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Rosuvastatin plus N Acetylcysteine to Prevention of Contrast Induced Acute Kidney Injury in Patients with Low Mehran Risk Score

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Abstract

Objective: Contrast induced acute renal injury is the third leading cause of hospital-acquired acute kidney injury, several protective treatments options have been developed among patients undergoing percutaneous coronary intervention (PCI). Our trial aimed to comparison between high dose rosuvastatin versus rosuvastatin plus N acetylcysteine to prevention of contrast induced acute kidney injury in patients undergoing elective PCI at Alshifa hospital in Gaza.

Methods: Randomize control trial included 100 patients who undergoing elective PCI at Alshifa hospital in Gaza, Group A: (N:50) patients received 40 mg rosuvastatin orally once daily for 3 days, on dose before undergoing PCI and two dose after PCI. Group B (N: 50) patients received 40 mg rosuvastatin orally once daily for 3 days, on dose before PCI and two dose after PCI plus N-acetylcysteine 1200 mg orally twice daily every 12 hours for two days, the first dose before PCI and other 3 doses after PCI. All patients were measuring serum creatinine level, creatinine clearance and blood urea nitrogen (BUN) before PCI and (2-3) days after procedure.

Result: In Group A: nonsignificant reduction of serum creatinine level (P: 0.90), creatinine clearance (P: 40) but significant reduction of BUN was seen after treatment (P: 0.017). In Group B: Significant reduction of serum creatinine level, and BUN (P; 0.001). But creatinine clearance not significant changes were seen after treatment (P:0.72). On other hand comparison between two group was significant reduction of serum creatinine level (P: 0.046) in group B, but not significant changes in creatinine clearance and BUN were not significant (0.41, 0.34) respectively.

Conclusion: High dose rosuvastatin plus N-acetylcysteine compared rosuvastatin had significant reduction of creatinine level among patients undergoing PCI.

Keywords: Rosuvastatin; NAC; Contrast Induced Acute Kidney Injury

Abbreviations

CIN: Contrast Induced Nephropathy; RCTs: Randomized Clinical Trials; CrCl: Creatinine Clearance; NYHA: New York Heart Association.

Introduction

Rosuvastatin is high-intensity statins commonly used in patients with very high or high risk atherosclerotic cardiovascular disease. At same time also have pleiotropic

effects additionally to the lipid-lowering effect. Rosuvastatin hydrophilic form of statin and may be better potential for prevention of contrast induced nephropathy (CIN) than other statin forms, probably owing to stronger anti-inflammatory effect and longer plasma half-life than other statins. Contrast-induced acute kidney injury is the major risk for hospital acquired acute renal failure and is associated with high mortality rate may be led to persistent worsening of renal function and end stage renal disease [1,2].

Several medications have examined how to prevent contrast induced acute renal injury. Among patients who need contrast media for diagnostic or therapeutic procedures. Studies using N-acetylcysteine have been debated widely [3]. But high dose N-acetylcysteine shown clinical efficacy for prevent contrast induced acute kidney injury [4].

Many randomized clinical trials (RCTs) have failed to show beneficial effects of statin for prevent contrast induced acute kidney injury [5-10]. Conversely, some trials have suggested that pretreatment of rosuvastatin can reduce the prevalence of CIN in patients undergoing PCI because it can reduce inflammation and oxidative stress to a greater extent.

Statins have renoprotective effects in patients with kidney disease [11]. The latest report of European Society of Cardiology guidelines on myocardial revascularization advises the use of statins to prevent Contrast induced acute kidney injury, especially in patients with high-risk for acute renal injury after contrast administration [12]. Hence, in our prospective trial we make comparison between high dose rosuvastatin versus rosuvastatin plus N acetylcysteine to prevention of Contrast induced kidney injury in patients with low Mehran risk score who undergoing elective PCI at Alshifa hospital in Gaza – Palestine.

Methods

Study population

Our study was a single-center, prospective, randomized trial performed on patients with ischemic heart disease undergoing elective PCI from October 2022 to July 2023, all patients admitted to cardiology department at Alshifa hospital in Gaza were considered for enrollment in the study. The aim of our trial was to evaluate comparison of efficacy between rosuvastatin alone or rosuvastatin plus N acetylcysteine therapy for prevention of contrast induced acute kidney injury in patients with ischemic heart disease and undergo elective PCI.

Our trial included patients with age between 18 to 70 years who had stable ischemic coronary artery disease and not received any statin treatment for at least one-week prior undergoing elective PCI.

Exclusion criteria were hypersensitivity to statins, current statin treatment; acute coronary syndrome within the previous 15 days, baseline serum creatinine level > 3 mg/dl, end-stage renal failure requiring dialysis, contrast medium administration within the previous one weeks, pregnancy, class IV chronic heart failure as defined by the New York Heart Association (NYHA) functional classification system or refusal of consent form.

The calculation of estimated creatinine clearance (CrCl) was calculated from serum creatinine (sCr) concentrations by using the modified glomerular filtration rate estimating equation for patients with chronic renal disease [13]:

For Female: $CrCl = (140 - Age) * (Weight\ in\ Kg) / 72 * SC\ X0.85$

All patients provided written informed consent form before enrollment in our study. Block randomization with a block size of three patients were randomized to receive either rosuvastatin 40 mg every evening, from one day before to 2 days after contrast medium administration plus or to a control group.

Patients assigned to the group (A): Patients received only 40 mg Rosuvastatin orally once daily for 3 days, on dose before elective PCI and two dose after elective PCI or group (B): Patients received combination of 40 mg Rosuvastatin orally once daily for 3 days, on dose before elective PCI and two dose after elective PCI and N-acetylcysteine 1200 mg orally twice daily every 12 hours for two day, on dose before and 3 dose after PCI.

Hydration therapy was administered with isotonic saline (0.9% sodium chloride, 1 ml/kg/h, but in patients with Ejection Fraction less than 40% hydration rate was 0.5ml/kg/h) started 12hrs before and continued for 24hrs after contrasting medium administration. The iso-osmolar nonionic dimeric hydrophilic contrast agent (320 mg iodine/ml, omnipaque, GE Healthcare) was administered during all procedures. Blood samples were taken to measure urea and serum creatinine concentrations before randomization and 48-72hrs after contrast medium administration. Renal function was measured using creatinine clearance in all patients.

Definitions of Endpoints

The primary endpoint was defined as a change in serum creatinine, BUN or GFR after 48-72 hours of contrast medium administration.

Statistical Analysis

Normally distributed continuous variables, expressed as mean ± standard deviation, The Student's t test was used for continuous variables comparison between 2 groups. Categorical variables were analyzed using Chi-square test. P value lower than 0.05 was considered as statistically significant. All statistical analyses were performed by the (SPSS 26.0, Chicago, IL, The USA)

Results

Baseline clinical characteristics were well balanced between two groups, total male 72 patients, total female 28 patients. Mean age 58+9.5 years. Mehran risk score < 5 was in 85% patients, Mehran risk score 5-16 was in 15% of the patients (Table 1).

Baseline Clinical Characteristics	Group A	Group B
Age	58.4+9.7	57.6+9.4
Sex Male/female	33/17	39/11
Diabetes mellitus	17 (34%)	19 (38%)
Hypertension	24 (48%)	22 (44%)
Serum creatinine	0.98+0.19	0.99+0.19
Creatinine clearance	104.8+29.4	116.8+33.0
Blood urea nitrogen (BUN)	32.3+9.8	35.2+9.8
Mehran risk score		
<5	41 (82%)	44(88%)
16-May	9(18%)	6 (12%)
>16	0	0

Table 1: Baseline clinical characteristics.

Group A

Total 50 patients, 33 (66%) male, 17 (34%) female, mean age: 58.4+9.7 years. After intervention serum creatinine was decreased from 0.92+0.19 to 0.91+0.16 mg/dl. (P:0.4), creatinine clearance was decreased from 104.8+29.4 to 104.7+27.9 ml/min (P:0.9) and BUN reduced from 32.3+9.8 to29;6+7.0 (P 0.017) (Table 2).

Blood Plasma	Before	After	P Value
Serum Creatinine	0.98+0.19	0.97+0.16	0.4
Creatinine Clearance	104.8+29.4	104.7+27.9	0.9
Blood Urea Nitrogen (BUN)	32.3+9.8	29.6+7.0	0.017

Table 2: Serum creatinine, creatinine clearance and blood urea nitrogen before and 72 hours after PCI in group-A.

Group B

Total 50 patients, 39 (78%) male, 11(22%) females, mean age: 57.6+9.4 years. After intervention serum creatinine was decreased from 0.99+0.19 to 0.88+0.17 mg/dl. (P:0.001), creatinine clearance was decreased from 116.8+33.0 to 115.3+33.7 ml/min (P:0.72) and BUN from 35.2+9.9 to 31.3+10.4 (P 0.001) Table 3.

Blood Plasma	Before	After	P Value
Serum creatinine	0.99+0.19	0.88+0.17	0.001
Creatinine clearance	116.8+33.0	115.3+33.7	0.72
Blood urea nitrogen (BUN)	35.2+9.9	31.3+10.4	0.001

Table 3: Serum creatinine, creatinine clearance and blood urea nitrogen before and 72 hours after PCI in group A and B

Comparison between group A and group B

No significant difference between two group was seen in creatinine clearance and BUN, but significant decrease was seen in creatinine level (P:0.046) Table 4.

Blood Plasma	Time Interval	Group A	Group B	P value
Serum creatinine	Before	0.98+0.19	0.99+0.19	0.73
	After	0.97+0.16	0.88+0.17	0.046
Creatinine clearance	Before	104.8+29.4	116.8+33.0	0.07
	After	104.7+27.9	115.3+33.7	0.41
Blood urea nitrogen	Before	32.3+9.8	35.2+9.9	0.15
	After	29.6+7.0	31.3+10.4	0.34

Table 4: Serum creatinine, creatinine clearance and blood urea nitrogen before and 72 hours after PCI in group A and B.

Discussion

Our study is randomized, prospective trial to evaluate the efficacy of high intensity statin therapy plus N-acetylcysteine for the prevention of contrast induced kidney injury in patients with mild-to-moderate Mehran risk score who undergoing PCI comparison to statin alone.

In our trial, we observed that periprocedural administration of rosuvastatin, 40 mg daily for a short duration (3 days), and N acetylcysteine 1200 mg (2 days) suggesting that a short course of oral statin and NAC may reduce the incidence of contrast induced kidney injury after contrast medium injection in these patients. But rosuvastatin 40 mg daily for 3 days alone doesn't reduction creatinine level after PCI. These results are of clinical significance because contrast induced acute kidney injury is a severe complication in patients with previous have impaired renal function.

Despite of many metanalysis suggested benefit of statin pretreatment in prevention of contrast-induced nephropathy [14]. Kandula P, et al. [5] reported an observational study on 239 patients who received statins and 114 subjects who not received statins. They Toso A, et al. [15] suggested that statin therapy was not related to reduce contrast induced nephropathy prevention (P= 0.12) a short-time administration of high doses of atorvastatin before and after contrast medium exposure, in addition to intravenous hydration and oral N-acetylcysteine, does not decrease CIN occurrence in patients with pre-existing chronic renal disease.

Han Y, 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 divided to receive 10 mg rosuvastatin per day for 2 days before and 3 days after the diagnostic angiography procedure or 1 placebo. Hydration with isotonic saline was given according to treating doctor. The primary end point was contrast-induced Acute kidney injury.

The incidence of contrast-induced Acute kidney injury was significantly lower among patients in 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 not routine for all patients but was given according to treating physician. In our trial we used 40 mg rosuvastatin and routine hydration for all patients.

In the PRATO-ACS trial, Leoncini M, et al. [17], evaluates the effects of rosuvastatin on contrast induced acute kidney injury in patients with a non-ST elevation acute coronary syndrome. Patients were randomly to receive high dose rosuvastatin (40 mg on hospital admission then 20 mg per day until hospital discharge) or to placebo before undergoing angiography. All patients were received isotonic saline and N-acetylcysteine.

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 similar to our trial but in our trial control group was used 40 mg rosuvastatin and hydration.

Study Limitations

First, most of patients of our trial (85%) are low risk according to Mehran risk score. Second, this study the sample size was small. Small a sample size led to further limitations in statistical significance of subgroup data. Third, in addition, we used routine pre-treatment with N acetylcysteine and hydration was used in all patients. The association between N acetylcysteine and rosuvastatin 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 N acetylcysteine can reduce

contrast induced acute kidney injury.

Conclusion

Rosuvastatin at 40 mg per day for 3 days plus N acetylcysteine 1200 mg twice daily for 2 days compared with Rosuvastatin alone significant decrease in creatinine level but no significant difference was seen in creatinine clearance and BUN but in patients with low Mehran risk.

Declaration of Competing Interest: There is no conflict of interest.

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Declaration of Patient Consent: The authors certify that they have obtained all appropriate patient consent forms.

Author's Contribution: Mohammed habib (MH) gave a substantial contribution to the conception and design of the work, gave a substantial contribution of data and gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work.

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