Clin. Cardiol. 27, 607–610 (2004)

Role of N-Acetylcysteine in Prevention of Contrast-Induced Nephropathy after Cardiovascular Procedures: A Meta-Analysis

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Summary

Background: Contrast-induced nephropathy is one of the common causes of acute renal insufficiency after cardiovascular procedures.

Hypothesis: The objective of this paper was to analyze the published data on the usefulness of N-acetylcysteine in the prevention of contrast-induced nephropathy after these procedures.

Methods: Trials were selected if they were prospective, randomized, controlled, had selected patients with impaired renal function, used low-osmolality, nonionic contrast media intra-arterially, administered a total of four doses of N-acetylcysteine in addition to intravenous saline hydration, and had contrast-induced nephropathy as their primary outcome. Contrast-induced nephropathy was defined as an increase in serum creatinine concentration by > 0.5 mg/dl or a 25% increase above baseline at or within 48 h post procedure. Meta-analysis was performed using the Fisher's Combined Test with a measure of effect size. The magnitude of the N-acetylcysteine effect was estimated using random-effects models. Homogeneity was evaluated using the chi-square test of homogeneity and standard Q statistic. Reporting bias was explored by the Rosenthal method.

Results: The Fisher's Combined Test was significant at $p < 0.005$ in favor of N-acetylcysteine. The size of the N-acetylcysteine effect was to reduce contrast-induced nephropathy by 20%. There was a 62% relative risk reduction in contrast-induced nephropathy with N-acetylcysteine using a fixed-effects model, and a 70% relative risk reduction using the random-effects model. In addition, we found that 27 unpublished trials showing no effects of N-acetylcysteine would exist to overturn the combined significance of $p < 0.005$ of the five trials in our meta-analysis.

Conclusion: Oral administration of N-acetylcysteine in addition to intravenous saline hydration has a beneficial effect in the prevention of contrast-induced nephropathy after cardiovascular procedures in patients with impaired renal function.

Key words: N-acetylcysteine, contrast induced nephropathy, radio contrast dyes, renal failure, coronary angiography, percutanous coronary intervention, cardiac catheterization

Introduction

Contrast-induced nephropathy is one of the common causes of acute renal insufficiency in hospitalized patients. With an increasing number of patients undergoing cardiovascular procedures with significant comorbidities, there is a need for agents to prevent the incidence of contrast-induced nephropathy. The rate of contrast-induced nephropathy among all patients undergoing cardiovascular procedures has been reported to be anywhere from 7.8 to 17%.[1] Of these patients, 0.5 to 2% will require dialysis; this translates into longer hospital stays and increased health care costs.[2] The exact mechanism causing contrast-induced nephropathy is unknown; however, direct cytotoxicity of the contrast agents, apoptosis, and vasoconstriction of the renal vasculature with resultant decreased renal blood flow have all been proposed. The only established modality for the prevention of contrast-induced nephropathy is peri-procedure hydration.[3–5] The efficacy of N-acetylcysteine in preventing contrast-induced nephropathy has been studied in several small single-center trials. Its proposed mechanism of action could be related to its antioxidant properties, which might prevent oxidative tissue damage in the kidney, or

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Received: July 30, 2004
Accepted with revision: September 21, 2004

to its hemodynamic effects by improving endothelium-dependent vasodilatation.[6–8] Advantages of N-acetylcysteine are its low cost and lack of significant side effects. In this meta-analysis, our aim was to examine the usefulness of N-acetylcysteine in the prevention of contrast-induced nephropathy after cardiovascular procedures.

Trial Selection

Our meta-analysis included trials that focused on the role of N-acetylcysteine in the prevention of contrast-induced nephropathy after cardiovascular procedures. We identified trials by performing a MEDLINE search as well as by reviewing the references of the identified articles.[9–13] Trials were included if they were published in the English language and met the following criteria: design as prospective, randomized, controlled trials; inclusion of patients who were at high risk due to their renal status (impaired renal function); use of low-osmolality nonionic contrast media intra-arterially for diagnostic or therapeutic cardiovascular procedures; use of N-acetylcysteine to prevent contrast nephropathy in addition to intravenous saline hydration; administration of a total of four doses of N-acetylcysteine starting the day before procedure and continued through the day of procedure. All of the trials compared orally administered N-acetylcysteine and peri-procedural hydration (treatment group) to peri-procedural hydration alone (control group). In each of the selected trials, the endpoint of interest was contrast-induced nephropathy, which was defined as an increase in the creatinine concentration by > 0.5 mg/dl or a 25% increase above baseline creatinine at or within 48 h post administration of contrast agent.

Statistical Analysis

Meta-analysis was performed using the Fisher's Combined Test with a measure of effect size. This test has been shown to be more asymptotically optimal and more conservative than the other combination methods. This statistical test was accompanied with several indices of effect size to gain further insight as to the strength of the effect of N-acetylcysteine. The magnitude of the N-acetylcysteine effect was evaluated by estimating the population effect size using a random-effects model (both unweighted and weighted by the sample size of each trial). The pooled relative risk weighted by inverse variance (a quality weight that is the product of the precision) was also calculated using both the fixed-effects and random-effects models. Homogeneity of data was evaluated using the methods outlined by Hunter *et al.*[14] and McDaniel *et al.*,[15] which used a chi-square test of homogeneity and examined the absolute amount of residual variance, respectively. The standard Q Statistic was also calculated for comparison to the preceding. Finally, to explore the presence of reporting bias or publication bias, we used the method of Rosenthal[16] to calculate the number of no-effect findings that would have to exist unpublished to invalidate a significant overall p.

Results

Five trials were identified based on our search;[9–13] the trial data are summarized in Table I. The total number of patients included was 643, of which 319 patients were randomized to hydration alone (control group) and 324 to N-acetylcysteine and hydration (treatment group). The age of the patients ranged from 64 to 73 years and the baseline creatinine ranged from 1.36 to 2.8 mg/dl. The amount of contrast agent used ranged from 115 ± 48 to 200 ± 144 ml. N-acetylcysteine was administered as a twice-daily dose starting the day prior to procedure for a total of four doses in each trial.

The incidence of the primary endpoint of contrast-induced nephropathy was 11 to 45% in the control group versus 3 to 18% in the treatment group. Patients with greater severity of renal insufficiency in the study by Shyu *et al.*[10] demonstrated a remarkable reduction in contrast-induced nephropathy from 44% in the control arm to 8% in the treatment arm. Briguori *et al.*[12] did an analysis based on the volume of contrast used and divided the patients into two groups, those with < 140 ml of contrast administered (n = 60 in each control and treatment groups) and those with > 140 ml (n = 30 in the control group and 32 in the treatment group). They concluded that N-acetylcysteine was effective in preventing contrast-induced nephropathy only in the subgroup of patients who received < 140 ml of contrast agent.

The indicators of homogeneity showed that five trials had significant heterogeneity; however, including only the subgroup of patients who received < 140 ml of contrast in the Briguori trial, all of the tests of homogeneity agreed that this population was homogeneous (Table II). For further analysis, the subgroup of patients from the Briguori trial who received > 140 ml of contrast (n = 62 patients) was excluded. The Fisher's Combined Test was significant at $p < 0.005$ in favor of N-acetylcysteine (Table III). The size of the N-acetylcysteine effect illustrated by the pooled correlation coefficient (weighted mean r) was to reduce contrast-induced nephropathy by 20%. This meta-analysis showed a 62% relative risk reduction in patients given acetylcysteine using a fixed-effects model, and a 70% risk reduction using the random-effects model showing robustness. In addition, we found that 27 unpublished trials showing no effects of N-acetylcysteine would exist to overturn the combined significance of $p < 0.005$ of the five trials in our meta-analysis.

Discussion

Initially Tepel *et al.*[17] demonstrated the positive effect of the use of N-acetylcysteine in the prevention of contrast-induced nephropathy in patients undergoing computed tomography scans with an intravenous administration of 75 ml of contrast. The incidence of contrast-induced nephropathy in the control group was 21 versus 2% in the treatment arm.[1] Following this, there was an interest in the use of N-acetylcysteine for the prevention of contrast-induced nephropathy in patients undergoing cardiovascular procedures.

TABLE 1 Meta-analysis data

	Diaz-Sandoval *et al.* (9)	Shyu *et al.* (10)	Allaqaband *et al.* (11)	Briguori *et al.* (12)	Kay *et al.* (13)
Number of patients (n)					
Control group	29	61	40	91	98
N-acetylcysteine group	25	60	45	92	102
Contrast agent	Ioxilan	Iopamidol	Ioversol or Iodixal	Iopromide	Iopamidol
N-acetylcysteine dose	600 mg × 4	400 mg × 4	600 mg × 4	600 mg × 4	600 mg x 4
Angiography/angioplasty	Coronary	Coronary	Coronary, peripheral	Coronary, peripheral	Coronary
Volume of contrast (ml)					
Control group	189 ± 12	115 ± 48	122 ± 16	200 ± 144	120 (median)
N-acetylcysteine group	179 ± 8	119 ± 3	122 ± 16	194 ± 127	130 (median)
Baseline creatinine (mg/dl)					
Control group	1.56 ± 0.05	2.8 ± 0.8	2.03 ± 0.79	1.54 ± 0.36	1.36
N-acetylcysteine group	1.66 ± 0.06	2.8 ± 0.8	2.20 ± 0.73	1.52 ± 0.43	1.35
48-h creatinine (mg/dl)					
Control group	1.88 ± 0.09	3.1 ± 1.0	2.03 ± 48	1.53 ± 0.45	1.38
N-acetylcysteine group	1.53 ± 0.09	2.5 ± 1.0	2.22 ± 1.0	1.48 ± 0.36	1.22
P value (of change in creatinine)	< 0.0001	< 0.001	NS	NS	0.006
Contrast-induced nephropathy					
Control group (n) (%)	13/29 (44.8)	15/61 (24.6)	6/40 (15)	10/91 (11)	12/98 (12.2)
N-acetylcysteine group (n) (%)	2/25 (8)	2/60 (3.3)	8/45 (17.8)	6/92 (6.5)	4/102 (3.9)
P-value (of contrast-induced nephropathy)	0.005	< 0.001	0.73	0.22	0.03
Relative risk of contrast-induced nephropathy	0.18 (0.04,0.72)	0.14 (0.03,0.57)	1.18 (0.45,3.12)	0.59 (0.22,1.57)	0.32 (0.10,0.96)
Pearson's correlation coefficient (r) [a]	0.41	0.31	0.04	0.08	0.15
Measure of effect size (d)	0.90	0.65	0.08	0.16	0.30

[a] Pearson's correlation coefficient (r) is calculated for each study using the formula: $r = \sqrt{\chi^2/n}$, and then converted to a measure of effect size (d) using the formula: $d = 2r/(\sqrt{1-r^2})$.

TABLE II Data homogeneity results

Method	Results
Q statistic	9.4665 (with 4 df, p = 0.0504)
Random effects model	
Residual standard deviation	0.03849 (< 1/4 of the population effect size)
Observed variance accounted for by sampling error	84.3% (> 75% of the observed variance accounted for by sampling error)
Chi-square test of homogeneity	5.92956 (with 4 df, p = 0.2045)

Abbreviation: df = degrees of freedom.

TABLE III Meta-analysis results

Method	Results
Fisher's combined test	41.76 (with 10 df, p<0.005)
Estimate of effect size	
Pooled correlation coefficient	0.213
Weighted correlation coefficient [a]	0.196
Pooled relative risk weighted by inverse variance	
Fixed effects model	0.380 (95% CI: 0.214,0.676), p = 0.0010
Random effects model	0.299 (95% CI: 0.110,0.815), p = 0.0183

[a] Weighted by sample size.

Abbreviations: CI = confidence interval, df = degrees of freedom.

In this meta-analysis we combined data from a homogeneous group focusing on the trials that used low-osmolality, nonionic contrast media intra-arterially for cardiovascular procedures and administered a total of four doses of N-acetylcysteine. The size of the N-acetylcysteine effect was to reduce contrast-induced nephropathy by 20%, illustrated by the pooled correlation coefficient weighted by sample size. We estimated a significant reduction in the relative risk of contrast-induced nephropathy in patients given acetylcysteine (62% using the fixed-effects model and 70% using the random-effects model). Meta-analyses are subject to publication bias because they largely summarize the results of published positive trials that were more likely to be published than negative trials. Nonetheless, it would need 27 unpublished negative trials to overturn the results of this meta-analysis, which is a fairly large number of unpublished negative trials. By excluding the subgroup of patients who received > 140 ml of contrast

in the Briguori trial, we might have increased the positive effect found by our analysis, but it was realistic to exclude this group to have a homogeneity in the pooled data.

Contrast-induced nephropathy remains a major issue in the cardiovascular procedures, and the conflicting results have been reported by relatively small trials on the role of N-acetylcysteine, in addition to saline hydration, in the prevention of contrast-induced nephropathy. We have attempted to address this issue by gathering relatively narrow but specific data in this meta-analysis. However, meta-analysis in not a replacement for a large trial; therefore, larger trials are needed to clarify the role of N-acetylcysteine in the prevention of contrast-induced nephropathy after cardiovascular procedures. In addition, newer iso-osmolar contrast agents have been shown to reduce the incidence of contrast-induced nephropathy in high-risk patients with chronic renal insufficiency and diabetes, and the effect of N-acetylcysteine in addition to the use of these agents needs to be studied.[18] Recently, a study from United Kingdom has reported beneficial effects of an intravenously administered, accelerated dosing regimen of N-acetylcysteine in preventing contrast-induced nephropathy in patients undergoing cardiac catheterization and intervention when time urgency did not permit its oral administration;[19] however, the parenteral preparation of N-acetylcysteine is not available in United States.

Conclusion

Oral administration of N-acetylcysteine in addition to saline hydration has a beneficial effect in the prevention of contrast-induced nephropathy after cardiovascular procedures in patients with impaired renal function. Increased morbidity and higher health care costs associated with contrast-induced nephropathy can possibly be reduced by using N-acetylcysteine, which has minimal cost and has no major side effects.

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