ORIGINAL RESEARCH

Dehydration in acute stroke: Risk factors and outcome

[1]Dr. Aayush Jain, [2]Dr. Amandeep Kaur, [3]Dr. Sidak Paul Singh, [4]Dr. Birinder Paul Singh, [5]Dr. Dinesh Jain

[1]MBBS, Research fellow, DMC & Hospital, India
[2]M.D. Medicine, India
[3]MBBS (st.) DMC & Hospital, India
[4]DM Neurology, DMC & Hospital, India
[5]M.D. Professor of Medicine, DMC & Hospital, India

Corresponding Author
Dr. Birinder Paul Singh
DM Neurology, DMC & Hospital, India
Email: drbirinder06@yahoo.co.in

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ABSTRACT

Background-Among several factors reported to predict outcome of stroke, dehydrated appears to have poor functional outcomes. Unfortunately clinical methods to gauge hydration are not accurate, especially in geriatric patients hence, biochemical parameters like BUN/creatinine ratio(BUN/Cr) would be valuable marker for dehydration in stroke patients. **Aim-**To determine frequency and risk factors of dehydration in acute stroke patients, and impact on outcome at 30 days. **Methods-**An observational, prospective study conducted over 6-months. All adult patients presenting with acute stroke in first 24 hrs after symptom onset were included. Patients with previous history of stroke, TIA or congestive cardiac failure, renal failure and de-compensated cirrhosis of liver were excluded. Demographic, clinical and laboratory parameters were recorded. The primary outcome was determined at 30 days by modified Rankin Scale. **Results-**116 patients were enrolled in study with 103(88.7%) patients having ischemic stroke while 13(11.2%) had hemorrhagic stroke. Analyzing baseline factors, older age, higher stroke severity(NIHSS >16), low GCS(<8), and BUN/Cr>15 were significantly($p<0.001$) associated with dependency(mRS>2) or mortality at day 30. On multivariate analysis, dehyration (BUN/Cr>15) was found in 53.4% and was one of the independent predictors of poor short-term outcome. In this study, 53.4%patients had BUN/Cr ratio >15(Group I) while 46.6% with BUN/Cr ratio≤15(Group II). Mean age (64.4±12.15 years) was significantly higher in Group I compared to Group II(57.9±8.7 years). On univariate analysis, diabetes(48.4% vs 20.4%) and coronary artery disease(41.9% vs 18.5%) were statistically significant associated with dehydration at time of acute stroke. Higher NIHSS score and low GCS were also statistically significant in Group I. From multivariate analysis older age group, low GCS and CAD were independent predictors for hydration status at time of acute stroke. **Conclusion-** Our findings support that BUN/Cr ratio(rapid, cheap, and easily available parameter) should be included in routine assessment of all stroke patients and is one of the independent predictors of poor outcome.

INTRODUCTION

Stroke accounts for almost 10% of all deaths worldwide and 5% of all disability-adjusted life-years. [1] The bulk of this burden is more in the low-income and middle-income countries accounting for more than 75% of deaths from stroke and 80% of disability-adjusted life-years. [2] Several factors have been studied to predict the outcome of stroke, such as stroke severity at presentation, infarction volume, and presence of comorbidities.A large percentage of stroke patients who were found to be dehydrated at the time of stroke also appear to have poor functional outcomes.[3] Although hydration status can be gauged clinically via a variety of methods, stroke patients pose several challenges. The thirst may be missed due to altered mental status, language impairment, or diminished thirst mechanisms. [4] Unfortunately, the clinical assessment of dehydration by physicians is not always accurate, especially in geriatric patients. Hence, various investigators for the assessment of hydration status have used biochemical parameters like plasma osmolality, BUN/creatinine ratio, and urine-specific gravity, although none have been considered a gold standard. [5] A common marker used for the assessment of dehydration is the blood urea nitrogen to creatinine ratio (BUN/Cr). This marker has been used in multiple studies evaluating hydration status for differing disease processes. [4,6]

Studies also suggest that dehydration after stroke is a prevalent phenomenon, with a frequency of around 60% as measured with the BUN/Cr ratio associated with a poor outcome. [7] Blood urea nitrogen

(BUN)/creatinine (Cr) ratio, has been reported as an independent predictor of early neurological deterioration after acute stroke. [5]

Our aim was to determine the frequency and risk factors of dehydration in acute stroke, and its effects on the outcome 30 days after stroke, using a blood urea nitrogen (BUN)/creatinine (Cr) a biomarker of dehydration as a diagnostic tool.

METHOD

This was an observational prospective study in consecutive patients presenting to the Emergency Department with acute stroke, after fulfilling the inclusion criteria were included in the study. Inclusion criteria were adult patients (>18 years of age) presenting within the first 24 hours after symptom onset with the first episode of acute stroke (ischemic or hemorrhagic). Patients were excluded if there was history of previous episode of acute ischemic stroke, time between the onset of neurologic symptoms and presentation to the emergency department (ED) was >24 hours, patients with a transient ischemic attack or other co-morbid conditions like congestive cardiac failure (CCF), renal failure and decompensated cirrhosis of the liver. A written informed consent was obtained from the patients or their relatives for inclusion in the study. The institution's ethics committee approved the study protocol.

A detailed history was taken and a thorough general physical and systemic examination was performed. The details collected: on a predesigned performa included age, sex, signs and symptoms, Glasgow coma scale (GCS), history of diabetes, hypertension, coronary artery disease, dyslipidemia, diuretic usage, and smoking habits and alcohol intake. Laboratory investigations comprising complete blood count with hematocrit, blood urea nitrogen (BUN), serum creatinine, BUN/creatinine ratio, serum electrolytes, blood glucose. Plasma osmolality (calculated), serum bilirubin, lipid profile, glycated hemoglobin (HbA1C), D-dimer (qualitative assay), C-reactive protein (CRP, qualitative assay), urine specific gravity, non-contrast CT (NCCT) scan of head and electrocardiogram were performed within 24 hours of admission in all the patients. The neurological status of the patient and the severity of the stroke were assessed by using the NIHSS scoring system. Patients were divided into two groups. The first group included patients with BUN/Cr ratio >15 and the second group included those with BUN/Cr ratio ≤15. The two groups were compared for demographic characteristics, clinical characteristics, NIHSS score severity, GCS score severity, urine specific gravity and other lab parameters, disease severity, complications and outcome were compared between the two groups.

The patients were prospectively followed up after discharge, and those who were unable to come for an in-person visit were contacted on the phone for the modified Rankin Scale (mRS) score at thirty days. Primary outcome measures was determined at 30 days and categorized as, good (mRS ≤2) or poor (mRS >2 or death) at 30 days.

RESULTS

We enrolled 116 patients in our study. The mean age of presentation was 61.35 ± 11.14 years, with 61 (52.6%) < 60 years of age, 63 (54.3%) were males. More than two-thirds of the patients suffered from ischemic stroke (103) while only 13 (11.2%) had hemorrhagic stroke. Among the associated comorbidities, 68 (58.6%) patients were hypertensive, 40 (34.5%) were diabetic, 36 (31%) had coronary artery disease, dyslipidemia in 30 (25.9%). At the time of admission 62 (53.4%) patients had BUN/Cr ratio >15 suggesting a relatively dehydrated state.

We analyzed the demographic factors, type of stroke, neurological deficit and GCS at admission, BUN/Cr ratio, and hospital course for their potential influence on the functional neurological outcome at day 30 as defined by mRS. The results of univariate analysis showed that older age group, stroke severity (higher NIHSS >16), low GCS (<8), and BUN/Cr ratio >15 and urine specific gravity >1.010 were significantly ($p<0.001$) associated with dependency (mRS >2) or mortality at day 30. On multivariate logistical analysis BUN/creatinine >15 were found to be one of the independent risk predictors of poor outcome in patients with acute stroke.

Further we analyzed the factors for predicting volume-contracted state based on BUN/creatinine ratio by dichotomizing the acute stroke patients based on their hydration status; group I (BUN/Cr ratio of >15) and Group II (ratio of ≤15). The mean age (64.4 ± 12.15 years) was higher in Group I as compared to Group II (57.9 ± 8.7 years). Among the comorbid conditions that included DM, CAD, hypertension, univariate analysis, showed that DM (48.4% vs 20.4%) and CAD (41.9% vs 18.5%) were significantly ($p=0.002$ and 0.009 respectively). The prior use of diuretic medication for control of hypertension and history of addiction were similar in both the groups ($p=0.057$). Higher neurological deficit as assessed by NIHSS (>15) and correspondingly low GCS was statistically significantly noted in-group I as compared to the other group while other demographic factors were only comparable. Between the two groups there was a significant impact of volume-contracted state on duration of hospital stay, need of intensive care unit admission. On multivariate analysis age >60 years, low GCS (<8) and presence of coronary artery disease were the independent predictors for dehydration status (BUN/Cr ratio >15) in patients with acute stroke.

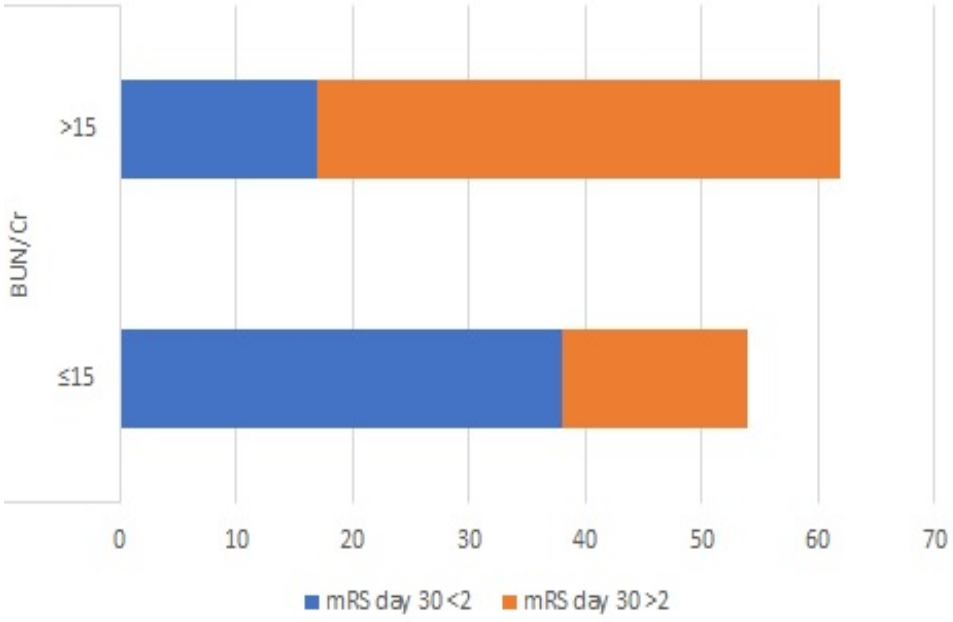
Table 1: Univariate analysis of all Clinical characteristics affecting functional outcome at day 30. DM-diabetes mellitus, HTN-hypertension, CAD-coronary heart disease, NIHSS-National, GCS-glassgow coma scale mRS-Modified Rankin scale, BUN/Cr-blood urea/Creatinine ratio.

Variables		Functional outcome day 30		p-Value
		mRS ≤2	mRS> 2	
Age group	Mean ± SD	59.87 ±8.73	62.39 ±12.15	**0.004**
Gender	F	30 (54.5)	23 (37.7)	0.093
	M	25 (45.5)	38 (62.3)	
GCS	≤8	0 (0)	50 (82)	**0.000**
	> 8	55 (100)	11 ()	
NIHSS	<15	55 (100)	8 ()	**0.000**
	≥15	0 (0)	53 (86.9)	
DM	N	37 (67.3)	39 (63.9)	0.706
	Y	18 (32.7)	22 (36.1)	
HTN	N	25 (45.5)	23 (37.7)	0.397
	Y	30 (54.5)	38 (62.3)	
CAD	N	39 (70.9)	41 (67.2)	0.667
	Y	16 (29.1)	20 (32.8)	
Dyslipidemia	N	37 (67.3)	49 (80.3)	0.109
	Y	18 (32.7)	12 (19.7)	
BUN/Cr	≤15	38 (69.1)	16 (26.2)	**0.000**
	> 15	17 (30.9)	45 (73.8)	
Urine specific gravity	<1.010	36 (65.5)	26 (42.6)	**0.016**
	>1.010	19 (34.5)	35 (57.4)	
Hospital Stay	≤10	54 (98.2)	21 (34.4)	**0.000**
	>10	1 (1.8)	40 (65.6)	

Table 2: Univariate analysis of Characteristics affecting hydration status, (BUN/Cr ratio).

Variables		BUN/Cr ratio		
		≤15	>15	p- value
Sex	F	26 (48.1)	27 (43.5)	0.62
	M	28 (51.9)	35 (56.5)	
DM	N	43 (79.6)	32 (51.6)	**0.002**
	Y	11 (20.4)	30 (48.4)	
HTN	N	23 (42.6)	25 (40.3)	0.605
	Y	31 (57.4)	37 (59.7)	
CAD	N	44 (81.5)	36 (58.1)	**0.009**
	Y	10 (18.5)	26 (41.9)	
Dyslipidemia	N	42 (77.8)	44 (71)	0.403
	Y	12 (22.2)	18 (29)	
Diuretic use	N	45 (83.3)	42 (67.7)	0.057
	Y	9 (16.7)	20 (32.3)	
Addiction	N	35 (64.8)	41 (66.1)	0.882
	Y	19 (35.2)	21 (33.9)	
ICU requirement	N	39 (72.2)	20 (32.3)	**0.000**
	Y	15 (27.8)	42 (67.7)	
Age		57.87 (8.73)	64.39 (12.15)	**0.001**
GCS		13.39 (2.64)	10.52 (3.39)	**0.000**
NIHSS		8.19 (7.06)	15.26 (8.45)	**0.000**
Urine specific gravity		1.01 (0)	1.020 (0.01)	**0.000**
Duration of hospital stay		7.7 (5.16)	10.23 (7.58)	**0.04**

Figure1: Depicting BUN/Cr ratio as an independent predictor of Poor Functional outcome in Acute Stroke.



DISCUSSION

Stroke is a significant cause of morbidity and mortality worldwide, and its incidence is increasing steadily. [8] Several risk factors have been evaluated to predict the prognosis of acute stroke, and dehydration is one of the important modifiable risk factors among them.

We enrolled 116 patients with stroke in our study, most of who were males (54.3%) and suffered from ischemic stroke (88.7%). In this study, the incidence of volume-contracted state was noted in more than 50% of the acute stroke patients at the time of admission as assessed by BUN/Cr ratio. On one hand, assessment tools such as dry skin or mucosa, and dark urine are subjective markers while on the other hand multi-frequency bioelectrical impedance is a cumbersome and not very effective method of assessing volume status. [9] Taking these facts into consideration we choose the ratio of BUN and serum creatinine as an easily available effective and reliable biomarker of dehydration in stroke to predict the short-term functional outcome. In this study, dehydration was an important independent predictor of poor outcome at 30 days. Volume contracted state or dehydration at the time of stroke results in an increase in blood viscosity and decreased blood pressure causing impaired collateral flow, thus reducing cerebral perfusion. The combination of these factors can potentially hinder the ability to salvage the ischemic penumbra, leading to an increased size of the infarcted core. As a result, there may be a greater loss of neural cells, resulting in more pronounced functional deficits. [11] In addition, we aimed to identify the factors predicting the hydration status of patients with acute stroke at admission.

Our findings also support that BUN/Cr ratio should be included in the routine assessment of patients with stroke for predicting hospital course as it is easily available parameters and even for following up the relative dehydration conditions. Because of dehydration there are multiple physiological changes such as electrolyte imbalances, hypotension, and reduced cerebral blood flow along with an ongoing pathological cascade of ischemia and cytotoxic edema in the brain. This can lead to worsening neurological deficits and additionally, dehydration can blunt cerebral auto-regulatory response and impair the body's ability to repair damaged tissues. [4]

Further, it was noted urine specific gravity was also a marker of the hydration status and it was also shown in studies that urine specific gravity >1.010 was also an important predictor of functional outcome which in line with our study though the assessment parameter were different. Interestingly, there are gaps in the literature regarding the utility of urine-specific gravity as the only marker of the hydration status of the acute stroke patients. Shih-Bin Su et al [12] and Eric Kyle O'Neal et al [13] reported urine-specific gravity as a good marker for evaluating hydration status while Anne Rowat et al [14] and Damir Zubac et al [15] did not find the marker to be useful.

Analyzing the factors for dehydration it was seen that older person with acute stroke was significantly dehydrated ($p = 0.001$). The reason for older people to be more prone for this volume-contracted state is due to multiple factors such as water deprivation, decreased thirst response with reduced kidney functioning, decreased total body water, and urinary incontinence. [16]

The presence of comorbidities like diabetes mellitus, and coronary artery disease were also significantly

associated with the presence of dehydration status (p = 0.002 and p = 0.009 respectively). This finding also echoes with results of previous studies. Oral hypoglycemic drugs are also one of the factors for reduced appetite with decreased consumption of water along with the presence of autonomic neuropathy in long-standing cases leading to gastroparesis, hence the reduced oral intake. Also, some oral hypoglycemics like SGLT-2 inhibitors work by glucosuria and polyuria further contributing to dehydration. [17] This class of drug is used in patients with coronary artery disease as well. Similarly, patients with coronary artery disease (who develop heart failure) are often advised to limit their oral fluid intake [18], which may lead to relative dehydration. The presence of hypertension as another common comorbidity was not seen to contribute to the volume contracted state in our study. Diuretics can exacerbate dehydration by increasing urine output, leading to electrolyte imbalances and hypotension however our results did not significant (p = 0.057) trend with prior use of diuretics. This may be due to the small number of patients on diuretics (29) in this study. Thus, we believe that these patients may be more susceptible to dehydration due to their underlying medical conditions, which led to impaired fluid balance.

Higher median NIHSS and low GCS scores at admission were found to be predictors of the volume contracted state. This may be because of impaired thirst mechanisms, dysphagia, and loss of consciousness (poor GCS) all of which result in reduced intake of oral intake of fluids. On the other hand the reverse may be also true, pre-existing subclinical volume contracted state because of the associated risk factors may have resulted in a large infarcted core resulting in larger artery stroke.

Our study has several limitations. First, it was a single-center study with a relatively small sample size. Second, we acknowledge that BUN/Cr ratio may be inaccurate in certain medical conditions such as coronary artery disease with compensated congestive cardiac failure (CCF), although we excluded clinically diagnosed CCF and renal failure patients from our study. Third, we have not serially measured the BUN/Cr ratio and only evaluated the hydration status of patients at the time of admission. Lastly, we have not evaluated the blood glucose levels in our study and only included the diagnosed cases of diabetes.

This study strengthens the existing evidence regarding the assessment of the hydration status of patients who present with acute stroke. It also establishes the consistency and reliability in monitoring the BUN/Cr ratio that needs to be emphasized in the management of acute stroke apart from using various antiplatelet and anticoagulant drugs. Identifying the predictors of dehydration state early may be helpful in the timely institution of corrective measures, thus preventing further worsening of neurological status, indirectly reducing the hospital stay as well as the cost of treatment with improved outcomes.

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