Research Paper

Efficacy of Atorvastatin in Prevention of Contrast-induced Nephropathy in High-risk Patients Undergoing Angiography: A Double-blind Randomized Controlled Trial

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Abstract

Objective: To evaluate the efficacy and safety of atorvastatin (ATN) 80 mg in the prevention of contrast medium- induced nephropathy (CIN) in high risk patients undergoing angiograph. **Materials and Methods:** This was a prospective, double-blind, two-arm, parallel group RCT. A total of 216 patients undergoing coronary angiography were screened, and 188 eligible patients were randomized to two treatment arms. Patients in Group A received tablet N-acetylcysteine (NAC) 1200 mg once daily, and patients in Group B received tablet atorvastatin 80 mg + NAC 1200 mg once daily, for 3 days before, and 2 days after angiography. **Results:** A total of 160 patients completed the trial. Postprocedure, nine and two CIN cases were found in Group A and B, respectively. The mean change in serum creatinine was 0.086 ± 0.168 in Group A and 0.021 ± 0.083 in Group B, which was statistically significant (P = 0.0289). Postprocedure, the estimated glomerular filteration rate was reduced by 19.52 in Group A and 13.55 in Group B (P = 0.003). **Conclusion:** This trial indicates the positive role of statins in preventive strategy against CIN along with NAC.

Keywords: Atorvastatin, contrast-induced nephropathy, N-acetylcysteine

Introduction

CIN is a common cause of acute renal dysfunction. The CIN is defined as an increase in serum creatinine concentration of 0.5 mg/dL or 25% above the baseline within 48 h after contrast administration.[1] Serum creatinine usually peaks 48–72 h following contrast media use and returns to the baseline within 14 days; however, some patients may progress to acute kidney injury requiring dialysis.[2] The common procedures associated with CIN are coronary angiography and contrast-enhanced computed tomography.[3] The incidence of CIN in the general population is 2%. In high-risk patients with chronic renal impairment, diabetes mellitus (DM), congestive heart failure, and old age, the incidence increases 20%–30%.[4-8] Interaction between inflammatory mechanisms and oxidative stress are involved in the pathogenesis of CIN.[9] Increase in adenosine, endothelin, and free radical-induced vasoconstriction and reduced nitric oxide (NO) cause ischemia in the deeper portion of outer medulla.[10] Statins may decrease inflammation and improve endothelial function, decreasing expression of endothelial adhesion molecules, and increasing NO bioavailability.[11-13] This trial was conducted to evaluate the efficacy and safety of atorvastatin (ATN) 80 mg in the prevention of CIN in high-risk patients undergoing angiography.

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Materials and Methods

This was a prospective, double-blind, randomized, two-arm, parallel group, controlled, clinical trial. The study protocol was approved by the Institutional Ethics Committee and conformed to the principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and Indian Council of Medical Research Guidelines for Biomedical Research on Human Subjects, 2006. Patients referred to the department of cardiology of a tertiary health-care center in Aurangabad for coronary angiography were recruited from January 2013 to December 2013. Patients of either gender, between 18 and 65 years of age, who had serum creatinine between 1 and 1.5 mg/dL or estimated glomerular filteration rate (eGFR) >60 mL/min/1.73 m^2 and suffering from controlled DM or hypertension (HT) were enrolled after written, vernacular, witnessed, informed consent to participate in the trial. Patients with a history of known structural heart disease, severe heart failure, or very low left ventricular ejection fraction were excluded from the study. Patients with eGFR <60 mL/min/1.73 m^2 or requiring hemodialysis, severe hepatic disease, exposed to iodinated contrast media within 7 days, or hypersensitivity to study medication were excluded from the study.

Methodology

All eligible patients underwent baseline evaluation for recording demographic details, medical history, general and systemic examination, and laboratory work which included hemogram, hepatic and renal function tests, and routine urine analysis. Each patient given a particular "patient number" and it identifies the patient throughout the study. For randomization, a list of computer-generated numbers for each treatment group was prepared and treatments given in accordance with the list. For double blinding, the investigator took similar white envelops for both groups of drugs and numbered them according to randomization sequence and handed over to the clinician. Afterward, the data sorted out depending on the randomization sequence chart. The enrolled patients were divided into two treatment groups. Thirty-four patients already taking statins were divided into both groups. Patients in Group A received tablet N-acetylcysteine (NAC) 1200 mg once daily, and patients in Group B received tablet ATN 80 mg + NAC 1200 mg once daily, for 3 days before and 2 days after angiography. All the patients were hydrated with standard 1000 mL saline infusion for 6 h after the procedure. Blood samples were drawn at baseline and 48 h after coronary angiography for measurement of serum creatinine. Modification of diet in renal disease equations was used to determine eGFR. All patients were followed up for efficacy and safety assessment on day 2 [Figure 1].

The efficacy of treatment was evaluated primarily on the basis of prevention of CIN occurrence. The secondary outcome parameters included mean change in serum creatinine and mean change in eGFR values from baseline.

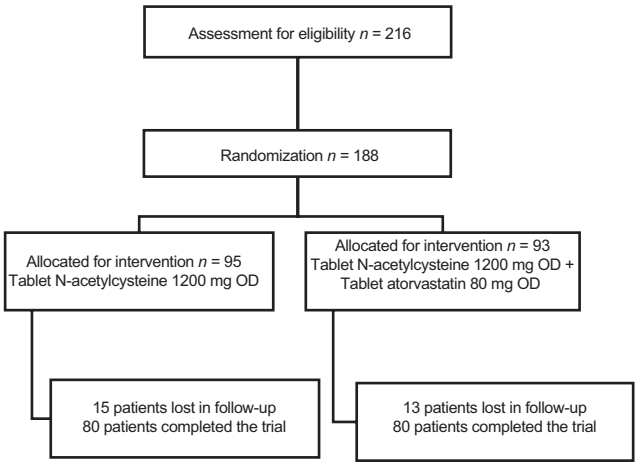

Figure 1: Flowchart showing the run-in of the intervention

Statistical analysis

The data were entered into Microsoft Excel from case record form for analysis. For comparing quantitative data between the study groups, Student's unpaired *t*-test was applied. Comparison of qualitative data between the study groups was performed using Fisher's exact test/Chi-square test. Statistical analysis was performed with the help of the software "Graph Pad Prism 5 for windows Version 5.01 August 2007 (GPW5-614601-RAG-1147)." $P < 0.05$ was considered as statistically significant.

Results

A total of 216 patients undergoing coronary angiography were screened, and 188 eligible patients were randomized into two treatment groups. In Group A 15 patients and in Group B 13 patients were lost to trial. Both groups were similar in demographic profile at baseline [Table 1]. Postprocedure, nine and two CIN cases were detected in Group A and B, respectively. The incidence of CIN was 11.25% in Group A and 2.5% in Group B and this difference was statistically significant ($P = 0.028$) [Table 2]. After calculating the absolute risk reduction, the number needed to treat (NNT) appeared 16.129 [Table 2]. Postprocedure levels of serum creatinine were significantly lower in Group A as compared to Group B. The mean change in serum creatinine was 0.086 ± 0.168 in Group A versus 0.021 ± 0.083 in Group B, which was statistically significant ($P = 0.028$) [Table 2]. Postprocedure, the eGFR was reduced by 19.52 in Group A and 13.55 in Group B ($P = 0.003$) which means that there was significantly less decrease in eGFR in Group B as compared to Group A. Patients with CIN were discharged when renal function returned to baseline after aggressive hydration. No Patients with CIN in either group required dialysis.

Discussion

The CIN is an important cause of mortality and morbidity in high-risk patients undergoing angiography.[9] After contrast

Table 1: Baseline characteristics of the two groups

Parameter	Group A (*n*=80) NAC	Group B (*n*=80) NAC + ATN	*P*
Age (years)	51.87±8.48	53.12±7.55	0.497†
Gender (*n*)			
Men	52	47	0.415‡
Women	28	33	
Blood pressure			
Systolic	132.65±6.205	134.55±4.619	0.120†
13 Diastolic	80.55±6.915	82.85±5.901	0.112†
Fasting blood sugar level	123.12±5.989	121.94±6.703	0.246†
Patients already on statins	16	18	0.566‡

Data presented as mean±SD and number. *Statistically significant, †Using two-tailed unpaired *t*-test, ‡Using Chi-square test. NAC=N-acetylcysteine, ATN=Atorvastatin, SD=Standard deviation

Table 2: Primary and secondary parameters

Incidence of CIN

Incidence of CIN	Group A (*n*=80) NAC	Group B (*n*=80) NAC + ATN	*P*‡
Number of patients developed CIN	9	2	0.028*
Number of patients not developed CIN	71	78	

Pre- and post-procedure serum creatinine and eGFR

Parameter	Mean±SD		*P* inter group†
	Group A NAC	Group B NAC + ATN	
Serum creatinine (mg/dL)			
Baseline	1.152±0.124	1.124±0.128	0.332
Postprocedure	1.236±0.131	1.146±0.167	0.009*
Mean change	0.086±0.168	0.021±0.083	0.028*
eGFR (mL/min/1.73 m^2)			
Baseline	87.27±14.13	86.87±13.96	0.901
Postprocedure	67.75±8.404	73.32±12.40	0.025*
Mean change	19.52±8.934	13.55±5.064	0.003*

Data presented as mean±SD and number. *Statistically significant, ‡Using Fisher's exact test, †Using two-tailed unpaired *t*-test. NAC=N-acetylcysteine, ATN=Atorvastatin, SD=Standard deviation, eGFR=Estimated glomerular filtration rate, CIN=Contrast-induced nephropathy

exposure, there is medullary hypoxia because of adenosine production from the macula densa, release of angiotensin, vasopressin, and endothelin-1, and decreased synthesis of NO.[14] Other organ injury processes may take place including oxidative stress, release of pro-inflammatory cytokines and complement activation, with subsequent cytoplasmic vacuolization, necrosis, interstitial inflammation, and tubular obstruction by protein precipitates.[15-17] Statins prevent endothelial dysfunction caused by hypoxia and oxidized low-density lipoprotein cholesterol by restoring endothelial NO synthase activity.[18-20] Statins increase the expression of tissue-type plasminogen activator and inhibit the expression of endothelin-1.[21,22] Statins enhance endothelium-dependent relaxation by inhibiting the production of reactive oxygen species, such as superoxide and hydroxyl radicals (antioxidant effects).[23] Statins attenuate angiotensin II-induced free radical production in vascular smooth muscle cells by inhibiting Rac1-mediated NADH oxidase activity and downregulating angiotensin AT1-receptor expression.[24] Recent review of a large insurance database has shown that statin therapy is associated with a lower incidence of CIN after percutaneous coronary intervention.[8,9,11] NAC is a potent antioxidant that scavenges a wide variety of oxygen-derived free radicals and prevents CIN by avoiding direct oxidative tissue damage and also by improving renal hemodynamics.[25]

Patti *et al*.[14] in ARMYDA-CIN trial reported that the incidence of CIN was significantly lower in patients randomized to ATN arm (5%, 6 of 120, vs. 13.2%, 16 of 121, in placebo arm, $P = 0.046$), and postprocedure levels of serum creatinine were significantly lower in the ATN arm (1.06 ± 0.35 vs. 1.12 ± 0.27 mg/dl in placebo group, $P = 0.01$). Ozhan *et al*.[9] demonstrated that seven and two patients developed CIN in NAC and ATN + NAC group, respectively. The mean change in creatinine was 0.06 ± 0.25 mg/dL in NAC group and 0.02 ± 0.13 mg/dL in ATN + NAC group ($P = 0.023$), and mean change in eGFR was 0.8 ± 16.8 mL/min in NAC group and 2.4 ± 16 mL/min in ATN + NAC group in Ozhan *et al*.[9] study. Yoshida *et al*.[11] reported that pravastatin treatment before contrast media exposure was associated with a reduction in CIN in patients with cardiovascular diseases and renal insufficiency. The studies performed by Khosravi *et al*.[26] and Bidram *et al*.[27] demonstrated that pretreatment with high-dose ATN significantly reduces the incidence of CIN in patient undergoing angiography.

The incidence of CIN was 11.25% in patients who received NAC alone and 2.5% in patients who received ATN along with NAC and this difference was statistically significant. The mean change in serum creatinine was 7.46% and 1.86% in NAC group and ATN and NAC group, respectively. Hence, there was a less increase in mean serum creatinine after the procedure in patients who have taken both drugs. After the procedure, eGFR reduced by 22.36% in NAC group and 15.59% in ATN and NAC group.

Conclusion

The Pleotropic effects of statin play important role in prevention of kidney damage caused by inflammatory and oxidative stress. The findings of our study indicate the positive role of statins in preventive strategy against CIN. High dose Atorvastatin along with NAC is effective in prevention of CIN in high risk patients.

Limitation

The sample size is small for the study, and because of the exclusion criteria, the external validity (generalizability) of the conclusion is limited to some extent.

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Conflicts of interest
There are no conflicts of interest.

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