Meta-analysis on allopurinol preventive intervention on contrast-induced acute kidney injury with random controlled trials

PRISMA

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Abstract

Objective: The objective of this meta-analysis on randomized controlled trials is to evaluate whether the administration of allopurinol with or without hydration will reduce contrast-induced acute kidney injury (CI-AKI) in patients undergoing contrast exposure.

Background: The efficacy of allopurinol in the prevention of CI-AKI after cardiac catheterization and percutaneous coronary intervention (PCI) is significantly related to the heterogeneous results.

Methods: Two investigators independently searched MEDLINE, EMBASE, the Cochrane Controlled Trials Registry, the China Wanfang Data, the China Biological Medicine Database and the China National Knowledge Infrastructure (CNKI) databases for randomized controlled trials (RCTs) comparing allopurinol with placebo or no allopurinol for the prevention of CI-AKI in patients from their inception to July 31, 2018. The primary outcome was the incidence of CI-AKI, and the secondary outcomes were the differences of serum creatinine (Scr), blood urea nitrogen (BUN), uric acid (UA), and estimated glomerular filtration rate (eGFR) levels between groups after contrast media exposure. We used fixed-effects or random-effects models according to I² statistics. The meta-analytic procedures were completed by Review Manager, version 5.3.

Achievements: Eight random controlled trials with 1141 patients were included for this analysis. Compared with the control, allopurinol was associated with a reduced risk of CI-AKI (Relative Risk (RR) 0.39, 95% confidence interval [CI] 0.20, 0.74, P = .004) and only a intend for decrease a post-procedure uric acid levels compared with the controlled ones at 48 hours (standardized mean difference (SMD) −0.72, 95% CI −1.44, 0.01, P = .05). But the difference of post-procedure uric acid levels was not statistically significant in allopurinol groups compared with controlled groups. There were lower post-procedure Scr and BUN levels in allopurinol groups compared with those in controlled groups. There were higher post-procedure eGFR levels in allopurinol groups than those in controlled groups (SMD −0.50, 95% CI −0.79, −0.21, P = .0009; SMD −0.40, 95% CI −0.60, −0.20, P < .0001; respectively). There were higher post-procedure eGFR levels in allopurinol groups than those in controlled groups (SMD 0.65, 95% CI 0.48, 0.83, P < .0001).

Conclusion: The main findings of this meta-analysis are focus on allopurinol may cause reduces in the incidence of CI-AKI in patients undergoing interventional coronary procedures. Further researches are still required for confirmation.

Abbreviations: BUN = blood urea nitrogen, CI = confidence interval, CI-AKI = contrast-induced acute kidney injury, CNKI = China National Knowledge Infrastructure, eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, RR = relative risk, Scr = serum creatinine, SMD = standardized mean difference, UA = uric acid.

Keywords: allopurinol, cardiac catheterization, contrast-induced acute kidney injury, Meta-analysis, percutaneous coronary intervention

1. Introduction

Contrast-induced acute kidney injury (CI-AKI), known as contrast-induced nephropathy, is a common complication of procedures with intravascular contrast medium and associated with prolonged hospitalization, increased health care costs, and a powerful predictor of unfavorable early and long-term outcome.[1–3] CI-AKI is mainly defined as an increase of 25% or absolute elevation of 44.2 μmol/L (0.5 mg/dl) of serum creatinine (Scr) from baseline within 2 to 3 days after the contrast application in the absence of other causes. CI-AKI is the third leading cause of acute renal injury-related health care, which led to around 10% of acute renal injury in hospitalized patients.[4] Therefore, the prevention of CI-AKI is beneficial for minimizing hospital costs, mortality and morbidity.

Currently, 2 precautions have been recommended for reducing CI-AKI such as reducing the amount of contrast media as much as
possible, using optimal hydration before and immediately after the procedure. Allopurinol has been investigated as a preventive treatment due to inhibiting XO activity and blocking the generation of oxygen radicals and the production of uric acid (UA). However, the benefits of allopurinol against CI-AKI have been inconsistent. Some studies have reported the benefits\(^5\)\(^6\) while others do not support the reno-protective effects of allopurinol.\(^7\) Therefore, in order to provide more evidences in the prevention of CI-AKI during cardiac catheterization and percutaneous coronary intervention (PCI), this meta-analysis to evaluate if allopurinol therapy with or without hydration effectively decreases the incidence of CI-AKI in patients undergoing interventional coronary procedures was performed.

2. Methods
This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.\(^8\) This study is a meta-analysis of RCTs and all data were collected from published trials, so an additional ethical approval is not necessary.

2.1. Search procedure
Two trained investigators independently searched MEDLINE, EMBASE, the Cochrane Controlled Trials Registry, the China Wanfang Data, the China Biological Medicine Database and the China National Knowledge Infrastructure (CNKI) databases from the date of their inception to July 31, 2018 with no language restrictions. We used the combinations of the terms like, ‘allopurinol’, ‘contrast media’, ‘contrast medium’, ‘renal insufficiency’, ‘nephropathy’, ‘contrast-induced nephropathy’, ‘acute kidney injury’, both as the test words and as MESH headings. All articles were available till July 31, 2018. Relevant studies were identified from the reference lists of selected articles and from review articles.

2.2. Study selection
Randomized controlled trials of allopurinol in the prevention of CI-AKI comparing with one or more control groups (either no allopurinol or placebo) in patients undergoing interventional coronary procedures with or without PCI were included with constraints on the time period till July 31, 2018. The processes of selection, data extraction, and quality assessment were independently executed by two reviewers. Disagreement was solved by reviewing the relevant studies for reach consensus.

2.3. Inclusion criteria
Eligible studies met the following PICOS criteria:

(1) population: adult hospitalized patients undergoing interventional coronary procedures with or without PCI
(2) intervention: allopurinol with or without hydration
(3) comparison intervention: one or more control groups (either no allopurinol or placebo)
(4) outcome: incidence of CI-AKI, Scr level, blood urea nitrogen (BUN) level, UA level, estimated glomerular filtration rate (eGFR)
(5) study design: randomized controlled trials.

2.4. Exclusion criteria
(1) observational study
(2) study not reporting the desired outcome
(3) overlapping populations and pediatric studies.

2.5. Data extraction
Data extraction from reports was processed in line with the protocol, by the reviewers; disagreements were resolved by negotiations. For each of the trials included in the review the following characteristics were recorded:

1. First author’s surname;
2. Year of publication;
3. Country where the study was performed;
4. Study design and characteristics;
5. Total number of participants;
6. inclusion and exclusion criteria;
7. Details about intervention arm;
8. Details about control arm;
9. type of contrast medium;
10. baseline eGFR;
11. definition of CI-AKI;
12. incidence of CI-AKI evaluated;
13. Other outcome variables evaluated;
14. Quality indicators.

2.6. Assessment of risk of bias
Each trial included was evaluated for risk of bias according to the Cochrane risk of bias tool\(^9\) that assesses the adequacy of randomization, the concealment of treatment allocation, the similarity of treatment groups at randomization, investigator blinding, and the description of withdrawals and dropouts. Disagreements were resolved by negotiation.

2.7. Statistical analysis
All of the meta-analytic procedures were conducted by Review Manager, version 5.3. Relative risk (RR) and 95% confidence interval (CI) were used to describe dichotomous data (incidences of CI-AKI), while standardized mean difference (SMD) and 95% CI to describe continuous data (the differences of Scr, BUN, UA, and eGFR levels between groups after contrast media exposure) for each study. Two-tailed \(P\) values <.05 were regarded as statistically significant. We used \(Q\) statistics, the related \(P\) values, and the \(I^2\) statistic to investigate the heterogeneity of each study. The \(I^2\) statistic is a quantitative measure that describing the percentage of total variations due to heterogeneity. The extracted \(I^2\) statistic value was utilized to assess the heterogeneity of each variable across studies. According to the Cochrane Handbook, heterogeneity of variables is indicating significant heterogeneity when the \(I^2\) square range from 50% to 90%. Therefore, an \(I^2\) square of <50% is considered acceptable. If the research results were not statistically different, the fixed effect model would be used for meta-analysis. If there is a statistical heterogeneity among the research results, the sources of heterogeneity will be needing further analysis. After excluding the obvious clinical heterogeneity, the random effects model was exploited in analyzing the Meta.
2.8. Achievements

The search strategy yielded 58 citations, 37 of them apparently irrelevant articles were excluded at the very beginning. Finally, 8 RCTs\(^{[5–7,10–14]}\) were reserved for analysis. The flow chart of selection is shown in Figure 1.

2.9. Study characteristics and quality

The study characteristics of the eight RCTs includes: published from 2013 to 2017, enrolling a total of 1141 patients are summarized in Table 1. In general, all the studies were RCT design with a meaningful follow-up duration of days and nights in 5 days and 3 of them\(^{[6,13,14]}\) are without hydration in both groups. The baseline demographic and medication characteristics are summarized in Table 1. Contrast medium related procedures were applied in all the studied patients. Coronary angiography or PCI in all the studies. One study\(^{[6]}\) had definitions of CI-AKI based on the changes of cystatin-c, which was defined as a ≥25% increase in serum cystatin-c relative to the patient’s baseline value in the first 24 hours after the exposure to the contrast agent. Therefore, the definitions of CI-AKI in the other studies is the 44.2 μmol/l (0.5 mg/dl) or 25% above baseline elevation of Scr levels following iodinated contrast administration without an alternative cause.\(^{[15]}\) The definitions of CI-AKI are presented in Table 1.

Two studies\(^{[6,10]}\) did not report the mean and standardized deviation of post-procedural Scr, the increase in Scr level from baseline are adopted instead according to the Cochrane Handbook for Systematic Reviews of Interventions. One study had more than 2 arms of studied groups,\(^{[10,11]}\) which had 3 arms (hydration, hydration+n-acetylcysteine, hydration+allopurinol300mg). We took the hydration arm as control group and took hydration+allopurinol300mg arm as one experimental group. The results of this study\(^{[10]}\) was divided into groups (Omnipaque and Visipaque). For a binary outcome (incidence of CI-AKI), combining the arms simply means adding the numbers...
Table 1

Summary of characteristics of randomized control trials included in the meta-analysis.

| Study          | Publication Year | Study Location | Sample Size | Intervention | Age | Follow-up Duration | Primary Outcome |
|----------------|------------------|----------------|-------------|--------------|-----|--------------------|-----------------|
| Erol et al[5]  | 2013             | Turkey         | 79          | Allopurinol (300 mg) 24 h before hydration alone | 65±9 | 96 h               | CIN, Scr, BUN and UA |
| Kumar et al[10]| 2014             | India          | 95          | Allopurinol (300 mg/ day) 24 h before hydration alone | 62.1±10 | 5 days             | CIN, Scr and BUN |
| Iranirad et al[7]| 2016            | Iran           | 54          | Allopurinol 600 mg 24 h before hydration alone | 59.3±11.7 | 24 h               | CIN, SCR, UA, Cystatin-C |
| Ghelich et al[6] | 2017            | Iran           | 102         | Allopurinol 100 mg 24 h before hydration alone | 59.2±5.3 | 48 h               | CIN, BUN, eGFR |
| Chen et al[8]  | 2016             | China          | 41          | Allopurinol 100 mg 24 h before hydration alone | 41.9±8.3 | 48 h               | CIN, BUN, UA, eGFR |
| Zhang et al[10]| 2017             | China          | 75          | Allopurinol 300 mg 24 h before hydration alone | 62.9±8.67 | 48 h               | CIN, Scr, UA and eGFR |

AMR=acute myocardial infarction, CABG=coronary artery bypass graft, CHF=congestive heart failure, eGFR=estimated glomerular filtration rate, PCI=percutaneous coronary intervention.
of events and total participants over all arms. In case of continuous data, combinations of different arms were carried out by the formulas provided by the Cochrane Handbook for Systematic Reviews of Interventions. One study\[6\] did not report the type of the contrast agent, however, in the other 7 studies, only nonionic contrast media were adopted (iohexol: omnipaque or visipaque, iodoxanol, iopamidol were used). The contrast volume was statistically similar between the allopurinol group and controlled group in each trial except for the 2 trials\[10,14\] (not reported), which were confirmed by our pooled analysis (MD 1.51, 95% CI –2.30, 5.32, \(P=0.44\); Fig. 2). The trials did not report the volume of contrast agent in each group, however, both articles are about patients undergoing PCI and the contrast volume may be similar in each group.

Among those eight RCTs, 2\[13,14\] enrolled patients with hyperuricemia has been associated with renal failure for a long time; 5\[5–7,11,12\] enrolled patients with impaired renal function (Scr \(\geq 1.1\) mg/dL, eGFR: 30–59 mL/min/1.73 m\(^2\); Scr \(\geq 2.0\) mg/dL, respectively); One study\[10\] included patients willing to complete the angiography and angioplasty with or without risk factors and patients with modies, there was insufficient information about some items to permit a definite judgment. Risk-generating information on the random sequence developing CI-AKI were included in 1 study.\[10\] Patients’ eGFR <15 mL/min/1.73 m\(^2\) or eGFR <60 mL/min/1.73 m\(^2\) were excluded in 2 study.\[6,7\]

The bias risk of included RCTs was assessed with Cochrane bias risk tool. Most items for all included studies indicated a low risk; however, randomization generation was reported in 3 studies.\[5,7,14\] One RCT\[6\] were double blinded, three studies were open label.\[7,10,11\] No other potential sources of bias was apparently presented except one study.\[12\] As shown in Figure 3.

2.10. Incidence of CI-AKI

Eight studies have evaluated the effect of allopurinol on Incidence of CI-AKI in patients with contrast exposure. Meta-analysis shows that \(I^2 = 57\%\), \(P = .02\), the heterogeneity was high, so a random effect model was used. Allopurinol comparing with controlled ones can significantly reduce the incidence of CI-AKI (RR 0.39, 95% confidence interval [CI] 0.20, 0.74, \(P = 0.004\); Fig. 4) in patients complicated with hyperuricemia or renal dysfunction after contrast exposure. Heterogeneity was reduced when restricts the analysis to the renal dysfunction patients (\(I^2 = 5\%\), \(P = .62\)), giving effect sizes that were similar in magnitude and direction to the overall estimates. (RR 0.56, 95% CI 0.35, 0.89, \(P = .01\); Fig. 4)

2.11. Change of Scr

There were no statistical differences in the baseline Scr and cystatin-c between allopurinol groups and controlled groups in all included studies except 2 studies (not reported).\[10,11\] This meta-analyses of the post-procedural Scr differences between allopurinol and controlled groups at 24 or 48 hours using a random effects model. The changes of post-procedural Scr concentration reflected the protection effect of allopurinol therapy in patients after contrast administration. Seven\[5–7,10,12–14\] of them covered the meta-
There was a significant difference between the allopurinol therapy and controlled arms in favor of allopurinol therapy, with an SMD (SMD = 0.50, 95% CI = 0.79, −0.21, P < .0001; I² = 82%; Fig. 5) in Scr change.

### 2.12. Change of BUN

The change of post-procedural BUN reflected the protection effect of allopurinol therapy in patients after contrast administration. Three studies[^7,10,12] were included in the meta-analysis of the changings in post-procedural BUN. There was a significant difference between the allopurinol therapy and controlled arms in favor of allopurinol therapy with an SMD (SMD = −0.40, 95% CI = −0.60, −0.20; P < .0001; I² = 0%; Fig. 6) in BUN changings.

### 2.13. Change of UA

Based on the data provided in 6 trials[^5–7,12–14] the pooled estimation for the SMD in 24 or 48-hour uric acid levels between

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[^7,10,12]: References should be included in the notes section.
the allopurinol and controlled groups was (SMD −0.72, 95% CI −1.44, 0.01, P = .05; Fig. 7). Meta-analysis showed that I² = 96%, P < .00001, the heterogeneity was high, so using a random effect model. This suggested a trend of a less uric acid elevation in allopurinol groups compared with controlled groups, but the difference was not of statistically significance.

2.14. Change of eGFR

Four studies[7,12–14] were included in the meta-analysis of post-procedural eGFR at 48 hours. There was a vital difference between the allopurinol therapy and controlled arms in favor of allopurinol therapy, with an SMD (SMD 0.65, 95% CI 0.48, 0.83, P < .0001; I² = 39%; Fig. 8) in eGFR change.

3. Discussion

There is an increasing number of performed contrast procedures, particularly cardiac catheterization with PCI.[16] CI-AKI represents the third leading cause of hospital-acquired acute kidney injury. The main mechanisms of contrast agent contributing to CI-AKI includes renal vasoconstriction, tubule toxicity of the contrast agent, generation of reactive oxygen species and medullary hypoxia.[17,18] Accumulated hypoxanthine after contrast exposure is metabolized into xanthine after the hypoxia improved, which contributing to the production of oxygen-free radicals.[19,20] Theoretically, the inhibition of the enzyme xanthine oxidase may blocking the generation of oxygen radicals and consequently may mitigate the nephrotoxic effect of contrast agents. Therefore, allopurinol may protect the kidneys by attenuate the production of oxygen free radicals caused by the xanthine inhibitory effects.

Currently, optimal hydration before and immediately after the procedure by administration of intravenous sodium chloride against CI-AKI are recommended. Hydration decreases the concentration of iodinated contrast within the kidney appear to reduce the risk of CI-AKI. Patients undergoing a contrast procedure, especially those with risk factors such as chronic kidney disease, accompanying with hypotension, contrast medium volume, congestive heart failure, aging, diabetes mellitus, and cardiovascular disease would be risky to develop mild to serious complications.[21,22] In this meta-analysis, it was found that the administration of periprocedural allopurinol could cause reduction in the incidence of CI-AKI in patients undergoing interventional procedures (RR 0.39, 95% confidence interval[CI] 0.20,0.74, P = .004; Fig. 3) which leading to a significantly lower level of Scr and BUN (SMD -0.50, 95% CI -0.79,—0.21, P = .0009; SMD -0.40, 95% CI -0.60,—0.20, P < .0001; respectively).

In 7 of the 8 studies, the definition of AKI incorporated the classical definition of >25% rise in Scr or a rise of 0.5 mg/dL of Scr within 72 hours. In 1 study,[6] CI-AKI was defined as a >25% increase in serum cystatin-c relative to the patient’s baseline value in the first 24 hours after exposure to the contrast agent. Although Scr is widely used in clinical practice, its several drawbacks have made it an unreliable biomarker. Levels of Scr can vary widely depending on a large number of nonrenal factors including age, sex, muscular mass and nutritional status. It will remain in the normal range until the GFR has decreased to half the normal value.[23] In this meta-analysis, we found that the administration of periprocedural allopurinol may case a reduction in the serum uric acid of CI-AKI in patients undergoing interventional procedures (SMD −0.72, 95% CI −1.44, 0.01, P = .05; Fig. 7). This indicates a trend of a less uric acid elevation in allopurinol groups compared with controlled groups, but the difference was not statistically significant. However, the administration of periprocedural allopurinol may preserve eGFR (SMD 0.65, 95% CI 0.48, 0.83, P < .0001; Fig. 8).

The mechanism by which UA may contribute to CI-AKI can be related to the uricosuric properties of radiocontrast. Uric acid is the end product of purine metabolism. Radiocontrast is known to induce marked uricosuria. First, after contrast media exposure,
the excretion of uric acid in the urine increased, which may predispose to crystallization, may induce tubular injury. Elevated serum UA levels are related to various pathologic processes such as endothelial dysfunction, inflammation, activation of the renin-angiotensin system, inhibition of the nitric oxide system and increased oxidative stress. All these pathologic processes are also risk factors for CI-AKI. Allopurinol presents antioxidant properties by reducing the production of reactive oxygen species derived from purine metabolism. Oxidative stress is an important factor that involved in endothelial dysfunction and ischemia-reperfusion injury and may be implicated in the pathogenesis of CI-AKI. Allopurinol may have a direct protective effect on the endothelial cells and improves simultaneously renal medulla perfusion, thus counterbalancing the direct and the ischemic effects induced by the contrast media. As study showing that among patients undergoing coronary angiography or percutaneous interventions elevated uric acid level is independently associated with an increased risk of CI-AKI. 

The failure to demonstrate the benefits of allopurinol in reduction in the serum uric acid in this study which may be caused by various reasons. On one hand, there might exist some bias in the studies we included were not so reliable conclusions. For example, Ghelich et al reported an evident difference in serum uric acid which was more likely related to the placebo status, rather than the additive effect of allopurinol 600 mg. On the other hand, our achievements also need to be interpreted carefully, for the achievements could be related to the different types of contrast medium, different application methods of allopurinol or other confounders which might lead to unpredictable bias.

The present meta-analysis has several significant strengths. First, to our knowledge, this is the first meta-analysis focusing on prophylactic allopurinol vs no allopurinol on CI-AKI. Second, the subjects enrolled in our study are from patients of different ages and baseline renal functions which are major risk factors for CI-AKI; however, the baseline of included study is comparable.

4. Limitations

First, the sample sizes in some of the studies were relatively small, with a number less than 200; thus some studies reported no events within groups and the estimated effect could not be calculated. Second, we did not have access to individual patient data to determine whether there are other risk factors, such as diabetes mellitus, congestive heart failure, chronic kidney disease and hypertension, which could influence the effect of hydration on CI-AKI risks. Thirdly, this meta-analysis contained trials with inconsistent definition of CI-AKI are not exactly the same administration method of allopurinol and population with different clinical features, which might also lead to some bias. Fourth, an obvious difference in controlled methods (hydration or placebo) might have affected all the whole statistical achievements. Finally, most enrolled trials in our study locates at a medium to high quality level, while there were still some studies with quality at a lower level, which might affect the power of the analysis. All of these may limit the validity of the achievements of our study, and we still need further investigation to draw a more definite conclusion.

5. Conclusion

The main findings of this meta-analysis is that allopurinol may reduce the incidence of contrast-induced acute kidney injury in patients undergoing interventional coronary procedures

Author contributions

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