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Hiponatrijemija u kroničnom zatajivanju srca

Hyponatremia in chronic heart failure

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SAŽETAK: Hiponatrijemija je biljeg povećanog rizika za neželjeni ishod u bolesnika s kroničnim srčanim zatajivanjem i klinički parametar koji u rutinskom radu zahtjeva posebnu pažnju. Uz terapijske opcije među kojima raspolažemo restrikcijom unosa tekućine, primjenom hipertonične otopine NaCl, diuretika Henleove petlje, ACE-inhibitora, antagonista AVP-receptora i njihovim kombinacijama te uz mnogobrojna otvorena pitanja, sada se ključnim nameće detaljna procjena bolesnika i individualna prilagodba terapijskog pristupa. Hipovolemijska hiponatrijemija samo je jedna od značajnih inačica ovog kliničkog stanja o kojoj moramo voditi računa pri liječenju. Očekuju se rezultati novih prospektivnih, dvostruko slijepih i placebom kontroliranih studija za konačno definiranje otvorenih pitanja unutar ovog iznimno značajnog područja suvremene kardiološke prakse.

KLJUČNE RIJEČI: srčano zatajivanje, hiponatremija.

SUMMARY: Hyponatremia is a marker of increased risk for adverse outcome in patients with chronic heart failure and a clinical parameter that requires special attention in routine practice. In addition to the treatment options including the restriction of fluid intake, by administering hypertonic saline, loop diuretics, ACE-inhibitors, antagonists of AVP-receptors and combinations thereof, in addition to numerous open questions, now the detailed assessment of patients and individual adaptation of the therapeutic approach is imposed as a crucial issue. Hypovolemic hyponatremia is just one of the most significant versions of this clinical condition which we have to take into account during the treatment. The results of new prospective, double-blind and placebo-controlled studies are expected as to finally define the open issues within this extremely important area of contemporary cardiology practice.

KEYWORDS: heart failure, hyponatremia.

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Kronično srčano zatajivanje — nova epidemija razvijenog svijeta

Srčano zatajivanje (SZ) je klinički sindrom koji nastaje kao posljedica različitih strukturnih i funkcionalnih poremećaja koji dovode do narušavanja srčane sposobnosti dostavljanja oksigenirane krvi i zadovoljavanja metaboličkih potreba tkiva unatoč normalnom tlaku punjenja ili samo pri značajno povišenom tlaku punjenja. Obzirom na napredak koji je tijekom posljednjih desetljeća postignut u liječenju akutnih kardioloških stanja, u prvom redu akutnog infarkta miokarda te dijelom zbog općeg produljenja očekivanog trajanja života, prevalencija SZ je sve veća u razvijenim zemljama te ono kao kompleksan i progresivan neuroendokrini klinički sindrom predstavlja sve veće socijalno i financijsko opterećenje kroz utjecaje na kvalitetu života i visoke zahtjeve u liječenju. Danas 1%-2% ukupne odrasle populacije ima SZ, a njegova je prevalencija ≥10% kod osoba starijih od 70 godina[1]. Multicentrična hrvatska studija *Polića i sur.* koja je obuhvatila 226 bolesnika sa SZ navodi prosječnu dob ovih bolesnika od 67 godina, zastupljenost muškog spola s 59%, ishemijsku etiologiju u 30% te kronični tijek bolesti u 68% svih hospitalizacija zbog SZ[2]. Ista je skupina autora 2011. god. objavila petogodišnju analizu Hrvatskog registra za zatajivanje srca koja je na uzorku od 1868 bolesnika hospitaliziranih zbog SZ utvdila udio muškaraca od 54,7% i prosječnu dob 71±11,9 god., dok su žene bile stare 77±9,9

Chronic heart failure — a new epidemic in the developed world

Heart failure (HF) is a clinical syndrome that occurs as a result of various structural and functional disorders that lead to the impairment of cardiac capability of delivering oxygenated blood and satisfying the metabolic needs of the tissue despite normal filling pressure or only at significantly elevated filling pressure. Given the significant progress that has been made over the past decade in the treatment of acute cardiac conditions, primarily acute myocardial infarction, and partly because of the general extension of life expectancy, the prevalence of HF is increasing in developed countries, and as a complex and progressive neuroendocrine clinical syndrome it represents ever greater social and financial burden by affecting the quality of life and the high demands of the treatment. Today 1% to 2% of the adult population has a HF, and its prevalence ≥10% in people older than 70 years[1]. The Croatian multicentric study *Polić et al.* which included 226 patients with HF reports a median age in these patients of 67 years, presence of males with 59%, ischemic etiology in 30% and a chronic course of the disease in 68% of all hospitalizations for HF[2]. The same group of authors published a five-year analysis of the Croatian Registry of Heart Failure in 2011, which on a sample of 1868 patients hospitalized for HF reported a frequency of men of 54.7% and a median age of 71±11.9, while the women were

god., a smrtnost tijekom analizirane hospitalizacije iznosila je 13,6%. Navedena je studija ukazala na usporedivost hrvatskih s europskim podacima[1,3].

Znanstvena područja koja se bave pojedinim aspektima SZ i njihovim dodirnim temama su vrlo dinamična. Rutinska klinička praksa, usprkos kontinuiranom napretku ističe neka od iznimno važnih područja kojima se ne polaže dovoljna pažnja i unutar kojih tek očekujemo velike, randomizirane, dvostruko slijepe prospektivne studije[4]. Jedno od njih je hiponatrijemija u bolesnika sa SZ koja predstavlja svakodnevnu dilemu kliničara.

Hiponatrijemija u kroničnom popuštanju srca

Hiponatrijemija je definirana kao serumska koncentracija Na niža od 136 mmol/L. Ona predstavlja najčešći elektrolitski poremećaj u nehospitaliziranih i hospitaliziranih bolesnika sa SZ i prema dosadašnjim saznanjima, iznimno je značajan klinički problem s jasnim utjecajem na tijek i prognozu bolesti. Sama prevalencija hiponatrijemije u SZ kreće se oko 35% iako podaci u literaturi široko variraju i u prvom redu ovise o vrijednostima koje su pojedina istraživanja odredila pri probiru[5]. Bez obzira na potrebu za dodatnim definiranjem navedenog, nedvojbena je visoka zastupljenost niskih vrijednosti Na i snažna negativna prognostička vrijednost u ovih bolesnika[4]. Osobe s manifestnim SZ i hiponatrijemijom imaju značajno povišen rizik od ranog neželjenog ishoda. Iako su hiponatrijemija i prateća smanjena osmolarnost plazme povezani sa sklonošću izazivanja edema mozga i neurološkim smetnjama, čini se da ovo nije vodeća opasnost u bolesnika s SZ. U ovisnosti o težini i brzini nastanka, hiponatrijemija je u ovoj populaciji povezana sa smrtnošću unutar mjesec dana od 5% do 50%. Vrijedno je naglasiti kako se same neurološke manifestacije mogu dodatno potencirati jatrogeno tj. pretjerano brzom korekcijom Na, a ovo dolazi do izraćaja posebno u žena starije dobi te u osoba sa istodobno prisutnom hipokalijemijom[5].

Nedavno objavljena meta-analiza *Rusinaru i sur.* obuhvatila je 22 studije i na ukupnom uzorku od oko 15.000 bolesnika ukazala na negativnu linearnu povezanost vrijednosti Na nižih od 140 mmol/L i smrtnosti unutar 3 godine[6]. Hiponatrijemija je također jasno povezana s dužim trajanjem hospitalizacije, povećanim rizikom rehospitalizacije i drugih značajnih komplikacija, te ukupno višim troškovima liječenja[7,8].

Osnove patofiziologije

Nizak udarni volumen koji je često prisutan u SZ, povezan je sa smanjenom arterijskom stimulacijom baroreceptora koja izravno potiče simpatičku stimulaciju te aktivaciju renin-angiotenzin-aldosteronskog (RAAS) i arginin-vazopresinskog (AVP) sustava. Navedno u kaskadi dovodi do smanjenja bubrežnog protoka, prateće povećane resorpcije Na i vode te razvoja osjećaja žeđi s pojačanim pijenjem, a opisani mehanizmi kumulativnim učincima dovode tako do smanjenja koncentracije natrija u serumu i razvoja klinički značajne hiponatrijemije. U skladu s navedenim, bolesnici sa SZ i hiponatrijemijom imaju više plazmatske koncentracije renina, angiotenzina II, aldosterona, norepinefrina, epinefrina i dopamina nego bolesnici sa SZ i primjerenim razinama Na[9]. Ovim mehanizmima valja dodati i poticaj što ga smanjivanju razina Na mogu dati lijekovi, u prvom redu tiazidski diuretici koji djeluju u distalnim tubulima. Iako oni u većini slučajeva potiču blago dodatno smanjenje razina Na, ono u pojedinim slučajevima može biti značajno. Zanimljivo je kako ovo tija-

77±9.9 years old, whereas mortality during the analyzed hospitalization was 13.6%. The above study pointed to the comparability of the Croatian with the European data[1,3].

The scientific fields that deal with specific aspects of HF and their related areas are very dynamic. Routine clinical practice, despite continuous progress highlights some of the very important areas which are paid sufficient attention and within which we expect only large, randomized, double-blind prospective studies[4]. One of them is hyponatremia in patients with HF being a daily dilemma of clinicians.

Hyponatremia in chronic heart failure

Hyponatremia is defined as the serum sodium concentration lower than 136 mmol/L. It is the most common electrolyte disorder in non-hospitalized and hospitalized patients with HF and according to current insights it is an extremely important clinical problem with a clear impact on the clinical course and prognosis of the diseases. The prevalence of hyponatremia itself in HF is around 35%, although the data in the literature significantly varies and primarily depends on the values that specific trials have determined in the screening[5]. Notwithstanding the need for further definitions of the foregoing, there is no doubt about a high prevalence of low sodium values and a strong negative prognostic value in these patients[4]. People with manifest HF and hyponatremia have a significantly elevated risk of early adverse outcome. Although hyponatremia and associated decreased plasma osmolality are associated with the propensity of causing brain edema and neurologic disorders, this does not seem to be the leading risk in patients with HF. Depending on the weight and speed of occurrence, hyponatremia is in this population associated with mortality within one month from 5% to 50%. It is worth emphasizing that the neurological manifestations may be further aggravated iatrogenically i.e. by overly rapid sodium correction, and this is especially pronounced in elderly women and in persons with concomitant hypokalemia[5].

A recently published meta-analysis *Rusinaru et al.* included 22 studies and on a total sample of around 15,000 patients it pointed out a negative linear correlation between the sodium values lower than 140 mmol/L and mortality within 3 years[6]. Hyponatremia is also clearly associated with a longer length of hospitalization, increased risk of rehospitalization and other significant complications and higher total costs of the treatment[7,8].

Basics of pathophysiology

Low stroke volume, which is often present in HF, is associated with reduced arterial baroreceptor stimulation, which directly stimulates the sympathetic stimulation and activation of the renin-angiotensin-aldosterone (RAAS) and arginine-vasopressin (AVP) system. In the cascade it leads to a reduction in renal flow, accompanied increased sodium and water reabsorption, and the development of a sense of thirst with increased drinking, while the described mechanism lead to a decrease in serum sodium concentration and the development of clinically significant hyponatremia by cumulative effects. Accordingly, the patients with HF and hyponatremia have higher plasma concentrations of renin, angiotensin II, aldosterone, norepinephrine, epinephrine and dopamine than patients with HF and appropriate sodium levels[9]. These mechanisms should also be added by the stimulation that can be given by medications in reducing so-

zidsko poticanje hiponatrijemije vrijedi i na indapamid. Ukoliko se uz tiazidske diuretike kombinira amilorid, rizik od hiponatrijemije dodatno raste zbog njegovog utjecaja na sabirne tubule — retiniranje K i pojačanu ekskreciju Na[10].

Terapijski pristup hiponatrijemiji

Ograničenje dnevnog unosa tekućine na 800-1100 ml jedan je od najjednostavnijih i najjefinijih postupaka liječenja koji međutim definira niska razina suradljivosti. Iako se smanjenje pijenja povezuje sa značajnom redukcijom postojećih i smanjenom incidencijom novih simptoma, njegov utjecaj na dugoročni ishod vrlo je slabo istražen[4].

Značajna akutna hiponatrijemija redovito je povezana s neurološkim simptomima (promjene motorike, kvantitativni i kvalitativni poremećaj svijesti) i zahtijeva neodgodivu parenteralnu korekciju. U navedenim je slučajevima iznimno značajno precizno doziranje hipertonične otopine NaCl s ciljem podizanja serumske razine Na za 1-2 mEq/L na sat do simptomatskog poboljšanja uz napomenu kako ukupna dnevna promjena razine Na u serumu ne bi smjela biti veća od 8m Eq/L[4].

Kod bolesnika s kroničnom hiponatrijemijom bez značajnih neuroloških ispada, upravo je ovaj dnevni limit jedina sigurna odrednica za primjerenu i maksimalno učinkovitu korekciju elektrolitskog statusa. Pri provedbi ovih terapijskih mjera valja također imati na umu da se jatrogeni učinci ne moraju javiti promptno, već je njihova pojava opisana u vremenskom odmaku do 72 sata od terapijskog zahvata. Centralna pontina mijelinoliza, naziv je sindroma koji polimorfnom neurološkom simptomatologijom predstavlja patološki odgovor na neprimjerenu, obično prebrzu terapijsku korekciju serumskog Na[11].

Kako imaju maksimalnu učinkovitost u klirensu čiste vode, diuretici Henleove petlje predstavljaju realnu terapijsku opciju u bolesnika kod kojih je hiperhidracija dio SZ kao razvijenog neuroendokrinog poremećaja. Primjena hipertonične otopine NaCl s istodobnim davanjem visokih doza diuretika Henleove petlje daje značajno povećanje razina serumskog Na i potencijalno poboljšanje u dugoročnom ishodu, a kombinacija inhibitora angiotenzin-konvertaze (ACE) i furosemida, u navedenom se iskazala posebno učinkovitom. U dugoročnoj korekciji hiponatrijemije kao dijela SZ, zanimljivo je kako je dodatak ACE u bolesnika sa SZ na prethodnoj terapiji furosemidom pri dugoročnom praćenju iskazao smanjenje simptomatologije, poboljšanje ishoda, ali i značajno manju hiponatrijemije[12,13].

Obzirom na značaj aktivacije sustava AVP (arginin-vazopresin, vazopresin, argipresin ili antidiuretski hormon) u SZ, danas je razvijena posebna skupina lijekova, antagonista AVP-receptora među kojima se ističu tolvaptan, liksivaptan i konivaptan. Iako se međusobno razlikuju u afinitetu za pojedine podtipove AVP-receptora (V1A, V1B, V2), svima je zajednički pozitivan utjecaj na hiponatrijemiju, te značajno pozitivno djelovanje na količinu izlučenog urina i promjenu tjelesne težine tijekom liječenja dekompenziranog srčanog zatajivanja. Rezultati utjecaja na patofiziološke osnove SZ kao kompleksnog poremećaja, sposobnost djelovanja na remodeling miokarda te dugoročni utjecaj na klinički tijek i ishod za sada se mogu promatrati kroz niz manjih kliničkih studija. Potrebna su dodatna istraživanja za konačno definiranje navedenih pitanja i formulaciju stava o poziciji ove skupine lijekova u ukupnom liječenju SZ[14-16].

dium levels, primarily by thiazide diuretics that exert effect on the distal tubules. Although in most cases they stimulate a slight additional reduction of sodium levels, in some cases it can be significant. If amiloride is combined with thiazide diuretics, the risk of hyponatremia additionally increases due to its impact on the collecting tubules — retinening of K and increased excretion of Na[10].

Therapeutic approach to hyponatremia

Restriction of daily fluid intake to 800-1100 ml is one of the simplest and cheapest methods of the treatment; however which is specified by a low level of compliance. Although the reduction in drinking is associated with a significant reduction of the current and reduced incidence of new symptoms, its impact on the long-term outcome has been very poorly investigated[4].

Significant acute hyponatremia is regularly associated with neurological symptoms (changes in motor skills, quantitative and qualitative disturbance of consciousness) and it requires an immediate parenteral correction. In these cases, a precise dosing of hypertonic saline is very important to increase serum sodium levels to the 1-2 mEq/L per hour until the symptomatic improvement is achieved, noting that the total daily change in serum sodium level should not exceed 8m Eq/L[4].

In patients with chronic hyponatremia without significant neurological deficits, this daily limit is the only certain determinant for appropriate and maximally effective correction of the electrolyte status. When implementing these therapeutic measures, we should also bear in mind that the iatrogenic effects need not occur promptly, but their occurrence is described in the time interval of up to 72 hours from the therapeutic intervention. Central pontine myelinolysis is the name of the syndrome which with polymorphic neurological symptomatology represents a pathological response to therapeutic sodium serum correction[11].

Since they have maximal efficiency in the clean water clearance, loop diuretics represent a realistic therapeutic option in patients with whom hyperhydration is a part of HF as the developed neuroendocrine disorder. The application of hypertonic saline with concomitant administration of high doses of loop diuretics produces a significant increase in serum sodium levels and potential improvement in the long-term outcome, while the combination of the angiotensin converting enzyme (ACE) inhibitors and furosemide proved to be very efficient for the above mentioned. In the long-term correction of hyponatremia as a part of the HF, it is interesting that the addition of ACE in patients with HF in the previous furosemide therapy in long-term follow-up showed a reduction of symptoms, improvement of outcomes, but also significantly lower prevalence of hyponatremia[12,13].

Considering the importance of the activation of AVP (arginine-vasopressin, vasopressin, argipressin or antidiuretic hormone) in HF, special group of drugs, AVP receptor antagonists has been developed today, among which tolvaptan, lixivaptan and conivaptan are to be emphasized. Although differing in affinity for certain subtypes of AVP receptors (V1A, V1B, V2), the thing that all of them have in common is a positive impact on hyponatremia, whereas their effect on the amount of excreted urine and body weight change during the treatment of decompensated heart failure is significant. The results of the impact on the pathophysiological bases of HF as a complex disorder, their ability to have effect on myocardial remodeling and the long-term impact on

Posebnu pažnju u korekciji hiponatrijemije kao dijela sindroma SZ valja posvetiti bolesnicima s hipovolemijskom hiponatrijemijom[4,17]. U njih ne bi trebalo koristiti antagoniste AVP-receptora, kao što pri primjeni ovih lijekova ne bi trebalo provoditi restrikciju unosa tekućine, niti ih primjenjivati pri akutnom ili kroničnom zatajivanju bubrega[3].

Zaključak

Hiponatrijemija je elektrolitski poremećaj s visokom prevalencijom u oboljelih od SZ koji je prepoznat kao biljeg povećanog rizika za razvoj komorbiditeta i uvjerljiv predskazatelj nepovoljnog ishoda. Iako dugoročni učinci primjerene korekcije sniženih serumskih razina Na nisu uvjerljivo dokumentirani, današnja saznanja ipak postavljaju precizne terapijske zahtjeve kod poremećaja serumskog Na u bolesnika sa zatajivanjem srca. Hiponatrijemiju u rutinskom radu u prvom redu ne smijemo previdjeti, već bolesnike u kojih se ona javlja valja identificirati kao pojedince povećanog rizika, a potom djelovati pažljivom korekcijom korištenjem dostupnih terapijskih mjera koje treba individualno prilagoditi svakom pojedinačnom bolesniku uz redovite kontrole laboratorijskih nalaza i trajan klinički nadzor čak i nakon korekcije Na u serumu.

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the clinical course and outcome can now be observed in series of small clinical studies. Additional trials are required to finally define these issues and to take an attitude towards the position of this group of drugs in the overall treatment of HF[14-16].

Particular attention is to be paid to the patients with hypovolemic hyponatremia in the correction of hyponatremia as a part of the HF syndrome[4,17]. AVP receptor antagonists should not be used in these patients, whereas the restriction of fluid intake should not be done when using these drugs and such drugs should not be used in acute and chronic renal failure[3].

Conclusion

Hyponatremia is the electrolyte disorder with a high prevalence in patients suffering from HF which is recognized as a marker of a higher risk for the development of comorbidities and is a convincing predictor of the adverse outcome. Although the long-term effects of an appropriate correction of reduced serum sodium levels have not been convincingly documented, the current insights, nevertheless, impose precise therapeutic requirements in sodium serum disorders in patients with heart failure. Hyponatremia in the routine work should not be overlooked in the first place, but the patients in whom it occurs should be identified as individuals at increased risk, followed by a careful correction by using available therapeutic measures that are to be individually tailored to each individual patient accompanied by doing regular controls of laboratory findings and ongoing clinical monitoring even after the serum sodium level is corrected.

Literature

1. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J. 2012; 33:1787-847.

2. Polić S, Zaputović L, Miličić D, Glavaš D. Croatian Heart Failure Registry: intial results - part II. Liječ Vjesn. 2007;129 Suppl 4:34.

3. Polić S, Glavaš D. Some specific features of identification and treatment of heart failure in the Republic of Croatia. Cardiol Croat. 2011;6(11):286-8.

4. Flilippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. World J Cardiol. 2013;5:317-28.

5. Schrier RW, Sharma S, Shchekochikhin D. Hyponatremia: more than just a marker of disease severity? Nat Rev Nephrol. 2013;9:37-50.

6. Rusinaru D, Tribouilloy C, Berry C, et al. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis: Meta-Analysis Global Group in Chronic heart failure (MAGGIC). Eur J Heart Fail. 2012;14:1139-46.

7. Rich MW, Beckham V, Wittenberg C, Leven CL, Freeland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. N Engl J Med. 1995;333:1190-5.

8. Callahan MA, Do HT, Caplan DW, Yoon-Flannery K. Economic impact of hyonatremia in hspitalized patients: a retrospecive cohort study. Postgrad Med. 2009;121:186-91.

9. Liamis G, Milionis H, Elisaf M. Blood pressure drug therapy and electrolyte disturbances. Int J Clin Pract. 2008;62:1572-80.

10. Hix JK, Silver S, Sterns RH. Diuretic-associated hyponatremia. Semin Nephrol. 2011;31:553-66.

11. Graff-Radford J, Fugate JE, Kaufmann TJ, Mandrekar JN, Rabinstein AA. Clinical and radiologic correlations of central pontine myelinolysis syndrome. Mayo Clin Proc. 2011;86:1063-7.

12. Elisaf M, Theodorou J, Pappas C, Siamopoulos K. Successful treatment of hyponatremia with angiotensin-converting enzyme inhibitors in patients with congestive heart failure. Cardiology. 1995;86:477-80.

13. Wehling M. Morbus diureticus in the elderly: epidemic overuse of a widely applied group of drugs. J Am Med Dir Assoc. 2013;14:437-42.

14. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated dystolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail. 2013;19:390-7.

15. Zmily HD, Khan NS, Daifallah S, Ghali JK. The potential role for lixivaptan in heart failure and hyponatremia. Expert Opin Investig Drugs. 2011;20:831-48.

16. Lehrich RV, Ortiz-Melo DI, Patel MB, Greenberg A. Role of vaptans in the management of hyponatremia. Am J Kidney Dis. 2013;62:364-76.

17. Vujičić B, Ružić A, Zaputović L, Rački S. Određivanje volumnog statusa u akutnom zatajivanju srca i bubrega. Acta Med Croatica, 2012:66.Supp.2:47-55.