Hyponatremia as a surrogate marker for optimal diuretic selection in acute heart failure

Despite the lack of clear evidence of a reduction in mortality and morbidity, diuretic therapy remains a mainstay for the management of patients with acute heart failure (AHF). Current guidelines recommend immediate use of loop diuretics to relieve signs and symptoms of congestion attributed to HF [1]. In fact, however, diuretic resistance often occurs under several mechanisms including the braking phenomenon, post-diuretic sodium reabsorption, and renal adaptation [Fig. 1]. This not only makes it difficult to mitigate fluid retention, but diuretic resistance per se is related to the worsening prognosis [2]. In such a clinical setting, a higher dose of loop diuretics or a combination of loop and thiazide diuretics is considered, and thiazide is shown to exert an adjunctive effect via sequential nephron blockade that suppresses increased sodium reabsorption due to renal adaptation [3]. Conversely, the combined use of thiazide exacerbates a risk for hypotension, worsening renal failure, and especially hyponatremia when the increase in urine sodium excretion is greater than the increase in urine water excretion [3]. Hyponatremia, defined as a serum sodium (Na) level < 135 mEq/L, is a common electrolyte abnormality in AHF, which accounts for 15–25% of admitted patients [4]. Hyponatremia is appreciated as a strong predictor for increased mortality after discharge as well as during admission in HF patients [5]. The pathophysiology of hyponatremia is complicated, and it is indeed difficult to distinguish between dilutional and depletional. In general, however, dilutional hyponatremia is more evident in AHF, that is attributable to the HF-related vasopressin release reducing water diuresis together with the use of potent diuretics [6]. Hyponatremia is also associated with activation of the renin-angiotensin-aldosterone system (RAS) possibly due to severe impairment in renal blood flow and glomerular filtration rate [7]. Moreover, recent studies have indicated that persistent or treatment-induced hyponatremia during hospitalization is associated with long-term outcomes in AHF [7,8]. Accordingly, it is proposed that high-dose loop diuretics or combined use of loop and thiazide may cause hospital-acquired hyponatremia and lead to worse prognosis in AHF, but this has not been fully clarified.

In this issue of the Journal of Cardiology, Yamazoe et al. [9] retrospectively analyzed the data from 1844 patients with AHF in the West Tokyo Heart Failure (WET-HF) registry and investigated whether diuretic use is an independent predictor for hospital-acquired hyponatremia and for long-term adverse outcomes in patients with AHF. They examined the change in serum Na level between on admission and at discharge, and hospital-acquired hyponatremia was defined as worsening hyponatremia in which serum Na level (≥ 135 mEq/L) at admission declined to <135 mEq/L at discharge. In their study, high-dose loop diuretics were not associated with the development of hyponatremia regardless of thiazide use. Although it appears to be unexpected, the finding is in line with sub-analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial, in which serum Na level was comparable among low (≤ 300 mg) and high (>300 mg) dose of loop diuretics [2]. Additionally, the authors demonstrated that the use of thiazide rather than high-dose loop diuretics was independently associated with hospital-acquired hyponatremia and mortality even after adjusting for confounding variables by multivariate analysis as well as propensity score matching [9]. The present study underscores the importance of proper diuretic selection to prevent hyponatremia concomitant with the alleviation of congestion. However, the question is raised as to whether hospital-acquired hyponatremia contributes directly to exacerbating outcomes in AHF or whether hyponatremia is simply a marker that represents thiazide use.

As for the prognostic influence of hyponatremia, previous studies have suggested that the impact on prognosis differs between hospital admission and discharge in AHF [7,8,10]. For instance, a large prospective AHF cohort in Korea has indicated that aggravated or persistent hyponatremia before discharge is associated with one-year mortality, irrespective of Na level on admission [8]. In contrast, a post hoc analysis of the ESCAPE trial has shown that hyponatremia at discharge is not linked to adverse composite endpoints for six months after discharge as long as the serum Na level at admission is normal [10]. Since hyponatremia, especially at hospital discharge, can develop due to various factors including compromised hemodynamics, neurohormonal activation, and diuretics, it is plausible that the worse prognosis in the thiazide group is attributable to factors other than hyponatremia.
[6]. One potential factor is the varying RAS activation depending on the different action site of diuretics on renal tubules [7]. Specifically, (pro)renin receptor, a novel component of RAS, is localized in distal nephron and is responsible for renal RAS activation [11]. This is further supported in that soluble form of (pro)renin receptor is increased in HF patients and correlates with renal dysfunction [12]. Given that the different diuretic action sites of the distal tubule and the loop of Henle contributes to the distinct patterns of RAS activation, it is possible that each effect on vasopressin release impairs free water excretion and results in diuretic class-dependent hyponatremia. As a novel diuretic that yields less activation of RAS, a vasopressin type 2 receptor antagonist, tolvaptan, has emerged in clinical settings [13]. In the sub-analysis of EVEREST (the efficacy of vasopressin antagonism in HF outcome study with tolvaptan) trial [14], tolvaptan has been shown to reduce the morbidity and mortality of patients with hyponatremia (serum Na < 130 mEq/L). These findings suggest that tolvaptan is promising in HF patients with hyponatremia and neurohormonal activation, and yet further studies are needed to verify the desirable effects of tolvaptan on long-term outcomes in HF.

On the other hand, whether thiazide administration itself is associated with higher mortality remains largely elusive because of small sample sizes in previous reports. The issues will be addressed by an ongoing large-scale, randomized, double-blind trial designed to examine the safety and efficacy of combination therapy with loop and thiazide diuretics in HF patients [15].

Several limitations must be noted. First, given the retrospective nature of this study, residual confounding cannot be excluded and causality is impossible to determine. Second, although the registry data include numerous patients with AHF, the final number of patients with or without thiazide after propensity score matching was limited to 103 of each group and therefore it remains elusive whether the detrimental clinical influences of thiazide apply to the whole HF population. Third, no information is available on the dose and type of thiazide that determines the bioavailability related to pharmacokinetics. Nevertheless, the present study has clinical relevance in identifying a combined therapy with thiazide as an independent risk factor for acquired hyponatremia that associates with prognosis in AHF. As a treatment strategy for AHF, not only improvement in fluid retention but also optimal diuretic selection targeted at preventing the development of hyponatremia is indispensable to improve long-term outcome post-discharge. In this regard, optimal combination of loop diuretics and tolvaptan is clinically useful to coordinate the balance between natriuresis and aquaresis [Fig. 1] and may provide further clinical benefits related to normalization of hyponatremia. While serum Na level is a simple and conventional value, this study highlights its role as a surrogate marker for selecting better diuretics in light of prognosis after discharge in AHF.

Conflict of interest

The authors declare no conflicts of interest.

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References


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