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ROLE OF ROSUVASTATIN PRETREATMENT IN PREVENTION OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY

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All the authors contributed significantly to the research that resulted in the submitted manuscript.

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ABSTRACT

Objective: The aim of this study was to assess the efficacy of short-term high-dose rosuvastatin pretreatment therapy for the prevention of contrast induced nephropathy.

Methodology: This study prospectively included two hundred patients who underwent coronary angiography, and were randomized into two groups: control group (included 100 patients who did not receive statin therapy) and statin group (included 100 patients who received rosuvastatin 20 mg/day 3 days before and 7 days after coronary angiography).According to recommendations of the National kidney foundation, results had been recorded using both serum creatinine and glomular filteration rate levels.

Results: There was statistically significant reduction in the occurrence of contrast-induced nephropathy in rosuvastatin pretreated patients ("22%" and "15%" of them developed contrast-induced nephropathy regarding the glomular filteration rate and serum creatinine levels respectively), compared to those in the control group ("35%" and "38%" regarding the glomular filteration rate and serum creatinine levels respectively) with P-value (<0.001 regarding serum creatinine and <0.042 regarding glomular filteration rate).

Conclusion: This study favors statin pretreatment for preventing contrast induced nephropathy in patients undergoing coronary angiography.

Key Words: Contrast Induced Nephropathy, Rosuvastatin, Angiography

INTRODUCTION

Contrast-induced nephropathy (CIN) remains one of the most important clinical complications associated with the intravascular administration of radio-contrast media.

Statins have recently been shown to possess pleiotropic effects and has been suggested to reduce the CIN risk because through having beneficial effects on endothelial function, maintaining nitric oxide production, and reducing oxidative stress. A lot of prospective and retrospective studies focused on statin therapy as specific prophylactic measure of contrast-induced nephropathy.[1,2]

Strategies for reducing the CIN risk remain a highly topical subject for years and the main focus of them stills the adequate hydration. Utilization of the invasive radiological techniques for both diagnostic and therapeutic procedures is growing up and the radio-contrast media used in these procedures may cause a reversible form of acute renal failure.[3] Although these trials studied the role of different types of statins (atorvastatin, simvastatin and pravastatin) in prevention of CIN, only Massimo Chello et al, tested the role of rosuvastatin on only 7% of included patients.[4]

In this current study, the aim was to assess the efficacy of short-term high-dose rosuvastatin pretreatment therapy for the prevention of contrast induced nephropathy.

METHODOLOGY

Two hundred sequential patients who underwent coronary angiography (CA) at (El-Agouza police hospital) were included in the trial. Patients were randomized into two groups:1-Control group (CG): included 100 patients who did not receive statin therapy: 2-Statin group (SG): included 100 patients who received rosuvastatin 20 mg/day 3 days before and 7 days after CA. All included patients were subjected to: Taking full history about chronic diseases especially diabetes mellitus and hypertension. Hydration with isotonic saline (1.0 ml/kg IV administration per hour starting 4 h before and continued 24 h after contrast exposure) and all of them received the same nonionic contrast medium; Iopromide (Ultravist) and contrast doses had been recorded.[1] Determination of renal function: Blood samples had been obtained before contrast exposure (baseline) and after 48 hours of contrast exposure to measure serum creatinine and glomerular filteration rate (GFR).Serum creatinine had been assayed using (Olympus AU) Modular Analyzer (Germany) and GFR had been determined using Cockcroft-Gault equation, which is used to estimate creatinine clearance from age, weight and serum creatinine as follow.[5]

140-"age per year" × "weight per kg" ×GF/S.Creatinine × 72

("GF" means gender correction factor, it equals 1 in males and 0.85 in females).

According to recommendations of the National kidney foundation (NKF), results had been recorded using both serum creatinine and GFR levels.Rise in serum creatinine greater than 25 percent or greater than 0.5 mg/dl from baseline and GFR less than 90 ml/min/1.73 m^2 after intra-vascular administration of contrast were considered as CIN (according to National kidney foundation definition of CIN).[6] Both groups were compared as regards contrast volume, serum creatinine , eGFR before, after the procedure.

Patients were excluded if they had chronic liver failure, chronic renal failure requiring dialysis, stage III–IV heart failure, contrast exposure history within 3 months preceding the procedure, active infections or Malignancies.

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 9.0. Windows, SPSS Inc., Chicago, Illinois, US). Continuous variables had been compared with the Student t-test. Categorical variables were assessed by Fisher's exact two-tailed test.

Descriptive statistics were done for numerical parametric data as mean, standard deviation and minimum& maximum of the range and for numerical non parametric data as median and 1st & 3rd inter-quartile range, while they were done for categorical data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with parametric data and Mann Whiteny U in cases of two independent groups with non parametric data. Inferential analyses were done for qualitative data using Fisher's Exact test for independent variables with small expected. While correlations were done using Spearman Rho test for numerical non parametric.

The level of significance was taken at P value < 0.05 is significant, otherwise is non significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance in the population, if it actually present.

RESULTS

It is a prospective study evaluating development of contrast induced nephropathy in patients underwent coronary angiography who received short-term pretreatment rosuvastatin therapy (statin group "SG") compared to those who did not receive statins (control group "CG").

Patients enrolled in the present work had an average age of 53.450±10.809 years, (ranging from 21-81 years). Female patients constituted 26.5% (28% in statin group and 25% in control group) and males were 73.50% (72% in statin group

Table 1: Baseline Demographic Findings

Variables		Rosuvastatin Pretreatment		P- value
		Yes (n = 100)	No (n = 100)	
	Age (years)	54.780±10.926	52.120±10.692	0.017
Gender	Male	72 (72%)	75 (75%)	0.631
	Female	28 (28%)	25 (25%)	
	Weight	83.600±7.576	80.700±7.569	0.077
	Smoking	53 (53%)	64 (64%)	0.114
	Diabetes Mellitus	49 (49%)	37 (37%)	0.087
	Hypertension	71 (71%)	63 (63%)	0.229
	RI	3 (3%)	2 (2%)	0.651

and 75% in control group) of the studied patients. As demonstrated in Table 1, there was no statistically significant difference in demographic data between two groups except in age.

There was no statistically significant difference in the average of contrast media doses in studied patients. The doses were between 75 -150 CC (120.750 ± 17.786 CC in statin group and 122.500 ± 16.088 CC in control group) of Iopromide (Table 2) .

Table 2: Dose of Contrast Media

Variables	Rosuvastatin Pretreatment		P- value
	Yes (n=100)	No (n=100)	
Contrast amount/ CC	120.750±17.786	122.500±16.088	0.466

Serum creatinine (S.Cr) measurements were between (0.6 to 2.94 mg/dl), with mean (0.808±0.195 mg/dl in statin group and 0.809 ± 0.308 mg/dl in control group) and GFR measurements were between (36 to 212 ml/min/1.73 m^2), with mean (123.010 ± 34.970 ml/min/1.73 m^2 in statin group and 125.251 ± 35.754 ml/min/1.73 m^2 in control group) in studied patients before CA (Table 3).

After coronary angiography, serum creatinine measurements were between (0.7 to 3.6) mg/dl, with mean (0.971 ± 0.302) mg/dl in statin group and (1.024 ± 0.380) mg/dl in control group and GFR measurements were between (25 to 182 ml/min/1.73 m^2), with mean (104.281 ± 29.781) ml/min/1.73 m^2 in statin group and (98.107 ± 26.167) ml/min/1.73 m^2 in control group.

All these laboratory data were statistically non-significant as regards the two groups.

The study showed statistically significant lower incidence of contrast nephropathy in the statin group (15% of the patients developed CIN), compared to those in control group (38% of them developed CIN), regarding to serum creatinine levels, and P-value was (<0.001) (Figure 1). Regarding to the GFR measurements statin group showed (22%) incidence of CIN, compared to (35%) in the control group and P-value was <0.042 (Figure 2).

DISCUSSION

The current study is a prospective study evaluating the effects of short-term pretreatment rosuvastatin therapy on the development of renal function deterioration following CA.

The present study showed statistically significant reduction in the incidence of CIN (P-value <0.001) in rosuvastatin pretreated patients. As in 100 patients (mean age was 54 ± 10.926 years, 49% were diabetic and mean contrast dose was 120 ± 17.786 cc of Iopromide) received rosuvastatin 20 mg/day 3 days before and 7 days after CA {Statin group}, "22%" and "15%" of them developed CIN regarding to the GFR and serum creatinine levels respectively, compared to patients who did not receive rosuvastatin

Table 3: Baseline Laboratory Findings

Variables	Rosuvastatin Pretreatment		P- value
	Yes (n=100)	No (n=100)	
S.Cr Before (mg/dl)	0.808 ± 0.195	0.809 ± 0.308	0.991
S.Cr After (mg/dl)	0.971 ± 0.302	1.024 ± 0.380	0.269
GFR Before (ml/min)	123.010 ±34.970	125.251 ± 35.754	0.655
GFR After (ml/min)	104.281 ±29.781	98.107 ± 26.167	0.121

Figure 1: Percentage of CIN According to S.Cr Level

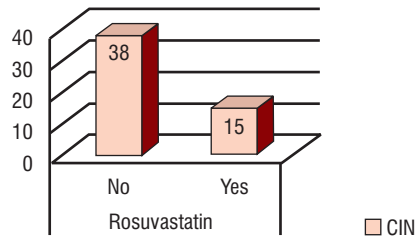
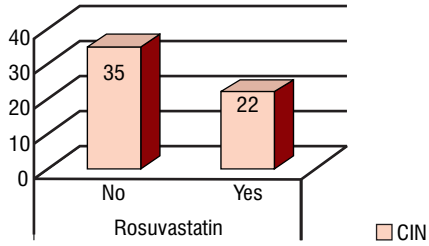


Figure 2: Percentage of CIN According to GFR Level



{Control group} in which "35%" and "38%" developed CIN regarding to the GFR and serum creatinine levels respectively. These findings relatively coincided with findings of Patti et al who collected 241 patients who were candidate for CA, 120 of them (30% were diabetic with mean age 65 years old and mean contrast dose was 209 cc iobitridol) received atorvastatin 80 mg (12 hours before) + 40 mg (2 hours before), 40 mg for 2days after procedure, and 121 patients (25% were diabetic, mean age 66 years old and mean contrast dose was 213 cc iobitridol) did not receive statin before angiography and he found that 6 patients "5%" in atorvastatin group developed CIN, compared to 16 patients "13%" in no statin group.[7] This relative difference in results might be due to higher percentage of diabetic patients in our study.

Also these results are in agreement with the data reported by Ozhan et al, who collected 130 candidates for CA, 60 patients received atorvastatin, 80 mg 1 day pre-procedure and 2 days post-procedure+600 mg NAC pre-procedure (SG) and 70 patients received only 600 mg NAC pre-procedure (CG) and he found that 2 patients "3.3%" in atorvastatin group developed CIN, compared to 7 patients "10%" in no statin group.[8] Also this relative difference in results might be due to higher number of patients and percentage of diabetes mellitus in our study.

Toso et al, showed non-statistically significant reduction, as she collected 304 patients were candidate for CA, 152 patients received atorvastatin 80 mg/day 2 days pre-procedure and 2 days postprocedure plus NAC 1200 mg/day, from 1 day before to 1 day post-procedure (SG) and 152 patients only received NAC 1200 mg/day (no statin group) and she found that 15 patients "9.8%" in atorvastatin group developed CIN, compared to 16 patients "10.5%" in no statin group.[9] This difference in results might be due to higher percentage of diabetic patients in our study, different type of statin administrated, and difference in patients' demographics, environmental circumstances.

Other preventive strategies applied in the previous two studies might led to less statistically significant CIN reduction, as the patients received oral N-acetylcysteine which is considered the most effective drug at decreasing the incidence of CIN.[10] Statins and N-acetylcysteine might share the same mechanism for renal protection.[11]

Also the current study coincided with cohort studies comparing the incidence of CIN in a chronic statin therapy compared to a statin-naive group. Most studies have suggested that chronic use of statins have a preventive effect against CIN and a beneficial effect in reducing the incidence of dialysis and long-term mortality. Massimo Chello et al, collected 434 patients who were candidate for CA, 260 of them (37% were diabetic with mean age 65±10 years old and mean contrast dose was 221±100 cc iobitridol) received statins (153 patients (59%) were taking atorvastatin, 77 (30%) simvastatin, 19 (7%) rosuvastatin and 11 (4%) pravastatin) with mean duration of statin pretreatment was 10.6 ± 9.1 months. And 174 patients (37% were diabetic, mean age 67±10 years old and mean contrast dose was 234±105 cc iobitridol) did not receive statin before angiography and he found that 8 patients "3%" in statin group developed CIN, compared to 47 patients "27%" in no statin group.[6] Also Zhao et al, collected 279 candidate patients for CA, 56 of them chronically received statins (pravastatin "41 %", simvastatin "37 %" and atorvastatin "22 %"). And 223 patients did not receive statin before angiography and he found that 4 patients "7 %" in statin group developed CIN, compared to 45 patients " 20 %" in no statin group.[12]

Results also relatively coincided with cohort studies comparing the incidence of CIN in patients received high dose statin therapy compared to a low statin therapy group. Xinwei et al, collected 228 candidate patients for CA, 113 of them received high dose simvastatin therapy (80 mg 4 times the day before, 20 mg the day after procedure (>460 mg), and 115 patients received low dose: 20 mg 4 times (>160 mg before angiography) and he found that 6 patients "5%" in high dose group developed CIN, compared to 18 patients "15%" in low-dose statin group.[2] This relative difference in results might be due to higher percentage of diabetic patients in our study, different type of statin administrated, and difference in patients' demographics, environmental circumstances.

Only one study by Kandula et al, reported a null effect for statin use and an even higher incidence of CIN in the statin group, as he collected 353 patients who were candidate for coronary angiography, 239 patients (41% were diabetic with mean age 72.1±10.4 years old and mean contrast dose was 217.1±106.8 cc of unreported type of contrast media) received atorvastatin (32.7%), simvastatin (31.0%), pravastatin (22.2%), others (statin group), and 114 patients (34.2% were diabetic, mean age 72.7±11.3 years old and mean contrast dose was 182.1±85.4 cc of unreported type of contrast media) received no statins (no statin group) and he found that 59 patients "24.7%" in statin group developed CIN, compared to 16 patients "14%" in no statin group. Higher contrast volume administered in the statin group might have contributed to this result, but when adjusted for the amount of contrast used, no differences in the incidence of CIN were noted.[13]

Limitation: No single or gold standard protocol for the diagnosis of contrast induced nephropathy so the study depended on measurement of both GFR and serum creatinine levels.

CONCLUSION

Short-term use of rosuvastatin 20mg prior to coronary angiography appears to have reno-protective effects and is associated with significant decrease in the incidence of contrast induced nephropathy.

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