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Original Investigation

Comparative Effectiveness of 12 Treatment Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis

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Background: To simultaneously evaluate the relative efficacy of multiple pharmacologic strategies for preventing contrast-induced acute kidney injury (AKI).

Study Design: Systematic review containing a Bayesian network meta-analysis of randomized controlled trials.

Setting & Population: Participants undergoing diagnostic and/or interventional procedures with contrast media.

Selection Criteria for Studies: Randomized controlled trials comparing the active drug treatments with each other or with hydration alone.

Intervention: Any of the following drugs in combination with hydration: *N*-acetylcysteine (NAC), theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E_1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), tocopherol (vitamin E), α-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide.

Outcomes: The occurrence of contrast-induced AKI.

Results: The trial network included 150 trials with 31,631 participants and 4,182 contrast-induced AKI events assessing 12 different interventions. Compared to hydration, ORs (95% credible intervals) for contrast-induced AKI were 0.31 (0.14-0.60) for high-dose statin plus NAC, 0.37 (0.19-0.64) for high-dose statin alone, 0.37 (0.17-0.72) for prostaglandins, 0.48 (0.26-0.82) for theophylline, 0.62 (0.40-0.88) for bicarbonate sodium plus NAC, 0.67 (0.54-0.81) for NAC alone, 0.64 (0.41-0.95) for vitamins and analogues, 0.70 (0.29-1.37) for natriuretic peptides, 0.69 (0.31-1.37) for fenoldopam, 0.78 (0.59-1.01) for bicarbonate sodium, and 0.98 (0.41-2.07) for low-dose statin. High-dose statin plus NAC or high-dose statin alone were likely to be ranked the best or the second best for preventing contrast-induced AKI. The overall results were not materially changed in metaregressions or subgroup and sensitivity analyses.

Limitations: Patient-level data were unavailable; unable to include some treatment agents; low event rates; imbalanced distribution of participants among treatment strategies.

Conclusions: High-dose statins plus hydration with or without NAC might be the preferred treatment strategy to prevent contrast-induced AKI in patients undergoing diagnostic and/or interventional procedures requiring contrast media.

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INDEX WORDS: Contrast-induced acute kidney injury (CI-AKI); contrast media; kidney disease; acute kidney failure; AKI prevention; statins; hydroxymethylglutaryl-CoA reductase inhibitor; statin; atorvastatin; rosuvastatin; simvastatin; *N*-acetylcysteine (NAC); serum creatinine; cardiovascular events; systematic review.

With the steady increase in rates of diagnostic and/or interventional procedures with contrast media, contrast-induced acute kidney injury (AKI) has become the third most common cause of AKI in hospitalized patients.[1] Contrast-induced AKI leads to prolonged hospitalization, increased costs, and increased morbidity and mortality.[2] Factors associated with the risk for contrast-induced AKI include pre-existing decreased kidney function, diabetes, hypertension, chronic heart failure, advanced age, volume depletion, hemodynamic instability, use of concurrent nephrotoxic medications, and large volume or high osmolality of contrast media.[3,4]

Minimization of the contrast media dose and the use of iso-osmolar or low-osmolar contrast media are recommended as nonpharmacologic precautions, and

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numerous pharmacologic strategies for preventing contrast-induced AKI have been evaluated. In 2008, a comprehensive meta-analysis of randomized controlled trials (RCTs) concluded that *N*-acetylcysteine (NAC) in combination with hydration was more effective than hydration alone.[5] However, due to the lack of head-to-head comparisons between treatment agents, traditional pairwise meta-analyses could not be used to simultaneously synthesize all evidence and generate clear hierarchies for the efficacy of different treatments.[5-8] As a consequence, the choice of the best treatment in practice is generally based on subjective judgment. Thus, objective information regarding the relative efficacy of different interventions would help the development of clinical practice guidelines for preventing contrast-induced AKI.

Bayesian network meta-analysis (ie, mixed treatment comparison) enables indirect comparison using a common comparator and combines direct and indirect comparisons to synchronously assess multiple treatments.[9-11] The usefulness of this method has been demonstrated in many studies of various medical conditions and interventions.[12-14] This study therefore aims to compare the relative efficacy of different pharmacologic interventions for preventing contrast-induced AKI by means of systematic review and network meta-analysis within a Bayesian framework.

METHODS

Data Sources and Searches

This systematic review was performed according to a prespecified protocol (Item S1, available as online supplementary material) and the reporting was in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.[15] We searched MEDLINE via Ovid (1946 to May 2016), Embase (1966 to May 2016), and the Cochrane Library database (CENTRAL [Cochrane Central Register of Controlled Trials]; before May 2016) for RCTs of contrast-induced AKI prevention, without language restrictions (see Item S1 for full search terms). The ClinicalTrials.gov website was also searched for RCTs that were registered as completed but not yet published.

Study Selection

We included RCTs that evaluated any of the following drugs in combination with hydration: NAC, theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E_1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), vitamin E or its analogues (tocopherol), α-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide. RCTs comparing the mentioned active drug treatments to each other or to hydration were eligible. We excluded studies that contained only one or none of the mentioned treatments. Eligible participants were those who underwent diagnostic and/or interventional procedures with contrast media, such as diagnostic coronary or peripheral arterial angiography or percutaneous intervention, ventriculography, enhanced computed tomography, intravenous pyelography, and other relevant procedures.

Treatment groups were classified into 12 categories according to drug species and/or dose: (1) the natriuretic peptide category comprised atrial natriuretic peptide, B-type natriuretic peptide, and carperitide; (2) the vitamins and analogues category comprised ascorbic acid, tocopherol, and α-lipoic acid; (3) the high-dose statin category comprised simvastatin, 40 to 80 mg; rosuvastatin, 20 to 40 mg; and atorvastatin, 40 to 80 mg; (4) the low-dose statin category comprised simvastatin, 10 to 20 mg; rosuvastatin, 10 mg; and atorvastatin, 10 to 20 mg; (5) the prostaglandin category comprised iloprost, alprostadil, misoprostol, and prostaglandin E_1; the other 7 treatment categories were: (6) theophylline (aminophylline); (7) NAC; (8) fenoldopam; (9) bicarbonate sodium; (10) bicarbonate sodium plus NAC; (11) high-dose statin plus NAC; and (12) hydration.

Data Extraction and Quality Assessment

Study selection, data extraction, and quality assessment were performed independently by 2 investigators (X.S. and X.X.) according to the prespecified study protocol (Item S1). The 2 investigators screened titles and abstracts of records identified by the search strategies for eligibility. Disagreements were resolved by discussion with a third reviewer (L.L.). Data for prespecified variables from the included studies were extracted into a computerized spreadsheet.

The outcome used was the development of contrast-induced AKI, defined as an absolute increase in baseline serum creatinine level of >44.2 μmol/L (>0.5 mg/dL) or a relative increase of >25%, typically within 48 to 72 hours after contrast injection.[16,17] If data were not available for the first 48 to 72 hours after the treatment, we used data obtained within the first 5 days of treatment (the data point closest to 48-72 hours was given preference).[18] If a different measurement index (eg, estimated glomerular filtration rate or creatinine clearance) or standard was applied, we extracted data according to one defined by authors of the included studies.

We assessed sources of bias using the Cochrane Collaboration risk-of-bias tool,[19] including an assessment of financial conflicts of interest.[20] We developed operational definitions for high, low, and unclear risk of bias for each of the 8 validity domains (Item S2).

Data Synthesis and Analysis

We used odds ratio (OR) and its 95% credible intervals to measure the relative effect of different treatments on contrast-induced AKI outcome. Before conducting network meta-analysis, we conducted conventional pairwise meta-analyses for treatments that were directly compared in RCTs. We used a fully Bayesian method, assuming a binomial likelihood on the log-odds scale, in pairwise meta-analyses through WinBUGS, version 1.4.3 (Medical Research Council Biostatistics Unit).[21,22] To investigate heterogeneity in conventional pairwise meta-analysis, we used STATA, version 12.0 (StataCorp LP), to conduct metaregression of direct comparisons based on empirical Bayes method and estimated I^2, τ^2, and Q value.

Network meta-analysis was conducted by using a random-effects model within a Bayesian framework, assuming a binomial likelihood and using WinBUGS 1.4.3 and R2WinBUGS package of R statistical software, version 3.1.1 (R Foundation for Statistical Computing), according to a predefined protocol (Item S1). We used noninformative priors with vague normal (mean, 0; variance, 100,000) and uniform (0-5) prior distributions for parameters such as means and standard deviations, respectively.[11] For each analysis, we generated 200,000 simulations for each of the 2 sets of different initial values and discarded the first 80,000 simulations as the burn-in period. Convergence was reached when Rhat, the potential scale reduction factor, is close to 1 for each of the parameters using the Brooks-Gelman-Rubin statistic.[23] We