RENOPROTECTIVE EFFECT OF HIGH PERIPROCEDURAL DOSES OF ORAL N-ACETYLCYSTEINE IN PATIENTS SCHEDULED TO UNDERGO A SAME-DAY ANGIOGRAPHY

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ABSTRACT

BACKGROUND: Few studies that have assessed the effect of abbreviated oral N-acetylcysteine (NAC) regimens in radiocontrast-induced nephropathy (RCIN) yield mixed results. OBJECTIVE: To evaluate the renoprotective effect of high periprocedural oral doses (HPOD) of NAC in patients with chronic renal impairment undergoing a same-day angiography. METHODS: Sixty one patients with renal impaired function scheduled to undergo a same-day angiography were randomly assigned to NAC 1200 mg orally 3 hours before and 3 after the procedure, or a placebo. All patients received 0.9% saline intravenous. RCIN was defined as an increase in SCC > 0.5 mg/dl 48 hours after the procedure. RESULTS: The mean baseline SCC for all patients was 1.44 ± 0.42 mg/dl. A significant difference in SCC change at 48 hours after the angiography was found (-0.07 mg/dl NAC, 0.09 mg/dl placebo, P=0.04). RCIN occurred in 1 (3%) patient of NAC group and in 2 (7.1%) patients of placebo group (P=0.59). Adverse effects were similar in both groups. CONCLUSIONS: In patients with mild renal impairment patients undergoing angiographic procedures, HPOD of NAC were more effective than placebo in preventing SCC change 48 hours. A non significant benefit in RCIN incidence was found.

KEY WORDS: N-acetylcysteine, contrast media, angiography, acute renal failure.

RESUMEN

ANTECEDENTES: Los escasos estudios q ue han evaluados los efectos de regimenes abreviados de N-acetilcisteína (NAC) oral en la nefropatía por contraste (NC) han encontrado resultados contrapuestos. OBJETIVO: Evaluar el efecto renoprotector de altas dosis orales periprocedimiento (ADOP) de NAC en pacientes con insuficiencia renal con angiografía programada el mismo día. MATERIAL Y METODOS: Sesenta y un pacientes con insuficiencia renal y angiografía programada para el mismo día fueron asignados aleatoriamente a 1200 mg de NAC 3 horas previas y 3 horas posteriores al cateterismo o un placebo. Todos los pacientes recibieron hidratación endovenosa con solución salina al 0.9%. La NC se definió como el aumento en la creatinina sérica (CS) > 0.5 mg/dl a las 48 horas del procedimiento. RESULTADOS: La CS media en todos los pacientes fue 1.44 ± 0.42 mg/dl. Se encontró una diferencia significativa entre ambos grupos en el cambio de CS a las 48 horas de la angiografía (-0.07 mg/dl NAC, 0.09 mg/dl placebo, P=0.04). La NC se presentó en 1 (3%) paciente del grupo NAC y en 2 (7.1%) pacientes del grupo placebo (P=0.59). Los efectos adversos fueron similares en ambos grupos. CONCLUSION: En pacientes con insuficiencia renal leve sometidos a angiografía en el mismo día, las ADOP de NAC fueron más efectivas que el placebo en la prevención del cambio de CS a las 48 horas del procedimiento. Se

encontró un beneficio no significativo en la incidencia de NC.

PALABRAS CLAVE: N-acetilcisteína, medio de contraste, angiografía, insuficiencia renal aguda.

INTRODUCTION

Radiocontrast agent administration during angiographic procedures often induces a renal function reduction.[1,2] Even though it is usually mild and reversible, it is associated with extended hospital stay and adverse clinical outcomes, including the occasional requirement of dialysis.[1,3] The ability to effectively prevent RCIN would result in a significant public health benefit, especially now that the ongoing advances of catheter-based technologies are steadily increasing the volume of diagnostic and therapeutic angiographic procedures.[2]

The precise mechanism of RCIN is not well understood, but there is evidence that it is related to alteration in renal hemodynamics and direct toxic effects on the renal tubular cells mediated by oxygen free radicals.[4] Except for intravenous hydration and low osmolality contrast media, no other strategies have proven clearly to be efficacious in preventing RCIN.[2,4-6]

Since Tepel *et al*[7] reported that N-acetylcysteine (NAC), an antioxidant agent, was effective in preventing RCIN among patients undergoing CT with angiographic contrast, several studies have assessed the effectiveness of NAC preventing RCIN after diagnostic and/or interventional angiographic procedures, with mixed results.[8-14] In most of these trials, NAC was started the day before the angiogram, precluding patients with clinical presentations that require angiographic procedures the same day.

Considering that high oral doses of NAC do not increase the incidence of side effects[15], and peak serum levels are achieved within 2 hours after the administration[16], we investigate the renoprotective effects of high periprocedural oral doses (HPOD) of NAC in patients with chronic renal impairment undergoing a same-day angiography.

METHODS

Study Population

This prospective, randomized double blind, placebo-controlled trial was conducted from Febrary-2002 through January-2004. Patients scheduled to undergo a same-day coronary or peripheral angiographic diagnostic or interventional procedure were eligible if they were 18 years or older and had a stable serum creatinine concentration (SCC) above 1.5 mg/dl or an estimated creatinine clearance using Cockroft-Gault formula below 50 mL/min. Exclusion criteria were: dialysis, acute renal failure (ARF), hemodynamic instability (systolic blood pressure < 80 mmHg or on vasoactive drugs), congestive heart failure, pregnancy, lactation, severe asthma and contrast medium use within the previous 10 days. The local ethics committee approved the study protocol and all patients gave written informed consent.

Study Protocol

Patients were randomly assigned to receive either NAC or placebo using a computer generated randomization list. A 1200 mg-oral dose of NAC (Fluimucil; Zambon Group, Barcelona, Spain) was given 3 hours before and 3 hours after catheterization. NAC was diluted in 125 ml of orange juice. The placebo was simply 125 ml of orange juice with similar appearance and taste. Both groups received intravenous hydration with 0.9% saline at a rate of 4 ml/kg/hr for 3 hours before the angiogram and at a rate of 2 ml/kg/hr for 6 hours after radiocontrast exposure. Liberal fluids intake was encouraged to all subjects after the angiographic procedure. The administration of theophylline, dopamine or mannitol was not allowed during the study. The angiographic procedures were performed with ionic (amidotrizoate or ioxitalamate), nonionic (iopamidol or iohexol) or both types of contrast agents. The dose and the type of radiocontrast used, as well as the adjunctive drug therapies given, were left at the discretion of the physician performing the procedure. Participants and all study personal including physicians, nursing staff, assessors and

data analysts, were blinded to treatment assignment. No request for unblinding was implemented. All patients were evaluated 48 hours after procedure. Hospital registers were screened up to 30 days after the procedure and followed for 30 days after the angiographic procedure to detect readmissions due to ARF, requirement for dialysis or death.

Endpoints

The primary endpoint was RCIN defined as an increase in SCC > 0.5 mg/dl 48 hours after the procedure. Secondary endpoints were: a) SCC change at 48 hours, b) length of hospitalization measured from admission to discharge or up to a vascular procedure, c) combined event rate of readmission for ARF, dialysis requirement or death within 30 days.

Statistical Analysis

Based on previous data showing a RCIN incidence of 28.5% in a similar population pretreated with hydration plus low and/or high-osmolar mediums [6], 28 patients in each group would be required to detect a similar RCIN reduction after NAC treatment as a previous study [7](two-sided significance level of 5% and 80% power). A final sample of 60 participants was planned. Data were expressed as mean + SD or percentages. Continuous data were analyzed with paired or unpaired t-test and discrete variables with $\div^2$ test or Fisher's exact test. All statistical tests were two-tailed and analysis followed an intention-to-treat approach. *P* value < 0.05 was indicative of significance. Calculations were performed with Stat View Statistical Program (version 4.5, Abacus Concepts, CA, USA).

RESULTS

A total of 61 patients were included. Baseline characteristics were similar between both groups (Table I). Angiographic and procedural

Table I. Baseline Characteristics.

Characteristic	Placebo group (n=28)	NAC group (n=33)	*P* value
Age, years	69.7 (13.1)	71.7 (7.4)	0.81
Men, n (%)	18 (64.3)	23 (69.7)	0.66
Body mass index ($kg.m^{-2}$)	27.6 (4.1)	27.3 (5.4)	0.61
Blood pressure, mmHg			
Systolic	134.2 (24.3)	132.2 (17.9)	0.83
Diastolic	76.5 (11.9)	78.4 (9.6)	0.59
Serum creatinine concentration (mg/dl) *	1.42 (0.37)	1.46 (0.46)	0.91
Estimated CrCl (ml/min^{1}) †	42.8 (8.7)	41.7 (11,8)	0.68
Hypertension, n (%)	16 (57.1)	26 (78.8)	0.10
Diabetes mellitus, n (%)	5 (17.8)	8 (24.2)	0.57
Heart failure, n (%)	6 (21.4)	8 (24.2)	0.81
NYHA I-II	3 (50.0)	2 (25.0)	0.58
NYHA III	3 (50.0)	6 (75.0)	0.58
Previous myocardial infarction, n (%)	5 (17.8)	7 (21.2)	0.76
Previous CABG surgery, n (%)	5 (17.8)	6 (18.2)	0.98
Medications, n (%)			
Calcium channel blocker	5 (17.8)	8 (24.2)	0.57
Diuretic	9 (32.1)	14 (42.4)	0.42
NSAID	15 (53.6)	20 (60.6)	0.59
ACE inhibitor	11 (39.3)	12 (36.4)	0.82
Angiotensin II receptor inhibitor	4 (14.3)	6 (18.2)	0.74
Oral hypoglicemic	2 (7.1)	5 (15.1)	0.44
Insulin	3 (10.7)	4 (12.1)	0.99

Abbreviations: NAC, N-acetylcysteine; CrCl, creatinine clearence; NYHA, New York Heart Association; CABG, coronary artery bypass graft; NSAID, non steroidal antiinflamatory drugs; ACE, angiotensin-converting enzyme.
* To convert mg/dl to μmol.l· multiply serum creatinine concentration values by 88.4.
† To convert ml/min to ml.s· multiply values by 0.0167.

characteristics were similar in both groups (Table II). The type of radiocontrast used was similar in both groups with 70% of the patients receiving an ionic agent. Twenty one percent of the patients enrolled were diabetic. The mean baseline SCC for all patients was 1.44 ± 0.42 mg/dl. Mean SCC values at 48 hours after the catheterization were similar in both groups. There was a significant difference in SCC change at 48 hours after the procedure favor NAC (-0.07 mg/dl NAC, 0.09 mg/dl placebo, P=0.04) (Table III).

RCIN occurred in 1 patient (3.0%) from NAC group and in 2 patients (7.1%) from placebo group (RR 0.42, 95% CI 0.06-3.10, P=0.59) (Table III). There was no statistically significant difference in the incidence of RCIN between NAC and placebo in the following subgroups of patients: diabetics, baseline SCC > 2 mg/

Table II. Angiographic and procedural characteristics.

Characteristic	Placebo group (n=28)	NAC group (n=33)	P value
Angiographic procedure, n (%)			
Coronary angiography and LV	14 (50.0)	10 (30.3)	0.19
Coronary angiography and ad hoc PCI	6 (21.4)	5 (15.1)	0.74
Coronary angiography and peripherical angiography	3 (10.7)	5 (15.1)	0.71
PCI	1 (3.6)	0 (0)	0.46
Peripherical angiography	4 (14.3)	11 (33.3)	0.13
Peripherical angiography and angioplasty	0 (0)	2 (6.2)	0.49
LVEF <40%	4 (14.3)	7 (21.2)	0.53
Coronary angiographic diagnosis, n (%)			
Normal	5 (17.9)	2 (10.0)	0.23
Single-vessel disease	3 (12.5)	4 (20.0)	0.68
Double-vessel disease	6 (25.0)	3 (15.0)	0.48
Triple-vessel disease	6 (25.0)	7 (35.0)	0.99
Graft-disease	4 (16.7)	4 (20.0)	0.99
Contrast agent, n (%)			
High-osmolar	22 (78.6)	21 (63.6)	0.26
Low-osmolar	2 (7.1)	4 (12.1)	0.67
Both	4 (14.3)	8 (24.2)	0.52
Volume of contrast agent, ml	155.5 (108.1)	158.0 (60.5)	0.09
Volume of contrast agent per body weight, ml.Kg^{-1}	2.0 (1.1)	2.3 (1.3)	0.17
Iodine mount, mg	56.1 (39.8)	56.2 (20.6)	0.11
Intravenous hydration, ml	1487 (1263)	1800 (989)	0.11
Preprocedure plus procedure hydration time, hours	3.8 (1.7)	4.5 (3.5)	0.66
Posprocedure hydration time, hours	18.6 (16.3)	21.4 (18.7)	0.68

Abbreviations: NAC, N-acetylcysteine; LV, left ventriculography; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction.

Table III. Outcomes in both groups 48 hours after the angiography.

Characteristic	Placebo group (n=28)	NAC group (n=33)	P value
Mean SCC at 48 hours *	1.49 (0.60)	1.40 (0.49)	0.52
Change in SCC at 48 hours	0.09 (0.32)	-0.07 (0.26)	0.04
Incidence of RCIN, n (%)			
Rise of > 0,5 mg/dl in serum creatinine *	2 (7.1)	1 (3.0)	0.59
Rise of > 25% in serum creatinine	3 (10.7)	1 (3.0)	0.32
Rise > 1 mg/dl in serum creatinine *	1 (3.6)	0 (0)	0.46
Length of hospitalization, hours	39.0 (55.3)	39.7 (41.9)	0.98
Readmission for acute renal failure, n (%)	1 (3.6)	1 (3.0)	0.99
Dialysis, n (%)	1 (3.6)	0 (0)	0.46
Death, n (%)	1 (3.6)	0 (0)	0.46
Combined event, n (%)	3 (10.7)	1 (3.0)	0.32

Abbreviations: NAC, N-acetylcysteine; RCIN, radiocontrast-induced nephropathy.

* To convert mg/dl to μmol.l multiply serum creatinine concentration values by 88.4.

dl, amount or type of radiocontrast agent administered.

Length of hospitalization and the combined event rate were similar in both groups (Table III). There was no difference in RCIN incidence according to radiocontrast agent type (P=0.98). Adverse effects were similar in NAC and placebo groups (drowsiness 12.1% vs. 14.3%, chills 6.1% vs. 10.7%, nausea 0% vs. 3.6%).

DISCUSSION

This randomized study showed a significant difference in SCC change at 48 hours with HPOD of NAC plus hydration and hydration alone in patients with mild chronic renal impairment undergoing a same-day angiographic procedures. There was a not significant difference in RCIN incidence between the two strategies.

A difference in SCC change at 48 hours between both groups was found in the present trial. Comparable findings had been reported in other studies.[8,10,12] The values of the weighted mean increase of SCC at 48 hours reported in two meta-analysis were similar to our change.[17,18] However, clinical utility of SCC change at 48 hours is not confirmed, and this parameter may not be a reasonable surrogate for relevant outcomes such as need of dialysis and the length of hospitalization compared to RCIN, defined as an increase in SCC >0.5 mg or 25% at 48 hours.[1]

Several factors may explain the negative results in the present trial when RCIN was evaluated, but probably the main was the lower incidence of RCIN in the placebo group compared to other studies. The baseline SCC, a strong predictor of RCIN, was lower than the studies that have shown positive results and similar to the studies that have shown no significant preventive benefit with NAC.[8-13] Similarly, the percentage of diabetics (<18% in placebo-treated patients), a subgroup of special interest, was lower than most of the positive trials.[8,10,12] It could be possible that the beneficial effects of NAC become more evident in high risk populations.[10] In contrast, the rate of RCIN in patients treated with NAC in this study was similar to other studies, but since the rate of RCIN in the placebo group was much lower than it was expected, the study lacked the necessary power to detect significant differences in RCIN between both groups.

While several studies have assessed the effectiveness of oral NAC preventing RCIN after diagnostic and/or interventional angiographic procedures, the effect of periprocedural NAC use in patients that require a same-day procedure has been evaluated in few ones. Ochoa *et al* [19], assessed an abbreviated regimen of NAC, 1000 mg-oral dose one hour before and 4 after the procedure, RCIN occurred 3 of 36 (8%) patients of the NAC group vs 11 of 44 (25%) in the control group (P=0.051). SCC remained stable in NAC group, but a significant increased occurred in the controls. Durham *et al* [20] found no significant difference in RCIN with 1200 mg-oral dose one hour before and 3 after the procedure respectively. The reason for the lack of a clear benefit in RCIN observed with abbreviated regimens is not clear. Although serum levels of NAC should be adequate 1 to 2 hours after administration and the doses of NAC used were similar to Tepel *et al*'s [7] regimen, it cannot be ruled out that NAC may have a metabolite that exerts its favorable effects in renal function requiring a longer period of time before becoming active.[15, 20] The RAPPID trial, which evaluated a periprocedural regimen of very high intravenous NAC, showed favorable effects in RCIN, although NAC infusion was terminated early in three patients due to side effects.[21] Webb *et al* [22] found no difference in RCIN with periprocedural intravenous NAC in a large randomized trial.

NAC is a thiol-containing antioxidant.[23] Interest in NAC for prevention of RCIN was greatly stimulated by Tepel et al's publication.[7-23] There is evidence that renoprotective effects of NAC may be due to its ameliorating effect on the expected contrast-induced reduction of nitric oxide and by an antioxidant mechanism.[23-25]

Given the sharply divergent published study results, NAC efficacy in RCIN and the optimal administration regimen are not completely established.[23] Two meta-analysis yielded a risk reduction of RCIN with NAC use[17,26], although a systematic

revision (15 trials, 1776 patients) revealed a borderline benefit and highlight the lack of studies reporting long term outcomes.[18] Finally, the recent non-randomized trial yielded that NAC could affect SCC determinations without altering glomerular filtration evaluated with cystatin C levels.[27]

The present trial has several limitations. The sample size was small and it was a single center study. SCC was only measured at baseline and 48 hours after the procedure, although a 30-day follow up was performed. Finally the influence of different renal pathologies in NAC effectiveness in RCIN prevention was not explored.

CONCLUSION

We conclude that in patients with mild renal impairment patients undergoing a same-day angiographic procedures, HPOD of NAC were more effective than placebo in preventing SCC change 48 hours, although this benefit was not significant in RCIN incidence.

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