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URIC ACID LOWERING TREATMENT OF PATIENTS WITH CHRONIC HEART FAILURE

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ჰიპერურიკემიის მკურნალობა გულის ქრონიკული უკმარისობის მქონე პაციენტებში

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რეზიუმე

ჰიპერურიკემია მნიშვნელოვან თანმხლებ პათოლოგიას წარმოადგენს გულის უკმარისობის მქონე პაციენტებში და ასოცირდება კლინიკური მდგომარეობის გაუარესებასთან და დაავადების ცუდ გამოსავალთან. ჩვენი კვლევის მიზანს წარმოადგენს ალოპურინოლის კლინიკური უსაფრთხოება და ეფექტურობა გულის უკმარისობის და ჰიპერურიკემიის მქონე პაციენტებში. გამოვიკვლიეთ გულის უკმარისობის მქონე 75 პაციენტი, რომელთაც აღენიშნებოდათ ჰიპერურიკემია; 50-მა პაციენტმა (ჯგუფი-1) მიიღო ალოპურინოლი, პაციენტთა უმრავლესობაში საწყისი დოზა იყო 200მგ/დღეში და მცირდებოდა მათი თირკმლის ფუნქციის ან შარდმჟავას დონის მიხედვით. 25 პაციენტი (ჯგუფი-2) – საკონტროლო ჯგუფი. მკურნალობის ხანგძლივობა იყო 6 თვე. პაციენტებს უტარდებოდათ კლინიკურ-ლაბორატორიული კვლევები, დატვირთვის მიმართ ტოლერანტობა ისაზღვრებოდა 6-წუთიანი სიარულის ტესტით.

ალოპურინოლის კლინიკური უსაფრთხოება და ეფექტურობა სარწმუნო იყო გულის უკმარისობის და ჰიპერურიკემიის მქონე პაციენტებში. პაცინეტებს, რომლებიც იღებდნენ ალოპურინოლს, შარდმჟავას დონის შემცირებასთან ერთად აღენიშნებოდათ გულის უკმარისობის მოვლენების შემცირება, ექოკარდიოგრაფიული მონაცემების გაუმჯობესება (განდევნის ფრაქცია, დარტყმითი მოცულობა, მარცხენა პარკუჭის მასის ინდექსი და მოცულობა); ალოპურინოლის გამოყენება (განსაკუთრებით მაღალი დოზებით) ასოცირებული იყო გულ-სისხლძარღვთა სისტემის მოვლენების დაბალ სიხშირესთან, განსხვავებით იმ პაციენტებისგან, რომლებსაც არ ჰქონდათ დანიშნული ალოპურინოლი. პაციენტებს შორის, რომლებსაც აქვთ გულის უკმარისობა და შრატში შარდმჟავას მაღალი დონე, ალოპურინოლის გამოყენება უსაფრთხოა და მტკიცედ უკავშირდება გაუმჯობესებულ შედეგებს. მაშასადამე, ალოპურინოლი შეიძლება განხილულ იყოს, როგორც მნიშვნელოვანი თერაპია, გულის უკმარისობის მქონე პაციენტების გარკვეულ ჯგუფებში.

Hyperuricemia is often accompanied by heart failure (HF), since 47-56% of patients with heart failure has been reported to associate with hyperuricemia [1,2]. In patients with HF, the prevalence of hyperuricemia ranges from 30 to 60% [3]. Ogino et al [2] reported that the prevalence of hyperuricemia increased in line with the NYHA classification and that the level of serum uric acid correlated to insulin resistance and renal function. Hyperuricemia was also an indicator of poor prognosis in HF [4] A meta-analysis of observational studies showed that hyperuricemia was associated with an increased risk of HF and the risk of all-cause mortality and the composite endpoint, respectively [5].

Despite advances in our understanding of its pathology and improvements in its management, heart failure (HF) remains a common disease with high morbidity and mortality and is a significant public health burden on healthcare systems [6,7]. Inflammatory systems and oxidative stress are involved in the development and progression of HF [2–6]. Various oxidative stress markers, such as 8-hydroxy-20-deoxyguanosine (8-OHdG), advanced glycation end products, nicotinamide adenine dinucleotide phosphate oxidase, and xanthine oxidase (XO), were investigated to evaluate HF severity [9,10,12,13]. During purine metabolism, XO catalyses the final two steps (from hypoxanthine to xanthine and xanthine to uric acid [UA]). XO produces oxygen-derived free radicals [14] and is a major source of ROS in human physiology. The final product UA is a non-specific marker for oxidative stress. Excessive activation of XO induces hyperuricemia, and XO activity is upregulated in patients with HF [15]. XO inhibitors are used for treating hyperuricemia and have been shown to improve myocardial energetic efficiency. Allopurinol, an inhibitor of xanthine oxidase, may be a novel therapeutic agent for HF. Allopurinol reduces uric acid levels, prevents acute gout, and acts as an antioxidant, which could be beneficial among HF patients [16].

In animal models of HF, allopurinol has been shown to improve cardiac function [17] reduce left ventricular dimensions [18-19] and reduce mortality [20].

The purpose of the present study was to evaluate a UA-lowering and prognostic effects of allopurinol in patients with chronic HF and hyperuricemia.

Material and Methods

We studied 75 patients with HF and increased UA levels, who have been admitted to hospital. All patients aged 18 years and older were eligible, provided a left ventricular ejection fraction of 45% or less was documented on echocardiography during the enrolment visit and signs and symptoms of chronic heart failure were present. All patients gave written informed consent. All patients with clinicaл of acute infection, autoimmune disorders, severe renal disease (an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m2), hepatic disease and with suspected malignancy were excluded from the present study.

Patient baseline assessment included a standardized HF history regarding HF aetiology (classified as ischemic or non-ischemic) and co-morbidities. All patients underwent a standardized clinical evaluation, including physical examination, determination of NYHA class, determination of body weight. Blood samples were drawn from an antecubital vein in the morning for the assessment of a full blood count and clinical chemistry.

Renal dysfunction was diagnosed if the glomerular filtration rate (eGFR) was below 60 ml/min/1.73 m^2, diabetes mellitus, if patients reported a history of diabetes or were on anti-diabetic drugs, and chronic obstructive pulmonary disease (COPD), if patients were on anti-obstructive pharmacotherapy or reported that COPD had been previously diagnosed. Hyperuricemia was defined according to World Health Organization criteria as uric acid level >5.7 mg/dl in women and >7 mg/dl in men. Echocardiographic parameters included interventricular septum thickness (IVS), posterior wall thickness (PW), left ventricular dimension (LVEDd), left ventricular diastolic function (LVDF), left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF). The LVEF vas calculated using a Simpson's method. Assessment of exercise capacity was performed by a 6-min walk test. Exercise capacity was categorized as reduced, if patients performed below the median walking distance during the 6-min walk test. Quality of life was studied using the Minnesota Quality of Life Questionnaire.

Patients were divided in to two groups: 50 patients (group 1) received allopurinol. The initial dose of in most patients was 200 mg/day and it was reduced according to their renal function or UA level. 25 patients (group 2) – controlled group. Treatment duration was 6 months.

Statistical analyses

Continuous variables are given as means with standard deviations. Non-normally distributed variables (serum uric acid, serum creatinine, serum C-reactive protein) were long-transformed to achieve normal distribution before analysis. Student's *t* test was used to test for between-group differences. *P* values of <0.05 were considered statistically significant.

Results: Baseline characteristics are given in **Table 1**.

Characteristics	Group 1 (N=50)	Group 2 (N=25)
NYHA class II	3 (6%)	2 (8%)
NYHA class III	39 (78%)	20 (80%)
NYHA class IV	7 (14%)	9 (36 %)
LVEF (%)	38.7±2.7	36.4±2.5
Serum uric acid	6.2±1.8	8.7±1.5
Serum creatinine (μmol/L)	106.8±17.6	104.6±15.8
eGFR (ml/min 1.73m^2)	48.7±3.2	49.5±4.6
NT-proBNP (pg/ml)	710±10.9	717±9.7
6-MWT (m)	211.8±10.7	224.4±6.8
CRP (mg/dl)	4.0±1.2	4.9±1.1
LV mass index g /m^2	110.8± 20.5	120.7± 20.4
LV end-diastolic dimension, mm	44.7 ± 8.7	47.7±9.4
Interventricular septum thickness (IVS). mm	10.49±2.9	10.93±1.64
Posterior wall thickness, mm	11.3± 2.2	11.4 ± 3.7
QoL	56.4±0.9	54.6±0.6

Mean age of patients was 73.2±9.1 years, 55% were men. Coronary artery disease was the primary aetiology of HF in 73% of patients. The median level of NT-proBNP at the time of enrolment was 710-717 μmol/L and the median LVEF was 38-36% in both groups.

At the end of 3 months medical history was again recorded, patients underwent a physical examination, assessed laboratory tests, a 6-minute walk test, and completed quality of life questionnaire.

Repeated studies after 3 months showed the following results:

1. Uric acid treatment improved the echocardiographic parameters: LV mass index decreased from 118.7±5.2 to 110.8±20.5 vs 112.6±3.2 in group 2. LV end-diastolic dimension, decreased – from 48.8±7.6 to 44.7±8.7 vs 46.4±6.7 in group 2.
2. Uric acid correction reduced NT-proBNP from 710±10.9 to 235±5.2 vs 535±5.6 in group 2. Also improved renal function: serum creatinine from 106.8±17.6 to 88.7±9.1 vs 91.8±4.1 ($p<0.1$) and eGFR from 48.7±3.2 to 54.1±4.1 vs 52.7±5.1 in group 2 ($p<0.5$).
3. Improved NYHA functional class: the number of patients with NYHA II increased from 3 (6%) to 25 (55%) vs 2 (9 %) to 10 (38.6%) in group 2. LVEF increased from 38.2±2.9 to 42.1±1.9 vs 40.1±3.5 to 42.1±2.2 ($p<0.5$). Increased the 6-minute walk distance from 211.8±10.7 to 289±9.1 vs 224.4±6.8 to 247±5.3 in group 2 ($p<0.5$). Improves QoL from 56.4±0.9 to 37.5±0.3 vs 54.6±0.6 to 49.5±1.3 in group 2 ($p<0.05$).

Discussion

There are different recommendations for pharmacological treatment of asymptomatic hyperuricemic patients between Western countries and Asian country Japan. The European and American guidelines 60 do not recommend use of uric acid lowering agents (ULAs) for asymptomatic hyperuricemia to prevent gout, renal dysfunction and cardiovascular events. In contrast, Japanese guideline recommend use of ULAs for asymptomatic hyperuricemia [21].

In the present study we demonstrated the clinical safety and efficacy of allopurinol in patients with HF and hyperuricemia. Several studies have reported the association between hyperuricemia and various cardiovascular diseases. Large-scale studies have revealed that the serum UA level was an independent predictor of mortality in patients with acute myocardial infarction. In addition, an elevated UA level is associated with low LVEF, stroke volume, and cardiac output and cardiac remodelling [22] and is a risk factor for atrial fibrillation. These hemodynamic and electrophysiological influences on the heart lead to HF, and several studies have reported that a high UA level is a strong and independent predictor of mortality in patients with not only mild to moderate chronic HF [23] but also acute HF [24] Allopurinol is widely used to treat gout or hyperuricemia, and a number of clinical studies have reported the effects of allopurinol in patients with cardiovascular disease, including HF. In a large-scale clinical study targeting more than 2000 older adult patients with hypertension, allopurinol use was associated with lower rates of cardiovascular events, particularly at higher doses, compared with patients without allopurinol.

Conclusion

Among patients with HF and elevated serum uric acid levels, allopurinol use was safe and strongly associated with improved outcomes. So, allopurinol may be an important therapeutic consideration in certain groups of patients with HF.

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ЛЕЧЕНИЕ ГИПЕРУРИКЕМИИ У БОЛЬНИХ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ

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РЕЗЮМЕ

Гирепурикемия (ГУ) - важные и распространённые коморбидность, которые часто сосуществуют у пациентов с сердечной недостаточностью (СН) и независимо связаны с плохим клиническим статусом и худшими исходами. Целью наших исследований было клиническая безопасность и эффективность аллопуринола у больных с сердечной недостаточностью и гирерурикемией. Обследовали 75 больных с сердечной недостаточностью, у которых было ГУ; 50 пациентов (группа 1) получили аллопуринол, у большинства пациентов начальная доза составляла 200 мг. в сут и уменьшалась в зависимости от их функции почек или уровня мочевой кислоты. 25 пациентов (группа-2) были включены в контрольную группу. Продолжительность лечения составила 6 месяцев. Больным проводили клинико-лабораторные исследования, переносимость нагрузки определяли с помощью 6 - минутной пробы ходьбы.

Клиническая безопасность и эффективность аллопуринола были достоверными у пациентов с сердечной недостаточностью и гиперурикемией. У больных, получавших аллопуринол, при снижении уровня мочевой кислоты отмечалось снижение частоты сердечной недостаточности, улучшение эхо кардиографических данных (фракция выброса, ударный объем, индекс массы левого желудочка); Применение аллопуринола (особенно в высоких дозах) ассоциировалось с меньшей частотой сердечно-сосудистых событий, в отличие от пациентов которым аллопуринол не назначался. У пациентов с сердечной недостаточностью и высоким уровнем мочевой кислоты в сыворотке использование аллопуринола было безопасным и ассоциировалось с улучшением исходов. Таким образом, аллопуринол можно рассматривать как важным терапевтическим фактором для определённых групп пациентов с СН.

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SUMMARY

Hyperuricemia (HU) is important and common comorbidity that often coexist in patients with heart failure (HF). High values of serum uric acid are associated to severe heart failure. The purpose of the present study was to evaluate a UA-lowering and prognostic effects of allopurinol in patients with chronic HF and hyperuricemia.

We studied 75 patients with HF and increased UA levels, who have been admitted to hospital. All patients aged 18 years and older were eligible, provided a left ventricular ejection fraction of 45% or less was documented on echocardiography during the enrolment visit and signs and symptoms of chronic heart failure were present. Patient baseline assessment included a standardized HF history regarding HF aetiology (classified as ischemic or non-ischemic) and co-morbidities. All patients underwent a standardized clinical evaluation, including physical examination, determination of NYHA class, determination of body weight. Blood samples were drawn from an antecubital vein in the morning for the assessment of a full blood count and clinical chemistry. Patients were divided in to two groups: 50 patients (group 1) received allopurinol. The initial dose of in most patients was 200 mg/day and it was reduced according to their renal function or UA level. 25 patients (group 2) – controlled group. Treatment duration was 6 months.

Repeated studies after 3 months showed the following results: Uric acid treatment improved the echocardiographic parameters (LVEF, LV mass index, IVS, PW, stroke volume), reduced NT- proBNP, improved renal function, Improved NYHA functional class;

6-minute walking test distance improved significantly in the UA- treatment group and quality of life. The QoL parameters that was improved included reduced physical limitation, improved mobility, selfcare, increased daily activities and reduced discomfort, anxiety and depression.

Among patients with HF and elevated serum uric acid levels, allopurinol use was safe and strongly associated with improved outcomes.

Keywords: Serum uric acid, Hyperuricemia, Exercise capacity, Heart failure, Prevalence