100.00%	0.00%	0.00%	<0.05
Normal		0	0	1	
%		0.00%	0.00%	33.30%	
HCT Day5					
Increased		0	2	0	
%		0.00%	50.00%	0.00%	
Decreased		2	0	0	
%		33.30%	0.00%	0.00%	<0.05
Normal		4	1	0	
%		66.70%	25.00%	0.00%	
Albumin Day 5					
Decreased		1	0	0	
%		16.70%	0.00%	0.00%	<0.05
Normal		5	3	0	
%		83.30%	75.00%	0.00%	
Urine Sodium					
Increased		6	4	1	
%		100.00%	100.00%	33.33%	
Decreased		0	0	2	
%		0.00%	0.00%	66.67%	<0.05

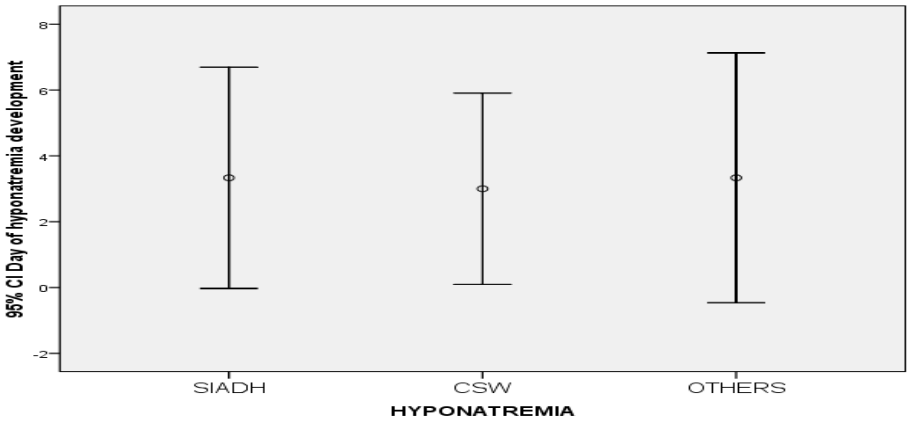
		Mean	SD	95% CI for Mean		Minimum	Maximum	Maximum
	Hyponatremia			Lower	Upper			
Na Day 1	With	127.08	3.252	125.11	129.04	117	130	
	without	139.03	4.2	137.63	140.43	130	148	<0.001
	Total	135.92	6.602	134.04	137.8	117	148	
Plasma Osmo	With	270.52	16.17	260.75	280.30	248	299	

Table – 3 Clinical Variables Mean

Table 4. Mean Day Of Hyponatremia Development

	Mean	SD	95% CI for Mean		Minimum	Maximum	Sig
Hyponatremia	[Days]		Lower	Upper			
SIADH	3.3	3.2	0.0	6.7	1	9	
CSW	3.0	1.8	0.1	5.9	1	5	
Others	3.3	1.5	-0.5	7.1	2	5	>0.05
Total	3.2	2.4	1.8	4.7	1	9	

Chart 1. Mean Day Of Hyponatremia Development

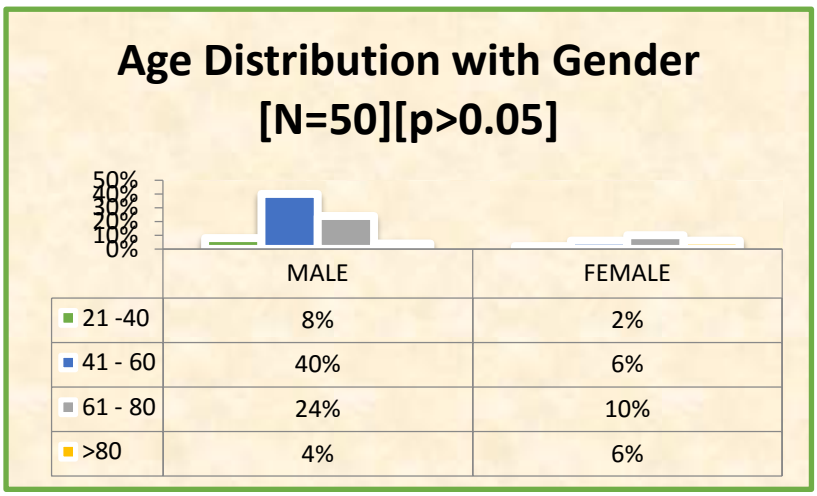


The mean day of development of hyponatremia was 3.2 days and there was no significant difference in the day of development of hyponatremia between the various groups. (p>0.05)

Table 5. Age Distribution

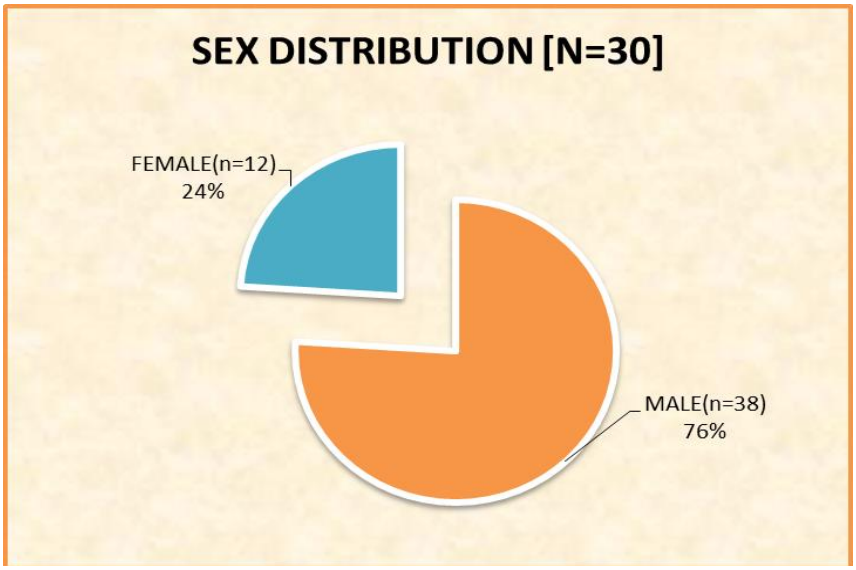
	GENDER			
AGE	MALE	FEMALE	TOTAL	(%)
21 -40	4	1	5	10%
41 – 60	20	3	23	46%
61 – 80	12	5	17	34%
>80	2	3	5	10%
TOTAL	38	12	50	

Chart 2. Comparision Of Age Distribution With Gender



In our set of stroke patients, the majority of the patients, around 46% (n= 23) belonged to the middle aged group (40 – 60 years of age), 10% of patients belonged to the extreme age groups, <40 years and >80 years.
The majority of males belonged to 40-60 years age group, (n=20). The prevalence of stroke in females was most seen to be in the 60 to 80 year age group (n=5)

Chart 3. Sex Distribution

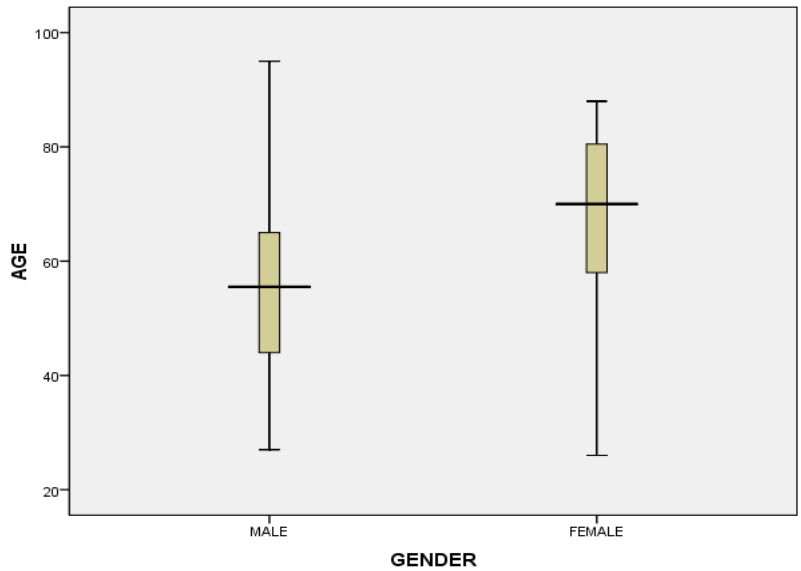


Of the 50 stroke patients 76% (n= 38) are male and 24% (n= 12) were female

Table 6. Mean Age With Gender Comparision

Mean Age with Gender							
	Mean	SD	95% CI for Mean		Minimum	Maximum	Sig
Gender	[Years]		Lower	Upper			
MALE	56.2	14.5	51.4	61.0	27	95	
FEMALE	66.9	17.3	55.9	77.9	26	88	<0.05
Total	58.8	15.8	54.3	63.2	26	95	

Chart 4. Box Plot Of Age Vs Gender

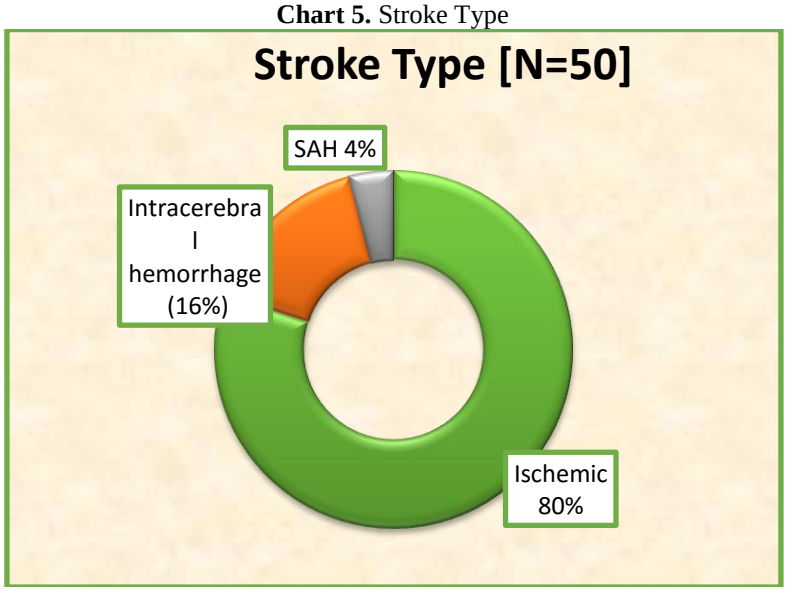


In our study group patients, we found
The mean age of males with stroke to be 56.2 (± 14.5)
The mean age of the females with stroke to be 66.9 (± 17.3)

Table 7. Stroke Type

STROKE TYPE	n	(%)
Ischemic	40	80%
IntracerebralHemorrhage	8	16%
Subarachnoid Hemorrhage	2	4%
Total	50	100%

Chart 5. Stroke Type

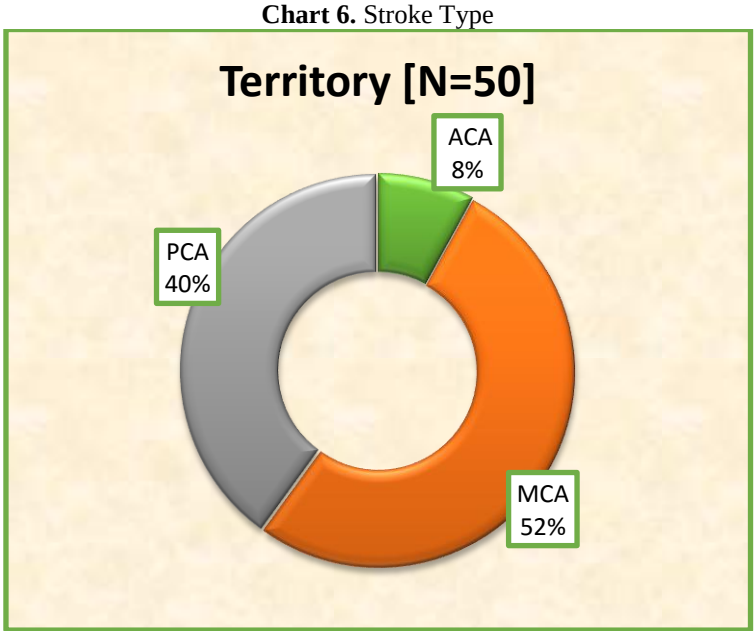


In our study, the majority of the patients had ischemic stroke around 80% (n=40), of which 6 patients had lacunar stroke, 5 patients had a massive infarct.
Hemorrhagic stroke was seen in 10 patients, with 8 patients (16%) having intracerebral bleed
In 4 patients with intra cerebral bleed, the cause of haemorrhage was accelerated hypertension.
2 patients with hemorrhagic stroke had aneurysmal bleed presenting sub-arachnoid haemorrhage (4%)

Table 8. Stroke Territory

TERRITORY	n	(%)
ACA	4	8%
MCA	26	52%
PCA	20	40%
Total	50	100%

Chart 6. Stroke Type

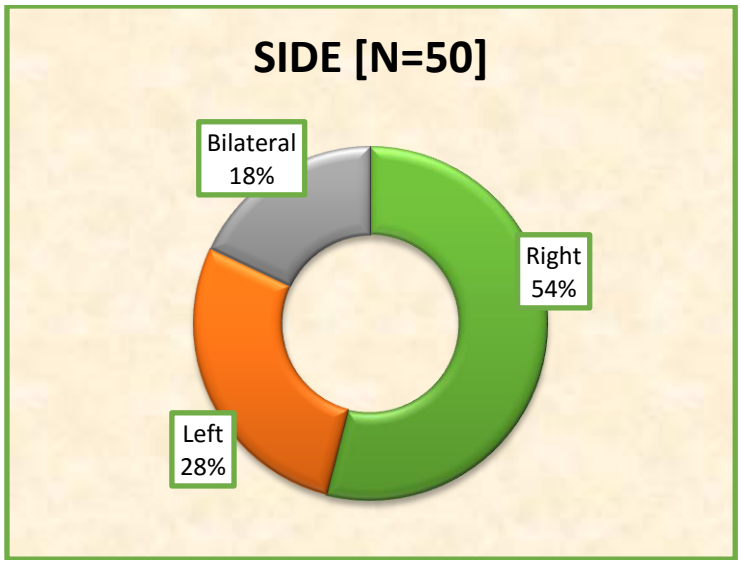


The majority of patients in our study i.e., 26 patients (52%), had stroke corresponding to the Middle Cerebral Artery territory, followed by 20 patients (40%) with Posterior cerebral artery involvement and 4 patients (8%) with Anterior Cerebral circulation involvement.

Table 9. Side Of The Stroke

SIDE	**N**	**(%)**
Right	27	54%
Left	14	28%
Bilateral	9	18%
Total	50	100%

Chart 6. Side Of Stroke

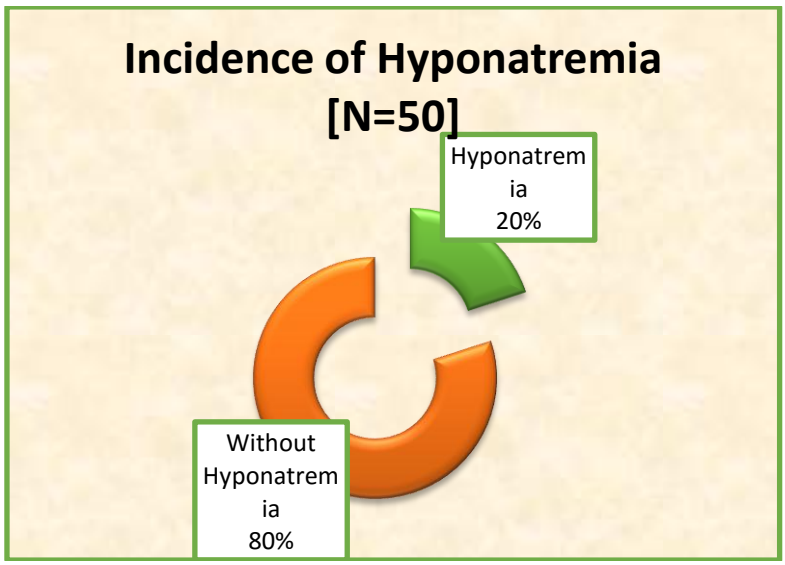


In our study, most of the patients had Right sided stroke 54% (n=27), 28% had left sided stroke (n=14) and 18% (n=9) had bilateral involvement.

Table 10. Incidence Of Hyponatremia

	n	**(%)**
Hyponatremia	10	20%
Without Hyponatremia	40	80%
Total	50	100%

Chart 7. Incidence Of Hypoatremia



The occurence of hyponatremia due to cerebral causes was noted in 20% of the 50 studied stroke patients (n=10)

Table 11. Incidence Of Siadh And Csw

	n	**(%)**
SIADH	6	12%
CSW	4	8%
Others	3	6%
Total	13	26%

Chart 8. Incidence Of Siadh And Csw

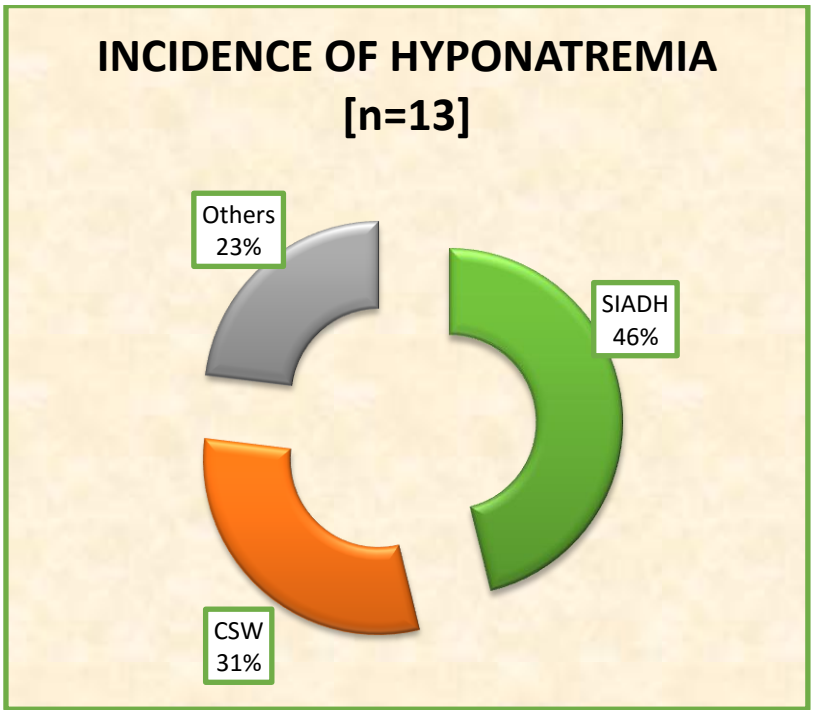
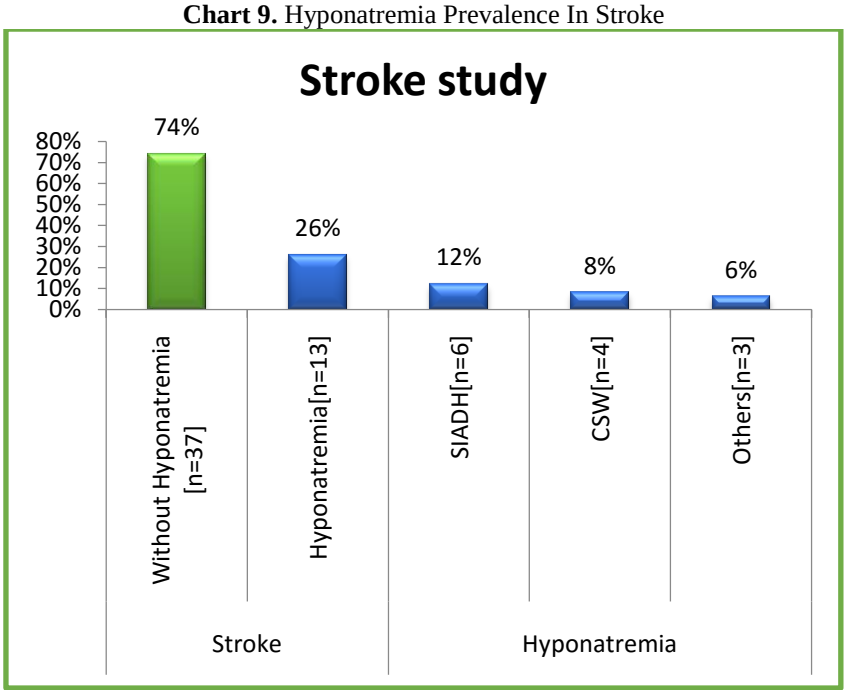


Chart 9. Hyponatremia Prevalence In Stroke

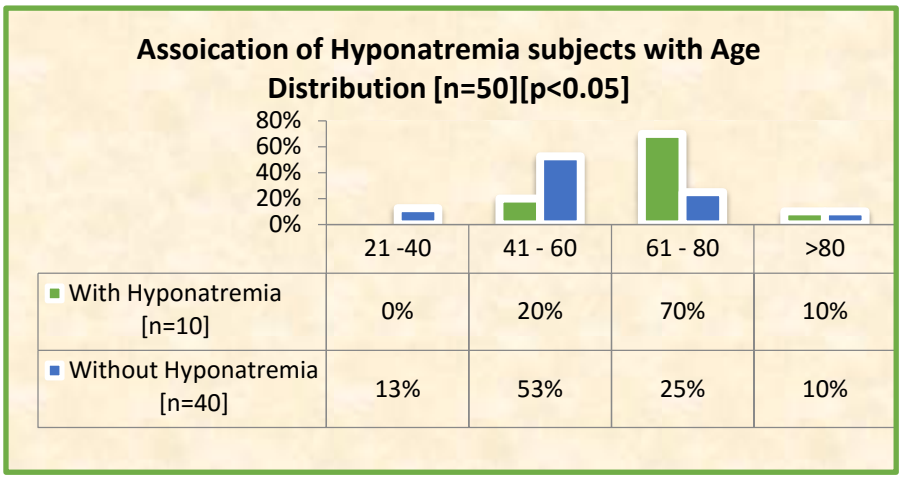


Of the 50 patients, 12% had SIADH (n=6) and 8% had CSW (n=4),Other causes of hyponatremia were found in 6% (n=3) which were attributed to diarrhoea (n=1), renal failure (n=1) and congestive cardiac failure (n=1).

Table 12. Age Distribution

	HYPONATREMIA			
AGE	WITH	WITHOUT	TOTAL	(%)
21 -40	0	5	5	10%
41 - 60	2	21	23	46%
61 - 80	7	10	17	34%
>80	1	4	5	10%
TOTAL	10	40	50	

Chart 10. Age Distribution



In general, the occurrence of hyponatremia due to cerebral causes was noted most in the 61-80 year age group i.e., 70% (n=10).

The occurrence of hyponatremia was 20% in 41-60 year age group and 10% in the > 80 year age group. The difference in the hyponatremia prevalence among the various age groups reached statistical significance ($p<0.05$)

Table 13. Age Distribution Of Siadh And Csw

	Hyponatremia				
Age	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
41 - 60	2	0	0	2	15%
61 - 80	4	3	3	10	77%
>80	0	1	0	1	23%
Total	6	4	3	13	

Chart 11. Age Distribution Of Siadh And Csw

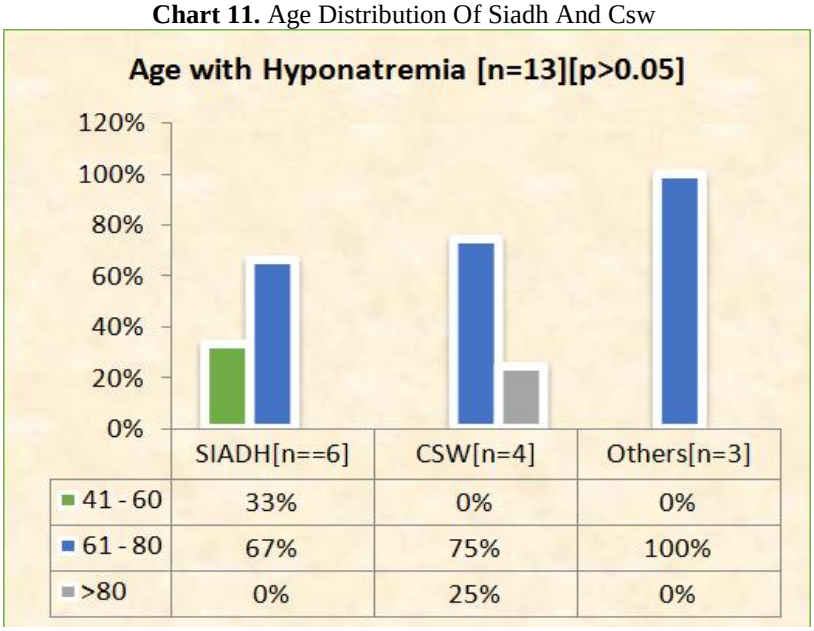
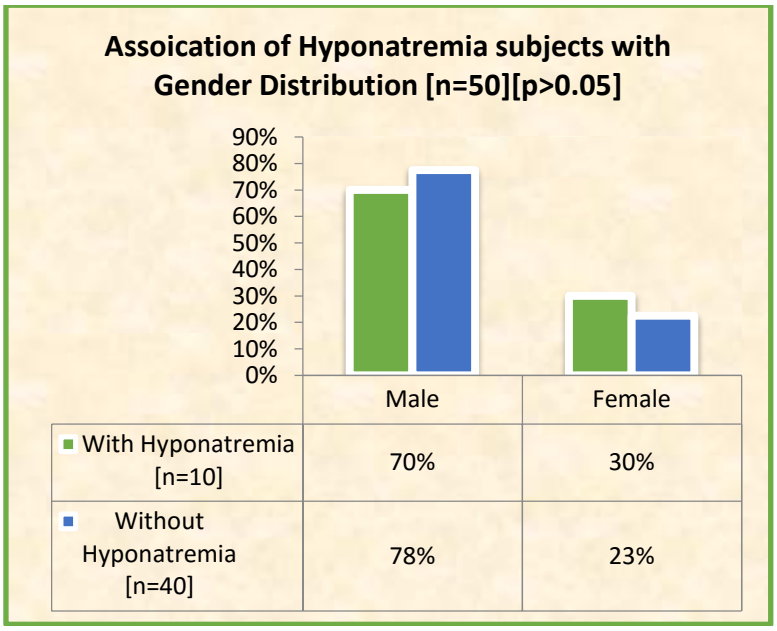


Table 14. Gender Distribution

	Hyponatremia				
Gender	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
Male	4	3	1	8	62%
Female	2	1	2	5	23%
Total	6	4	3	13	

Chart 12. Gender Distribution



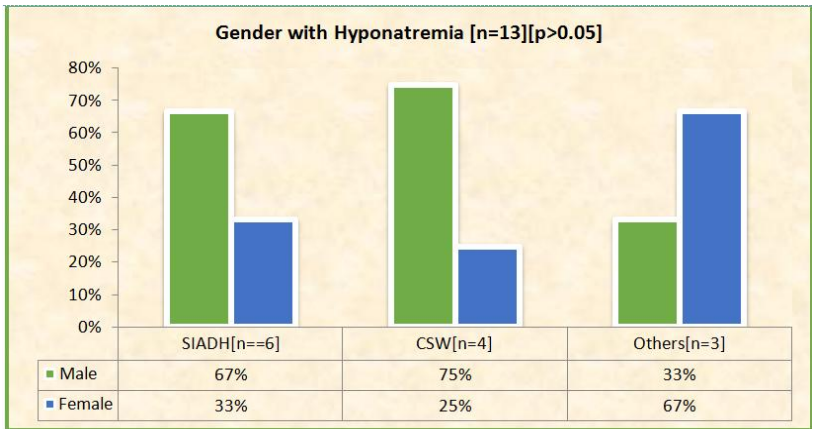
Of the patients with hyponatremia due to cerebral cause , 70% (n=7) were males and 30%(n=3) were females

There was no significant difference in the incidence of hyponatremia based on the gender (p>0.05)

Table 15. Gender Distribution Of Siadh And Csw

	HYPONATREMIA			
Gender	WITH	WITHOUT	TOTAL	(%)
Male	7	31	38	76%
Female	3	9	12	24%
TOTAL	10	40	50	

Chart 13. Gender Distribution Of Siadh And Csw



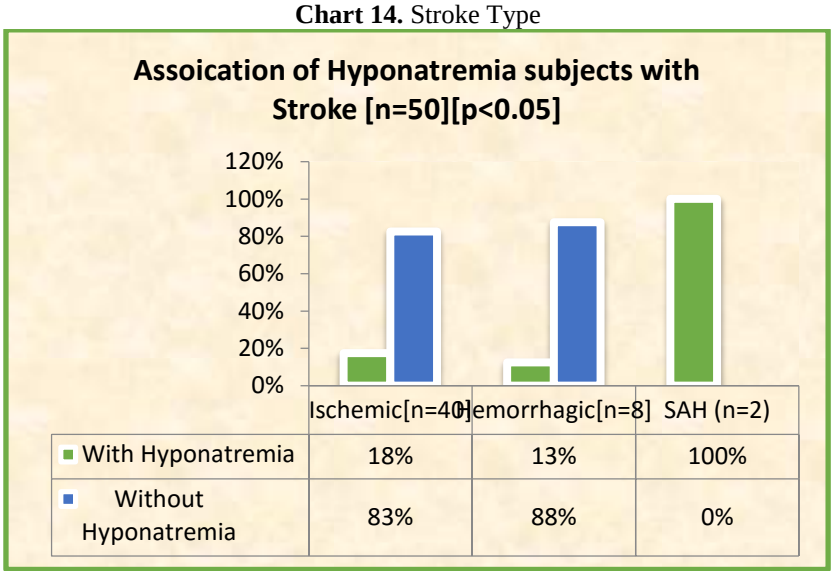
In the SIADH group, the majority of patients were males 67% (n=4) and females comprised of 33% (n=2).

In the CSW group also the gender of majority of the patients was male 75% (n=3), whereas females comprised about 25% (n=1). The variation in sex distribution among the various groups did not reach statistical significance.($p > 0.05$)
In the group of patients who had other causes of hyponatremia, the majority were females, 67%.

Table 16. Stroke Type

	HYPONATREMIA			
STROKE TYPE	WITH	WITHOUT	TOTAL	(%)
Ischemic	7	33	40	80%
Intracerebral hemorrhage	1	7	8	16%
SAH	2	0	2	4%
TOTAL	10	40	50	

Chart 14. Stroke Type

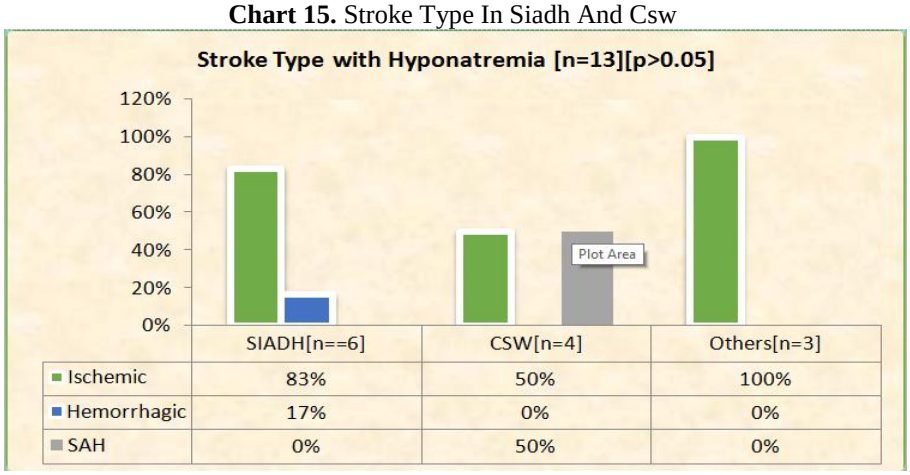


All the subarachnoid haemorrhage patients in our study developed hyponatremia(n=2)
Out of the Ischemic stroke patients 18% had hyponatremia. (n=7).
Hyponatremia was seen in 13% of patients with intracerebral haemorrhage.

Table 17. Stroke Type In Siadh And Csw

	Hyponatremia				
Stroke Type	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
Ischemic	5	2	3	10	77%
Hemorrhagic	1	0	0	1	8%
SAH	0	2	0	2	23%
Total	6	4	3	13	

Chart 15. Stroke Type In Siadh And Csw

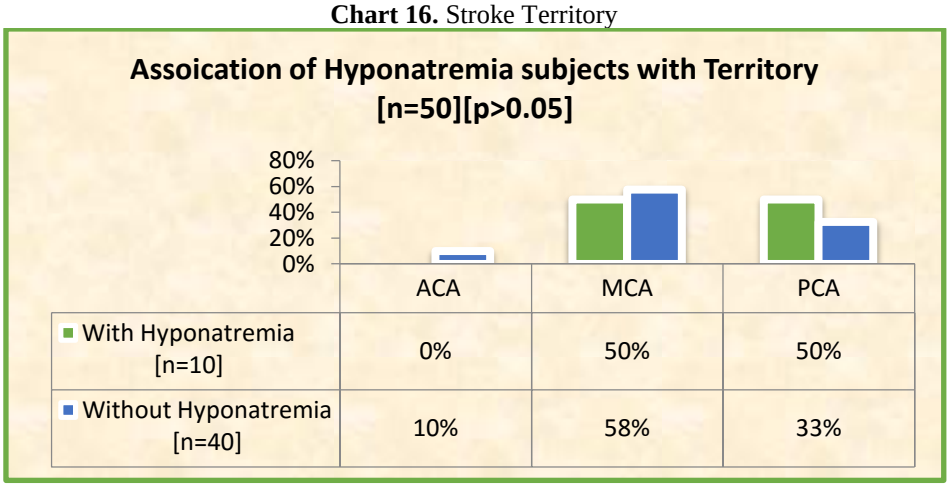


Among patients with hyponatremia, 77% had ischemic stroke (n=10), 8% had intra-cerebral haemorrhage (n=1), and 23% (n=2) had sub-arachnoid haemorrhage.Among SIADH patients, 73% had ischemic stroke and 18% had intra cerebral hemorrhage. Among cerebral salt wasting patients, ischemic stroke was found in 50% of patients and SAH was found in 50% patients.
The difference in stroke type seen in the various conditions did not however, reach statistical significance.

Table 18. Stroke Territory

Association of Hyponatremia subjects with Territory				
	HYPONATREMIA			
TERRITORY	WITH	WITHOUT	TOTAL	(%)
ACA	0	4	4	8%
MCA	5	23	28	56%
PCA	5	13	18	36%
TOTAL	10	40	50	

Chart 16. Stroke Territory



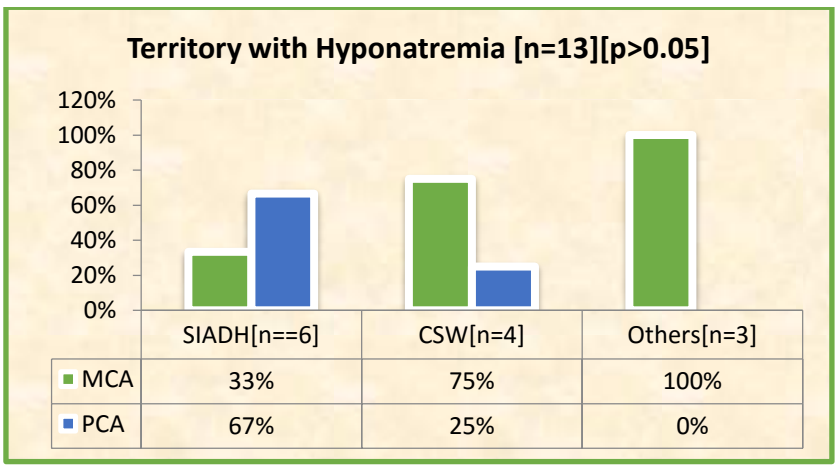
In the MCA territory stroke patients, 50% developed hyponatremia.
Hyponatremia was seen in 50% of the Posterior Cerebral Artery territory stroke

None of our patients with ACA territory stroke developed hyponatremia

Table 19. Territory In Siadh And Csw

	Hyponatremia				
Territory	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
MCA	2	3	3	8	62%
PCA	4	1	0	5	23%
Total	6	4	3	13	

Chart 17. Territory In Siadh And Csw

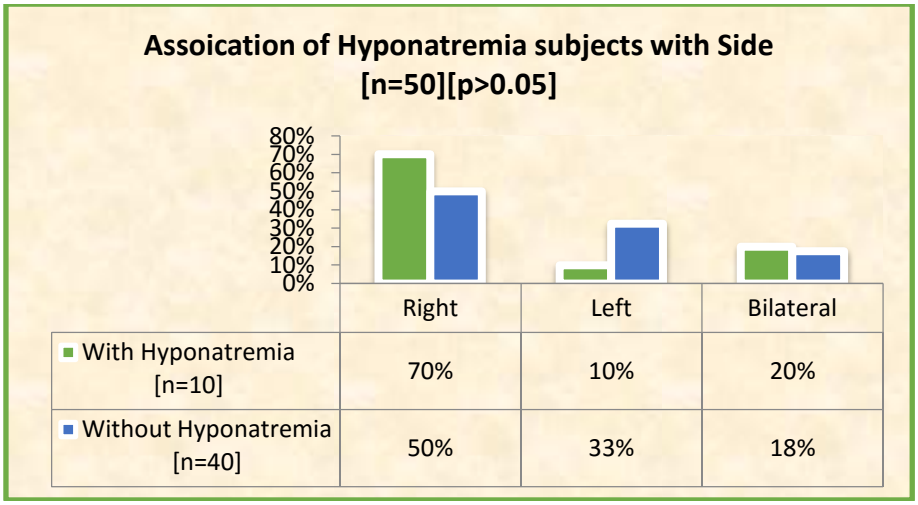


The majority of patients with SIADH had aposteriorcirculation stroke, 67% (n= 4), and 33% (n=2 had Middle Cerebral Territory stroke.
In CSW, 75% (n=3) had Middle Cerebral Artery territory involvement and
25% had posterior circulation stroke.

Table 19. Side Of Cerebral Involvement

Association of Hyponatremia subjects with Side				
	HYPONATREMIA			
SIDE	WITH	WITHOUT	TOTAL	(%)
Right	7	20	27	54%
Left	1	13	14	28%
Bilateral	2	7	9	18%
TOTAL	10	40	50	

Chart 18. Side Of Cerebral Involvement



Of the patients with cerebral cause of hyponatremia, 70% had a right sided involvement, 20% had bilateral and 10% had left sided involvement.

Table 20. Side Vs Siadh And Csw

	Hyponatremia				
SIDE	**SIADH**	**CSW**	**Others**	**TOTAL**	(%)
Right	4	3	0	7	54%
Left	1	0	1	2	15%
Bilateral	1	1	2	4	23%
Total	6	4	3	13	

4 patients with SIADH and 3 patients with CSW had right sided involvement. Left sided involvement was seen in 1 patient with SIADH.
2 patients (1- SIADH and 1- CSW) had bilateral arterial involvement.

Table 21. Duration Of Hospital Stay

Mean Duration of Hospital Stay							
	Mean	SD	95% CI for Mean		Minimum	Maximum	Sig
Hyponatremia	[Days]		Lower	Upper			
WITH	17	34.247	-3.7	37.7	1	130	
WITHOUT	3.73	1.866	3.11	4.35	1	10	<0.05
Total	7.18	18.01	2.06	12.3	1	130	

The mean duration of hospital stay was significantly different in patients with hyponatremia 17 days as against 3.73 days in normonatremic patients
The maximum duration of stay seen in one of the hyponatremic patients was 130 days.

Chart 19. Duration Of Hospital Stay

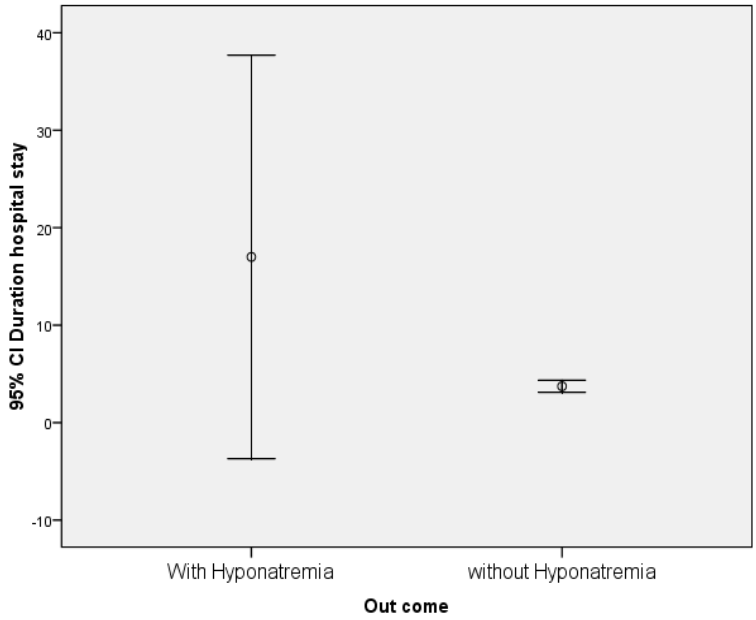


Table 22. Survival Time

Kaplan-Meier							
Means and Medians for Survival Time							
Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
92.411	13.566	65.823	119	130	0	.	.
a. Estimation is limited to the largest survival time if it is censored.							

Chart 20. Survival Time

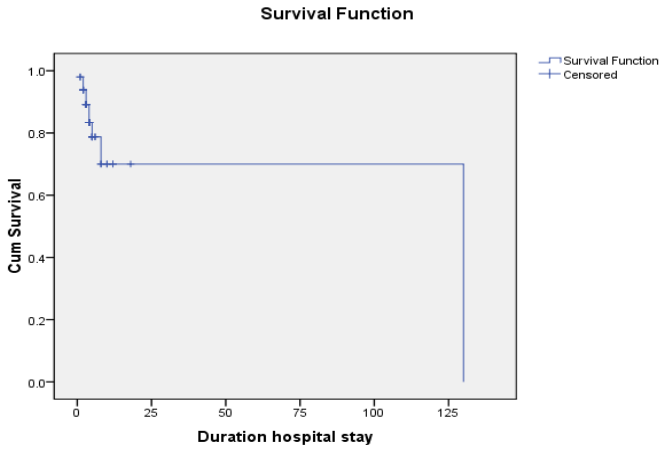


Table 23. Survival Time Vs Age

Means and Medians for Survival Time vs Age							
Mean[a]				Median			
Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound			Lower Bound	Upper Bound
80.899	3.106	74.812	86.986	81	4.865	71.464	90.536
a. Estimation is limited to the largest survival time if it is censored.							

Chart 21. Survival Time Vs Age

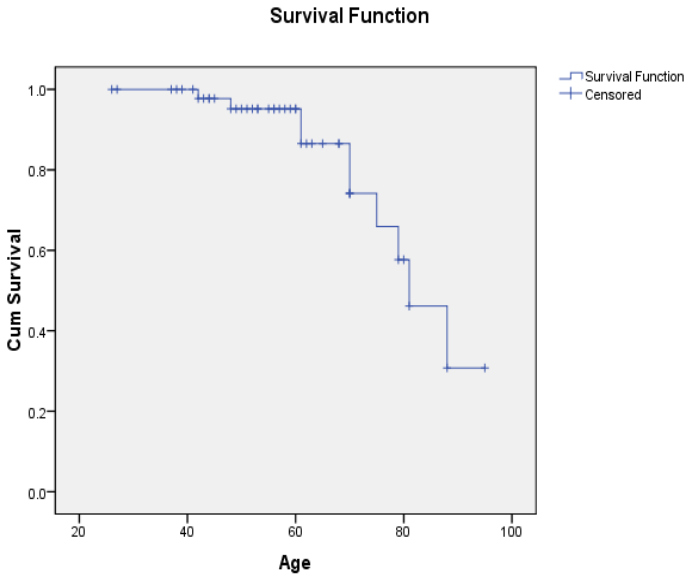
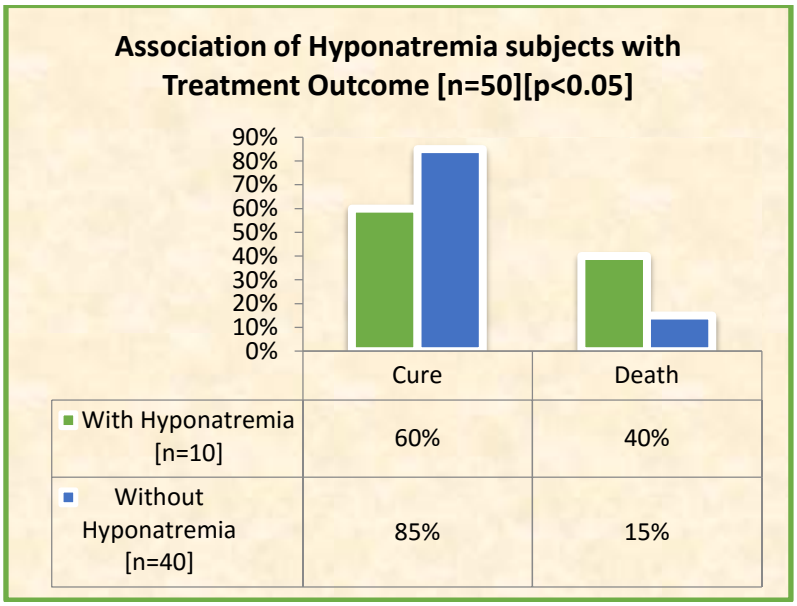


Table 24. Treatment Outcome

Association of Hyponatremia subjects with Outcome				
	HYPONATREMIA			
Outcome	WITH	WITHOUT	TOTAL	(%)
Cure	6	34	40	80%
Death	4	6	10	20%
TOTAL	10	40	50	

Among the stroke patients, 80% were cured and 20% succumbed to the illness.

Chart 22. Treatment Outcome

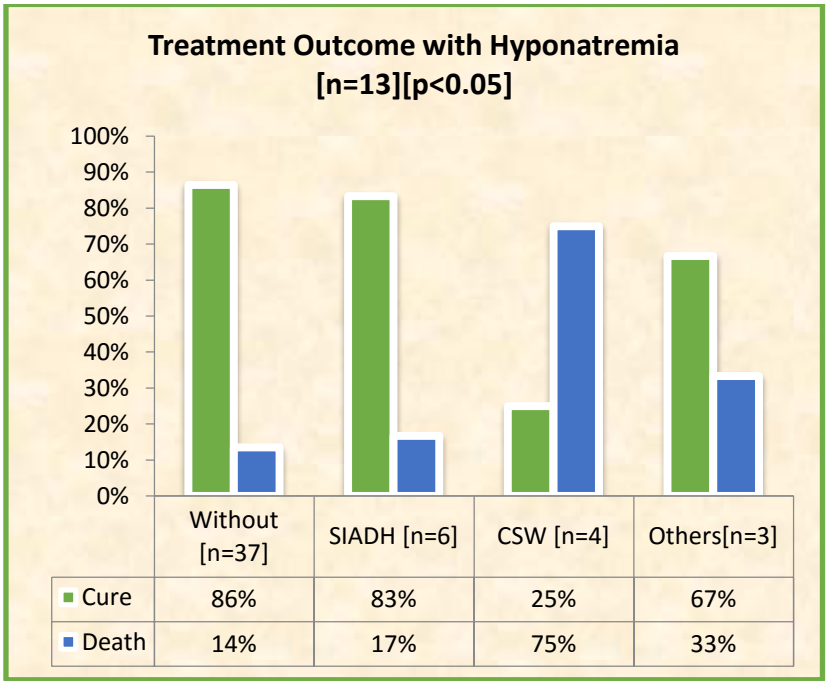


In normonatremic stroke patients, an 85% cure rate and 15% death rate was seen. In hyponatremic patients, there was 60% cure and 40% death. The cure and death rate between the two groups reached a statistical significance. ($p<0.05$)

Table 25. Treatment Outcome Of Siadh Vs Csw

Treatment Outcome in Hyponatremia					
	HYPONATREMIA				
Out Come	**Without [n=37]**	**SIADH [n=6]**	**CSW [n=4]**	**Others[n=3]**	**Total**
Cure	32	5	1	2	40
Death	5	1	3	1	10
Total	37	6	4	3	50

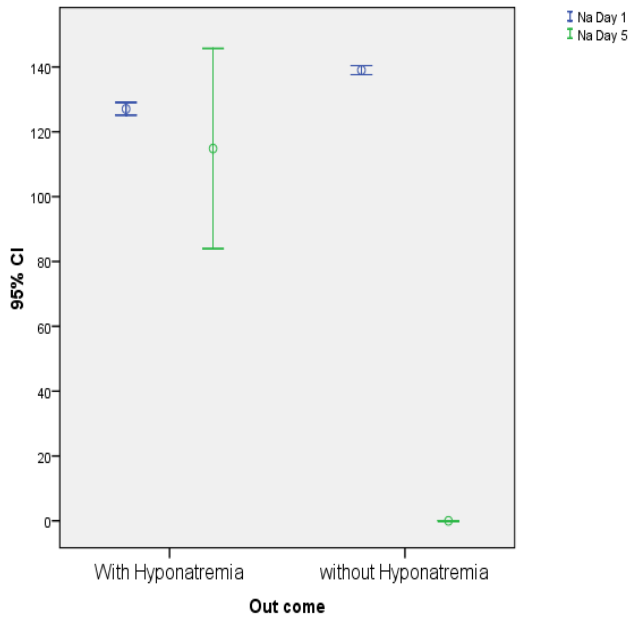
Chart 23. Treatment Outcome In Siadh Vs Csw



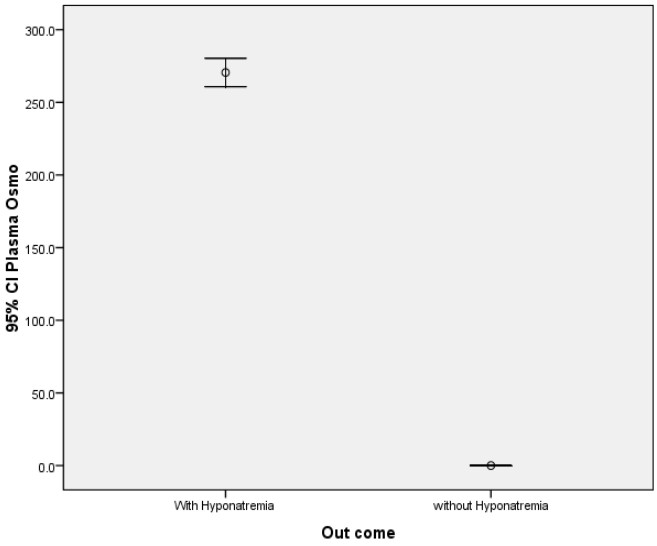
In the SIADH group, 83% were cured of hyponatremia with treatment and 17% patients succumbed. But in the CSW group, only 25% survived and 75% succumbed to the illness. The difference in outcome between the two groups reached statistical significance ($p< 0.05$)

24. Box Plots- Treatment Outcome

24.A



24B.



V. Discussion

The consequences of salt depletion was first described by McCance in 1936 [1].
In 1950, Peters et al [2] at Yale described three neurologic patients with hyponatremia. Both patients had increased urine sodium loss and dehydration inspite of high sodium diet. In 1952, Cort [3] in Yale described another similar patient as having Cerebral salt wasting syndrome.

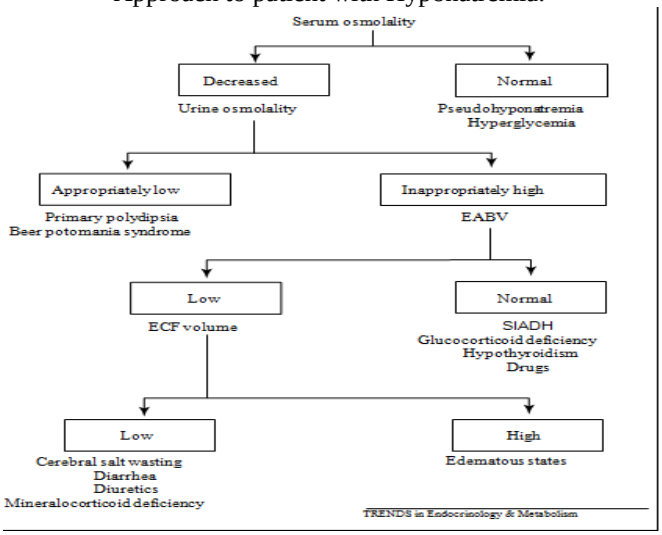
Schwartzet al [4] published the paper on SIADH which became a milestone. For over two decades theterm CSW vanished from literature.In 1981,Nelson etal [5] reintroduced the term based on his findings in patients with sub-arachnoid haemorrhage, finding volume contraction in those patients in spite of hyponatremia.

Hyponatremia is the most common electrolyte disturbance in neurologicpatients [7]Hyponatremia is defined as sodium level of less than 130 meq/L and occurs in 20% of hospitalised patients [8] and the in-hospital mortality rate is found to be 1.5 fold higher than those with normal sodium levels [9].

Water and sodium homeostasis are tightly regulated and thus disturbances in water homeostasis can lead onto sodium imbalance.

Sodium being the major extracellular ion is the principal determinant of serum osmolality. Thus the interplay between circulating vasopressin and water intake plays a key role in regulating the serum osmolality. Relative sodium concentration thus changes with water homeostasis and hence absolute plasma sodium values do not suffice to tell about the volume status of the patient. Hyponatremia is a very common disorder occurring in upto 22% of inpatients.

Approach to patient with Hyponatremia:



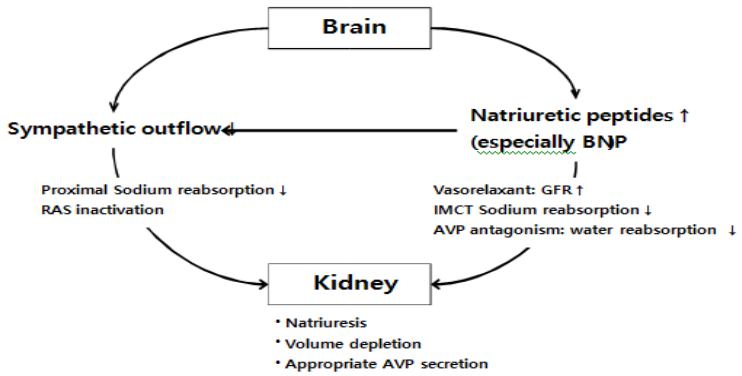
Syndrome of Inappropriate Anti-diuresis

In SIADH, ECFexpansion is not accompanied by overt signs of hypervolemia likeneck vein distension or peripheraledema, but has increased GFR and increased renal blood flow. Due to decreased proximal tubular reabsorption, uric acid and urea, both of which are proximally reabsorbed, are also seen to decrease in blood [10]
Decreased effective osmolality (<275 mOsm/kg of water)
Urinary osmolality >100 mOsm/kg of water during hypotonicity
Clinical euvolemia
No clinical signs of volume depletion of extracellular fluid
No orthostasis, tachycardia, decreased skin turgor, or dry mucous membranes
No clinical signs of excessive volume of extracellular fluid No edema or ascites
Urinary sodium >20 mEq/L with normal dietary salt intake
Normal thyroid and adrenal function
No recent use of diuretic agents
Plasma uric acid <4 mg/dL
Blood urea nitrogen <10 mg/dL
Fractional sodium excretion >1%; fractional urea excretion >55% Failure to correct hyponatremia after 0.9% saline infusion
Correction of hyponatremia through fluid restriction Abnormal result on test of water load (<80% excretion of 20 mL of water per kilogram of body weight over a period of 4 hours), or inadequate urinary dilution (<100 mOsm/kg of water)
Elevated plasma AVP levels, despite the presence of hypotonicity and clinical euvolemia

Cerebral Salt Wasting Syndrome:

CSW is a volume-depleted state hypothesised to be due to decreased sympathetic nervous system outflow in patients with a CNS insult. Also shown to be implicated are increased levels of natriuretic factors like atrial natriuretic peptide and brain natriuretic peptide.

Pathophysiology of Cerebral Salt Wasting



Difference between SIADH and CSW:

The primary difference lies in the effective arterial blood volume (EABV), which is increased in SIADH and vice versa in CSW. Since EABV is a clinical entity it can only be indirectly measured by levels of urine sodium excretion and ECF volume. Thus the differentiation of SIADH and CSW requires a panel of physical and laboratory investigations.

Physical features:

SIADH shows features of normal to increased ECF volume whereas
CSW shows dry skin and mucosa , orthostasis, flat neck veins, and a negative fluid balance [10]

Laboratory Features:

Thus in CSW aggressive salt and fluid replacement is necessary to maintain intravascular volume. Intravenous saline (isotonic or hypertonic), salt tablets or agent with mineralocorticoid activity like fluodrocortisone are the various treatment options [11, 12]

On the other hand, SIADH requires fluid restriction as the treatment.

Intravenous saline given in this volume-expanded state could lead to symptomatic hyponatremia, and worsening clinical condition.

So the osmolality of the administered fluid should exceed the osmolality of urine [8].

More targeted therapies would include AVP receptor antagonists [13] The other treatment options would include drugs like frusemide, demeclocycline and lithium.

Patients with acute sodium reductions and severe neurologic symptoms may need initial rapid sodium correction with hypertonic saline, but caution is necessary to prevent against osmotic demyelination during correction [14,15]

In patients with stroke, hyponatremia can be a cause of persistent altered sensorium. Neurologic dysfunction in hyponatremia occurs due to cerebral edema and due to cerebral autoregulation. The complications of hyponatremia are more marked with acute and severe Sodium reductions [16].

If the fall in sodium levels occur within a span of three days, cerebral edema is marked.

The symptoms of nausea and malaise occur at sodium levels 125-130mEq/L. Headache, obtundation, seizures, coma, respiratory failure and non-cardiogenic pulmonary edema can occur at levels 115-120mEq/L. Hyponatremia by resulting in adverse situations like seizures and coma can cause further deterioration of the patient.

Hyponatremia in stroke is mostly hypo-osmolal and is due to either SIADH or CSW [17].

Precipitating factors include dietary sodium restriction, diuretics and infections.

In a study by Sheikh et al, the incidence of hyponatremia in stoke was found to be 35% out of which 67% had SIADH and 33% had CSW. Hyponatremia had significant impact on the outcome especially in patients with CSW [16].

In another study by Huang WY et al, hyponatremia in acute stroke was seen in 11.6%. Hyponatremia was also a predictorof three-year mortality in acute ischemic stroke patients [17].

In our study we analysed 50 patients with acute stroke to study the occurrence of hyponatremia. The majority of stroke patients, about 46%, belonged to the middle age i.e., 40 – 60 years of age. The mean age of stroke occurrence in males was 56.2 (± 14.5) and that of the females was 66.9 (± 17.3). This is comparable to the population based study by Dalal et al (18) in Mumbai where the mean age for stroke was 66 years, and in Trivandrum by Sridharan et al (19) where the mean age was 67 years.

The majority of males belonged to 40-60 years age group. The prevalence of stroke in females, however was higher in the 60 to 80 year age group. Thus a higher age stratified prevalence for females was found, which is comparable to the data from the 2008 Mumbai stroke registry (42) where a mean of 63.4 years was recorded for females.

Of the stroke patients in our study group, 76% were male and 24% were female

The prevalence of ischemic stroke was higher (80%), of which 6 patients had lacunar stroke, 5 patients had a massive infarct. Hemorrhagic stroke was seen in 20%, with 16% having intracerebral bleed and 4% having sub-arachnoid haemorrhage. This is comparable to the Mumbai stroke registry (18), where 80% of strokes were attributed to be ischemia and 17.7% to haemorrhage. Accelerated hypertension was the cause of haemorrhage in 4 patients with intra cerebral bleed. 52% had stroke corresponding to the Middle Cerebral Artery territory, 40% with Posterior cerebral artery involvement and 8% with Anterior Cerebral circulation involvement.

The prevalence of hyponatremia due to cerebral causes was noted in 20% of the acute stroke patients. The prevalence is slightly higher than the study by Kuramatsu et al (20) where prevalence was 15%. Rodrigues B (19) reported a prevalence of 16% and Soiza et al (21) 13.8% Of the hyponatremic patients, there was a higher prevalence of SIADH (46%). CSW contributed to 31%. The study by Saleem et al (22) showed the respective prevalences to be 67% and 33% The prevalence of hyponatremia was the most in the 61-80 year age group (70%). The prevalence was lower among other age groups and this reached statistical significance ($p<0.05$). 67% of the patients who developed SIADH were of the 61-80 years age group. All the patients who developed Cerebral Salt Wasting on the other hand belonged to a higher age group (> 65 years). ($p<0.05$)

The trend of hyponatremia prevalence was more in males (70%) but did not reach statistical significance ($p>0.05$) Both SIADH and CSW showed a higher male prevalence, 67% and 75% respectively.

All the subarachnoid haemorrhage patients in our study developed hyponatremia Out of the Ischemic stroke patients 18% had hyponatremia. Hyponatremia was seen in 13% of patients with intracerebral haemorrhage. The most common stroke type seen in hyponatremic patients was ischemic stroke (77%) Among SIADH patients, 73% had ischemic stroke and 18% had intra cerebral hemorrhage. Saleem et al (22) in his study, showed 35% and 65% respectively.

Among cerebral salt wasting patients, ischemic stroke was found in 50% of patients and SAH was found in 50% patients. In the study by Saleem et al 33% and 67% were the prevalence. (22) Hyponatremia was seen in 50% of the MCA and 50% of Posterior Cerebral Artery territory stroke. None of our patients with ACA territory stroke developed hyponatremia. The majority of patients with SIADH had a posterior circulation stroke, 67%, and 33% had Middle Cerebral Territory stroke. Saleem et al (22) however, reported 13% and 86% respectively In CSW, 75% had Middle Cerebral Artery territory involvement and 25% had posterior circulation stroke.

This was comparable with Saleem et al's study (15%) who reported 85% and 15% respectively.

The mean duration of hospital stay was significantly different in patients with hyponatremia 17 days as against 3.73 days in normonatremic patients The maximum duration of stay seen in one of the hyponatremic patients was 130 days. A poorer discharge disposition was seen in the hyponatremia group in the study by Rodrigues (19) In normonatremic stroke patients, an 85% cure rate and 15% death rate was seen. In hyponatremic patients, there was 60% cure and 40% death. This is similar to the death rate reported by Saleem et al, 40%. (22) In both the studies, the presence of hyponatremia was found to significantly alter the treatment outcome in patients with stroke ($p<0.05$) Kuramatsu et al showed that in-hospital mortality was roughly doubled in hyponatremia compared with nonhyponatremia patients (40.9% vs 21.1%), translating into a 2.5-fold increased odds ratio ($P<0.001$). Also, Multivariable analyses identified hyponatremia as an independent predictor of in-hospital mortality ($P=0.037$) (20)

In the SIADH group, 83% were cured of hyponatremia with treatment and 17% patients succumbed. But in the CSW group, only 25% survived and 75% succumbed to the illness. CSW was significantly associated with higher death rate. ($p<0.05$)

Survival Curves

The Kaplan Meier analysis showed a significant increase in duration of hospital stay poorer survival in patients with hyponatremia.

Huang W.-Y proved that hyponatremia in the acute stroke stage was associated with higher mortality in hospital (P = .039) and at 3-month (P = .001) and 12-month follow-ups (P = .001), and that it is an independent predictor of 3-year mortality in patients with acute first-ever ischemic stroke.(23)

VI. Conclusion

Hyponatremia in the setting of acute stroke occurs in 10-20% patients. The prevalence is higher in males and among the middle aged. Hyponatremia, attributed to CSW is more common in stroke patients with sub-arachnoid haemorrhage. Hyponatremia occurs more with Middle and Posterior cerebral arterial territories involvement. SIADH has a higher prevalence than Cerebral Salt Wasting.

Hyponatremia and especially, cerebral salt wasting is an independent predictor of short and long term mortality in stroke. It also predisposes to a longer duration of hospital stay and poorer discharge disposition.

Thus, a clear distinction between the two entities ought to be made and the appropriate treatment be carried out, to reduce the morbidity, short and long term mortality in acute stroke patients with hyponatremia.

VII. Summary

This study is an observational descriptive study carried out to emphasise the importance of hyponatremia in the setting of a stroke and the impact it can have on the prognosis of the patient. This study was carried out in the premises of Coimbatore Medical College Hospital during a one year period. 50 cases of strokewere selected in random basis and were followed up for occurrence of hyponatremia.

The prevalence of hyponatremia was found to be 20%. The causes of hyponatremia especially Cerebral Salt Wasting and SIADH were studied. It was found that hyponatremia per se, and Cerebral Salt Wasting in stroke resulted in poorer discharge disposition and longer duration of in-hospital stay and significantly impacted on the short term in-hospital mortality. The pathophysiology of the two conditions (SIADH and CSW) being entirely different need a completely differing treatment regime and hence the distinction between the two is of utmost importance in neurologic cases with hyponatremia

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