Hyponatremia in Acute Stroke: To Treat or Not to Treat?

Dear Editor,

Hyponatremia is the most common electrolyte disorder both in hospitalized patients and individuals from the community with a reported incidence mounting up to 30% and 8%, respectively.[1,2] Its association with increased risk of mortality has been well-established.[3-5] Several meta-analyses have demonstrated that hyponatremia increases mortality in patients with common clinical conditions, such as acute myocardial infarction, heart failure, cirrhosis, and chronic kidney disease,[3-5] while "correction" of serum sodium levels improves survival.[6-8]

Hyponatremia is frequently observed in patients with stroke either upon their admission (3.9%-45.3%) or during hospitalization (40%-45%).[9] In this context, Chen et al have recently published a well-designed meta-analysis investigating the association of hyponatremia with the risk of short- and long-term mortality in patients with acute ischemic or hemorrhagic stroke.[9] Therein the authors included 12 observational studies with 21,973 subjects and concluded that hyponatremia increases the risk of all-cause mortality both short-term (hazard ratio [HR]: 1.78; 95% confidence interval [CI]: 1.19-2.75) and long-term following a stroke (HR: 2.23; 95% CI: 1.30-3.82).[9]

By scrutinizing the available literature, 2 significant studies are apparently missing.[8,10] Lasek-Bal et al published a study of 464 patients with chronic kidney disease who experienced a first-ever ischemic stroke showing that hyponatremia was associated with worse neurological outcomes and increased mortality at 1 month (odds ratio: 3.41, 95% CI: 1.66-7.04).[10] Likewise, in another prospective study by Shah et al evaluating the impact of incident hyponatremia on short-term mortality in patients with hemorrhagic stroke (n = 234), hyponatremia during hospitalization was associated with increased in-hospital mortality (odds ratio: 10.21, 95% CI: 3.81-27.37).[8,11]

There are several causes accounting for hyponatremia in patients with acute stroke. First, hyponatremia may be related with patients' comorbidities, such as type 2 diabetes, chronic kidney disease and heart failure as well as with concomitant drug treatment, including thiazide diuretics, antidepressants, and nonsteroidal anti-inflammatory drugs.[2,12] Moreover, during hospitalization, "inappropriate" administration of hypotonic solutions, poor solute intake, complicating infections and drugs, such as mannitol, may lower serum sodium levels.[13-15] In the acute stroke setting, secondary adrenal insufficiency due to pituitary ischemia or hemorrhage, syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting should be considered in the diagnostic approach of hyponatremia.[16] Chen et al acknowledged the fact that most data of the studies included in their analysis was not adjusted for all these potential confounding factors, which represents a major limitation.[9] Consequently, there is no 'safe' answer to the question whether hyponatremia independently affects survival of stroke patients or it is merely a marker of major comorbidities worsening the prognosis.

Stroke physicians should keep in mind evidence suggesting that the correction of hyponatremia improves survival in patients with heart failure or subarachnoid hemorrhage regardless of the underlying cause.[6-8] Therefore, despite the lack of guidelines for the management of hyponatremia in patients with acute stroke, implementing an effective treatment strategy would be in the benefit of patients. This strategy should include: (1) restoration of fluids and electrolytes in volume-depleted hyponatremia, (2) hypertonic solutions in cases of symptomatic hyponatremia, and (3) treating the underlying cause in cases of hyper- and euvolemic hyponatremia (eg, withdrawal of an offending drug). Fluid restriction and/or drugs like loop diuretics, urea, and vasopressin-receptor antagonists (vaptans) are also available therapeutic options.[17-19] All things considered, whether correcting or restoring serum sodium levels in patients with acute stroke would improve short and long-term prognosis remains to be answered in future studies.

Conflict of Interest

The authors report no conflicts of interest associated with the present work.

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References

1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med 2006;119(7 Suppl 1): S30-S35.

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2. Liamis G, Rodenburg EM, Hofman A, et al. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med 2013;126:256-263.
3. Corona G, Guiliani C, Parenti C, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. PLoS One 2013;8:e80451.
4. Ma QQ, Fan XD, Li T, et al. Short- and long-term prognostic value of hyponatremia in patients with acute coronary syndrome: a systematic review and meta-analysis. PLoS One 2018;13:e0193857.
5. Sun L, Hou Y, Xiao Q, et al. Association of serum sodium and risk of all-cause mortality in patients with chronic kidney disease: a meta-analysis and sysematic review. Sci Rep 2017;7:15949.
6. Wang J, Zhou W, Yin X. Improvement of hyponatremia is associated with lower mortality risk in patients with acute decompensated heart failure: a meta-analysis of cohort studies. Heart Fail Rev 2019;24:209-217.
7. Corona G, et al. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. PLoS One 2015;10:e0124105.
8. Shah K, Turgeon RD, Gooderham PA, et al. Prevention and treatment of hyponatremia in patients with subarachnoid hemorrhage: a systematic review. World Neurosurg 2018;109:222-229.
9. Chen Z, Jia Q, Liu C. Association of hyponatremia and risk of short- and long-term mortality in patients with stroke: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2019;28:1674-1683.
10. Lasek-Bal A, Holecki M, Kret B, et al. Evaluation of influence of chronic kidney disease and sodium disturbances on clinical course of acute and sub-acute stage first-ever ischemic stroke. Med Sci Monit 2014;20:1389-1394.
11. Shah A, Sabir S, Artani M, et al. Significance of hyponatremia as an independent factor in predicting short-term mortality in patients with hemorrhagic stroke. Cureus 2019;11:e4549.
12. Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. Int J Clin Pract 2008;62:1572-1580.
13. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis 2008;52:144-153.
14. Liamis G, Filippatos TD, Elisaf MS. Correction of hypovolemia with crystalloid fluids: individualizing infusion therapy. Postgrad Med 2015;127:405-412.
15. Liamis G, Milionis HJ, Elisaf M. Hyponatremia in patients with infectious diseases. J Infect 2011;63:327-335.
16. Hannon M, Behan LA, O'Brien MM, et al. Hyponatremia following mild/moderate subarachnoid hemorrhage is due to SIAD and glucocorticoid deficiency and not cerebral salt wasting. J Clin Endocrinol Metab 2014;99:291-298.
17. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol 2014;170:G1-47.
18. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013;126(10 Suppl 1):S1-42.
19. Filippatos T, Elisaf M, Liamis G. Pharmacological management of hyponatremia. Expert Opin Pharmacother 2018;19:1337-1344.