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SYSTEMATIC REVIEW

Prevention of Radiocontrast Nephropathy With *N*-Acetylcysteine in Patients With Chronic Kidney Disease: A Meta-Analysis of Randomized, Controlled Trials

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● ***Background:*** **Radiocontrast nephropathy (RCN) is a common cause of hospital-acquired acute renal failure. Results of several studies using *N*-acetylcysteine (NAC) for the prevention of RCN have yielded conflicting results. We performed a meta-analysis of group data extracted from previously published studies to assess the effect of NAC on the prevention of RCN in patients with pre-existing chronic kidney disease (CKD). *Methods:* Ovid's multidatabase search for MEDLINE, Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, and HealthSTAR were used to identify candidate articles. Abstracts from proceedings of scientific meetings also were screened. We selected blinded and unblinded randomized controlled trials (RCTs) performed in humans 18 years and older with pre-existing CKD, defined by a mean baseline serum creatinine level of 1.2 mg/dL or greater (≥106.1 μmol/L) or creatinine clearance less than 70 mL/min (<1.17 mL/s). The overall risk ratio (RR) for the development of RCN was computed using a random-effects model. *Results:* Eight RCTs (n = 885 patients) published in full-text articles were included in the primary analysis. In the control group, the overall rate of RCN was 18.5% (95% confidence interval [CI], 15 to 22). In the primary analysis, overall RR for RCN associated with the use of NAC was 0.41 (95% CI, 0.22 to 0.79; *P* = 0.007). In a sensitivity analysis that included 4 additional RCTs published in abstract form, RR remained significant at 0.55 (95% CI, 0.34 to 0.91; *P* = 0.020). *Conclusion:* NAC reduces the risk for RCN in patients with CKD. *Am J Kidney Dis* 43:1-9.**

INDEX WORDS: Acute renal failure (ARF); contrast media; *N*-acetylcysteine (NAC); radiocontrast nephropathy (RCN); chronic kidney disease (CKD); meta-analysis.

RADIOGRAPHIC contrast media is the third leading cause of hospital-acquired acute renal failure, accounting for approximately 11% of cases.[1] The incidence of radiocontrast nephropathy (RCN) reported in the literature has ranged between 1% and 45%,[2-4] largely depending on the comorbidity of the study population and parameters used to define RCN. However, the incidence of RCN in low-risk populations (ie, without known risk factors for RCN) ranges from 1% to 3%.[5,6] Risk factors for the development of RCN have been described previously.[7,8] Diabetes mellitus[6,7] and pre-existing chronic kidney disease (CKD)[3,5,7,9] appear to be the most important predictors of RCN.

RCN is associated with both short- and long-term morbidity and mortality. Estimates of in-hospital mortality rates are as high as 34% in

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patients who develop acute renal failure compared with 7% in those who do not.[10,11] Duration of hospitalization and health care expenditures also are elevated in those who develop RCN.[12,13]

The pathophysiological state of RCN is not fully elucidated, and alterations in both kidney hemodynamics and free radical damage have been described.[14-16] *N*-Acetylcysteine (NAC), a free radical scavenger[17,18] with additional vasodilating effects,[17,19] may have a protective role in the prevention of RCN and has been used in a variety of experimental and clinical models of ischemic and nephrotoxic renal tubular injury.[17-22]

Results of several studies using NAC for the prevention of RCN have yielded conflicting results. The primary objective of this meta-analysis is to address whether administration of NAC prevents RCN in patients with CKD.

METHODS

Selection

Studies considered for inclusion in the current analysis were double-blinded and unblinded randomized controlled trials (RCTs) using NAC for the prevention of RCN in humans older than 18 years with CKD. Three-arm trials in which NAC and placebo were 2 of the arms were included. For the purpose of this study, pre-existing CKD is defined as a mean serum creatinine level of 1.2 mg/dL or greater ($\geq$106.1 μmol/L) or creatinine clearance less than 70 mL/min ($<$1.17 mL/s). Intravenous fluid administration was considered standard prophylaxis against RCN for both patient groups. Studies may have been published in either full or abstract format and in any language.

Literature Search

Ovid's multidatabase search for MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and HealthSTAR were used to identify candidate articles by using several search terms alone and in combination. For search purposes, we used the key words radiocontrast nephropathy or contrast-induced renal failure, as well as a combination of the key words acetylcysteine, Parvolex®, or Mucomyst®, with the following entries: nephropathy, renal failure, hospital-acquired renal failure, hospital-acquired renal insufficiency, or chronic kidney disease.

We also searched proceedings of annual scientific meetings of the following societies: American Society of Nephrology (1999 to 2002), American College of Cardiology (1999 to 2003), American Society of Hypertension (2000 to 2003), American Heart Association (2000 to 2002), and Transcatheter Cardiovascular Therapeutics (2001 and 2002).

References of published articles also were examined to identify other candidate studies. Assessment of abstracts from proceedings and published articles by the same investigators were critically appraised to avoid duplication. Abstracts were not considered if they represented partial or complete results of a later published full-text article.

Data Abstraction

Data abstracted included type of diagnostic/therapeutic procedure, number of patients, percentage with diabetes mellitus, inclusion criteria, definition of RCN, intravenous fluid administration protocol, NAC dose protocol, mean contrast volume, radiocontrast type (ionic versus nonionic and low versus high osmolar), and number of RCN events. Of note, if the mean value for the entire study population was not provided, it was calculated by averaging values of the treatment and control groups. Data were verified at least twice before further analysis.

Quantitative Data Synthesis

We used a random-effects model to calculate the risk ratio (RR) for RCN.[23] This model generally is more conservative because it includes in its calculations between-study differences in treatment effects, leading to wider confidence intervals (CIs) when a given level of heterogeneity in treatment effect is observed.[24]

The primary analysis was limited to studies published in full-text articles. We also performed 3 sensitivity analyses to assess the robustness of results. In the first analysis, we excluded 1 study[25] in which patients underwent computed tomography using the same contrast volume for all patients. Of note, this also was the only study in which intravenous rather than intra-arterial contrast was administered. In the second analysis, we excluded the study by Baker et al[26] because it was the only study that used intravenous NAC. In the third analysis, we included studies published in abstract form.

Finally, we performed 2 independent subgroup meta-analyses in all studies (including abstracts) to assess whether there was a difference in the effect of NAC in patients with different levels of kidney function, as well as in studies with different mean volumes of radiocontrast administered. For the former analysis, we chose a creatinine level of 1.9 mg/dL (168.0 μmol/L) as the cutoff value because it divided the studies into 2 equal groups. For the latter, we arbitrarily chose a contrast volume cutoff value of 140 mL because NAC was found to be of benefit only below this level in 1 study.[27]

We also calculated the number needed to treat (NNT = 1/risk difference). This numerical expression of results was used to estimate the number of patients that need to be treated with NAC to prevent 1 case of RCN.[28] All RRs are reported with 95% CIs.

RESULTS

Study Selection Diagram

A schematic representation of the process of selection of studies for this meta-analysis is shown in Fig 1.[2,25-27,29-45] A total of 8 studies published in full-text articles were considered for the primary analysis.[2,26,27,42-46] Four additional

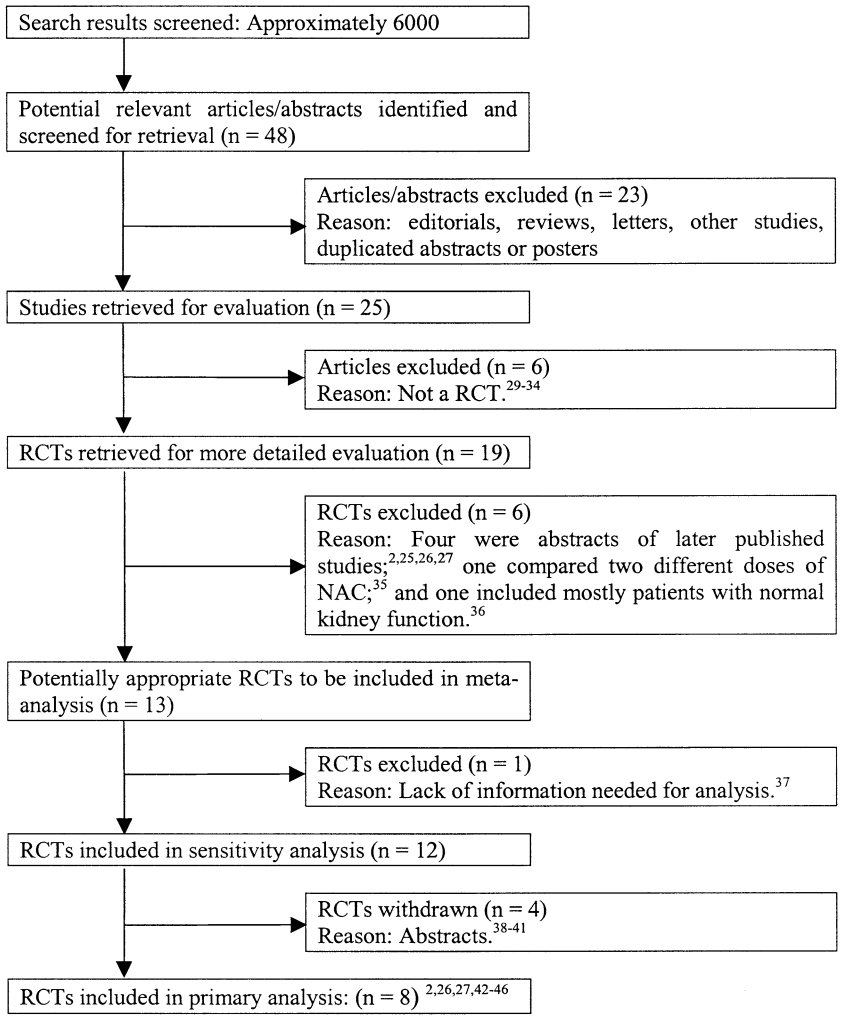

Fig 1. Study selection diagram.

studies published in abstract form were included in a sensitivity analysis.[38-41]

Study Characteristics

Characteristics of the 8 full-text articles included in the primary analysis are listed in Table 1. In brief, all but 3 studies were performed in patients exclusively undergoing cardiac catheterization. One study was performed in patients undergoing computed tomography,[25] and 2 studies included patients undergoing peripheral arterial and coronary artery angiography.[27,42] All studies included patients with pre-existing CKD. Dialysis patients were excluded in all studies.

Mean patient age ranged from 64 to 71 years. Thirty-two percent to 64% of patients had diabetes mellitus. Mean baseline serum creatinine levels ranged from 1.3 to 2.8 mg/dL (114.9 to 247.5 μmol/L). Only 3 studies provided baseline data on left ventricular ejection fraction, and 2 studies provided data on severity of coronary artery disease.

As listed in Table 1, criteria used to define RCN varied among the individual studies. Four studies defined RCN as an increase in baseline serum creatinine level of 0.5 mg/dL or greater ($\geq$44.2 μmol/L) within 48 hours after radiocontrast exposure,[25,42-44] 3 studies considered a 25% increase in serum creatinine level,[26,27,45] and 1 study considered either an increase in serum creatinine level of 0.5 mg/dL or greater, or a 25% increase.[2]

Intravenous fluid administration was considered standard therapy in all studies. However, as listed in Table 1, different regimens were fol-

Table 1. Characteristics of Studies Included in the Meta-Analysis

Reference	No. of Patients	Diagnostic Procedure	Inclusion Criteria	Mean Creatinine (mg/dL)	Diabetes Mellitus (%)	Radiocontrast Characteristics		RCN Definition	IV Fluid Protocol			NAC Dose Protocol
						Type	Volume (mL)		Saline Strength (%)	Rate or Volume	Timing	
Full-text articles												
Tepel et al[25]	83	CT	sCr >1.2 mg/dL or CrCl < 50 mL/min	2.4 ± 1.3	32	LO, NI	75	sCr ↑ ≥ 0.5 mg/dL	0.45	1 mL/kg/h	12 h pre + 12 h post	600 mg orally 2 × d × 2 d
Durham et al[43]	79	CC	sCr >1.7 mg/dL	2.2 ± 0.5	48	LO, NI	81	sCr ↑ ≥ 0.5 mg/dL	0.45	1 mL/kg/h	≤12 h pre + ≤12 h post	1,200 mg orally 1 h pre + 3 h post
Briguori et al[27]	183	CC/PA	sCr >1.2 mg/dL, CrCl < 70 mL/min	1.5 ± 0.43	38	LO, NI	197	sCr ↑ ≥ 25% or dialysis	0.45	1 mL/kg/h	12 h pre + 12 h post	600 mg orally 2 × d × 2 d
Diaz-Sandoval et al[2]	54	CC	sCr ≥1.4 mg/dL or CrCl < 50 mL/min	1.6 ± 0.29	39	LO, NI	184	sCr ↑ ≥ 0.5 mg/dL or > 25%	0.45	1 mL/kg/h	2-12 h pre + 12 h post	600 mg orally 2 × d × 2 d
Shyu et al[44]	121	CC	sCr ≥ 2 or < 6 mg/dL or CrCl < 40 mL/min	2.8 ± 0.8	64	LO, NI	117	sCr ↑ ≥ 0.5 mg/dL	0.45	1 mL/kg/h	12 h pre + 12 h post	400 mg orally 2 × d × 2 d
Allaqaband et al[42]	85*	CC/PA	sCr ≥ 1.6 mg/dL, or CrCl ≤ 60 mL/min	2.1 ± 0.6	50	LO, NI	~124	sCr ↑ ≥ 0.5 mg/dL	0.45	1 mL/kg/h	12 h pre + 12 h post	600 mg orally 2 × d × 2 d
Kay et al[45]	200	CC	sCr ≥ 1.2 mg/dL or CrCl < 60 mL/min	1.3 ± 0.44	38	LO, NI	139	sCr ↑ > 25%	0.9	1 mL/kg/h	12 h pre + 6 h post†	600 mg orally 2 × d × 2 d
Baker et al[26]	80	CC	sCr > 1.3 mg/dL or CrCl < 50 mL/min	1.8 ± 0.51	42	IO, NI	227	sCr ↑ > 25%	0.9	1 mL/kg/h	12 h pre + 12 h post†	150 mg/kg IV 30 min pre, 50 mg/kg over 4 h post‡
Abstracts												
Azmus et al[39]	204	CC	CKD or age > 69 y or diabetes	1.2‖	49	HO, I	NA	sCr ↑ > 25%	0.9	2,000 mL	NA	NA
Ochoa et al[41]	80	CC	CrCl < 50 mL/min	1.9 ± 0.6	NA	LO, NI	141	sCr ↑ > 0.5 mg/dL or > 25%	0.45	≥1,000 mL	Pre + post	1,000 mg orally 1 h pre + 4 h post
Loutrianakis et al[38]	47*	CC	sCr > 1.5 mg/dL	1.9 ± 0.35	NA	NA	NA	sCr ↑ ≥ 0.5 mg/dL or > 25%§	0.45	1 mL/kg/h	Pre + post	600 mg orally 2 × d × 2 d
Oldemeyer et al[40]	96	CC	CrCl < 50 mL/min	1.6‖	NA	NA	130	sCr ↑ > 0.5 mg/dL or > 25%	0.45	1 mL/kg/h	12 h pre + 12 h post	1,500 mg orally 2 × d × 2 d

NOTE. Values expressed as mean ± SD unless noted otherwise. To convert creatinine in mg/dL to μmol/L, multiply by 88.4; creatine clearance in mL/min to mL/s, multiply by 0.01667.

Abbreviations: sCr, serum creatinine; CrCl, creatinine clearance; DM, diabetes mellitus; CC, cardiac catheterization; CT, computed tomography; PA, peripheral angiography; IV, intravenous; LO, low osmolar; HO, high osmolar; IO, iso-osmolar; NI, nonionic; I, ionic; NA, not available.

*Excluding fenoldopam group.

†Liberal oral intake also was permitted.

‡NAC was administered in 500 mL of 0.9% saline.

§As a conservative estimate the 25% definition was used for the current meta-analysis because in particular for this value, placebo was found to be better than NAC.

‖Data on SD are not available from the abstract.

Table 2. Conclusions Drawn in Individual Studies Included in the Meta-Analysis

Reference*	Year	RCN (cases/no. of patients) NAC	RCN (cases/no. of patients) Control	Rate of RCN (%)	RR (95% CI)†	Conclusion of Investigators‡
Full-text articles						
Briguori et al[27]	2002	6/92	10/91	11	0.59 (0.23-1.57)	No benefit with NAC
Kay et al[45]	2003	4/102	12/98	12	0.32 (0.11-0.96)	Benefit with NAC
Allaqaband et al[42]	2002	8/45	6/40	15	1.19 (0.45-3.12)	No benefit with NAC
Tepel and Zidek[46]	2000	1/41	9/42	21	0.11 (0.02-0.86)	Benefit with NAC
Baker et al[26]	2003	2/41	8/39	21	0.24 (0.05-1.05)	Benefit with NAC
Durham et al[43]	2002	10/38	9/41	22	1.20 (0.55-2.63)	No benefit with NAC
Shyu et al[44]	2002	2/60	15/61	24	0.14 (0.03-0.57)	Benefit with NAC
Diaz-Sandoval et al[2]	2002	2/25	13/29	45	0.18 (0.04-0.72)	Benefit with NAC
Abstracts						
Oldemeyer et al[40]	2003	4/49	3/47	6	1.28 (0.30-5.41)	No benefit with NAC
Loutrianakis et al[38]	2003	8/24	2/23	8	3.83 (0.91-16.18)	No benefit with NAC
Azmus et al[39]	2002	11/104	17/100	17	0.62 (0.31-1.26)	No benefit with NAC
Ochoa et al[41]	2002	4/36	11/44	25	0.44 (0.12-1.28)	No benefit with NAC

*Studies listed in ascending order by rate of RCN in the control group.
†Risk ratio (RR) based on random-effects model.
‡Investigators' conclusion based on relative risk for RCN (as defined in the current meta-analysis) in individual studies.

lowed. Six studies followed a very similar protocol, consisting of 0.45% saline up to 12 hours before and up to 12 hours after administration of radiocontrast. In the remaining 2 studies, patients were administered 0.9% saline 12 hours before and 6 to 12 hours after contrast exposure.[26,45]

Mean radiocontrast volume ranged from 75 to 230 mL. Seven studies used low-osmolar nonionic contrast media, whereas the remaining study used iso-osmolar nonionic contrast.[26]

NAC was administered orally in 7 studies. In 5 studies, a dose of 600 mg twice daily for 2 days was used, starting the day before the procedure.[2,27,42,45,46] In 2 studies, NAC was administered orally as either a 400-mg dose twice a day for 2 days[44] or 1,200 mg just before contrast exposure.[43] In the last study, an intravenous dose of 150 mg/kg of NAC was administered 30 minutes before the procedure, followed by 50 mg/kg over 4 hours.[26]

Among the 4 studies published in abstract form and included in the sensitivity analysis (Table 1), NAC administration protocols included an oral dose of 600 mg twice daily for 2 days,[38] a 1,000-mg dose orally 1 hour before and 4 hours after radiocontrast exposure,[41] and a 1,500-mg dose twice daily for 2 days.[40] One study failed to mention the dose or route of NAC administration.[39]

Table 2 lists conclusions drawn in the individual studies included in the meta-analysis.

Quantitative Data Synthesis

Primary analysis. The primary analysis included the 8 full-text published RCTs, totaling 885 patients (Fig 2). The NAC and control groups had a total of 444 and 441 patients, respectively. There were 35 cases of RCN in the NAC groups and 82 cases in the control groups. The overall weighted rate of RCN in the control group was 18.5% (95% CI, 15 to 22). Overall RR associated with the NAC use was 0.41 (95% CI, 0.22 to 0.79; $P = 0.007$). The estimated number needed to treat with NAC to prevent 1 case of RCN was 8 (95% CI, 5 to 23).

Sensitivity analyses. In the first sensitivity analysis that excluded the study by Tepel et al,[25] RR was essentially unchanged at 0.46 (95% CI, 0.24 to 0.88; $P = 0.020$). In the second sensitivity analysis that excluded the study by Baker et al,[26] RR also was essentially unchanged at 0.44 (95% CI, 0.22 to 0.88; $P = 0.020$). In the third sensitivity analysis (Fig 3), which was inclusive of the 4 abstracts listed in Tables 1 and 2, a total of 12 studies (n = 1,312) were combined. The overall weighted RCN rate in the control group was 18% (95% CI, 15 to 21). Overall RR for RCN associated with the use of NAC was 0.55 (95% CI, 0.34 to 0.91; $P = 0.020$).

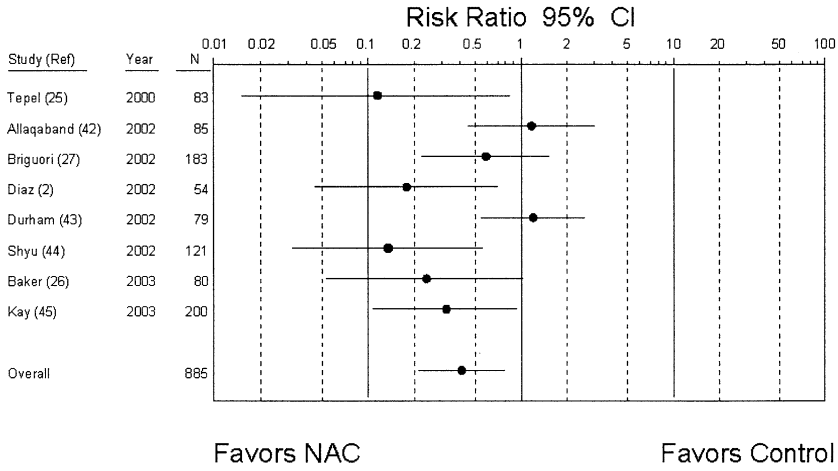

Fig 2. Primary analysis for the prevention of RCN with NAC in patients with CKD. The primary analysis was limited to the 8 RCTs published in full-text articles and performed using the DerSimonian & Laird random-effects model. Data presented as RRs with 95% CIs. Overall RR for RCN was 0.41 (95% CI, 0.22 to 0.79; *P* = 0.007) in favor of NAC.

Subgroup analyses. Table 3 lists results of independent subgroup meta-analyses. RRs for RCN were 0.66 (95% CI, 0.27 to 1.61; $P = 0.360$) and 0.47 (95% CI, 0.29 to 0.76; $P = 0.002$) in patients with a mean baseline creatinine level of 1.9 mg/dL or greater (≥168.0 μmol/L) or less than 1.9 mg/dL, respectively.

Among patients administered 140 mL or less of contrast material, RR for RCN associated with the use of NAC was 0.54 (95% CI, 0.24 to 1.21; $P = 0.140$), whereas among those administered greater than 140 mL, RR was 0.38 (95% CI, 0.21 to 0.68; $P = 0.001$).

DISCUSSION

Results of this meta-analysis suggest that NAC prevents RCN in subjects with CKD. This finding is important from the perspective of both patients and health care expenditure. RCN is associated with greater morbidity and mortality and often is associated with increased expenditures because of prolonged hospitalizations and the need for additional diagnostic testing.[13] Consequently, the result of this meta-analysis, which shows a beneficial effect of NAC in preventing RCN, is an important public health finding.

Although independent subgroup meta-analyses noted some differences in the benefit of NAC depending on either mean volume of radiocontrast administered or mean baseline level of kidney function, it is difficult to know whether these are caused by true differences or statistical differences secondary to power limitations. That

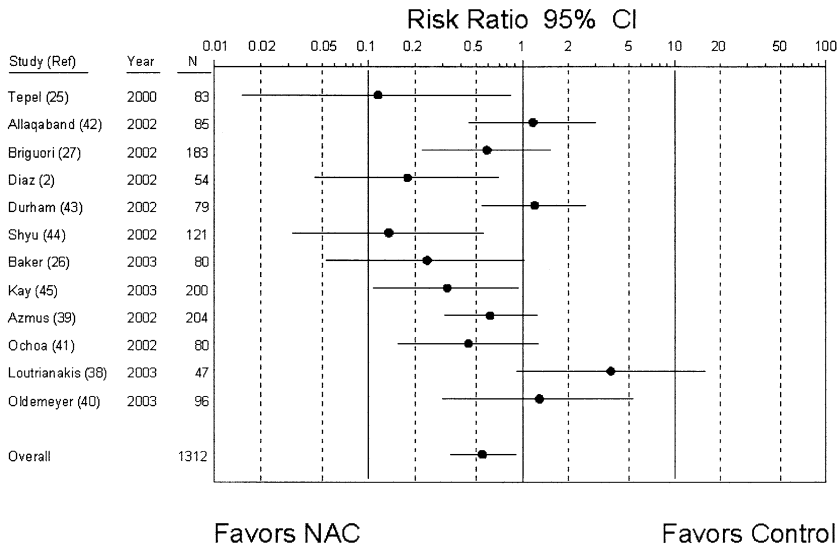

Fig 3. Sensitivity analysis for the prevention of RCN with NAC in patients with CKD. Sensitivity analysis included 4 additional RCTs published in abstract form and was performed using the DerSimonian & Laird random-effects model. Data presented as RRs with 95% CIs. Overall RR for RCN was 0.55 (95% CI, 0.34 to 0.91; *P* = 0.020). *Abstract.

Table 3. Subgroup Analyses

Category	No. of Studies	No. of Patients	RR (95% CI)	*P*
Mean baseline serum creatinine (mg/dL)				
≥1.9	6	495	0.66 (0.27-1.61)	0.360
<1.9	6	817	0.47 (0.29-0.76)	0.002
Mean radiocontrast volume* (mL)				
>140	4	397	0.38 (0.21-0.68)	0.001
≤140	6	664	0.54 (0.24-1.21)	0.140

NOTE. Independent subgroup meta-analyses were performed after classifying studies according to baseline mean serum creatinine level and contrast volume. To convert creatinine in mg/dL to μmol/L, multiply by 88.4.

*Mean radiocontrast volume was not available in 2 studies.[38,39]

is, RR for NAC was less than 0.7 in all subgroups of patients (Table 3).

Among the 8 studies included in the primary analysis, 3 studies failed to show a benefit of NAC. In the study by Durham et al,[43] we can only speculate about whether the oral administration of NAC only 1 hour before cardiac catheterization may have been the reason for lack of efficacy. Although in healthy subjects, serum NAC levels have peaked 1 to 2 hours after oral administration,[47] absorption may have been erratic in this patient study group because of comorbidity. Furthermore, because CKD is associated with glutathione peroxidase depletion, measured by low levels in plasma, urine, and kidney parenchyma,[48] it remains to be determined whether repletion of this important intracellular antioxidant with NAC would require longer oral therapy. It is worth noting that the study by Baker et al,[26] which used an intravenous dose of NAC 30 minutes before contrast exposure, was beneficial in preventing RCN. Therefore, length of dosing and route of administration may have a role in the efficacy of NAC.

There are several potential limitations to our meta-analysis. First, the studies included in this meta-analysis are heterogeneous with respect to patient population and type of radiological intervention. Patients with various degrees of kidney impairment and comorbid conditions were administered either intravenous or intra-arterial radiocontrast at various volumes and different protective doses and routes of administration of NAC. However, our findings strengthen the notion that physicians are more likely to encounter heterogeneity in clinical practice. Second, the definition of RCN adopted in this analysis was derived from the different definitions used in the individual studies. This clearly calls for the need to develop uniform criteria to define RCN for research purposes, which would allow better comparison among studies. Third, publication bias is always a potential limitation in a meta-analysis. In other words, negative studies are not published because they either have not been submitted or accepted for publication. We attempted to partially account for this limitation by including abstracts in the sensitivity analysis because negative studies may be more likely to remain unpublished after being presented in abstract form.[49] Finally, this meta-analysis is limited to summary measures of unadjusted RCN rates. A pooled analysis of individual patient-level data therefore would be important to enable adjustment of analyses for variables that potentially are important risk factors for RCN. Furthermore, individual patient data would allow assessment of risk factors for RCN, which is not possible in a meta-analysis of summary data.

To date, most preventive strategies for RCN have been associated with increased health care costs.[13,50-52] For example, the use of low-osmolar nonionic contrast medium costs greater than $100/100 mL, which is approximately 10 times the cost of conventional ionic agents.[53] Replacement of ionic agents by nonionic or low-osmolar contrast media for all radiographic procedures was estimated to add more than $1 billion to the annual US health care budget.[13,53,54] Similarly, fenoldopam, an experimental drug under current investigation to prevent RCN, may cost $200/d to $1,000/d and has potential serious side effects, including hypotension.[55] Conversely, NAC has limited side effects, and a 2-day treatment of 600

mg twice daily costs approximately $24.[56] Therefore, although no formal cost-effectiveness analyses have been performed, it would appear reasonable to conclude that in addition to intravenous fluid administration of saline, NAC is an ideal agent to prevent RCN in patients with CKD.

In summary, NAC is effective in preventing RCN in adult patients with pre-existing CKD who undergo procedures involving intravascular administration of iodinated radiocontrast material. Although cost-effectiveness analyses are lacking, NAC is inexpensive and has limited adverse side effects and therefore should be recommended to subjects at high risk for RCN.

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