Clinical research

Combination of atorvastatin plus N-acetylcysteine versus atorvastatin alone to prevent contrast-induced nephropathy

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Submitted: 24 July 2024; **Accepted:** 10 November 2024
Online publication: 31 December 2024

Arch Med Sci Atheroscler Dis 2024; 9: e207–e211
DOI: https://doi.org/10.5114/amsad/195767

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Abstract

Introduction: Contrast-induced acute renal injury is the third leading cause of hospital-acquired acute kidney injury. Our trial aimed to compare high-dose statin versus statin plus N-acetylcysteine (NAC) to prevent contrast-induced nephropathy.
Material and methods: Randomized control trial included patients who undergoing elective percutaneous coronary intervention (PCI) at Alshifa Hospital in Gaza, the first group (statin: 50 patients) received 80 mg of atorvastatin orally once daily for 3 days. The second group (statin + NAC: 50 patients) received 80 mg of atorvastatin orally once daily for 3 days, plus NAC 1200 mg orally twice daily every 12 h for 2 days. All patients underwent measurement of serum creatinine and urea level before PCI and 2–3 days after the procedure. The primary endpoint was to compare development of contrast-induced nephropathy between the two groups.
Results: The total group comprised 100 patients: 71 male patients and 29 female patients. Mean age was 59 ±9.8 years. After intervention serum creatinine decreased from 1.02 ±0.27 mg/dl to1.01 ±0.29 mg/dl in the statin group, while it decreased from 1.08 ±0.36 mg/dl to 0.92 ±0.13 mg/dl in the statin + NAC group. The difference between the two groups was significant (p = 0.048). Also, the urea plasma level in the statin group decreased from 34.5 ±9.7 mmol/l to 30.6 ±8.7 mmol/l after PCI, while in the statin + NAC group it decreased from 36.4 ±9.9 mmol/l to 26.2 ±10.6 mmol/l; the difference between the two groups was significant (p = 0.017). Contrast-induced nephropathy was seen in 9 (18%) patients in the statin group and in 2 (4%) patients in the statin + NAC group (p = 0.025).
Conclusions: The combination of high-dose atorvastatin plus NAC compared to atorvastatin alone was associated with a significant reduction of contrast-induced nephropathy in patients undergoing PCI.

Key words: atorvastatin, N-acetylcysteine, contrast-induced acute kidney injury.

Introduction

Atorvastatin is a high-intensity statin commonly used in patients with coronary heart disease and/or cerebrovascular diseases and/or peripheric vascular diseases. It has pleiotropic effects additionally to the lipid-lowering effect, probably owing to a stronger anti-inflammatory effect and reduced C-reactive protein (CRP) level in these patients. Contrast-induced acute kidney injury including elevated level of urea and creatinine

48 h after contrast media administration or development of contrast-induced nephropathy (CIN) is the major risk for hospital-acquired acute renal failure. It is associated with a high mortality rate and may lead to persistent worsening of renal function [1, 2].

Several medications have examined how to prevent contrast-induced acute renal injury. Among those approaches, studies using N-acetylcysteine (NAC) have been debated widely [3]. But high-dose NAC has shown clinical efficacy for prevention of contrast-induced kidney injury [4].

Many randomized clinical trials (RCTs) have failed to show beneficial effects of statin to prevent contrast-induced acute kidney injury after exposure to contrast media [5–10].

Statins have reno-protective effects in patients with kidney disease [11]. The latest report of the European Society of Cardiology guidelines on myocardial revascularization advises the use of statins to prevent contrast-induced acute kidney injury, especially in patients at high risk for acute renal injury [12]. Hence, in our prospective trial we compared high-dose atorvastatin versus a combination of atorvastatin and NAC for prevention of contrast-induced nephropathy among patients with a mainly low to high Mehran risk score who were undergoing elective percutaneous coronary intervention (PCI) at Alshifa Hospital in Gaza, Palestine.

Material and methods

Study population

Our study was a single-center, prospective (Registration No: 079-2022. Alshifa Hospital – ethics committee) randomized trial performed on patients with ischemic heart disease undergoing elective PCI between October 2022 and July 2023. All patients admitted to the cardiology department at Alshifa Hospital in Gaza were considered for enrollment in the study. The allocation ratio was 1 : 1 in a trial comparing two treatments group. The randomization was 1 : 1. The aim of our trial was to evaluate comparison of safety and efficacy between atorvastatin alone or a combination of atorvastatin plus NAC therapy for prevention of contrast-induced nephropathy in patients with ischemic heart disease and undergoing elective PCI.

Our trial included patients aged between 18 and 70 years who had not received any statin treatment for at least 1 week prior to exposure for contrast medium administration.

Exclusion criteria were hypersensitivity to statins, current statin treatment, acute coronary syndrome within the previous 30 days, acute renal failure or baseline serum creatinine level > 3 mg/dl, end-stage renal failure requiring dialysis, contrast medium administration within the previous 1 to 2 weeks, pregnancy, class III-IV chronic heart failure as defined by the New York Heart Association (NYHA) functional classification system or refusal of consent.

All patients provided written informed consent before enrollment in our study. Patients were randomized to receive either atorvastatin 80 mg every evening, from one day before to 2 days after contrast medium administration, or to a control group.

Patients assigned to the statin group received only 80 mg of atorvastatin orally once daily for 3 days, one dose before PCI and two doses after PCI. Patients assigned to the statin + NAC group received a combination of 80 mg of atorvastatin orally once daily for 3 days, one dose before PCI and two doses after PCI and NAC 1200 mg orally twice daily every 12 h for 2 days, one dose before and 3 doses after PCI.

Hydration therapy was administered with isotonic saline (0.9% sodium chloride, 1 ml/kg/h, but in patients with the ejection fraction less than 40% the hydration rate was 0.5 ml/kg/h) started 12 h before and continued for 12 h after contrast medium administration. Blood samples were taken to measure urea and serum creatinine concentrations before randomization and 48–72 h after contrast medium administration.

Cardiac catheterization with coronary angiography and/or percutaneous coronary intervention was performed according to local standards using the radial or femoral approach. The iso-osmolar nonionic dimeric hydrophilic contrast agent (320 mg iodine/ml, Omnipaque, GE Healthcare) was used in all cases. Adjunctive therapy and the dose of contrast agent were left to the discretion of the interventional cardiologist.

Operator definitions

CIN was defined as an increase in serum creatinine concentration of 0.5 mg/dl or ≥ 25% of the baseline value within 48 h after the procedure.

End stage renal disease was defined as estimated glomerular filtration rate ≤ 15 ml/min per 1.73 m^2.

Mehran score was calculated for all patients, which Mehran *et al.* [13] defined. It is calculated by summing the scores from the following findings: hypotension (5 points, if systolic blood pressure < 80 mm Hg for at least 1 h requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive heart failure (5 points, if class III/IV in NYHA classification or history of pulmonary edema), age (4 points, if > 75 years), anemia (3 points, if hematocrit < 39% for men and < 36% for women), diabetes mellitus (DM)

(3 points), contrast media volume (1 point per 100 ml), and estimated glomerular filtration rate (GFR; in ml/min per 1.73 m^2; 2 points, if GFR 60 to 40; 4 points, if GFR 40 to 20; 6 points, if GFR < 20). It is categorized into 4 groups: low risk, ≤ 5 points; moderate risk, 5–10 points; high risk; 11–16 points, and very high risk ≥ 16 points.

Definition of primary endpoint

The primary endpoint was to compare development of contrast-induced nephropathy between two groups.

Statistical analysis

Normally distributed continuous variables are expressed as mean ± standard deviation. Student's *t* test was used for comparison of continuous variables between 2 groups. Categorical variables were analyzed using the χ^2 test. A *p*-value lower than 0.05 was considered as statistically significant. All statistical analyses were performed using SPSS Statistics 26.0 (IBM Corp., USA).

Results

Baseline clinical characteristics were well balanced between the two groups. In total there were 71 male patients and 29 female patients. Mean age was 59 ±9.8 years. Mehran risk score was ≤ 5 in 73% of patients, 5–16 in 22% of the patients, and only 5% of the patients had a Mehran risk score more than 16 (Table I).

Statin group

Total 50 patients, 34 (68%) male, 16 (32%) female, mean age: 59.3 ±9.6 years. After intervention serum creatinine was decreased from 1.02 ±0.27 to 1.01 ±0.29 mg/dl (p = 0.18), urea plasma level was decreased from 34.5 ±9.7 mmol to 30.6 ±8.7 mmol (p = 0.037) (Table II).

Statin + NAC group

Total 50 patients, 37 (74%) male, 13 (26%) female, mean age: 58.7 ±10.2 years. After intervention serum creatinine was decreased from 1.08 ±0.36 mg/dl to 0.96 ±0.13 mg/dl (p = 0.029), urea plasma level was decreased from 36.4 ±9.9 mmol to 26.2 ±10.6 mmol (p = 0.001) (Table III).

Comparison between statin group and statin + NAC group

After intervention serum creatinine decreased from 1.02 ±0.27 mg/dl to 1.01 ±0.29 mg/dl in the statin group, while it decreased from 1.08 ±0.36 mg/dl to 0.92 ±0.13 mg/dl in the statin + NAC group. The difference between the two groups was significant (p = 0.048). Also, the urea plasma level in the statin group decreased from 34.5 ±9.7 mmol/l to 30.6 ±8.7 mmol/l after PCI, but in the statin + NAC group it decreased from 36.4 ±9.9 mmol/l to 26.2 ±10.6 mmol/l; the difference between the two groups was significant (p = 0.017) (Table IV).

Table I. Baseline clinical characteristics

Parameter	Statin group	Statin + NAC group
Age	59.3 ±9.6	58.7 ±10.2
Sex male/female	34/16	37/13
Diabetes mellitus	16 (32%)	19 (38%)
Hypertension [mm Hg]	23 (46%)	27 (54%)
Serum creatinine [mg/dl]	1.02 ±0.27	1.08 ±0.36
Urea plasma level [mmol]	34.5 ±9.7	36.4 ±9.9
eGFR	88.1 ±20.9	87.9 ±21.2
Mean contrast medium volume	171.5 ±50.7	189.5 ±53.3
Mehran risk score		
Low ≤ 5	34 (68%)	39 (78%)
Moderate-high 5–16	12 (24%)	10 (20%)
Very high ≥ 16	4 (8%)	1 (2%)

eGFR – estimated glomerular filtration rate (ml/min per 1.73 m^2).

Table II. Creatinine, creatinine clearance and blood urea nitrogen before and 72 h after PCI in statin group

Parameter	Before	After	*P*-value
Serum creatinine [mg/dl]	1.02 ±0.27	1.01 ±0.29	0.18
Urea plasma level [mmol]	34.5 ±9.7	30.6 ±8.7	0.037

Table III. Creatinine, creatinine clearance and blood urea nitrogen before and 72 h after PCI in statin + NAC group

Parameter	Before	After	*P*-value
Serum creatinine [mg/dl]	1.08 ±0.36	0.92 ±0.13	0.004
Urea plasma level [mmol]	36.4 ±9.9	26.2 ±10.6	0.001

Table IV. Creatinine, creatinine clearance and blood urea nitrogen before and 72 h after PCI in statin group and statin + NAC group

Parameter	Statin group	Statin + NAC group	*P*-value
Serum creatinine (mg/dl):			
Before	1.02 ±0.27	1.08 ±0.36	0.35
After	1.01 ±0.29	0.92 ±0.13	0.048
Urea plasma level (mmol):			
Before	34.5 ±9.7	36.4 ±9.9	0.33
After	30.6 ±8.7	26.2 ±10.6	0.017

Primary endpoint

Contrast-induced nephropathy was seen in 9 (18%) patients in the statin group and in 2 (4%) patients in the statin + NAC group (p = 0.025).

Discussion

Our study was a randomized, prospective trial to evaluate the efficacy of combination of high-intensity statin therapy plus NAC for the prevention of contrast-induced kidney injury in patients with a low-to-high Mehran risk score who were undergoing PCI in comparison to statin alone.

In our trial, we observed that periprocedural administration of atorvastatin, 80 mg daily for a short duration (3 days), and NAC 1200 mg (2 days), suggested that a short course of oral statin and NAC may reduce the incidence of contrast-induced renal injury after contrast medium injection in these patients. However, atorvastatin 80 mg daily for 3 days alone does not reduce the creatinine level after PCI. These results are of clinical significance because contrast-induced acute kidney injury is a severe complication in patients with previous impaired renal function.

Although many meta-analyses have suggested a benefit of statin pretreatment in prevention of contrast-induced nephropathy [14], Kandula *et al.* [5] reported an observational study on 239 patients who received statins and 114 subjects who did not receive statins. Their findings suggested that statin therapy was not associated with reduced contrast-induced nephropathy (p = 0.12). Toso *et al.* [15] reported that short-term administration of high doses of atorvastatin before and after contrast medium exposure, in addition to intravenous hydration and oral NAC, does not decrease CIN occurrence in patients with pre-existing chronic renal disease.

Han *et al.* [16] enrolled patients with type 2 diabetes mellitus or kidney disease stage 2 or 3 from 53 clinical centers in China. Patients were randomly assigned to a group that received 10 mg rosuvastatin per day for 2 days before and 3 days after the diagnostic angiography procedure or placebo. Hydration with isotonic saline was given according to the treating doctor. The primary endpoint was contrast-induced acute kidney injury. The incidence of contrast-induced acute kidney injury was significantly lower among patients in the rosuvastatin group than those in the placebo group (2.3% vs. 3.9%, p = 0.01). In this trial low dose statin was used, and hydration was not routine for all patients but was given according to the treating physician. In our trial we used 40 mg of rosuvastatin and routine hydration for all patients.

The PRATO-ACS trial [17] evaluated the effects of rosuvastatin on contrast-induced acute kidney injury in patients with a non-ST elevation acute coronary syndrome. Patients were randomly assigned to a group that received high dose rosuvastatin (40 mg on hospital admission then 20 mg per day until hospital discharge) or to placebo before undergoing angiography. All patients received isotonic saline and NAC. The incidence of contrast-induced acute kidney injury was significantly lower among patients treated with rosuvastatin than those in the placebo group (6.7% vs. 15.1%, p = 0.003). This study was like our trial, but in our trial the control group used 80 mg of atorvastatin and hydration.

Ju Han Kim *et al.* reported that the combination of high-dose atorvastatin plus NAC was associated with lower incidence of CIN in patients with ST elevation myocardial infarction who underwent primary PCI compared to statin only. This study's results were similar to those of our trial. However, this study was performed in ST elevation myocardial infarction patients who underwent primary PCI, while in our study the patients were elective [18].

Study limitations. First, most of the patients in our trial (73%) were low risk according to the

Mehran risk score. Second, this study was an open-label trial, and the sample size was small. The small sample size led to further limitations in statistical significance of subgroup data. Third, in addition, we used routine pre-treatment with NAC and hydration was used in all patients. The association between NAC and atorvastatin may not rule out the possibility of an interaction or a synergistic effect. Thus, results from previous studies and from our study strongly suggest that use of statins and NAC can reduce contrast-induced acute kidney injury.

In conclusion, combination of atorvastatin at 80 mg/day for 3 days plus NAC 1200 mg twice daily for 2 days compared with atorvastatin alone revealed a significant decrease in creatinine and urea level and a decrease of development of contrast-induced nephropathy among patients with low to high Mehran risk.

Funding

No external funding.

Ethical approval

Not applicable.

Conflict of interest

The author declares no conflict of interest.

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