

Prednisone in Uric Acid Lowering in Symptomatic Heart Failure Patients with Hyperuricemia — The PUSH-PATH3 Study

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ABSTRACT. Objective. To determine the safety and efficacy of prednisone in patients with symptomatic heart failure (HF) and hyperuricemia.

Methods. Prednisone therapy was administered for a short time to 191 symptomatic HF patients with hyperuricemia (serum uric acid > 7 mg/dl).

Results. Prednisone significantly reduced serum uric acid by 2.99 mg/dl ($p < 0.01$) and serum creatinine by 0.17 mg/dl ($p < 0.01$). These favorable effects were associated with a remarkable increase in urine output, improvement in renal function, and improvement in clinical status.

Conclusion. Prednisone can be used safely in symptomatic HF patients with hyperuricemia. (First Release March 15 2015; J Rheumatol 2015;42:866–9; doi:10.3899/jrheum.141037)

Key Indexing Terms:

HEART FAILURE HYPERURICEMIA PREDNISONE RENAL FUNCTION

Growing evidence shows that inflammatory activation is an important pathway in disease progression in heart failure (HF), and raised plasma levels of cytokines predict worse prognosis in patients with HF¹. Inflammatory activation also plays an important role in cardiorenal syndrome¹. Tubulointerstitial inflammation and oxidative stress enhance local angiotensin II generation and compromise dopamine D1 receptor, leading to proximal and distal tubule sodium reabsorption². Uric acid is a marker of impaired renal function in HF^{3,4}. Therefore, patients with HF frequently present with hyperuricemia. Moreover, gout, as an inflammatory disease, is not uncommon in this population. But chronic drug interaction between HF therapy and pharmacological agents used for hyperuricemia and gout is a challenging problem⁵.

We found that prednisone, a commonly used antiinflammatory agent, could not only lower serum uric acid (SUA) but also improve renal responsiveness to diuretics in patients with HF, in a randomized clinical trial⁶ with a small sample.

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To further determine its safety and efficacy when used in the short term (< 2 weeks), we retrospectively reviewed data from 191 symptomatic HF patients with hyperuricemia treated with prednisone and assessed its effects in SUA lowering and renal function improvement.

MATERIALS AND METHODS

Patients. Our hospital committee on medical research ethics approved the study protocol. This study complied with the Declaration of Helsinki. Inclusion criteria were adult symptomatic HF patients with New York Heart Association function Class III-IV, fasting SUA > 7.0 mg/dl. Patients with active myocarditis and patients who were taking xanthine oxidase inhibitors were excluded. From January 2010 to November 2013, 191 symptomatic HF patients with hyperuricemia were enrolled. Table 1 lists the demographic characteristics of the patients at baseline.

Methods. Patients were treated with prednisone as bridge therapy between decompensated HF to compensated HF because prednisone can improve renal function and renal responsiveness to diuretic therapy^{6,7,8,9,10}. The dose of prednisone was based on clinical status judged by caregiving physicians, and median dose was 50 mg/day (interquartile range 30 mg–60 mg). Daily urine output was recorded. Concentrations of SUA and serum creatinine (SCr) were recorded at baseline, timepoint 1 (5th to 7th day after treatment initiation), and timepoint 2 (10th to 14th day after treatment initiation).

Statistical analysis. Continuous variables are expressed as mean \pm SD, unless stated otherwise. We used 1-way repeated measures ANOVA to test the treatment effects. Paired t-test was used to analyze differences in variables before and after treatment. Mixed linear models for repeated measures data with time varying covariate was used to determine the correlation of SCr and SUA. All statistical tests were performed with 2-sided alternatives and with a type I error of 0.05 and the use of SPSS software (version 16.0).

RESULTS

Effect of prednisone on SUA levels. Prednisone was given to 191 symptomatic HF patients with hyperuricemia. At

Table 1. Clinical characteristics of 191 patients with symptomatic HF and hyperuricemia. Data are expressed as mean \pm SD or n (%).

Variables	Value
Age, yrs	52.1 \pm 16.1
Male	149 (78.0)
HTN	32 (16.8)
AF	49 (25.7)
DM	30 (15.7)
Etiology of HF	
CAD	34 (17.8)
IDC	132 (69.1)
VHD	16 (8.4)
Others	9 (4.7)
NYHA functional class	
III	28 (15.7)
IV	163 (85.3)
LVEF \geq 45%	34 (17.8)
Laboratory test	
SUA, mg/dl	10.39 \pm 2.51
SCr, mg/dl	1.17 \pm 0.38
Medication	
Furosemide	179 (93.7)
HCTZ	110 (57.6)
Spironolactone	159 (83.2)
Digitalis	76 (39.8)
ACE I	118 (61.8)
ARB	14 (7.3)
β -blocker	148 (77.5)

HTN: hypertension; AF: atrial fibrillation/flutter; DM: diabetes mellitus; CAD: coronary artery disease; IDC: idiopathic dilated cardiomyopathy; VHD: valvular heart disease; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; SUA: serum uric acid; SCr: serum creatinine; HCTZ: hydrochlorothiazide; ACE I: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

timepoint 1, SUA was measured for 165 patients, and at timepoint 2, for 168 patients. Only 3 patients did not have data at either timepoint 1 or timepoint 2, because of 2 early deaths and 1 patient lost to followup. Prednisone reduced SUA concentration in symptomatic HF patients with hyperuricemia by 1.69 mg/dl at timepoint 1 and 2.99 mg/dl at timepoint 2 compared with baseline (Table 2).

Effect of prednisone on renal function. It is noteworthy that the reduction of SUA was accompanied by dramatic SCr reduction (Table 2). Consistent with a previous finding, there

Table 2. The effects of prednisone on SUA level and clinical improvement.

	Baseline, n = 191	Timepoint 1, n = 165	CFB at Timepoint 1, n = 165	Timepoint 2, n = 168	CFB at Timepoint 2, n = 168
SUA, mg/dl	10.39 \pm 2.51	8.50 \pm 2.44*	-1.69 \pm 2.43#	7.48 \pm 2.41*	-2.99 \pm 2.73#
SCr, mg/dl	1.17 \pm 0.38	1.06 \pm 0.39*	-0.08 \pm 0.31#	1.01 \pm 0.35*	-0.17 \pm 0.26#
Serum potassium, mmol/l	4.15 \pm 0.70	4.21 \pm 0.73	-0.07 \pm 0.95	4.21 \pm 0.57	-0.08 \pm 0.87
Serum sodium, mmol/l	135.03 \pm 5.51	135.52 \pm 4.87	-0.77 \pm 4.83	135.42 \pm 5.35	0.07 \pm 6.16
NYHA functional class	3.85 \pm 0.35	3.06 \pm 0.58*	-0.80 \pm 0.50#	2.53 \pm 0.70*	-1.33 \pm 0.71#
Body weight, kg	71.02 \pm 14.76	68.75 \pm 13.56*	-2.27 \pm 3.88#	67.88 \pm 12.82*	-3.30 \pm 4.46#

* p < 0.01 compared with baseline; # p < 0.01. SUA: serum uric acid; CFB: change from baseline; SCr: serum creatinine; NYHA: New York Heart Association.

was a clear correlation between SCr and SUA (Figure 1A). Adding prednisone to standard HF treatment did not cause fluid retention, and the hematocrit was increased from 36.5 \pm 8.3% to 38.5 \pm 7.9% after prednisone initiation (n = 47). Rather, it induced a slow but more potent diuresis (Figure 1B) without increasing the dose of furosemide (41.6 \pm 33.5 mg/day at baseline compared with 37.7 \pm 29.1 mg/day at the last time when the SUA was recorded).

Safety and tolerability. There were 8 deaths (4.2%) within 30 days in patients with symptomatic HF and hyperuricemia. Clinical status was improved in 172 patients (90%), remained unchanged in 4 patients (2.1%), and deteriorated in 7 patients (3.7%). Twenty-one out of 165 patients (12.7%) at timepoint 1 and 10 out of 168 patients (6.0%) at timepoint 2 had transient hypokalemia. All patients with diabetes mellitus had transient severe hyperglycemia, but it subsided when doses of insulin were adjusted. There was no acute gout attack recorded during prednisone treatment. Overall, prednisone was well tolerated in the symptomatic HF patients with hyperuricemia.

DISCUSSION

Prednisone resulted in a striking SUA reduction, as well as a significant improvement in renal function in the symptomatic HF patients with hyperuricemia. These favorable effects induced by prednisone were accompanied by a dramatic increase in urine output and an improvement in clinical status. We used prednisone as an add-on therapy. Therefore, our data did not support the use of glucocorticoids (GC) in lieu of diuretics.

Uric acid is the final product of purine degradation with xanthine oxidase, an enzyme implicated as a mechanistic participant in oxidant stress. About 70% of the uric acid is excreted through the kidneys and 30% through the gastrointestinal tract¹¹. Hyperuricemia results from either over-production or reduced excretion of uric acid, or both. In decompensated HF, glomerular filtration and tubular excretion of UA are impaired as a result of venous congestion^{3,12}. The level of SCr reduction was well correlated with the level of SUA, indicating renal function improvement contributed much to SUA lowering in HF. Additionally, gout is a common comorbidity in patients with HF⁵. However,

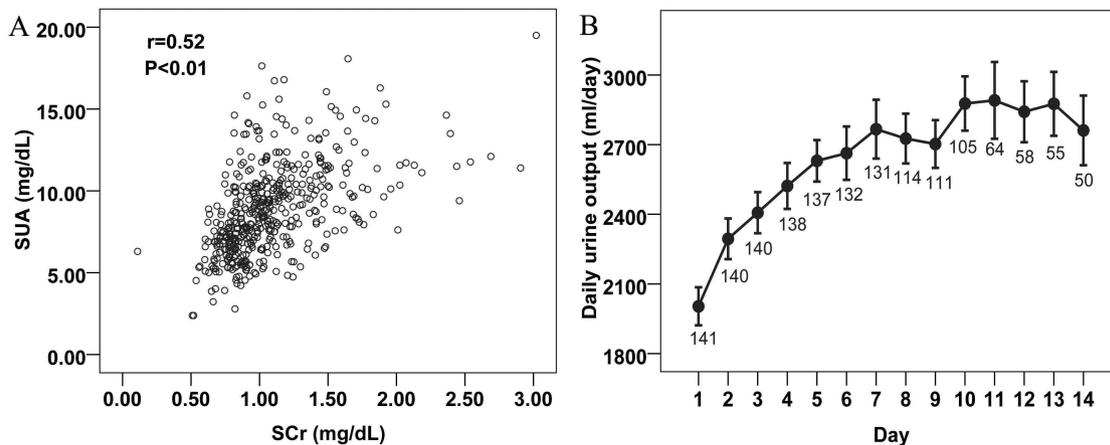


Figure 1. Correlation between SUA and SCr, and potentiating diuretic effect of prednisone on symptomatic HF patients with hyperuricemia. A. Correlation between SUA and SCr (Pearson correlation); $SUA = 3.03 + 5.60 \times SCr$ (Equation obtained by mixed linear models with time varying covariate; intercept, $p < 0.01$; SCr, $p < 0.01$). B. Effect of prednisone on daily urine output; annotations below the markers are no. patients who had urine output recorded. Data in panel B were expressed as mean and standard error.

drug options are restricted. HF therapy and pharmacological agents used for gout exclude nonsteroidal antiinflammatory drugs because of their nephrotoxicity. Therefore, a drug that can lower UA and treat gouty arthritis as well as induce potent diuresis will be ideal in this setting.

It is noteworthy that renal-protective effects induced by prednisone were accompanied by a potent diuresis in symptomatic patients with systolic HF. Coupled with the newly emerging evidence that oral prednisolone and naproxen are equally effective in the initial treatment of gouty arthritis¹³, prednisone might be the drug of choice for HF patients with hyperuricemia or gouty arthritis.

The role of GC in HF has changed. Using corticosteroids to treat HF was first reported in the 1950s⁷. With the advent of a potent diuretic such as furosemide, intractable cardiac edema became less intractable and GC vanished from the treatment of HF^{7,8}. However, data show that GC can successfully overcome diuretic resistance in the patients who fail to respond to loop or combined diuretic therapy^{7,14}. We demonstrated that GC could improve renal responsiveness to atrial natriuretic peptide by upregulating natriuretic peptide receptor-A expression in the inner medullary collecting duct cells both *in vivo* and *in vitro*, and produce a potent diuretic action in decompensated HF¹⁵. Moreover, there is evidence demonstrating that GC can dilate renal vasculature and increase renal plasma flow and glomerular filtration rate, a process that involves multiple pathways such as increased renal prostaglandin, nitric oxide, and dopamine production^{7,8}.

Inflammation and cardiorenal interaction in HF. In HF, several proinflammatory cytokines in response to neurohormones and sympathetic activation can be detected at high levels in the tissues and blood¹. Inflammatory response, in turn, may further worsen the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system,

and cause renal injury¹. Therefore, the antiinflammatory role of the glucocorticoid in attenuating diuretic resistance in HF cannot be excluded and merits further investigation.

The safety of corticosteroid treatment in patients is a major concern. Longterm or short-term corticosteroid use poses a high cardiovascular risk in the general population. However, HF patients with hyperuricemia have a 2-year mortality rate of about 40%^{16,17}. For such a high-risk population, prednisone might have a role in improving their longterm survival⁸.

Study limitations. The major limitation of our study was an inability to exclude contribution of placebo effects because of the lack of a control group. Second, the effect of prednisone on longterm mortality was also not evaluated. Third, there is still much to be done before this experimental approach to treat HF could become a common practice; efficacy and safety must be established. A dose-comparison study to determine the optimal dose of prednisone is needed, as are large-scale randomized controlled trials to establish its efficacy and safety. Fourth, the mechanism of UA-lowering effect induced by prednisone is speculative¹⁸. Preliminary data suggest corticosteroids might increase renal UA excretion^{6,19}. But this hypothesis is to be examined in a current ongoing trial. Finally, the urate-lowering effect induced by prednisone might, theoretically, trigger acute flares. However, as a potent antiinflammatory agent, systematic prednisone administration is recommended by international guidelines to prevent acute gout flares when initiating urate-lowering therapy in patients with chronic gout²⁰. Whether prednisone could trigger acute gout flare still needs further investigation in patients with symptomatic HF.

Prednisone can be safely used by symptomatic HF patients with hyperuricemia or acute gouty arthritis in the short term without worsening HF. Further large randomized controlled trials are warranted to corroborate these results.

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