The relationship between Hyperuricemia and Contrast-induced acute kidney injury undergoing primary percutaneous coronary intervention: the protocol of secondary analysis for ATTEMPT RESCIND-1 study

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Study protocol

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Abstract

Background Contrast-induced acute kidney injury (CI-AKI) contributes toward unfavorable clinical outcomes after primary percutaneous coronary intervention (pPCI). We assessed whether hyperuricemia is an independent predictor of CI-AKI and outcomes in patients undergoing pPCI. Methods/design Our study was a secondary analysis for the database from ATTEMPT study, enrolling 560 ST-segment elevation myocardial infarction (STEMI) patients undergoing pPCI. Eligible patients received peri-procedural either via aggressive (left ventricular end-diastolic pressure guided) or routine (<=500ml) intravenous hydration with the isotonic solution (0.9% NaCl) with randomization. The primary endpoint was CI-AKI, defined as >25% or 0.5 mg/dL increase in serum creatinine from baseline during the first 48-72 hours post-procedurally. Patients were divided into 2 groups according to the admission serum uric acid (SUA) level. Hyperuricemia was defined as a SUA level >7 mg/dL (417 mmol/L) in males and >6 mg/dL (357 mmol/L) in females. Multivariate analyses for CI-AKI and long-term mortality were performed using the logistic regression and Cox regression analyses, respectively. Discussion This study will determine the predictive value of hyperuricemia for the development of CI-AKI and outcomes in patients with STEMI undergoing pPCI. We predict that hyperuricemia will be associated with a risk of CI-AKI in patients with pPCI. Furthermore, after adjusting for other variables, long-term mortality after pPCI was higher in those with hyperuricemia than in those with normouricemia. Results of this study may provide scientific evidence for the effect of hyperuricemia on CI-AKI and long-term outcomes, thereby offering the potential possibility of lowering SUA on the development of CI-AKI and outcomes.

Background

ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (pPCI) are commonly complicated by contrast-induced acute kidney injury (CI-AKI) [1]. CI-AKI is associated with higher hospitalization rates, long-term morbidity, and mortality[2]. Therefore, patients recognized with high-risk factors of CI-AKI should be carefully monitored and treated with appropriate prophylactic strategies. Based on previous study, chronic kidney disease, diabetes, hypotension, contrast volume, congestive heart failure, advanced age, and anemia have been identified as risk factors CI-AKI[3].

Uric acid is the final product of purine metabolism, which is metabolized by xanthine oxidase[4]. In previous studies, we reported that hyperuricemia was an independent risk factor for CI-AKI after PCI[5,6]. However, the conclusion remains controversial[7-14]. In addition, only a limited number of studies reported that hyperuricemia was an independent predictor of CI-AKI in STEMI patients undergoing pPCI. Moreover, it was uncertain about the role of uric acid in the long-term outcome[15-17].

We aimed to investigate the association of hyperuricemia with CI-AKI in patients with high-risk STEMI undergoing pPCI, and to determine the predicting role in prognosis.

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Methods/design

Study design and population

This is a secondary analysis of aggressive hydration in patients with STEMI undergoing pPCI to prevent contrast-induced nephropathy, the first study for reduction of contrast-induced nephropathy following cardiac catheterization (ATTEMPT RESCIND-1 study). 560 patients aged 18 years or older, treated with pPCI and provided written informed consent were included from 15 medical research centers in China. Inclusion and exclusion criteria were described elsewhere[18].

Study protocol

Baseline Data includes demographics, diagnosis, medical history, laboratory parameters, medications, and physical examination. Hyperuricemia was defined as serum uric acid (SUA) level >7 mg/dL (417 mmol/L) in male and >6 mg/dL (357 mmol/L) in female. The primary outcome, CI-AKI, was defined as a 25% or 0.5 mg/dL increase in serum creatinine from baseline at 48-72 hours after pPCI[13]. The secondary endpoints were different definitions of CI-AKI, persistent renal impairment, major adverse clinical events during hospitalization, total hospitalization costs, and length of hospital stay.

Follow-up adverse events were recorded by trained investigators via office visits or telephone interviews at 3, 6, 12, 18, and 24 months after the pPCI. Long-term outcomes are major adverse cardiovascular events (MACEs), including mortality, stent restenosis, non-fatal myocardial infarction, and target vessel revascularization.

All data are collected with standardized electronic case report forms. At the time of enrollment, the data management team of Guangdong General Hospital conducts consistency checks and issues data clarification forms to deal with discrepant data.

All data were collected after the approval by the ethics committee of all participating centers. An independent data monitoring committee reviewed the ongoing safety events of every paticipant.

Statistical Analysis

Continuous variables were presented as the mean ± standard deviation if normally distributed and median plus interquartile ranges if nonnormally distributed. They were compared by t-test or Wilcoxon rank sum test according to distribution. The categorical data, expressed as a percentage were analyzed using the Pearson chi-square test or Fisher's exact test. The association between risk predictors and CI-AKI, as well as long-term mortality were performed using multivariate logistic regression and Cox regression analysis. Kaplan-Meier curve and Log-rank test were performed on the survival time of the hyperuricemia group and the normouricemia group. These data were analyzed on the basis of valid cases. A Two-tailed *p*-value <0.05 was considered statistically significant.

All statistical analyses were performed using SAS version 9.4 or later (SAS Institute, Cary, NC, USA) and R software (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria).

Discussion

CI-AKI is closely associated with prolonged hospital stay, long-term morbidity, and mortality in patient undergoing PCI. The incidence of CI-AKI is about 2% in the general population and over 50% in high-risk population[3]. Previous study supported the relationship between CI-AKI and higher incidence of adverse short- and long-term cardiovascular outcomes, including mortality[19]. Patients with STEMI are likely to present with hypotension, or even cardiogenic shock, higher volume of contrast media, and impossibility of renal prophylactic therapy, which are associated with an increased risk of CI-AKI[20].

Advanced age, diabetes, dehydration, hypotension, sepsis, cardiovascular disease, underlying acute kidney injury, chronic kidney disease, and concomitant use of nephrotoxic drugs were identified as well-known risk factors for CI-AKI[3,21]. In previous studies[5,6], we reported that hyperuricemia was an independent risk factor for CI-AKI in PCI patients, which was consistent with other studies[7-12]. However, other studies did not show the same conclusion[13,14]. Several studies explored the effect of serum uric acid (SUA) on CI-AKI among risk high-risk patients such as STEMI undergoing primary PCI. Elbasan et al. showed that SUA was associated with CI-aki in STEMI patients undergoing pPCI (mean SUA=6.2±0.9 mg/dL, 95% CI, 1.877- 3.236; P=0.002)) [15]. In another study, Mendi MA et al. demonstrated that SUA ≥ 5.4 mg/dL was an independent risk factor for CI-aki (OR 1.26, 95% CI, 1.10-1.42; 16 P < 0.001) [16]. Saritemur M et al. showed that elevated uric acid was lined with CI-AKI in multivariate analysis after adjusting for potential confounding factors (OR 1.01, 95% CI, 1.00-1.01; 17 P = 0.01) [17]. However, even though they reported that high SUA was an independent predictor of CI-AKI in STEMI patients, there was

no uniform standard for the definition of hyperuricemia. In our study, we employed the definition consistent with our previous study.

In addition, these studies did not compare the prognosis between CI-AKI group and nonCI-AKI group in STEMI patients undergoing PCI. Some observational studies proved the relationship between hyperuricemia and clinical outcomes in the presence of gout, but not for asymptomatic hyperuricemia[22,23]. Nevertheless, a recent study by Pagidipati et al, including the PLATO and TRACER study population, demonstrated a significant association between uric acid (UA) and short-term adverse outcomes, independent of the presence of gout[24]. Regarding the relationship between UA and long-term prognosis, the data also supported the relationship between elevated UA and long-term prognosis in patient with acute coronary syndromes and treated with PCI[25]. Therefore, whether hyperuricemia is still a predictor of poor long-term prognosis after adjusting for CI-AKI should be studied in STEMI patients receiving pPCI.

Although the pathophysiological mechanisms of adverse reactions to hyperuricemia has not been fully elucidated, it appears to be multifactorial. In experimental models, hyperuricemia was linked to a variety of proatherogenic processes, including increased oxidative stress[26], vascular smooth muscle cell proliferation[27], inflammation[28], and endothelial dysfunction[29].

Limitations

Our current secondary analysis is subject to the following restrictions. First, its sensitivity was lower due to the definition of >0.5 mg/dL because it was less selective for patients with higher risk of mortality and morbidity. Second, a single baseline SUA measurements were used to predict CI-AKI and long-term mortality. However, a number of previous studies have used this method as well. Third, the measurement of serum creatinine (SCr) was standardized at 72 hours after pPCI rather than at random, which might lead to the ignorance at the increase in delayed SCr (>72 hours). Finally, it is a secondary analysis that is not capable of testify a causal relationship.

In conclusion, our study will determine the association between hyperuricemia and contrast-induced acute kidney injury (CI-AKI) after primary percutaneous coronary intervention (pPCI), and will identify if Hyperuricemia is a risk factor for long-term death after adjusting for CI-AKI.

Trial status

The first patient was included in the RESCIND –1 ATTEMPT Trial (Protocol version 2.0, 11th June 2014) on 1st July 2014 and expected to complete recruitment in December 2018. As of October 24, 2018, recruitment is ongoing with 555 patients randomized at 15 centers in China.

Abbreviations

CI-AKI: Contrast-induced acute kidney injury; pPCI: primary percutaneous coronary intervention. STEMI: ST-segment elevation myocardial infarction; SUA: serum uric acid; SCr: serum creatinine.

Declarations

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Authors' contributions

NT and YL are the principal investigator. WG, FES and SQC is the main coordinator of the project. GLS and JL participated in the development of the protocol. LZ and JYC provided the basic suggestions for the study. WG drafted the manuscript of the present paper. All the authors were involved in the manuscript's revision and approved the final version.

Ethics approval and consent to participate

The study protocol has been approved by the Guangdong General Hospital Ethics Committee. All the participants will sign an informed consent form. Summary data will be used only for statistical analysis to ensure that personal information is not leaked.

Competing interests

The authors declare that they have no competing interests.

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Figures

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT	Day -1~0	Day 0	Day 1	Day 2	Day 3	Day 7	Day 90	Year 1
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
[General hydration]		X						
[Aggressive hydration]		X						
ASSESSMENTS:								
[Baseline variables]	X	X						
[CI-AKI]			X	X	X			
[Mortality]			X	X	X	X	X	X

Figure 1

The schedule of enrolment, interventions, and assessments.

Supplementary Files

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