JVIN | Journal of Vascular and Interventional Neurology

OFFICIAL JOURNAL OF ZEENAT QURESHI STROKE INSTITUTE

Hyperchloremia in Acute Stroke: A target intervention to improve stroke outcomes

Sajid Hameed[1], MBBS, FCPS, Mohammad Wasay[1,*], MD, FRCP, FAAN, FEAN

[1] Department of Neurology, Aga Khan University, Karachi, Pakistan

Acute stroke care has evolved significantly over the years, yet one of its most fundamental interventions remains intravenous fluid therapy. Adequate hydration supports cerebral perfusion, and hypertonic saline is central to the management of cerebral edema and intracranial hypertension.[1,2] However, the chloride content of these commonly administered solutions may not be physiologically neutral. Increasing evidence suggests that hyperchloremia may contribute to acute kidney injury (AKI), metabolic acidosis, and worse clinical outcomes in critically ill patients.[3] In stroke populations, where systemic complications directly influence neurological recovery, this possibility deserves attention.

Hyperchloremia is defined as a serum chloride concentration >110 mmol/L. In hospitalized patients, particularly in neurocritical care, it most often results from chloride-rich intravenous fluids. Normal saline contains 154 mmol/L of chloride, higher than physiological plasma levels (95-110 mmol/L). Hypertonic saline solutions deliver even greater chloride loads. In patients with intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), prolonged or continuous hypertonic therapy can result in significant cumulative exposure. Thus, in many stroke patients, hyperchloremia is not incidental but it is treatment related.

The broader critical care literature has already raised concerns about chloride burden. In the SMART trial, 15,802 critically ill adults were randomized to balanced crystalloids or saline. Balanced crystalloids reduced major adverse kidney events within 30 days compared with saline (14.3% vs. 15.4%; OR 0.91; 95% CI 0.84–0.99; P=0.04; absolute risk reduction 1.1%).[4] Similarly, in the SALT-ED trial of 13,347 noncritically ill adults, balanced crystalloids lowered major adverse kidney events (4.7% vs. 5.6%; adjusted OR 0.82; 95% CI 0.70–0.95; P=0.01).[5] Although the absolute benefits in both trials were modest and the populations did not specifically include stroke patients, the consistency of the results across different care settings highlight the broader clinical relevance.

Data from stroke populations further strengthens the argument. In acute ischemic stroke, Qureshi et al. showed that early and sustained hyperchloremia independently predicted poor functional outcome at 90 days, with more than a twofold increase in the odds of death or disability (adjusted OR 2.6; 95% CI 1.6–4.1).[6] In ICH, Riha et al. reported that moderate hyperchloremia (Cl^- ≥115 mmol/L) during continuous hypertonic saline therapy was independently associated with higher in-hospital mortality (34% vs. 14%; adjusted OR 4.4; 95% CI 1.4–13.5).[7] In SAH, Sadan et al. demonstrated that increasing mean serum chloride independently predicted AKI (adjusted OR 7.39 per 10 mmol/L increase; 95% CI 3.44–18.23), and AKI in this population was strongly associated with mortality.[8] Across ischemic and hemorrhagic subtypes, hyperchloremia consistently tracks with renal dysfunction and adverse outcomes.

The biological plausibility is compelling. Hyperchloremia induces renal vasoconstriction through activation of tubuloglomerular feedback, reducing renal blood flow and glomerular filtration.[3] Elevated chloride levels contribute to hyperchloremic metabolic acidosis, which may impair cellular metabolism and amplify systemic inflammation. In acute stroke, even modest renal dysfunction can complicate osmotherapy, anticoagulation decisions, and hemodynamic management. What appears to be a biochemical shift may in fact alter the trajectory of stroke recovery.

Potential effects may extend beyond the kidney. Chloride gradients are fundamental to γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission. Disturbances in chloride homeostasis can alter neuronal excitability.[9] Systemic hyperchloremic acidosis may also influence cerebral vascular tone, potentially reducing cerebral blood flow in already compromised territories.[8,10] Although direct clinical evidence of chloride-mediated neuronal injury remains limited, the convergence of acid–base, vascular, and electrophysiological considerations suggests that excess chloride is unlikely to be inert in the injured brain.

Vol.16, No. 1, pp. 35-36, Published April, 2026.

All Rights Reserved by JVIN. Unauthorized reproduction of this article is prohibited.

*Corresponding Author: Mohammad Wasay, Aga Khan university, Karachi. Email: Mohammad.wasay@aku.edu.

Importantly, hyperchloremia in stroke care is often avoidable. The Randomized, Double Blinded, Pilot Clinical Trial to Compare the Safety and Efficacy of Sodium Chloride and Sodium Acetate Combination Intravenous Fluids in Acute Stroke Patients (ACETatE trial) provides proof of concept that chloride burden can be reduced without compromising osmotic efficacy.[10] In patients with aneurysmal SAH, a low-chloride hypertonic solution combining sodium chloride (NaCl) with sodium acetate (16.4% NaCl plus sodium acetate) significantly reduced AKI compared with conventional 23.4% NaCl (12% vs 53%; p= 0.01), while achieving comparable intracranial pressure control. Sodium acetate, a metabolizable anion, limits chloride exposure and mitigates hyperchloremic acidosis. Although ACETatE was a pilot study and underpowered for long-term neurological outcomes, it demonstrates that the chloride component of hypertonic therapy is neither inevitable nor benign.

In a recent 2026 study, Qureshi et al. compared 0.9% NaCl alone with balanced solutions containing NaCl and sodium acetate in varying ratios (3:1, 2:1, and 1:1) among patients with acute stroke (n = 80; 64 ischemic strokes, 16 ICH). Sodium acetate–containing formulations were associated with significantly lower mean serum chloride levels in a dose-dependent manner, with the lowest concentrations observed in the 1:1 group, without an increase in adverse safety outcomes. Functional independence at 90 days appeared highest in the 2:1 group.[11]

The evidence does not support complete abandonment of saline-based therapies. Normal saline and hypertonic saline remain essential tools in stroke management. However, accumulating data challenges the longstanding assumption that chloride serves merely as a passive counterion. In both general critical care trials and stroke-specific observational studies, elevated chloride levels have been consistently associated with AKI and poorer clinical outcomes. The reproducibility of this association argues against therapeutic complacency.

Stroke care has increasingly prioritized the prevention of secondary brain injury by avoiding hypotension, hypoxia, hyperglycemia, and fever. Chloride exposure may belong in this same category. Routine monitoring of serum chloride, careful assessment of renal function, and thoughtful consideration of fluid composition represent low-cost interventions with potentially meaningful impact. Where feasible, limiting unnecessary chloride administration or considering chloride-sparing alternatives may reduce iatrogenic harm.

Iatrogenic hyperchloremia is common in acute stroke and consistently associated with adverse outcomes. Whether it is merely a marker of severity or a modifiable mediator of injury remains to be definitively proven. Yet the weight of current evidence suggests that excess chloride should not be dismissed as benign. In the injured brain, even modest systemic derangements can exert outsized effects. Chloride deserves to be regarded not as a routine laboratory value, but as a potentially modifiable determinant of prognosis in acute stroke. Future randomized controlled trials comparing normal saline to sodium acetate may be valuable in identifying better intravenous fluids in acute stroke care.

REFERENCES

1. Oddo M, Poole D, Helbok R, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. Intensive Care Med 2018;44(4):449–63. doi: 10.1007/s00134-018-5086-z. Epub 2018 Mar 2.
2. Vincent JL. Fluid management in the critically ill. Kidney International 2019;96(1):52–7. doi: 10.1016/j.kint.2018.11.047.
3. Rein JL, Coca SG. "I don't get no respect": the role of chloride in acute kidney injury. Am J Physiol Renal Physiol 2019;316(3):F587–605. doi: 10.1152/ajprenal.00130.2018. Epub 2018 Dec 12.
4. Semler MW, Self WH, Wanderer JP, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med 2018;378(9):829–39. doi: 10.1056/NEJMoa1711584. Epub 2018 Feb 27.
5. Self WH, Semler MW, Wanderer JP, et al. Balanced Crystalloids versus Saline in Noncritically Ill Adults. N Engl J Med 2018;378(9):819–28. doi: 10.1056/NEJMoa1711586. Epub 2018 Feb 27.
6. Qureshi AI, Huang W, Gomez FE, et al. Early Hyperchloremia and Outcomes After Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 2022;31(8):106523. doi: 10.1016/j.jstrokecerebrovasdis.2022.106523. Epub 2022 May 25.
7. Riha HM, Erdman MJ, Vandigo JE, et al. Impact of Moderate Hyperchloremia on Clinical Outcomes in Intracerebral Hemorrhage Patients Treated With Continuous Infusion Hypertonic Saline: A Pilot Study. Crit Care Med 2017;45(9):e947–53. doi: 10.1097/CCM.0000000000002522.
8. Sadan O, Singbartl K, Kandiah PA, et al. Hyperchloremia Is Associated With Acute Kidney Injury in Patients With Subarachnoid Hemorrhage. Crit Care Med 2017;45(8):1382–8. doi: 10.1097/CCM.0000000000002497.
9. Pressey JC, de Saint Rome M, Raveendran VA, et al. Chloride transporters controlling neuronal excitability. Physiol Rev 2023;103(2):1095–135. doi: 10.1152/physrev.00025.2021. Epub 2022 Oct 27.
10. Sadan O, Singbartl K, Kraft J, et al. Low-chloride- versus high-chloride-containing hypertonic solution for the treatment of subarachnoid hemorrhage-related complications: The ACETatE (A low ChloriE hyperTonic solution for brain Edema) randomized trial. J Intensive Care 2020;8:32. doi: 10.1186/s40560-020-00449-0.
11. Qureshi AI, Wasay M, Saleem S, et al. A randomized, double blinded, pilot trial to compare the safety and efficacy of sodium chloride and sodium acetate combination intravenous fluids in acute stroke patients. J Clin Neurosci 2026;147:111915.