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Febuxostat combined with hydration for the prevention of contrast-induced nephropathy in hyperuricemia patients undergoing percutaneous coronary intervention
A CONSORT-compliant randomized controlled trial

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Abstract

Background: To assess the efficacy of febuxostat combined with hydration on contrast-induced nephropathy (CIN) in coronary heart disease patients with hyperuricemia undergoing percutaneous coronary intervention (PCI).

Methods: Patients with hyperuricemia who underwent PCI were randomly assigned to 2 groups. The control group was given hydration only, and the febuxostat group received febuxostat 40 mg daily before administration of contrast agent and hydration. The primary endpoint of the study was the incidence of CIN, defined as an increase in baseline serum creatinine concentration by 25% at 2 days after contrast media administration, and variations in the serum levels of creatinine, neutrophil gelatinase-associated lipocalin, uric acid, and estimated glomerular filtration rate were compared.

Results: A total of 202 patients with hyperuricemia were randomly assigned to either the febuxostat group (n = 100) or the control group (n = 102). The baseline characteristics of the 2 groups were similar. The incidence of CIN was 6.0% (6/100) in the febuxostat group and 14.71% (15/102) in the control group.

  The levels of neutrophil gelatinase-associated lipocalin at 6-hour and serum creatinine and uric acid at 48-hour in the febuxostat combined hydration group were lower than those in the control group after surgery, and the level of estimated glomerular filtration rate was higher than that in the control group (all $P < .05$). Multivariate logistic regression analysis revealed that febuxostat was an independent predictor of CIN.

Conclusion: Our study demonstrated that prophylactic treatment with febuxostat combined with hydration can reduce the incidence of CIN in patients with coronary heart disease and hyperuricemia after PCI.

Abbreviations: CIN = contrast-induced nephropathy, eGFR = estimated glomerular filtration rate, NGAL = neutrophil gelatinase-associated lipocalin, PCI = percutaneous coronary intervention.

Keywords: contrast-induced nephropathy, coronary heart disease, febuxostat, hyperuricemia

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1. Introduction

Contrast-induced nephropathy (CIN) remains a common and serious adverse complication following cardiac catheterization and is associated with an increased risk of serious adverse outcomes. It prolongs hospitalization, increases health care costs, and is a powerful predictor of unfavorable early and long-term outcome.[1–3] Hence, prevention of CIN is important, particularly in high-risk patients, such as patients with pre-existing renal disease, hyperuricemia, diabetes mellitus, congestive heart failure, or undergoing arterial and interventional contrast procedures with a larger amount of contrast media.[4,5] Currently, 2 precautions have been recommended for reducing CIN, such as reducing the amount of contrast media as much as possible, using optimal hydration before and immediately after the procedure.

  The pathogenesis of CIN is complex and not completely understood, but 2 aspects of its pathophysiologic mechanism have been suggested: the direct cytotoxicity of contrast media and tissue hypoxia due to altered renal hemodynamics and increased osmotic load.[6–8] Reactive oxygen species play a pivotal role in CIN.[9] Serum uric acid is the final product of purine metabolism and is related to various diseases, such as metabolic syndrome, cardiovascular disease, diabetes mellitus, and renal disease.[10]

The protective effects of febuxostat observed by ameliorating oxidative stress have been demonstrated in a diabetic rat model.[11] Studies showing the beneficial effects of febuxostat in CIN are lacking. In the present study, we sought to demonstrate the efficacy of prophylactic administration of febuxostat for CIN prevention in a prospective, randomized trial in patients with hyperuricemia undergoing planned percutaneous coronary intervention (PCI).

2. Methods

2.1. Ethical approval of the study protocol

The Ethics Review Board of The First Affiliated Hospital of Henan University approved the study protocol. Informed consent was obtained from all patients.

2.2. Study population

Patients scheduled for an elective PCI admitted to the Department of Cardiology, The First Affiliated Hospital of Henan University between January 2019 and December 2020 were eligible to participate if they were at least 18 years of age, with serum uric acid levels ≥420 µmol/L. Exclusion criteria; contraindications to the class of drugs under study; use of febuxostat or allopurinol before elective PCI; acute myocardial infarction requiring primary coronary intervention; severe renal insufficiency (defined as estimated glomerular filtration rate [eGFR] <30 mL/min; eGFR = [140−age] × weight (kg)/[0.818 × Scr (µmol/L)] (× 0.85 if female), heart failure with left ventricular ejection fraction <30% or cardiogenic shock, acute renal failure, recent exposure to contrast agent within 2 weeks, hepatic failure, concomitant use of nicorandiol or trimetazidine, hemodialysis.

2.3. Study protocol

Eligible patients were randomly assigned to receive febuxostat (40 mg, p.o., 1 day before and 3 days after the operation) and intravenous hydration (1 mg/kg/h saline for 12 hours postcontrast), or intravenous hydration alone (1 mg/kg/h saline for 12 hours postcontrast). Computer-generated random numbers determined randomization. Hydration is recognized as the gold standard prophylactic measure for preventing CIN, and all recruited patients were encouraged to drink as much water as if they were thirsty. Drug delivery and hydration were conducted by the nurses. All patients were treated with a nonionic, low-osmolarity iodinated contrast medium during the procedure.

2.4. Laboratory parameters

Blood samples were collected to measure the baseline values of serum creatinine, neutrophil gelatinase-associated lipocalin (NGAL), and uric acid levels in all patients before administration of the contrast agent. The postoperative levels of serum creatinine at 48 hours, serum NGAL at 6 hours, eGFR = (140−age) × weight (kg)/[0.818 × Scr (µmol/L)] (× 0.85 if female).

2.5. Study end points and definitions

The primary endpoint of the study was the incidence of CIN, defined as an absolute increase in serum creatinine by 0.5 mg/dL (44.2 mmol/L) or a relative 25% increase from baseline within 48

hours after contrast media administration.[12] Additionally, variations in the serum levels of creatinine, NGAL, uric acid, and eGFR were compared.

2.6. Statistical analyses

Continuous variables with a normal distribution were presented as mean ± standard deviation. The unpaired Student t test was performed to determine the differences between the mean values for continuous variables, if appropriate. Serum reatinine, NGAL, eGFR, and uric acid concentrations were normally distributed; categorical variables were analyzed using the chi-square test as appropriate. *Statistical significance was set at $P < .05$.* Investigators used multivariate logistic regression analysis as a means to exclude the presence of confounding factors (contrast volume, hypertension, diabetes, febuxostat, age). CIN was used as the dependent variable to exclude confounding factors, and multivariate logistic regression analyses were performed to analyze the protective factors for CIN after PCI, and odds ratios and corresponding 95% confidence intervals were calculated simultaneously. The rate of CIN was approximately 15% in the control group. Treatment with febuxostat has been hypothesized to reduce the incidence to 5%. Accordingly, at least 65 patients from each group were needed based on a beta error level of 0.10 and an α error level of 0.05. Data were analyzed using SPSS software version 20.0 (version 20.0; SPSS, Inc., Chicago, IL), and a 2-sided $P < .05$, was considered significant.

3. Results

3.1. Baseline characteristics

We enrolled 210 eligible patients in the trial and randomized them to either febuxostat or control group; 8 patients did not undergo the scheduled PCI and did not receive any study medication. A flowchart of the study flowchart is shown in Figure 1. Hence, 100 and 102 patients were allocated to the febuxostat and control groups, respectively, and the baseline demographic, clinical, and procedural characteristics were well balanced between the 2 groups (Table 1). No significant differences were found between the 2 groups regarding age, sex, weight, left ventricular ejection fraction, past medical and medication history, and smoking status.

3.2. Incidence of CIN, NGAL level, and multivariate logistic regression analysis

According to the statistical analysis, CIN occurred in 21 patients (10.4%), including 6 patients (6%) in the febuxostat group and 15 patients (14.71%) in the control group ($P < .05$) (Table 2). The baseline level of NGAL was 95.82 ± 19.73 ng/mL in the febuxostat group and 94.31 ± 18.32 ng/mL in the control group ($P = .43$). After PCI, the level of NGAL in the febuxostat group was increased to 106.25 ± 17.92 ng/mL in febuxostat group and 112.76 ± 19.12 ng/mL in the control group was statistically significant (Table 3). In each group, the increase in NGAL level was significant when compared with their baseline values (95.82 ± 19.73 ng/mL; $P < .05$ in the febuxostat group, and 94.31 ± 18.32 ng/mL; $P < .05$, in the control group) (Table 3).

Multivariate logistic regression analysis was conducted to identify factors related to the development of CIN, such as contrast volume, diabetes, hypertension, age, and febuxostat
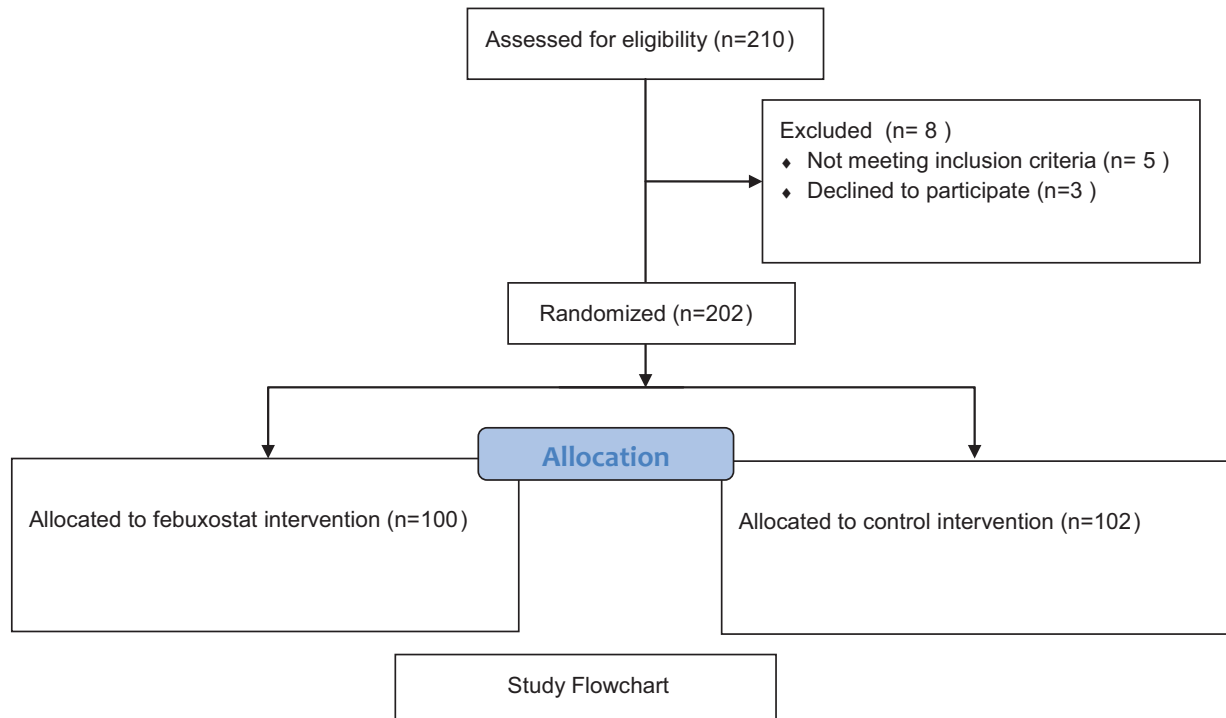
Figure 1. Study flowchart.

(Table 4). CIN was used as the dependent variable to exclude confounding factors (contrast volume, hypertension, diabetes, febuxostat, and age). Multivariate logistic regression analysis revealed that febuxostat was associated with a reduction in CIN compared to the control group (odds ratio = 0.918, 95% confidence interval = 0.767–0.982, P = .039) (Table 4).

3.3. Changes in serum creatinine, uric acid, and eGFR

The baseline serum reatinine levels were $81.42 \pm 17.33\,\mu$mol/L in the febuxostat group and were $83.37 \pm 19.12\,\mu$mol/L in the control group (P = .69). After the procedure, serum reatinine level increased to $85.13 \pm 18.53\,\mu$mol/L in febuxostat group and $89.36 \pm 19.07\,\mu$mol/L in the control group, which was statistically significant (P = .032). In each group, the increase in serum reatinine level was significant when compared with their baseline values ($85.13 \pm 18.53\,\mu$mol/L; $P < .05$) in the febuxostat group, and $89.36 \pm 19.07\,\mu$mol/L; $P < .05$ in the control group) (Table 3).

The baseline uric acid levels were $461.52 \pm 51.26\,\mu$mol/L in the febuxostat group and were $457.36 \pm 53.52\,\mu$mol/L in the control group (P = .83). After the procedure, uric acid level decreased to

Table 1

Baseline characteristics.

Parameters	Febuxostat group (n = 100)	Control group (n = 102)	t or χ^2	P
Age (yr)	66.46 ± 5.84	67.32 ± 5.40	−1.09	.28
Male (%)	60 (60)	63 (61.76)	0.066	.80
Hypertension (%)	62 (62)	66 (52.63)	0.16	.69
Diabetes mellitus (%)	24 (24)	30 (29.41)	0.76	.39
Total cholesterol (mmol/L)	3.68 ± 0.77	3.58 ± 0.88	0.88	.38
Smoking (%)	54 (54)	59 (57.84)	0.30	.58
Body mass index (kg/m^2)	26.90 ± 2.58	27.24 ± 2.64	−0.92	.36
LVEF (%)	49.17 ± 5.07	50.63 ± 6.00	−1.86	.064
Previous PCI (%)	21 (21)	19 (18.63)	0.18	.67
Medications	−	−	−	−
B-blockers (%)	80 (80)	84 (82.35)	0.18	.67
ACEI/ARB (%)	60 (60)	69 (67.65)	1.28	.26
Calcium antagonists (%)	23 (23)	26 (25.50)	0.17	.68
Statins (%)	93 (93)	92 (90.20)	0.52	.47
Diuretics (%)	11 (11)	14 (13.73)	0.35	.56
Contrast volume (mL)	187.84 ± 28.49	182.63 ± 26.83	−0.24	.83
GP llb/llla inhibitors (%)	22 (22)	20 (19.61)	0.18	.68

Variables are summarized mean (SD).

ACEI = angiotensin-covering enzyme inhibitor, ARB = angiotensin receptor blocker, LVEF = left ventricular ejection fraction, PCI = percutaneous coronary intervention, SD = standard deviation.

Table 2

Comparison of the incidence of CIN in control group and febuxostat group after PCI n (%).

Group	Total cases	Incidence of CIN
Control group	102	15 (14.71)
Febuxostat group	100	6 (6)
χ^2 value	4.108	
P	.042	

CIN = contrast-induced nephropathy, PCI = percutaneous coronary intervention.

436.37 ± 59.78 µmol/L in febuxostat group and increased to 473.25 ± 55.14 µmol/L in the control group, which was statistically significant (P = .035). In each group, the change in uric acid level was significant when compared with their baseline values (461.52 ± 51.26 µmol/L; P < .05) in the febuxostat group, and 457.36 ± 53.52 µmol/L; P < .05 in the control group) (Table 3).

The baseline eGFR levels were 86.76 ± 11.10 mL/min/1.73 m^2 in the febuxostat group and were 87.61 ± 13.35 mL/min/1.73 m^2 in the control group (P = .68). After the procedure, eGFR level decreased to 85.92 ± 10.76 mL/min/1.73 m^2 in febuxostat group and decreased to 84.86 ± 11.12 mL/min/1.73 m^2 in the control group, which was statistically significant (P = .029) (Table 3).

4. Discussion

Based on the results of the present study, febuxostat may reduce the incidence of CIN when compared to the control group. In addition, the prophylactic administration of febuxostat attenuated the increase in NGAL, a marker of renal injury, and decreased the incidence of uric acid increase compared with the control in patients with hyperuricemia undergoing PCI.

It has been shown that uric acid plays a pathogenic role in CIN. The main mechanism of CIN includes contrast agent renal tubular toxicity and renal hemodynamic changes resulting in medullary hypoxia.[13,14] The generation of oxygen free radicals plays a key role in the development of CIN.[9] The mechanism by which uric acid may contribute to CIN may be related to the uricosuric properties of radiocontrast. Uric acid is the end product of purine metabolism. Radiocontrast induces marked uricosuria. First, after exposure to contrast media, the excretion

Table 3

Changes in serum creatinine, eGFR, NGAL, and uric acid.

Parameters	Febuxostat group (n = 100)	Control group (n = 102)	t	P
serum creatinine (µmol/L)				
Baseline	81.42 ± 17.33	83.37 ± 19.12	−0.32	.69
48 h after procedure	85.13 ± 18.53*	89.36 ± 19.07*	−2.15	.032
eGFR (mL/min/1.73m^2)				
Baseline	86.76 ± 11.10	87.61 ± 13.65	−0.52	.68
48 h after procedure	85.92 ± 10.76*	84.86 ± 11.12*	2.21	.037
NGAL (ng/mL)				
Baseline	95.82 ± 19.73	94.31 ± 18.32	0.83	.43
6 h after procedure	106.25 ± 17.92*	112.76 ± 19.12*	−2.06	.029
Uric acid (µmol/L)				
Baseline	461.62 ± 51.26	457.36 ± 53.52	0.23	.83
48 h after procedure	436.37 ± 59.78*	473.25 ± 55.14*	−2.16	.035

Variables are summarized mean (SD).
eGFR = estimated glomerular filtration, NGAL = neutrophil gelatinase-associated lipocalin, SD = standard deviation.
* Compared with baseline, P < .05.

Table 4

Multiple logistic regression analysis.

Variables	OR	95% CI	P
Contrast volume	1.002	0.992–1.010	.638
Hypertension	1.335	0.803–2.313	.3
Diabetes	1.431	0.857–3.021	.22
Febuxostat	0.918	0.767–0.982	.039
Age	1.011	0.978–1.142	.13

P < .05.
CI = confidence interval, OR = odds ratio.

of uric acid in the urine increased, which may predispose to crystallization and may induce tubular injury. Elevated serum uric acid levels are related to various pathological processes, such as endothelial dysfunction, inflammation, activation of the renin angiotensin system, inhibition of the nitric oxide system, and increased oxidative stress.[15–17] All these pathologic processes are also risk factors for CIN, and allopurinol presents antioxidant properties by reducing the production of reactive oxygen species derived from purine metabolism. Oxidative stress is an important factor involved in endothelial dysfunction and ischemia-reperfusion injury and may be implicated in the pathogenesis of CIN. Allopurinol may have a direct protective effect on endothelial cells and simultaneously improve renal medullary perfusion, thus counterbalancing the direct and ischemic effects induced by the contrast medium, and allopurinol may reduce the incidence of contrast-induced acute kidney injury in patients undergoing interventional coronary procedures.[18]

Febuxostat, structurally difering from allopurinol, is a novel selective xanthine oxidase inhibitor, which is metabolized by the liver and excreted via both urine and feces.[19] Febuxostat has a renoprotective effect in patients with chronic kidney disease. A clinical study compared the efficacy of renal-protective function between febuxostat and allopurinol in patients afflicted with chronic kidney disease and hyperuricemia, and this study reported that febuxostat was superior to allopurinol in delaying the progression of renal impairment in these patients afflicted with chronic kidney disease and hyperuricemia.[20] Febuxostat had a superior urate-lowering efficacy to allopurinol in patients with hyperuricemia and chronic kidney disease stages 3 to 5. Compared with allopurinol, febuxostat can exert an effect on uric acid lowering without serious adverse events, which has been suggested as a priority for hyperuricemia patients with renal impairment.[21,22] One study showed that among patients undergoing coronary angiography or percutaneous interventions, elevated uric acid levels are independently associated with an increased risk of CIN.[23]

Currently, the commonly used clinical measures to reduce the incidence of CIN are to reduce the amount of contrast medium and to perform perioperative hydration.[24] In this study, all patients received standardized hydration treatment. Compared with simple hydration, febuxostat combined with hydration can reduce the incidence of postoperative contrast nephropathy in patients with high uric acid levels, as well as increase the 6-hour NGAL and 48-hour serum creatinine and serum uric acid levels, as well as the decrease in glomerular filtration rate.

The commonly used indicators for the clinical evaluation of renal function injury are serum creatinine and glomerular filtration rate. In this study, NGAL was used to evaluate contrast media-induced acute renal function injury. NGAL has been an indicator of acute kidney injury in recent years. When renal

ischemia or injury occurs, NGAL reabsorption in the proximal convoluted tubules results in significantly elevated blood or urine levels, and the increase in serum NGAL levels 6 hours after surgery appeared earlier than the increase in serum creatinine and the decrease in eGFR 48 hours postoperatively, which provides a better reference for the timely treatment of acute renal function injury and has good application prospects in the early diagnosis of CIN.[25]

4.1. Limitations of the study

This study had some limitations: it was a single-center study with a small sample size. It was not sufficiently powered to conclusively analyze the potential effects of patient-related or doses of febuxostat-related factors on the incidence of CIN or any differences in these effects between the febuxostat group and the control group. Moreover, although we observed statistical differences in the incidence of CIN between febuxostat and control groups, more cases are needed to prove the explicit renal protective effect of febuxostat on CIN, and the relatively low dose of the radiocontrast agent used could also have been a limitation of the study.

5. Conclusions

In conclusion, febuxostat can not only reduce the incidence of CIN, but also reduce postoperative serum uric acid levels and improve renal function. CIN may be related to the type and dosage of contrast agent used, basic renal function level, chronic renal insufficiency, and other factors. Although all studies used iodoxanol as a contrast agent, there were differences in the amount of contrast agent and the complications associated with the patients. Therefore, larger randomized controlled trials are needed to confirm these results.

Author contributions

Conceptualization: Guang Ma.
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Formal analysis: Xiaojv Zhai.
Investigation: Guang Ma, Min Li.
Methodology: Wei Teng.
Project administration: Guang Ma.
Resources: Zhaohui He, Zhenhua Xia.
Writing – original draft: Guang Ma.

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