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The effectiveness of *N*-acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: a meta-analysis of randomized controlled trials

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Abstract
Background *N*-Acetylcysteine (NAC) is reported to have potential for preventing of contrast-induced nephropathy (CIN) in patients undergoing coronary angiography. However, the effectiveness of NAC in preventing CIN in patients undergoing contrast-enhanced computed tomography (CT) is still controversial. We conducted a meta-analysis of relevant randomized controlled trials (RCTs) to further examine this issue.
Methods RCTs were identified by computerized searching in PubMed, EMBASE, SCOPUS, and Cochrane databases. Two reviewers independently assessed the methodological quality of each study. A meta-analysis was performed to evaluate the effectiveness of NAC in preventing CIN in patients undergoing CT. The primary outcome was the incidence of contrast-induced nephropathy, and the requirement for dialysis. The secondary outcome was the change of serum creatinine.
Results Six randomized controlled trials were identified with a total of 496 patients meeting the criteria for this study. Prophylactic administration of NAC in patients with serum creatinine above 1.2 mg/dL undergoing contrast-enhanced CT, along with hydration, reduced the risk of CIN (relative risk 0.20; 95 % confidence interval: 0.07–0.57). Requirement for dialysis was not significantly different between the NAC group and the control group.
Conclusions This review provides evidence of the efficacy of NAC in preventing the incidence of CIN

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and recommends that NAC be more widely used in high-risk patients undergoing contrast-enhanced CT. On the basis of the evidence reviewed, further research involving large RCTs may be warranted.

Keywords *N*-Acetylcysteine · Contrast-induced nephropathy · Computed tomography · Meta-analysis

Introduction

Contrast-induced nephropathy (CIN) is a major complication of intravenous administration of an iodine contrast medium and is usually defined as an increase in serum creatinine greater than 25 % or 44.2 μmol/L (>0.5 mg/dL) within 3 days of intravascular contrast administration in the absence of an alternative cause [1]. Contrast-induced nephropathy (CIN) is uncommon in patients with normal renal function, ranging from 0 to 10 % [2]. However, the incidence is perhaps as high as 50 % in patients with preexisting renal impairment or certain risk factors [3]. The most critical risk factors for CIN include preexisting renal insufficiency, old age, diabetes mellitus, reduced left ventricular systolic function, advanced congestive heart failure, kidney transplantation, reduced effective arterial volume, and concurrent administration of nephrotoxic drugs or drugs that interfere with the regulation of renal perfusion, such as angiotensin-converting-enzyme inhibitors [1]. Administering a large dose of intravenous contrast and using high-osmolar contrast agents in patients with renal impairment also increase the risk for CIN [4]. Despite a high rate of renal function recovery following CIN, the consequences of this complication include prolonged hospitalization, increased risk for renal failure and association with dialysis, increased health care cost, potentially irreversible reduction in renal function, and higher mortality [3]. Therefore, preventive measures for CIN are crucial.

The effects of various interventions in preventing CIN have been evaluated in clinical trials. The results of several studies have demonstrated a considerable reduction in the incidence of CIN using adequate intravenous fluid hydration, low-osmolality contrast media instead of high-osmolar agents and iso-osmolar agents instead of low-osmolar agents [5]. The previous studies have elevated the use of theophylline, calcium antagonists, dopamine, atrial natriuretic peptide, and other agents as preventive strategies in CIN; the results have been heterogeneous and are difficult to compare across different treatment strategies [6]. Accumulating evidence indicates that reactive oxygen species have a role in the renal damage caused by contrast agents [7]. Several randomized controlled trials (RCTs) and meta-analyses evaluating the antioxidative agent *N*-acetylcysteine (NAC) in preventing CIN in patients undergoing coronary angiography have yielded promising results [8]. However, the effectiveness of NAC in preventing CIN in patients undergoing contrast-enhanced computed tomography (CT) is still controversial. In this report, we systematically review the data from randomized trials to evaluate the effect of NAC in the preventing CIN in the study population.

Methods

Review protocol

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, explanation and elaboration document, and checklist to guide our methodology and reporting [9]. The systematic review described herein was accepted by the online PROSPERO international prospective register of systematic reviews of the National Institute for Health Research (CRD42012002094).

Search methods

The studies were identified by computerized searching in the PubMed, EMBASE, SCOPUS, and Cochrane databases. The following MeSH search headings were used: *acetylcysteine, radio induced or contrast induced, renal insufficiency or renal failure or kidney injury or nephropathy*, and *computed tomography*. These terms and their combinations were also searched as text words. All included studies were also entered into the PubMed 'related articles' function and the science citation index. In addition, we attempted to identify other studies by hand-searching the reference sections of these papers and by contacting known

experts in the field. Finally, unpublished trials were sought in the ClinicalTrials.gov registry (http://clinicaltrials.gov/). No language restrictions were applied. The final search was performed in October 2012. The full search strategies are available in the "Appendix".

Study selection

To be included in our analysis, studies were required to meet the following criteria: RCTs that have evaluated the efficacy of acetylcysteine, administered orally or intravenously, versus a control group with hydration alone to prevent CIN in patients undergoing contrast-enhanced CT, have documented clearly the inclusion and exclusion criteria used for patient selection, have adequately documented the administration of acetylcysteine, and have precisely documented the definition and evaluation of CIN. The studies were excluded from the analysis if any one or more of the following conditions applied: patients enrolled in the trials had undergone other contrast-enhanced diagnostic and therapeutic procedures concomitantly; trials compared NAC with another active treatment. When duplication papers using overlapping data sets were published, the study with the larger population was included.

Data extraction and quality assessment

Two reviewers (M.Y. Wu and K.W. Tam) independently extracted the following information from each study: study population characteristics, study design, inclusion and exclusion criteria, experimental drug administration, assessment of CIN, and complications. The individually recorded decisions of the two reviewers were compared, and any disagreements were resolved by a third reviewer (M.S. Yao). The authors of the studies were contacted for additional information when necessary.

The risk of bias in the included trials was assessed according to individual domains, reporting the following aspects: adequacy of randomization, allocation concealment, blinding, length of follow-up, number of drop-outs and whether intention-to-treat (ITT) analysis was conducted.

Data synthesis and analysis

We used the following outcomes to evaluate the efficacy of NAC in preventing CIN for patients undergoing contrast-enhanced CT: the incidence of CIN, the requirement for dialysis, changes of serum creatinine, and cystatin C level.

We conducted the analysis using the statistical package Review Manager, Version 5.1 (Cochrane Collaboration, Oxford, England). We statistically analyzed the dichotomous outcomes using risk ratios (RRs) as the summary statistic. Continuous outcomes were analyzed using the weighted mean difference (WMD). Both types of summary statistics were reported with 95 % confidence intervals (CIs). A pooled estimate of the RR was computed using the DerSimonian and Laird random-effect model [10], which provides a more appropriate estimate of the average treatment effect when trials are statistically heterogeneous, and usually yields wider CIs, thereby resulting in a more conservative statistical claim. χ^2 statistics tests (Q statistics) and I^2 test were used to test for heterogeneity between controlled trials.

Results

Characteristics of the trials

Figure 1 shows a flowchart for selecting trials. Our initial search strategy yielded 386 citations, 254 of which were ineligible based on our screening of titles and abstracts; thus, we retrieved the full text of 132 studies. Of these, 37 were excluded because of different comparisons; 34 were prospective or retrospective but not randomized studies; 3 used questionnaire surveys; and 52 did not meet the eligibility criteria because they were non-computed tomography studies. Consequently, 6 eligible trials remained [11–16]. Of these, all trials were peer-review articles, though the Burns study was a letter to the editor [11].

Characteristics and patient demographic data from each of the 6 trials included in our review are shown in Table 1. The studies were published between 1996 and 2012 and had sample sizes ranging from 30 to 209. Four trials had evaluated patients who had a history of chronic renal insufficiency and with a serum creatinine concentration

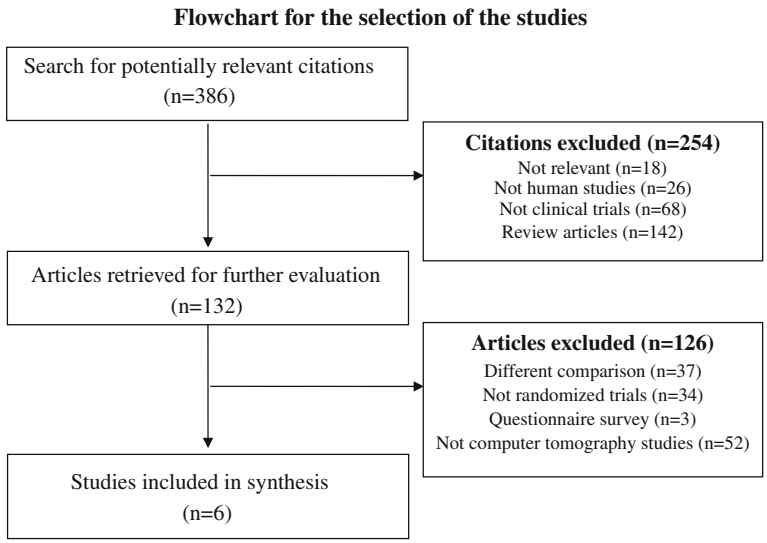

Fig. 1 Flowchart for selection of trials

above 1.2 mg/l (106 μmol/l) [11, 12, 14, 16]. One trial recruited type 2 diabetic patients with normal renal function (mean serum creatinine <1.2 mg/l) [13]. Patients included in three studies underwent CT with a nonionic low-osmolality (iopromide ultravist) radiographic contrast agent [12, 14, 16]. Patients requiring intravenous contrast media (100 mg of iohexol) administration for abdominal CT were eligible in one study [13]. Baseline characteristics were balanced between the 2 treatment groups in the 6 included RCTs. All patients received hydration before and after CT and were then assigned to NAC groups or control groups. One study randomized the patients to either vitamine E, NAC or control groups [16]. Administration of NAC varied considerably across trials: NAC was administered orally in 3 trials [13, 14, 16], and patients received NAC intravenously in 23 studies [11, 12, 15]. The dosages of NAC and hydration were adjusted according to various protocols.

The methodological quality of the 6 included RCTs is displayed in Table 2. Two studies clearly documented the use of random allocation [11, 12]. One study described whether or how patient allocation to treatment groups was concealed from the participants [15]. Two reported the blinding of the patients and researchers who assessed the outcomes [12, 16]. Two studies that we included based their analyses on the intention-to-treat principle [13, 14]. Loss to follow-up was acceptable (<20 %) in all studies. Other biases that existed in the studies included stopping the study early because of slow recruitment [11]; a total of 9 patients deaths before the final measurement (Day 4) because the enrolled patients were particularly in emergency [12]; significant differences in body weight, amount of contrast material administered, and the presence of chronic kidney disease between groups [16]; and no accurate amount of volume infusion provided [13].

The incidence of CIN

The definition of CIN varied considerably across trials. The incidence of CIN was proportional to the number of patients in whom nephrotoxicity developed after CT, defined as an increase of 0.3–0.5 mg/dL and/or an increase of 20–25 % over baseline creatinine at 2–5 days after the administration of a contrast agent. We performed subgroup analysis on populations with serum creatinine above or below 1.2 mg/dL. In high-risk patients, our analysis revealed that a significant difference between the 2 treatment groups, with more patients in the control group experiencing greater incidence of CIN (RR = 0.20; 95 % CI 0.07–0.57). In low-risk patients, we found no significant difference between the 2 groups (RR = 0.46; 95 % CI 0.21–1.02), although the incidence of CIN was lower in the NAC group (Fig. 2). No significant heterogeneity was observed among these trials ($I^2 = 0$ %). The number of people needed to receive the treatment before 1 person would experience a beneficial outcome [number needed to treat (NNT)] was 8.73.

Sar et al. [13] cannot provide the real delivered amount of saline in each group, which could

Table 1 Characteristics of studies fulfilling inclusion criteria in the meta-analysis

Study [references]	Inclusion criteria	No. of patient (% of male)	Age, years, mean ± SD	Baseline serum creatinine, mg/dl	Hydration/intervention	Contrast type, volume, ml
Burns et al. [11]	Serum creatinine >1.2 mg/dL or urine output <0,5 ml/kg over 4 h	A: 21 C: 21	NA	A: 1.15 ± 0.46 C: 1.34 ± 0.30	NS 12 h before and 24 h after CT A: 5 g IV post-randomization and 2 doses of 2.5 g at 6 h and 12 h after CT C: D5 W instead of NAC	NA
Kitzier et al. [16]	Serum creatinine >1.25 mg/dL for males and 1.09 mg/dL for females	A: 10 (20) E: 10 (60) C: 10 (50)	A: 76.6 ± 9.5 E: 73.3 ± 11.9 C: 74 ± 8.5	A: 1.37 ± 0.51 E: 13.7 ± 0.2 C: 1.33 ± 0.12	0.45 % saline 1 ml/kg 12 h before and 12 h after CT A: Orally, 1,200 mg 12 and 6 h before and 6 and 12 h after CT E: 540 mg IV 12 and 6 h before and 6 and 12 h after CT C: 0.45 % saline instead of NAC and vitamin E	Iopromide ultravisit 100 ml
Hsu et al. [15]	Patients received abdominal or chest CT in the emergency department	A: 106 (74) C: 103 (76)	A: 79.7 ± 8.5 C: 79.3 ± 11.1	A: 1.59 ± 0.56 C: 1.61 ± 0.63	A: 600 mg IV in 3 ml/kg NS 1 h before CT and NS 1 ml/kg 6 h after CT C: only hydration	Iohexol or iopromide or iobitridol
Poletti et al. [12]	Patients with serum creatinine >1.2 mg/dL admitted to emergency department	A: 44 (59) C: 43 (67)	A: 66 ± 11 C: 65 ± 15	A: 1.65 ± 0.40 C: 1.67 ± 0.41	0.45 % saline 5 ml/kg 1 h before and 1 ml/kg 12 h after CT A: 900 mg IV diluted in 50 ml D5 W 1 h before and in 0.45 % saline 1 ml/kg 12 h after CT C: 50 ml of NS instead of NAC	Iopromide ultravisit 100 ml
Sar et al. [13]	Diabetic patients with serum creatinine <1.2 mg/dL or creatinine clearance >60 ml/min	A: 25 (52) C: 20 (55)	A: 60 ± 11.3 C: 53.5 ± 9.9	A: 0.83 ± 0.15 C: 0.81 ± 0.17	NS 12 h before and 24 h after CT A: Orally, 1,200 mg before and 2 days after CT C: Only hydration	Iohexol 100 ml
Tepel et al. [14]	Serum creatinine >1.2 mg/dL or creatinine clearance <50 ml/min	A: 41 (58.5) C: 42 (54.8)	A: 66 ± 11 C: 65 ± 15	A: 2.5 ± 1.3 C: 2.4 ± 1.3	0.45 % saline 1 ml/kg 12 h before and 12 h after CT A: Orally, 600 mg BID on the day before and on the day of CT C: Only hydration	Iopromide ultravisit 75 ml

A *N*-acetylcysteine, *C* control, *CT* computer tomography, *E* vitamine E, *NA* not available, *NS* normal saline

strengthen the observation regarding the protective effect of NAC by ruling out any confounding factor related to the volume infusion, and hence, clinicians must interpret the results of our meta-analyses with caution. However, when we excluded the findings of Sar et al. from our meta-analysis, the pooled result did not change on exclusion of this study from our analysis.

Table 2 Methodological quality assessment of included trials

Study [references]	Allocation generation	Allocation concealment	Double blinding	Data analysis	Duration of follow-up	Loss to follow-up (%)	Other bias
Burns et al. [11]	Random number table	Unclear	Unclear	PP	5 days post-contrast	0	Stopped early due to slow recruitment
Kitzier et al. [16]	Block randomization scheme	Unclear	Adequate	PP	48 h post-contrast	0	Low risk
Hsu et al. [15]	Computer-generated	Adequate	Unclear	PP	72 h post-contrast	13 %	Significant differences in body weight, amount of contrast material administered, and the presence of CKD between groups
Poletti et al. [12]	Serial enrollment	Unclear	Adequate	PP	4 days post-contrast	2.1 at day 2 4.6 at day 4	9 patients died before final measurement
Sar et al. [13]	Unclear	Open-label	Inadequate	ITT	72 h post-contrast	0	No real amount of volume infusion provided
Tepel et al. [14]	Unclear	Unclear	Unclear	ITT	48 h post-contrast	0	Low risk

CKD chronic kidney disease, *ITT* intention-to-treat, *PP* per protocol

Requirement for dialysis

Three studies have provided data on the requirement for dialysis [11, 14, 15]. Hsu et al. [15] reported that the incidence of temporary renal replacement therapy was 0 % in the NAC group and 1.0 % in the control group. None of the patients required dialysis in the other 2 studies [11, 14].

Changes in creatinine

Three studies have provided data on the increase in creatinine as a protective effect of NAC therapy [12–14, 16]. Serum creatinine was measured from admission to 48, 72 h or 96 h after the administration of the contrast agent, and changes in each study were calculated accordingly. A significant difference was found between the 2 groups, with a greater improvement of changes in creatinine level in the NAC group (WMD = −0.22; 95 % CI −0.41 to −0.03) (Fig. 3). We discovered significant heterogeneity between the trials for changes in creatinine level ($I^2 = 87$ %; $\chi^2 = 23.95$; $P < 0.0001$).

Changes in cystatin C

Cystatin C appears to be more sensitive than creatinine in detecting mild decreases in the glomerular filtration rate (GFR) and is, therefore, an earlier indicator of acute renal failure [17]. Only 1 study investigated the changes of serum cystatin C [12]. Cystatin C was measured at admission and on Days 2 and 4 after CT. A 25 % greater increase in serum cystatin C concentration was found in 9 (22 %) of 40 patients in the control group and in 7 (17 %) of 41 patients in the NAC group ($P = 0.59$). No significant differences were observed in mean cystatin C concentration in either group on Days 2 and 4.

Discussion

Contrast-induced nephropathy is associated with medical resource use and mortality risk. According to Weisbord et al. [2], the incidence of contrast-induced acute kidney injury was reported as being the lowest, following computed tomography (range,

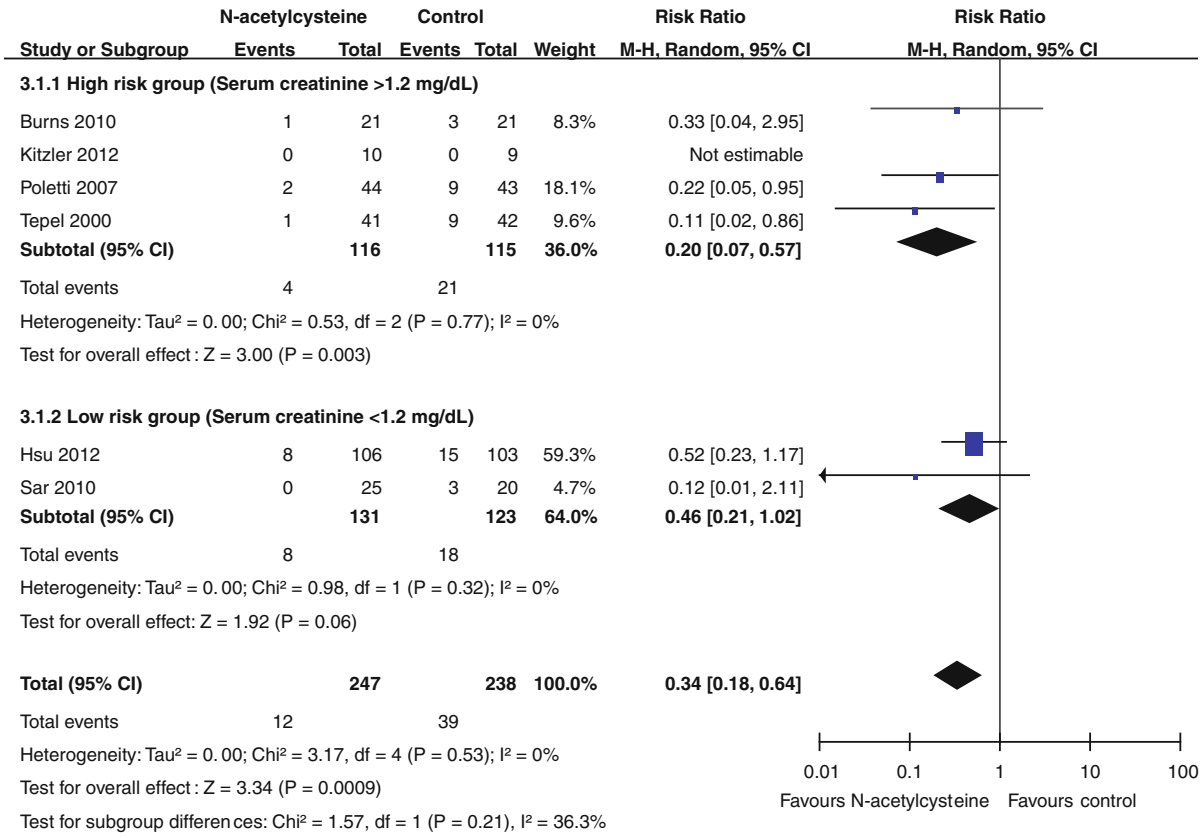

Fig. 2 Forest plot of comparison: *N*-acetylcysteine with hydration versus hydration. Outcome: the incidence of contrast-induced nephropathy

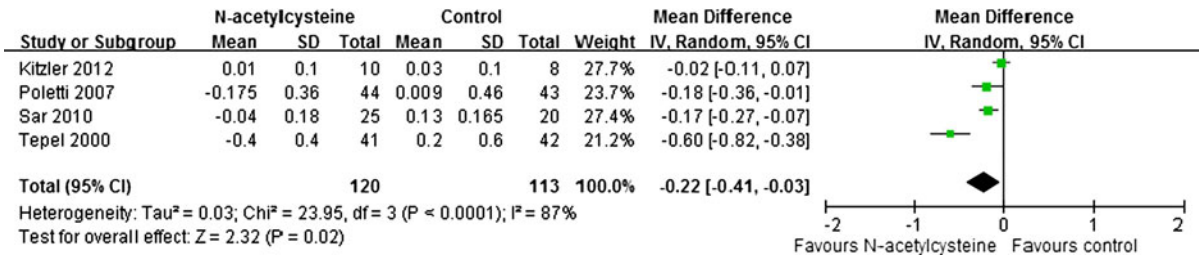

Fig. 3 Forest plot of comparison: *N*-acetylcysteine with hydration versus hydration. Outcome: change of serum creatinine

0.0–10.9 %), 0.0–12.1 % following coronary angiography, and was highest following non-coronary angiography (range, 1.9–34.0 %). The incidence of CIN is reported to be probably higher than predicted number for ambulatory population [3]. Several clinical trials have attempted to identify interventions that reduce the risk of CIN in high-risk patients receiving angiography. *N*-Acetylcysteine is inexpensive, readily available, easily administered, and rarely induces side effects or drug interactions. The efficacy of NAC in preventing CIN has been explored in numerous clinical studies and meta-analyses [8, 18]. The most recent meta-analysis studies have shown that NAC is the most effective agent in preventing CIN in patients with chronic renal insufficiency [8] and have suggested administering a high dose of NAC [18]. *N*-Acetylcysteine, as a routine intervention for prophylaxis of CIN in high-risk patients, is generally recommended in angiography. Our meta-analysis focused on the efficacy of NAC to prevent CIN in

patients receiving CT. The findings from our study show that NAC decreases the risk of CIN and improves the changes of serum creatinine. Second, by analyzing individual study data, we showed that the change of serum creatinine is less through NAC prevention than through hydration alone.

The choice of contrast medium and route of administration are procedural risk factors in preventing CIN in patients undergoing contrast-enhanced image studies. The various osmolality iodinated radiocontrast agents have different levels of nephrotoxicity, with the lowest risk of toxicity associated with low- or iso-osmolar agents. Intravenous administration of a contrast medium for enhanced CT is usually provided at a lower dose than angiography, and lower concentrations of contrast medium reach the kidneys. The 2 major mechanisms of kidney injury are renal vasoconstriction, resulting in medullary hypoxemia, and direct cytotoxic effects of the contrast agents [7]. Contrast medium agents (iohexol, iopromide) used in the studies we included are nonionic and low osmolar (osmolality ranging from 521 mOsm/kg H_2O to −695 mOsm/kg H_2O). Intravenously injected low-osmolality or iso-osmolality contrast agents in high-risk patients undergoing CT are generally safe with a low incidence of CIN [5]. Nevertheless, our study revealed that NAC decreased the risk of CIN, despite using low-osmolar agents.

There is broad consensus that hydration reduces the risk of CIN based on improving renal blood flow, diluting contrast material, reducing the activation of the rennin–angiotensin system, suppressing the secretion of the antidiuretic hormone, and minimizing reductions in the renal production of endogenous vasodilators. The most effective protocol for intra-arterial procedures appears to be 1.0–1.5 ml/kg/h, 12 h before and 12 h after administering the contrast medium. However, evidence of optimal amount and rate of volume expansion is not clear regarding patients who have received CT. Normal saline appears to be more effective than half-normal saline in preventing CIN [19]. Hydration protocols in our included studies involved normal saline (0.9 %) or half-normal saline (0.45 %) for 13–36 h, and the amount of fluid administration has varied considerably among studies.

N-Acetylcysteine with antioxidant and vasodilatory properties is of potential benefit in preventing CIN because it minimizes both vasoconstriction and oxygen-free radical generation after administering a radiocontrast agent. The most popular protocol involves an oral NAC, 600 mg, twice daily for 24 h the day before and on the day of the procedure. It has been suggested that periprocedural doses exceeding 600 mg, or daily doses exceeding 1,200 mg, decrease the incidence of CIN [18]. Patients requiring emergency coronary angiography or procedures, in whom preventive therapy with oral NAC cannot be administered the day before, have been treated with intravenous NAC. The benefit of this approach remains uncertain because of possible side effects such as hypotension and bronchospasm at high dose. Furthermore, comparing the various trials is difficult because of differences in patient populations and dosing, or lack of an adequate control group [20]. The dosing, timing, and procedure for administering NAC in patients receiving CT varied in our meta-analysis. Half of the previous studies reviewed have used oral regimens, and the remainder have used intravenous administration. Results of common effects demonstrated that both administration methods are effective in reducing the risk of CIN without heterogenicity. In a recent meta-analysis, Brown et al. [21] reported that combining NAC and $NaHCO_3$ reduces the occurrence of CIN overall, but does not reduce the occurrence of dialysis-dependent renal failure. However, routine intravenous hydration with $NaHCO_3$ is inconvenient for outpatients receiving CT.

Serum levels of Cr, estimated glomerular filtration rate (GFR), and cystatin C are used as markers of renal function to assess the effect of NAC in preventing CIN. In our meta-analysis, the outcome measurements basically used the increase of serum Cr 20–25 % over baseline creatinine as the definition of CIN. Estimated GFR and cystatin C were measured in only one study [12]. Herts et al. [22] indicated that more patients are identified when estimated GFR values, rather than creatinine levels, are used as a screening tool for renal insufficiency. Cystatin C is reported as a more sensitive marker and clearer indicator of GFR than serum Cr in detecting potential kidney injury, especially in diabetic patients who have received computed tomography coronary angiography and who exhibit extremely low or high muscle mass, cirrhosis, or critical illness [17]. Cystatin C is influenced by non-GFR-dependent factors, such as age, sex, obesity, smoking, thyroid dysfunction, and microinflammation. Nevertheless, Rehman et al. [23] indicated that

the change of cystatin C is not confounded by effects of NAC. Using a sensitive tool to identify patients that may require renal protection strategies is critical in patient care.

Many pharmacological manipulations have been examined to prevent CIN including theophylline, fenoldopam, dopamine, calcium channel blockers, mannitol, and entothelin receptor antagonists; however, the findings are limited, conflicting, or even negative. Huber et al. [6] reported that among patients who were admitted to the intensive care unit and who received 100 ml or more of a contrast medium, theophylline was superior to NAC. However, in a recent meta-analysis, Kelly and colleagues found that, although theophylline showed a risk reduction for CIN, the effects were not statistically significant [8]. Using theophylline may have adverse effects because of its interaction with various drugs.

The variability of clinical factors and the non-uniform reporting of clinical parameters, including baseline serum creatinine, definitions of CIN, timing and methods in evaluating patients' renal function, and hydration and NAC protocols, all contributed to the heterogeneity encountered in our review. The findings from our study show that NAC is associated with decreased risk of CIN and changes of serum creatinine. The strengths of this review include our comprehensive search for eligible studies, systematic and explicit application of eligibility criteria, careful consideration of study quality and rigorous analytical approach. Nonetheless, all meta-analyses are prone to certain limitations, some of which were evident in our study. First, even with our comprehensive search strategy, the possibility of publication bias exists. Studies with null results are generally less likely to be published and are therefore more likely to be missed in a database search. Second, the studies that we included used small samples, ranging from 30 to 209 patients per group, and high-quality data from randomized controlled studies were sparse. Finally, all of the trials that we reviewed displayed inadequate methodological rigor, as evidenced by their lack of double-blinding and unclear descriptions regarding the concealment of patient allocation to different treatment group trials (Table 2).

In conclusion, clinical practice guidelines have recommended hydration as a policy in preventing CIN. Our meta-analysis focused on the question of combined hydration and prophylaxis with NAC, demonstrating a significant benefit in preventing CIN after CT. We recommend that NAC could be more widely used in high-risk patients undergoing CT. Finally and most importantly, clinicians should consider benefit and safety when NAC is administered for protection against CIN and remain cognizant of the volume of contrast and practice an effective hydration regimen.

Conflict of interest None.

Appendix: Search methods for identification of studies

Relevant trials will be obtained from the following sources without language restriction:-

For the MEDLINE and EMBASE search, we used the following combination of keywords:
[Renal failure or kidney failure to include all subheadings] and [contrast media or iopamidol or iodine or ioxaglic acid or iodine compounds or iohexol or urography or tomography or X ray computed] and [clinical trial or randomized controlled trial] and [N-Acetylcysteine or acetylcysteine].
For the PubMed, Cochrane Library Database, and Scopus searches, we used the search words:
Acetylcysteine, radio induced or contrast induced, renal insufficiency or renal failure or kidney injury or nephropathy, randomized controlled trial, and computed tomography.

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