ARTÍCULO ORIGINAL

Prevalence of Dehydration at Acute Ischemic Stroke Onset and the Impact of Dehydration Subtypes on Severity: A Prospective Observational Study

Prevalencia de la Deshidratación al Inicio del Ictus Isquémico Agudo y el Impacto de los Subtipos de Deshidratación en la Gravedad: Un Estudio Observacional Prospectivo

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Abstract

Background: Dehydration has been suggested to influence stroke severity and recovery through mechanisms like increased blood viscosity and thromboembolism risk. This study aims to estimate the prevalence of dehydration at acute ischemic stroke (AIS) onset and assess the impact of different dehydration subtypes on stroke severity.

Methods: This prospective observational study was conducted at a tertiary care center over a period of one year. Dehydration was assessed using specific biomarkers to check for intracellular dehydration (Group A using urine osmolarity, plasma osmolarity, urine/plasma osmolarity ratio >1.5),) and mixed dehydration (Group B using BUN/creatinine ratio >0.20) parameters. Stroke severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS).

Results: Out of 177 AIS admissions, 71 patients met the inclusion criteria (49 males, 22 females; average age: 61.1 years for males, 62.8 years for females). Dehydration was present in 65% of patients at stroke onset. Among dehydrated patients, 33.3% had abnormal Group A parameters, 30% had abnormal Group B parameters, and 36% had abnormalities in both groups. A significant correlation was found between the presence of multiple dehydration markers and increased stroke severity ($p < 0.005$).

Discussion: The high prevalence of dehydration in AIS patients at onset suggests it may be a potential trigger for stroke and exacerbates stroke severity. Dehydration subtypes, categorized into intracellular, mixed, and extracellular dehydration, have distinct physiological implications requiring specific management strategies. Further research into standardized protocols and innovative biomarkers for dehydration assessment is recommended to enhance patient outcomes.

Keywords: Dehydration, Acute Ischemic Stroke, Secondary prevention, Primary prevention, Intracellular dehydration, extracellular dehydration

Resumen

Antecedentes: Se ha sugerido que la deshidratación influye en la gravedad y recuperación del ictus isquémico agudo a través de mecanismos como el aumento de la viscosidad sanguínea y el riesgo de tromboembolismo. Este estudio tiene como objetivo estimar la prevalencia de la deshidratación al inicio del ictus isquémico agudo (IIA) y evaluar el impacto de los diferentes subtipos de deshidratación en la gravedad del mismo.

Métodos: Este estudio observacional prospectivo se llevó a cabo en un centro de atención terciaria durante un período de un año. La deshidratación se evaluó utilizando biomarcadores específicos para verificar la deshidratación intracelular (Grupo A, usando osmolaridad urinaria, osmolaridad plasmática, ratio osmolaridad orina/plasma >1.5) y la deshidratación mixta (Grupo B, usando el ratio BUN/creatinina >0.20). La gravedad del ictus se evaluó utilizando la Escala de Ictus de los Institutos Nacionales de Salud (NIHSS, por sus siglas en inglés).

Resultados: De 177 ingresos por IIA, 71 pacientes cumplieron los criterios de inclusión (49 hombres, 22 mujeres; edad promedio: 61.1 años para los hombres, 62.8 años para las mujeres). La deshidratación estuvo presente en el 65% de los pacientes al inicio del ictus. Entre los pacientes deshidratados, el 33.3% tenía parámetros anormales del Grupo A, el 30% tenía parámetros anormales del Grupo B y el 36% presentaba anormalidades en ambos grupos. Se encontró una correlación significativa entre la presencia de múltiples marcadores de deshidratación y una mayor gravedad del ictus ($p<0.005$).

Discusión: La alta prevalencia de deshidratación en pacientes con IIA al inicio, sugiere que puede ser un desencadenante potencial y que exacerba su gravedad. Los subtipos de deshidratación, categorizados como intracelular, mixta y extracelular, tienen implicaciones fisiológicas distintas que requieren estrategias de manejo específicas. Se recomienda realizar más investigaciones sobre protocolos estandarizados y biomarcadores innovadores para la evaluación de la deshidratación con el fin de mejorar los resultados de los pacientes.

Palabras clave: Deshidratación, Ictus Isquémico Agudo, Prevención secundaria, Prevención primaria, Deshidratación intracelular, deshidratación extracelular

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Introduction

Acute ischemic stroke (AIS) is a major cause of morbidity and mortality worldwide, characterized by well-defined risk factors, along with established primary and secondary prevention strategies. AIS can occur secondary to atherosclerosis due to chronic endothelial damage from vascular risk factors and inflammation, from emboli, or due to a prothrombotic state.[1] Within this context, the triggers for stroke onset described in literature include strenuous physical activity, straining, heavy eating acute illness, or emotional outbursts, though a specific trigger is absent in the majority of cases.[2] Dehydration or volume depletion has been investigated as a factor influencing the severity and recovery of stroke patients.[3,4] It has been linked to increased blood viscosity, reduced plasma volume, and a heightened risk of thromboembolism, all of which can theoretically initiate or exacerbate stroke effects.[5] Previous studies have not analyzed dehydration at AIS onset or categorized dehydration subtypes. Recent advancements in understanding dehydration have led to the classification of dehydration into three subtypes: intracellular dehydration (ID) involving hypoosmotic water loss, extracellular dehydration (ED) involving isosmotic water loss, and mixed dehydration (MD). Each subtype has distinct physiological impacts and requires specific management strategies. Investigative markers have also been identified to detect the presence of each subtype.[5] This study aims to estimate the prevalence of dehydration in patients with AIS at onset and to determine the correlation between dehydration markers and stroke severity. By elucidating these relationships, the study seeks to enhance primary prevention and clinical management strategies to improve outcomes for stroke patients.

Methods

This study was designed as a prospective observational study conducted over one year period from November 2018 to October 2019 at Sri Ramachandra medical College and Research Institute, Chennai after obtaining ethical clearance and approval from the university ethics committee. The summer months of April and may were excluded to avoid seasonal variations in dehydration rates that could confound the results. The study population included adult patients with anterior circulation ischemic stroke who presented to the emergency department within 24 hours of stroke onset to ensure that the study focused on patients whose dehydration status was probably not a consequence of stroke. The exclusion criteria was designed to exclude patients who could be dehydrated due to other causes or could affect the measured values (Table 1).

Table 1. Exclusion criteria for the study.

Exclusion Criteria	Rationale
Referred patients from other centres – referral bias	Excluded to avoid the inclusion of patients who have received fluids before transfer.
Strokes presenting beyond 12 hours	Excluded to eliminate the potential effects of prolonged stroke on dehydration status.
Chronic kidney disease (CKD) or altered renal profile	Excluded to avoid altered dehydration markers due to renal dysfunction.
Chronic obstructive pulmonary disease (COPD)	Excluded due to chronic hypoxia affecting renal mechanics.
Uncontrolled glycaemic status	Excluded as it can alter osmolarity values and by itself can cause dehydration
Posterior circulation stroke	Excluded as the NIHSS score is not completely reliable for these cases.
Patients on diuretics or other relevant drugs	Excluded to prevent drug-induced changes in renal function and dehydration markers.
Patients requiring fluids at presentation	Excluded to ensure initial dehydration status was unaltered by immediate fluid administration.
Recurrent stroke, old CAD, or other structural/haematological risk factors:	Excluded to eliminate the influence of previous conditions on current dehydration and stroke severity.
Patients with swallowing difficulties, or requiring ryles tube	Since a lack of fluid intake after stroke could have led to the patient's dehydration

Patients meeting the inclusion criteria were enrolled in the study after obtaining informed consent. Comprehensive data were collected, including demographic information, medical history, clinical presentation, baseline investigations, and brain and vessel imaging details. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Dehydration was assessed using specific biomarker groups; Group A: Urine osmolarity, plasma osmolarity, and a urine/plasma osmolarity ratio >1.50 which were indicative of ID; Group B: Blood urea nitrogen (BUN)/creatinine ratio >0.20 which were indicative of Mixed dehydration. Surrogate markers for extracellular dehydration which included IVC collapsibility, Fractional excretion of sodium (FeNa) and haematocrit were not analysed as their validity and cut off values in dehydration were not established.[5,6] Although not the primary focus, surrogate markers like urine specific gravity, urine sodium, serum chloride, and uric acid levels were also analysed. Based on the results, patients were categorized into (H) hydrated, (A) abnormal group A results, (B) abnormal group B results, and (A+B) those with abnormal group A and B results based on these surrogate markers. The study compared baseline characteristics and stroke severity (NIHSS score) across these categories.

Data were expressed as the number of participants or as a percentage of the study population. Other data were presented as mean ± SD, or median and interquartile range for skewed distributions. Potential confounders were identified. Chi-square tests compared categorical variables, while

t-tests compared continuous variables. Group differences were analysed using the Chi-square test, non-paired and paired Student's t-tests for parametric distributions, and the Wilcoxon signed-rank test and Mann–Whitney U-test for nonparametric distributions. Differences among the four clinical subtypes were assessed using analysis of variance combined with Fisher's protected least significant difference. P-values < 0.05 were considered statistically significant. Statistical analysis was performed using the IBM SPSS Statistics software, version 29.0.

Results

Out of 177 acute ischemic stroke (AIS) admissions, 71 patients met the inclusion criteria for this study. The cohort consisted of 49 males and 22 females, with an mean age of 61.1 years for males and 62.8 years for females. Table 2 presents the baseline characteristics of the patients, showing no significant variations across the different groups.

Table 2. Baseline characteristics.

	Hydrated (35%)	A (33.3% of D)	B (30% of D)	A+B (36% of D)
Number	25	15	14	17
Age (mean)	61.1	63.2	61.5	62.4
Diabetes	9	7	6	8
Hypertension	10	5	7	7
Both (DM+HT)	6	2	3	5
Dyslipidaemia	4	3	3	3
Smoking	**4**	2	**1**	**2**
BMI (mean)	28.3	28.9	27.6	27.9
NIHSS (Mean)	**4.1**	5.9	**6.5**	**9**
TOAST Stroke classification				
- LAA	4	3	3	2
- SAO	16	9	9	10
- CE	2	2	1	3
- SOC	1	1	0	1
- SUC	2	0	1	1
Stroke Distribution				
- Cortical	**9**	7	**6**	**8**
- Subcortical	**16**	8	**8**	**9**
Prior Structural/ haematological risk factors for stroke	**Nil**	Nil	**Nil**	**Nil**

The study revealed that 65% of the patients presenting with ischemic stroke were dehydrated at the onset of their condition. Dehydration was further categorized based on specific parameters. Among the dehydrated patients, 33.3% exhibited abnormal values in group A parameters, 30% had abnormalities in group B parameters, and 36% showed abnormal values in both group A and group B parameters.

A statistically significant correlation was found between the presence of multiple types of dehydration and increased stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS) at onset. This correlation, with a p-value of less than 0.005, suggests that patients with a higher number of abnormal markers, indicating the presence of both intracellular and mixed dehydration, experienced more severe strokes compared to those who were hydrated or had only a single dehydration marker abnormality (Figure 1). An age and risk factor adjusted linear regression analysis also confirmed a significant association between dehydration and higher NIHSS scores, especially in the group (A+B).

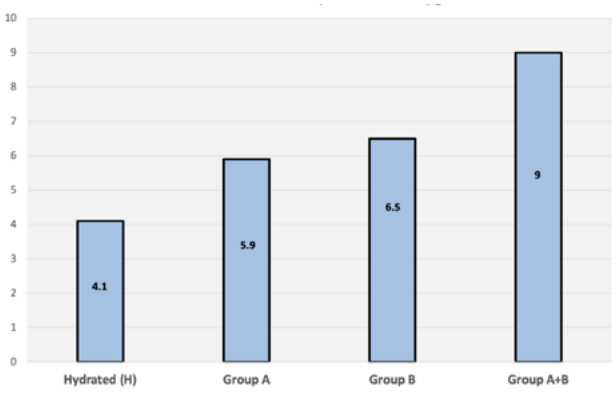

Figure 1. Average NIHSS in dehydration subtypes.

Discussion

Dehydration, which refers to the loss of body water, is a complex and dynamic clinical syndrome with significant physiological and pathological impacts.[5] Thirst, the subjective feeling of needing to drink fluids, is influenced by habitual, psychological, cultural, and importantly, regulatory drives.[7,8] Intracellular dehydration primarily triggers thirst through central osmoreceptors. In cases of extracellular dehydration, there must be at least a 2% increase in plasma osmolarity driven by sodium to cause a transcellular movement of water, resulting in intracellular dehydration.[9] The role of mechanoreceptors in directly stimulating thirst centres remains less clear.[8] Chronic dehydration further diminishes the thirst drive especially in older adults.[10] Beyond theoretical hypoperfusion, dehydration can increase blood viscosity, primarily influenced by haematocrit levels, which can promote or exacerbate thrombosis. Other additional mechanisms include orthostatic intolerance and activation of the coagulation cascade via the sympathetic autonomic system.[11] Environmental factors, like high humidity exacerbated by rising air pollution levels, can further worsen dehydration.[12,13]

The study revealed that 65% of ischemic stroke patients were dehydrated at onset, consistent with prior research showing dehydration in nearly 62% of hospitalized stroke patients at some stage during their hospitalization.[14] This high prevalence not only suggests a potential trigger for stroke but also emphasizes the critical need to monitor hydration status in stroke patients, as dehy-

dration can exacerbate outcomes. The study categorizes dehydration into three subtypes: intracellular dehydration (ID), mixed dehydration (MD), and extracellular dehydration (ED). Each subtype carries distinct physiological implications necessitating specific management strategies, supported by unique serological and urinary parameters for diagnosis (Figure 2). ID increases plasma osmolarity, potentially causing cellular shrinkage and dysfunction in vulnerable brain regions, thereby amplifying neuronal damage during ischemia. Simultaneously, extracellular dehydration increases blood viscosity due to reduced plasma volume, fostering a hypercoagulable state that may enhance thrombus formation or extension, an important factor in AIS progression. This dual effect could worsen cerebral hypoperfusion and expand the infarct area. Additionally, the compensatory activation of the renin-angiotensin-aldosterone system and sympathetic nervous system in response to volume depletion may heighten vascular resistance and endothelial stress, further aggravating the ischemic cascade.

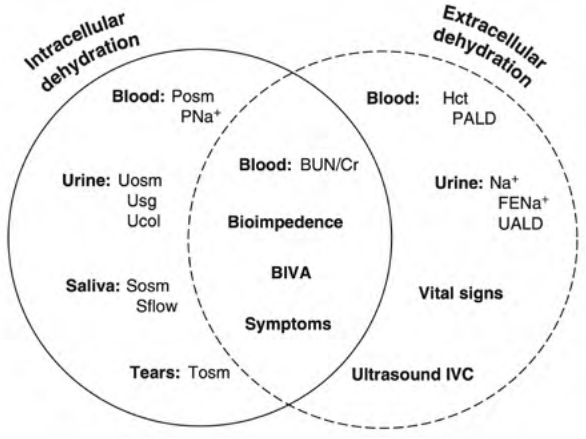

Figure 2. Dehydration assessment measures are categorized based on their physiological basis for detecting intracellular, extracellular, or both types of dehydration. Within each category, measurements are further subdivided by body fluid, technology, or technique.
This image has been reused with permission from author Samuel N. Cheuvront.

Previous studies have explored dehydration in ischemic stroke, linking it to adverse outcomes such as poor functional recovery and early neurological decline (END).[3,15] There is also evidence suggesting associations with cardioembolic stroke and increased risk of atrial fibrillation.[16] The THIRST study in 2009 was among the first to investigate dehydration as a potential contributing factor to stroke, particularly among the elderly. Conducted retrospectively over five years with 245 patients presenting with transient ischemic attack or acute ischemic stroke (AIS), it highlighted elevated plasma osmolality in elderly patients, indicative of a fluid-depleted state.[11]

ID is characterized by a hypoosmotic volume loss, while ED is characterised by a isosmotic volume loss.[5] Loss of hypoosmotic water produces a change in plasma osmolarity, and when this increases beyond 2%, it causes cells to shrink as water moves out across the cell membrane. Small changes in plasma osmolarity is buffered by large changes in urine osmolarity, making its measurement relevant for diagnosing ID separately. The Urine osmolarity/ Plasma osmolarity ratio was considered with a ratio of >1.5 as a baseline cut off.[17,18,19,20] The isosmotic water loss which occurs in ED causes insignificant change in Po per se but causes changes in extra cellular fluid volume. The potential markers of ED including haematocrit, vital signs, fractional excretion of sodium and ultrasound IVC parameters were all subject to variation, and demonstrated poor diagnostic accuracy and were not analysed in this study.[5,6,21] The BUN creatinine ratio represents a method to analyse dehydration stimulated by either osmotic or volume change as it uses creatinine which is relatively constantly excreted and BUN or the amount of reabsorbed BUN which is a inverse function of rate of urine flow controlled by AVP.[5,22-24]

The methodology in the present study was designed to exclude any cause which could potentially confound the measured assays, or could independently cause dehydration (e.g., CKD, uncontrolled diabetes, use of diuretics),to strengthen the study's validity by focusing on patients whose hydration status is directly linked to stroke onset. We also avoided enrolment during the summer months and ensured that the parameters were analysed form the initial samples obtained from the ER from patients presenting before 24 hours to prevent the effect of stroke on hydration from confounding the parameters. By these measures we aimed to possibly analyse the hydration status as close to the time of stroke onset as possible. Our study is one of the first studies to explore dehydration subtypes at stroke onset. However, the study has some limitations. The exclusion of patients who received fluids prior to admission or those presenting beyond 24 hours post-stroke onset may limit the generalizability of the findings. Additionally, the study did not track long-term outcomes of the patients, which would be important to understand the lasting impact of dehydration and rehydration therapy on stroke recovery. The sample size was also limited by the extensive exclusion criteria

Developing and validating standardized protocols for hydration assessment and management in stroke patients would help ensure consistent and effective care across different clinical settings. Including a broader range of patient populations in future studies, such as those with CKD, diabetes, or those presenting beyond 24 hours post-stroke onset, would enhance the generalizability of the findings.

This study underscores the high prevalence of dehydration in AIS patients at onset and its significant correlation with stroke severity. The categorization of dehydration into intracellular, mixed, and extracellular subtypes, and the use of specific biomarkers for assessment, provide a nuanced understanding of this condition. Integrating routine hydration assessment and tailored management strategies into clinical practice could mitigate stroke severity and enhance recovery outcomes. Importantly considering the significant presence of dehydration at stroke onset, and the effect of dehydration on coagulation dynamics, a role of dehydration in possibly triggering AIS should be acknowledged and the importance of adequate hydration in primary or secondary prevention of vascular events should be emphasized.

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