Comparison of Combined/Carvedilol Moderate Dose Atorvastatin to Single High Dose Atorvastatin for the Prevention of Contrast-Induced Nephropathy after Cardiac Catheterization

Original Article

Rabab A. EL-Gazar[a], Mohamed Seleem Mohamed[b], Soad zakaria[c], Nirmeen A. Sabry[d], Maggie M. Abbassi[d]

[a]Department of Clinical Pharmacy, Faculty of Pharmacy, October 6 University, [b]National Heart Institute, [c]Department of Pharmacology & Toxicology, Faculty of Pharmacy, October 6 University, [d]Department of Clinical Pharmacy, Faculty of Pharmacy, Cairo University, Kasr El-Aini, Egypt.

ABSTRACT

Background: Contrast-induced nephropathy (CIN) is associated with increased morbidity, and the need for short-term hemodialysis. Although several preventive measures have been used, the best approach to prevent CIN is still controversial.
Objectives: This study is intended to evaluate the protective effect of carvedilol/ medium dose statin compared to the recommended high dose atorvastatin on the development CIN in patients undergoing elective cardiac catheterization (CC).
Patients and Methods: A total of 144 patients planned for CC were randomly assigned to:
• Group (A): 49 patients received atorvastatin as single high dose 80 mg 12 hours before CC and another 40 mg of atorvastatin 2 hours before PCI.
• Group (B): 48 patients were prescribed carvedilol 12.5 mg twice daily for seven days before CC and continued for 24 hours post CC, plus 40 mg atorvastatin 12 hours before CC.
• Group (C): 47 patients received 40 mg atorvastatin 12 hours before CC.
Results: The baseline characteristics of the 3 groups were comparable. CIN incidence was the lowest in group A, but was not significantly different (*p=0.420*). CIN developed in 4(8.2%), 6(12.2%), and 8(17%) patients in groups A, B, and C respectively. Median change in CrCl 48 hours, and serum NGAL 4 hours post CC was significantly lower in group A compared to group C (*p=0.0330, p=0.0348* respectively).
Conclusion: The present study revealed that, combined carvedilol/statin regimen was comparable to single high dose atorvastatin in CIN prevention. However, short high dose of atorvastatin might be preferable in terms of kidney function preservation.

Key Words: Atorvastatin, Cardiac catheterization, carvedilol, CIN, NGAL.

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Corresponding Author: Maggie M. Abbassi, Department of Clinical Pharmacy, Faculty of Pharmacy, Cairo University, Kasr El-Aini, Cairo, Egypt. **Tel.:**: 002 01001589925, **E-mail:** Maggie.abbassi@pharma.cu.edu.eg

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INTRODUCTION

Diagnostic and invasive cardiac catheterization (CC) have been widely used in myocardial infarction (MI) patients.[1] Those patients are at increased risk of complications related to contrast media (CM) usage during CC procedure.[2] Contrast induced nephropathy (CIN), is one of the complications and one of the major causes behind hospital-acquired acute kidney injury.[3]

Pathogenesis of CIN is not clear but most studies suggested that, vasoconstriction of renal vessels, oxidative stress, free radical formation, and endothelial dysfunction are thought to be the major causes.[4] Length and amount of exposure to CM were found to be related to the degree of renal tubular cell death.[3]

CIN is defined as an increase in serum creatinine > 25% or > 0.5 mg/dL above the baseline value after systemic administration of iodinated contrast media following the exclusion of other factors that may induce nephropathy, such as nephrotoxins, hypotension, urinary obstruction, or atheromatous emboli.[5] Serum creatinine rises after 48 hours, peaks in 3-5 days and returns to normal in 21 days, in the absence of other causes of renal failure.[6] This might lead to dialysis, prolongation of hospitalization, and increase in morbidity and mortality.[2]

As serum creatinine rising in response to nephropathy might be delayed and also GFR might fall at any time within 3-5 days of CIN development,[7,8] recent studies proved that, the biomarker neutrophil gelatinase-associated lipocalin (NGAL) might be an alternative to creatinine in

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the early evaluation of acute kidney damage after exposure to CM.[9, 10] NGAL sharply rises in blood and urine within 2 to 4 hours from kidney injury as a compensatory response to defend against oxidative stress-mediated kidney toxicity, which may lessen the degree of damage on ongoing insult and mediate tissue protection.[7]

The best approach to prevent or reverse CIN is still controversial. The benefits of different strategies including intravenous hydration either with isotonic saline or sodium bicarbonate, statins, N- acetyl cysteine (NAC), iloprost, alprostadil, prostaglandin, theophylline, ascorbic acid, and tocopherol have been considered.[9] Despite all the previously mentioned interventions, hydration either orally or intravenously with isotonic saline is still believed to be the most efficient treatment for prevention of CIN.[3] Statins have proven efficacy to protect against CIN in patients at risk for development of CIN after CM exposure.[11] The reported significant decrease in CIN incidence among patients using statins makes it a highly recommended intervention in protection from CIN, especially short high dose atorvastatin which was recommended by European Society of Cardiology (ESC) for all patients with moderate to high risk for CIN.[3,12] High doses statins were defined as 20/40 mg rosuvastatin or 80 mg atorvastatin or 80 mg simvastatin.[3]

Beta-blockers are one the of recommended medication by the American Heart Association and American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) in the treatment of ischemic heart diseases even in patients who did not experience MI.[13,14] Carvedilol a member of beta-blockers family was found to have beneficial effect in CIN prevention.[15,16] Theoretically, it has this potential effect to protect from CIN due to its vasodilatory effect on renal blood vessels and its antioxidant activity.[17]

Up-to-date, there is no study that evaluated the possible reno-protective effect of combined beta-blocker with statin prior to CC in comparison to short high dose statins. Thus, the aim of this study is to compare the efficacy of carvedilol combined with moderate dose statin to short-term high dose atorvastatin in reducing the risk of CIN after cardiac catheterization in patients with moderate to high risk to CIN.

PATIENTS AND METHODS

A 2.1. Study population

This study was conducted in the National Heart Institute (NHI), Giza, Egypt, during the period between February 2016 and May 2017. The study protocol was approved by the Ethics Committee of the Faculty of Pharmacy, Cairo University, and scientific committee of the NHI. The study was conducted according to the Declaration of Helsinki principles.[18] Written informed consent was obtained from all the study participants (Clinicaltrials.gov Registration: NCT03867994).

All patients who were scheduled for elective CC were screened for eligibility to be included in the study. Patients aged between 18 and 65 years with serum creatinine ≤ 1.5 mg/dL, on moderate dose of atorvastatin 40 mg or equivalent, with moderate to high risk of CIN (Mehran score ≥ 6)[19] were included. Patients were excluded if they were suffering from ST-segment elevation myocardial infraction (STEMI), and needed immediate cardiac catheterization,[20] those with elevated liver enzymes aspartate aminotransferase (AST), and alanine aminotransferase (ALT) three times the upper limit of normal),[15] or with active infection, patients allergic to or have contraindication to contrast media, carvedilol, or atorvastatin. Patients vitamins, minerals, or any medication with antioxidant properties 7 days prior to CC, hemodynamically unstable patients (defined as abnormal or unstable blood pressure, especially hypotension (blood pressure less than 90/60 mm Hg),[21] patients who required dialysis, pregnancy, patients used carvedilol in the past three months, or those who used nephrotoxic agent in the past 48 hours or exposure to contrast agent in the past 7 days were also excluded.

All recruited patients were evaluated for the risk of CIN using Mehran risk score.[22] All risk variables were assessed and the score was at least 6 in all patients before they were included in the study except for the variable of volume of contrast media, whose points were added to the risk score after the CC procedure.

2.2. Study design

In this randomized, prospective, parallel controlled study, all recruited patients were randomly assigned to one of three groups:

- Group (A) included 49 patients who received high dose statin (80 mg atorvastatin) 12 hours before CC and 40 mg just 2 hours before CC.[23]
- Group (B) included 48 patients who received 12.5 mg carvedilol twice daily for 7 days before CC and continued for 24 hours after the CC, plus the moderate dose (40 mg) atorvastatin 12 hours before the CC.[24]
- Group (C) included 47 patients who received moderate dose (40 mg) atorvastatin 12 hours before CC as control group.

All recruited patients were hydrated with intravenous (IV) 0.9% sodium chloride (NaCl) at a rate of 0.5-1 mL/kg/hour for 4-6 hours before and 4-6 hours after CC.[25] The type of dye used for all study participants was nonionic low-osmolar contrast dye (iopromide).

Relevant demographic data, comorbidities and medication history were recorded for all study participants. All the patients were screened for the following parameters to determine the primary endpoint (CIN) and secondary endpoints (kidney function and serum NGAL):

- Serum creatinine (Cr) baseline (before initiating the hydration) and 48 hours after the CC procedure to

evaluate the incidence of CIN (defined as absolute rise in the baseline serum creatinine concentration by 0.5 mg/dL after 48 hours from CC).[26]

- Blood urea nitrogen (BUN) was measured before and 48 hours post-CC.
- Creatinine clearance (CrCl) was calculated using Cockcroft–Gault equation[27] on admission, and re-calculated 48 hours post CC using Cockcroft-Gault for all patients except for patients who showed > 0.5 mg/dL rise in SCR where Jelliffe and Jelliffe equation for unstable kidney function was used.[28]
- Serum NGAL baseline was measured before the initiation of hydration, and 4 hours after CC procedure. NGAL was assayed by enzyme-linked immunosorbent assay ELISA (Glory Science Co., Ltd, CHINA).

3.Statistical analysis

G power software was used to determine sample size, a minimum sample size of 34 patients in each group was recommended according to literature based on the incidence of CIN,[29] the power of the test was set at 0.8 and alpha of 0.05.

Statistical analysis was carried out using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA), and GraphPad Prism software (version 5.0; GraphPad Software, Inc., San Diego, CA, United States). Numerical data were presented as mean and standard deviation (SD) and median and inter-quartile range (IQR), while categorical data were described as frequency and percentage.[30] Chi-square test was used for comparison of nominal variables. Quantitative data were tested for normality using Shapiro-Wilk test. If the data was normally distributed one-way ANOVA followed by Tukey's test were used for comparison. For data that did not pass normality test Kruskal-Wallis followed by Dunn's test were used for comparisons.[30] Univariate analysis was performed to predict if any of study variables predicted CIN development.[31] Univariate analysis was performed by using Student t-test for normally distributed data or Mann-Whitney U test for data which did not pass normality test and Chi-square test for nominal variables.[31] For within group comparisons Wilcoxon test was used.[31] Correlation between numerical variables was tested by Spearman-rho method.[32] A *p-value < 0.05* was considered significant.[33]

RESULTS

Out of 1800 screened patients, a total of 173 patients were eligible and consented to take part in the study (Figure 1).

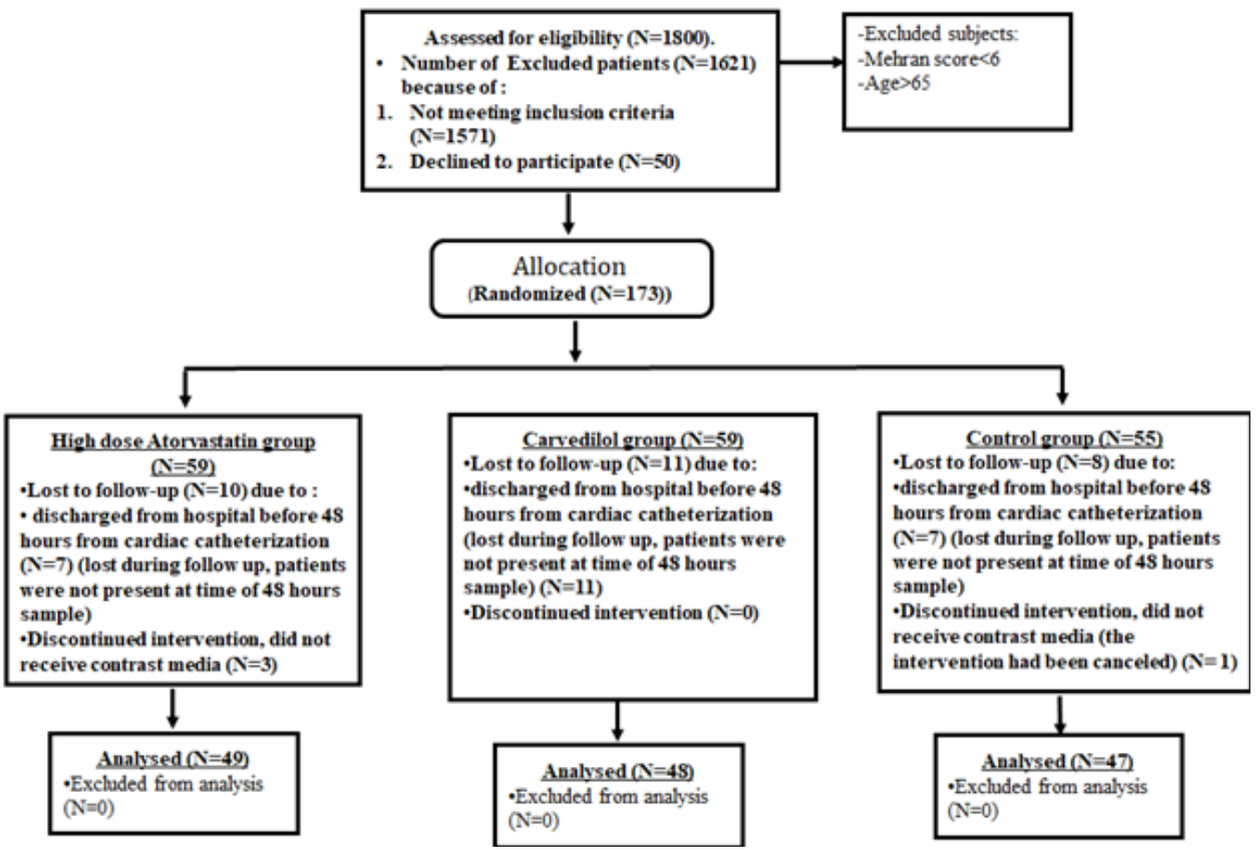

Fig.1: Patients selection and recruitment flow diagram.

The three groups were comparable with respect to their demographic data, clinical baseline data, and all pre-operative medication history except for the number of patients on furosemide which was significantly different between the three groups *p=0.030* (Table 1). However, univariate analysis for CIN development had been performed and revealed that furosemide did not influence the development of CIN (*p=0.488*).

Table 1: Demographic and clinical characteristics of the recruited patients in the three study groups

Parameter	Group A N=49	Group B N=48	Group C N=47	*P value*
Age (years), median (IQR)∞	55.26±6.239	54.50±9.265	57.56±7.781	0.13
Gender (Number of males (%))€	18(36.7)	28(58.3)	25(53.2)	0.08
Average weight (kg) ± SD¥	89.24±18.15	89.25±16.20	93.06±18.08	0.47
Average height (cm) ± SD¥	167.1±8.202	165.8±8.277	168.2±8.248	0.37
Body mass index BMI (kg/m2), median (IQR)∞	31.51(27.83-35.05)	32.16(29.09-34.44)	32.7(29.3-35.92)	0.46
Mehran score, median (IQR)∞	7(7-9)	7(6-9)	8(6-9)	0.35
Number of hypertensive patients (%)¥	49(100)	48(100)	47(100)	1
Number of anemic patients (%)¥	14(28.6)	18(37.5)	8(17)	0.08
Number of diabetic patients (%)¥	41(83.7)	39(81.3)	31(66)	0.08
Number of patients with heart failure class I and II (%)¥	15(30.6)	15(31.3)	20(72.6)	0.5
Number of patients with heart failure class III, and IV (%)¥	15(30.6)	9(18.8)	8(17)	0.22
Ejection fraction%, median (IQR)∞	37(75.5)	38(79.2)	32(68.1)	0.45
Systolic blood pressure (mmHg), median (IQR)∞	130(120-150)	130(120-150)	140) 130-150)	0.24
Diastolic blood pressure (mmHg), median (IQR)∞	80(70-90)	80(70-90)	90(80-90)	0.33
Number of patients undergoing angiography only (%)€	37(75.5)	38(79.2)	31(66)	0.32
Number of patients undergoing PCI (%)€	12(24.5)	10(20.8)	16(34)	0.32
Volume of contrast media (mL), median (IQR)∞	80(70-110)	80(62.5-100)	100) 70-50)	0.42
Volume of fluid administered before CC (mL), median (IQR)∞	240(172-360)	240(160-360)	231(172.360)	0.80
Volume of fluid administered after CC (mL), median (IQR)∞	240(160-360)	231(172.5-360)	240(172-360)	0.79
Patient medication history				
Number of patients on antiplatelets (%)€	48(100)	48(98)	47(100)	0.38
Number of patients on oral nitrates (%)€	45(91.8)	43(89.6)	43(91.5)	0.92
Number of patients on trimitazidine (%)€	21(42.9)	24(50)	23(48.9)	0.75
Number of patients on statins (%)€	49(100)	48(100)	47(100)	1
Number of patients on ACEIs (%)€	38(77.6)	37(77.1)	33(70.2)	0.65
Number of patients on ARBs (%)€	3(6.1)	2(4.2)	5(10.6)	0.45
Number of patients on CCBs (%)€	5(10.2)	10(20.8)	3(6.4)	0.09
Number of patients on furosemide (%)€	14(28.6)	20(41.7)	8(17)	0.030*
Number of patients on spironolactone (%)€	8(16.3)	12(25.5)	17(35.4)	0.1
Number of patients on anti-diabetics (%)€	41(83.1)	39(81.3)	31(66)	0.08
Number of patients on bisprolol (%)€	14(28.6)		7(14.9)	0.11

Data are presented as mean ± standard deviation, median, and interquartile range [25th–75th percentile], frequency and percent.
**P-values <0.05* were considered significant.
Anemia defined as hemoglobin <13g/dL for men and <12g/dL for women.[39]
Heart failure are classified according to New York Heart Association.[24]
ACEIs: angiotensin converting enzyme inhibitor.
ARBs: angiotensin receptor blockers.
CCBs: calcium channel blocker.
Type of statistical test: ∞ Kruskal-Wallis test followed by Dunn's test, € Chi-square test, ¥ one-way ANOVA followed by Tukey's.

Both the incidence of CIN and median of SCr elevation were not significantly different between the three groups ($p > 0.05$). Although the three groups were comparable with respect to CrCl at baseline, and 48 hours post intervention. The median change in CrCl was significantly lower in the group A which showed the lowest decline in kidney function (median change: -6.8 mL/min) compared to the group C (median change: -15.6 mL/min). Baseline serum NGAL was comparable between the three groups. At 4 hours post CC, group B had significantly lower level (23.7 µg/L) of serum NGAL when compared to group C (38.17 µg/L). However, the median change in serum NGAL, showed the least rise in the group receiving high dose atorvastatin (3.6499 µg/L) in comparison group C (10.60 µg/L) (Table 2, Figure 2).

Table 2: Renal biochemical and clinical parameters for recruited patients in the three groups during the study period

	Group A N=49	Group B N=48	Group C N=47	*P value*
Patients who developed CIN N (%)€	4 (8.2%)	6 (12.2%)	8 (17%)	0.42
SCr on admission (mg/dL), median (IQR)∞	1(0.7-1.25)	0.9(0.6-1.2)	0.8(0.67-1)	0.23
SCr after 48 hours (mg/dL), median (IQR)∞	1.2(0.9-1.4)	1.05(0.8-1.375)	1.1(0.9-1.36)	0.64
The median change in SCr (mg/dL), (IQR)∞	0.2(0.1-0.3)	0.175(0.1-0.3)	0.3) 0.1-0.4)	0.15
e-GFR (mL/min) on admission, median (IQR)∞	67.9(49.9-90.5)	73.05(59.58-95.38)	80.3(57.5-109.1)	0.12
e-GFR (mL/min) 48 hours post procedure, median (IQR)∞	67.9(41.7 -80.70)	64.2(50.33-77.98)	64.5(51.7-93.5)	0.65
The median change in e-GFR (mL/min), (IQR)∞	-6.8)-13.50-0.2)	-7.15(-17.88- -0.55)	-15.6(-26.30- -3.4)†	0.03*
Serum NGAL on admission (µg/L), median (IQR)∞	26.65(14.58-41.55)	17.53(10.03-27.36)	29.23(10.94-48.09)	0.06
Serum NGAL after 4 hours (µg/L), median (IQR)∞	31.24(13.44-46.56)	23.7(15.83-45.25)	38.17(26.81-65.73)$	0.03*
The median change in serum NGAL (µg/L), (IQR)∞	3.86(-4.647-10.94)	7.979(0.4469-13.73)	10.01(0.78-23.02)†	0.04*
BUN (mg/dL) on admission, median (IQR)∞	32(24.5-42.5)	30(24.25-38.25)	28(23.25-40.25)	0.46
BUN (mg/dL) 48 hours post procedure, median (IQR)∞	37(30-46)	37(29.25-45)	36.35(27.75-45.75)	0.844
The median change in BUN (mg/dl), (IQR)∞	5(-4-12)	5(2.25-12.75)	5(-1.250-10)	0.69

Data presented as frequency and percent or median and interquartile range [25th–75th percentile], **P-values <0.05* were considered significant.
CIN: contrast induce nephropathy, NGAL: neutrophil gelatinous associated lipocaline, SCr: serum creatinine, e-GFR: estimated glomerular filtration rate, BUN: blood urea nitrogen.
† Control group is significantly different from atorvastatin group.
$ Control group is significantly different from carvedilol group.
Type of statistical test: ∞Kruskal-Wallis test, € Chi

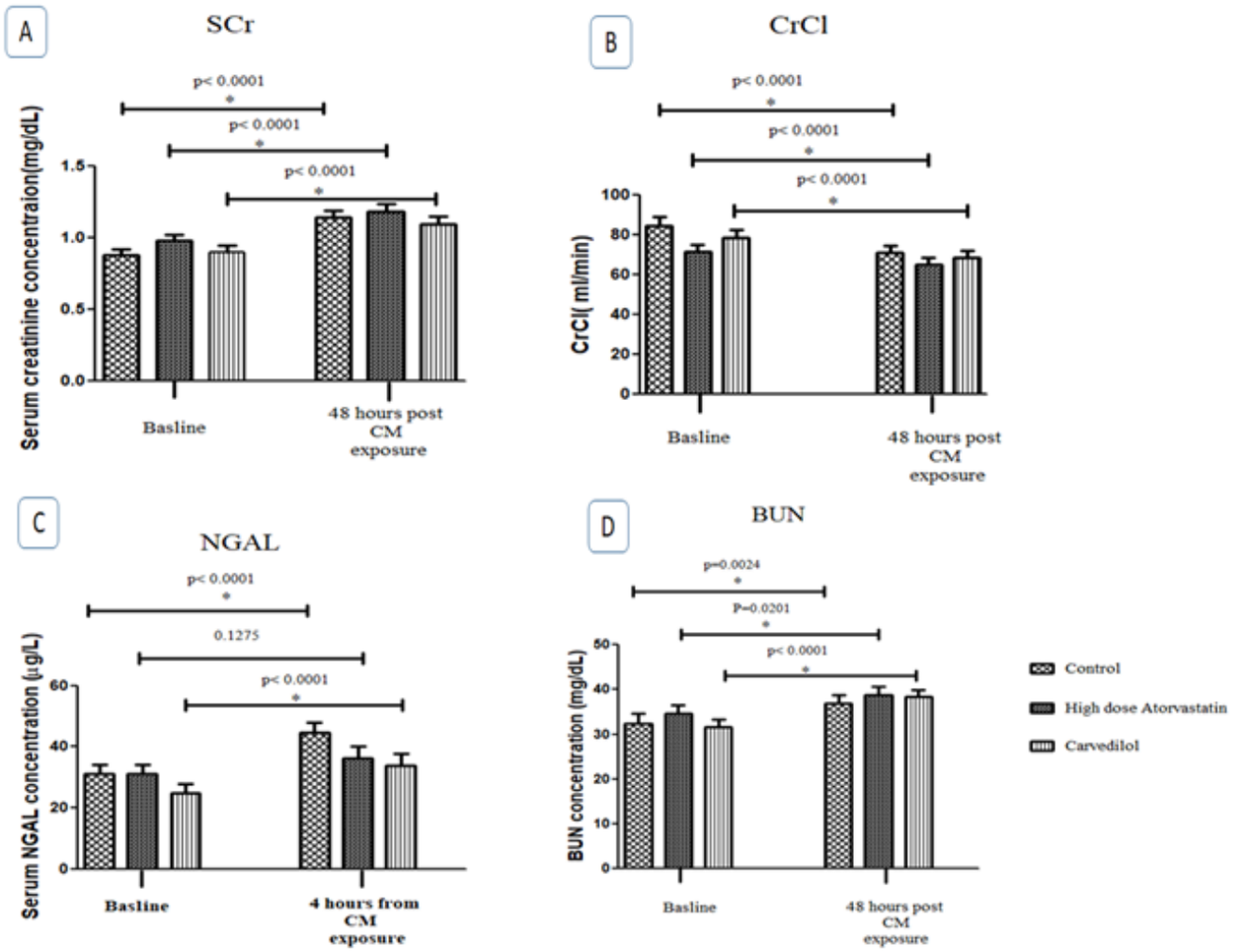

Fig. 2: Comparison of kidney function markers (A) SCr (B) Crcl (D) BUN, and (C) NGAL as acute kidney injury marker within each group before and after CC using the median values and Wilcoxon test, *$P<0.05$ was considered significant. A: Serum creatinine before and after CC in each group, B: Creatinine clearance before and after CC in each group, C: Serum NGAL before and after CC in each group and D: Blood urea nitrogen before and after CC in each group. CC: cardiac catheterization; Scr: serum creatinine, Crcl: creatinine clearance, NGAL: neutrophil gelatinous associated lipocaline ,BUN: blood urea nitrogen.

DISCUSSION

There was no significant difference in the incidence of CIN among the three groups. The definition used to describe CIN in this study was a 0.5 mg/dL absolute increase in serum creatinine,[3] since it was better correlated to mortality rate after 6 months.[26]

Wide ranges of CIN incidence had been reported, from 7% in patients with low or no risk for CIN development to reach 25% in patients with high risk for CIN.[34] The overall incidence of CIN development in the present study was 12.5%, which is considered relatively high incidence. This can be attributed to the high risk profile of the recruited patients: 77% of the patients had diabetes mellitus, 83(57.6%) patients had heart failure, 40(27.7%) patients had anemia, all patients had hypertension. On the basis of the risk score introduce by Mehran *et al*.,[22] the incidence of CIN development in patients with medium to high risk ranged between 14.1 and 26.1%.

The present study reported that, 7 preoperative days of carvedilol combined with moderate dose atorvastatin showed comparable results to short-term high dose of atorvastatin in the primary outcome which was the protection against CIN development. Otherwise, short-term high dose atorvastatin regimen was superior over conventional moderate dose atorvastatin in other outcomes as preserving CrCl 48 hours post CC and preventing serum NGAL rising 4 hours post CM exposure.

Statins have a proven efficacy to protect against CIN regardless of LDL cholesterol level of the patients,[11,12] and therefore, are considered one of the main CIN preventative measures according to the European Society of Cardiology CIN prevention guidelines.[3]

A meta-analysis by Su *et al*, analyzed 150 clinical trials evaluating 12 different interventions, comparing their protective effect against the development of CIN. The interventions included all of the following medications in combination with hydration: N-acetylcysteine (NAC), theophylline (aminophylline), fenoldopam, iloprost, alprostadil, prostaglandin E1, statins, statins plus NAC, bicarbonate sodium, bicarbonate sodium plus NAC, ascorbic acid (vitamin C), tocopherol (vitamin E), a-lipoic acid, atrial natriuretic peptide, B-type natriuretic peptide, and carperitide. The meta-analysis revealed that, high-dose statins plus hydration with or without NAC was the most preferable strategy to prevent CIN in patients undergoing CC[35].

Fan *et al*., concluded in their meta-analysis on 19 clinical trials that, all statins showed the same incidence of reducing CIN.[36] Another meta-analysis by Liu *et al*., analyzed nine randomized clinical trials showed that, patients using high dose (80 mg) atorvastatin had significantly lower incidence of CIN after coronary angiography.[37] Even a single high loading dose of atorvastatin administered within 24 hours prior CM exposure have proven its effect in reducing the rate of CIN.[38]

The results of the present study are also in line with the results of a multicenter study which evaluated 625 patients on chronic statins undergoing CABG. Patients were divided into two groups; one group was on regular statin therapy while the other one withheld statins 24 hours prior to CABG. Their results revealed that, preoperative statins had the ability to prevent kidney injury evidenced by the ability to inhibit plasma NGAL, and also other biomarkers of AKI as urine IL-8, urine NGAL, and urine KIM-1.[39]

Beta-blockers are among the most commonly prescribed anti-ischemic medication classes in coronary artery diseases specially prior to CC.[26,40] Several studies proved the nephroprotective effect of beta-blockers against oxidative stress mediated by CM in human and animal models of CI-AKI.[15,40,41] Carvedilol, metoprolol, and nebivolol were the most studied beta-blockers in the prevention of CIN.[42, 43]

Although metoprolol is still one of the most commonly prescribed beta-blockers by physicians,[43] it does not possess vasodilatory properties like carvedilol and nebivolol.[44] In randomized controlled trials, metoprolol did not prove to add any value over standard hydration regimen with IV 0.9% NaCl towards CIN prevention or even inhibiting serum creatinine peak rise two and five days post CM exposure.[43] Also, carvedilol and nebivolol had proven to be superior to metoprolol in the prevention of CIN.[15,45] However, the overall effect of nebivolol towards CIN prevention in humans was not found to be statistically significant when discussed in a meta-analysis by Thamcharoen.[42] The meta-ananlysis evaluated three clinical trials, and it reported that, pre-procedure administration of nebivolol was not superior over control group. Same incidence of CIN was reported when nebivolol was compared to carvedilol and metoprolol. also, it was reported that, nebivolol was superior over metoprolol in reducing incidence of CIN.

Carvedilol defensive properties over different condition affecting the kidney is well-recognized.[15,16,46] Yasar *et al*., proved that, carvedilol possessed reno-protective effect in ureteral obstruction in rats by preventing oxidative stress induced by obstruction ischemia.[47] Another study by Akindele *et al*., showed the same reno-protective effect of carvedilol in preventing nephrotoxicity mediated by oxidative stress of doxorubicin.[46] In addition to its antioxidant properties, nitric oxide (NO) releasing play a major role in reno-protective effect of carvedilol.[48]

Ozaydin *et al*.,[16] observed that, carvedilol synergized the beneficial effect of NAC in preventing AKI that resulted from oxidative stress and inflammation occurring during cardiac surgery in humans, in addition to the decreased incidence of CIN and peak serum creatinine rising after 5 days of procedure. Also, human trials showed promising results of carvedilol in the prevention of CIN,[15,16] and this was confirmed by the results of the present study.

The combination therapy of carvedilol and atorvastatin, which is widely used in patients with ischemic heart disease who are suspected to undergo CC, was proven to decrease mortality rate after MI, and after abdominal aortic aneurism surgery.[49] One study had evaluated the combination of carvedilol and atorvastatin in the protection of cyclosporine induced nephrotoxicity in animals, and revealed that, the combination reduced the nephrotoxicity of chronic use of cyclosporine and preserve kidney function when compared to each of them alone.[50]

In the present study, the combination of carvedilol to moderate dose atorvastatin showed comparable result to single high dose atorvastatin the prevention of CIN development, which could suggest the beneficial effect of the combination.

CONCLUSION

The incidence of CIN was not significantly different between carvedilol combined with moderate dose statin and single high dose atorvastatin, suggesting the non-inferiority of combined carvedilol/moderate dose atorvastatin to high dose atorvastatin in CIN protection. However, only short high dose of atorvastatin was found to be superior to moderate dose atorvastatin in terms of kidney function preservation by having the lowest decrease in CrCl, and unaltered serum NGAL level after exposure to CM.

STUDY LIMITATIONS

Some of included patients were not naïve beta-blocker which is considered as one of our study limitations, although they were on beta-blocker but they were on bisprolol and there is no evidence in the literature supporting the protective effect of bisprolol against CIN development.

Although measuring serum NGAL 4 hours post CC is a reliable test to estimation degree of the ongoing kidney insult, it was recommended to measure it at other time points as 12 hours and 24 hours after CC for confirmation. This was difficult to achieve due to the nature of the study which was self-funded. For the same reason investigators were unable assess kidney injury acute biomarker such as KIM-1, IL-18 to confirm the results.

RECOMMENDATIONS

Further trials on larger sample size might confirm the protective effect of carvedilol against CIN and the best regimen to be used before CC. In addition, a longer observation period will allow long-term outcome assessment.

If beta-blockers are recommended before CC, carvedilol in a dose of 12.5 mg given twice daily for 7 days before CC might add a clinical value in the prevention of CIN.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Slicker K, Lane WG, Oyetayo OO, *et al*. Daily cardiac catheterization procedural volume and complications at an academic medical center. Cardiovasc Diagn Ther. 2016;6(5):446-452. doi:10.21037/cdt.2016.05.02

2. Bartholomew BA, Harjai KJ, Dukkipati S, *et al*. Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am J Cardiol. 2004;93(12):1515-1519. doi:10.1016/j.amjcard.2004.03.008

3. Rear R, Bell RM, Hausenloy DJ. Contrast-induced nephropathy following angiography and cardiac interventions. Heart. 2016;102(8):638-648. doi:10.1136/heartjnl-2014-306962

4. Heyman SN, Reichman J, Brezis M. Pathophysiology of radiocontrast nephropathy: A role for medullary hypoxia. Invest Radiol. 1999;34(11):685.

5. Mohammed NA, Rafie I, Mahfouz A, Achkar K, Hajar R. Contrast-induced nephropathy. Hear Views. 2013;14(3):106. doi:10.4103/1995-705X.125926

6. Sv P, Jayakumar KP, Jayaprakash VL, *et al*. Contrast induced nephropathy a study of 850 patients undergoing cardiac catheterization laboratory procedures. Kerala Hear J. 2011;1:14-17.

7. De Geus HRH, Betjes MG, Bakker J. Biomarkers for the prediction of acute kidney injury: A narrative review on current status and future challenges. Clin Kidney J. 2012;5(2):102-108. doi:10.1093/ckj/sfs008

8. Mohammed NMA, Mahfouz A, Achkar K, *et al*. Contrast-induced Nephropathy. Heart Views. 2013;14(3):106-116. doi:10.4103/1995-705X.125926

9. Benzer M, Alpay H, Baykan Ö, *et al*. Serum NGAL, cystatin C and urinary NAG measurements for early diagnosis of contrast-induced nephropathy in children. Ren Fail. 2016;38(1):27-34. doi:10.3109/0886022X.2015.1106846

10. Tong J, Li H, Zhang H, *et al*. Neutrophil gelatinase-associated lipocalin in the prediction of contrast-induced nephropathy : A Systemic Review and Meta-analysis. Cardiovasc Pharmacol. 2015;66(3):239-245.

11. Barbieri L, Verdoia M, Schaffer A, *et al*. The role of statins in the prevention of contrast induced nephropathy : a meta-analysis of 8 randomized trials. J Thromb Thrombolysis. 2014;38(4):493-502. doi:10.1007/s11239-014-1076-3

12. Singh N, Lee JZ, Huang JJ, *et al*. Benefit of statin pretreatment in prevention of contrast-induced nephropathy in different adult patient population: Systematic review and meta-analysis. Open Hear. 2014;1(1):1-12. doi:10.1136/openhrt-2014-000127

13. Smith SC, Benjamin EJ, Bonow RO, *et al*. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124(22):2458-2473. doi:10.1161/CIR.0b013e318235eb4d

14. Cardiol RJ. 2013 ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology. Russ J Cardiol. 2014;111(7):7-79. doi:10.1016/j.rec.2013.11.008

15. Yilmaz M, Aydinalp A, Okyay K, *et al*. Comparison of carvedilol and metoprolol for preventing contrast-induced nephropathy after coronary angiography. CardioRenal Med. 2015;5(3):199-207. doi:10.1159/000381964

16. Ozaydin M, Peker T, Akcay S, *et al*. Addition of N-acetyl cysteine to carvedilol decreases the incidence of acute renal injury after cardiac surgery. Clin Cardiol. 2014;37(2):108-114. doi:10.1002/clc.22227

17. Dulin B, Abraham WT. Pharmacology of carvedilol. Am J Cardiol. 2004;93(9):3-6. doi:10.1016/j.amjcard.2004.01.003

18. Helsinki. World Medical Association Declaration of Helsinki. JAMA. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

19. Sgura FA, Bertelli L, Monopoli D, *et al*. Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. Circ Cardiovasc Interv. 2010;3(5):491-498. doi:10.1161/CIRCINTERVENTIONS.110.955310

20. Terkelsen CJ, Jensen LO, Tilsted HH, *et al*. Primary percutaneous coronary intervention as a national reperfusion strategy in patients with ST-segment elevation myocardial infarction. Circ Cardiovasc Interv. 2011;4(6):570-576. doi:10.1161/CIRCINTERVENTIONS.111.962787

21. Freeman R, Wieling W, Axelrod FB, *et al*. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72. doi:10.1007/s10286-011-0119-5

22. Mehran R, Aymong ED, Nikolsky E, *et al*. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. J Am Coll Cardiol. 2004;44(7):1393-1399. doi:10.1016/j.jacc.2004.06.068

23. Galal H, Nammas W, Samir A. Impact of high dose versus low dose atorvastatin on contrast induced nephropathy in diabetic patients with acute coronary syndrome undergoing early percutaneous coronary intervention. Egypt Hear J. 2015;67(4):329-336. doi:10.1016/j.ehj.2014.12.002

24. Akgüllü Ç, Eryılmaz U, Huyut A, Al E. Comparison of Carvedilol, Nebivolol and Metoprolol for the Prevention of Contrast Induced Nephropathy. J Am Coll Cardiol. 2013;62(18):223-224. doi:10.1016/j.jacc.2013.08.634

25. Maioli M, Toso A, Leoncini M. Effects of hydration in contrast-induced acute kidney injury after primary angioplasty a randomized, controlled trial. Circ Cardiovasc Interv. 2011;4:456-462. doi:10.1161/CIRCINTERVENTIONS.111.961391

26. Guillon B, Ecarnot F, Marcucci C, *et al*. Incidence, predictors, and impact on six-month mortality of three different definitions of contrast-induced acute kidney injury after coronary angiography. Am J Cardiol. 2018;121(7):818-824. doi:10.1016/J.AMJCARD.2017.12.029

27. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010;5(6):1003-1009. doi:10.2215/CJN.06870909

28. Jelliffe RW. Creatinine clearance: Bedside estimate. Ann Intern Med. 1973;79(4):604. doi:10.7326/0003-4819-79-4-604

29. Patti G, Nusca A, Chello M, *et al*. Usefulness of Statin Pretreatment to Prevent Contrast-Induced Nephropathy and to Improve Long-Term Outcome in Patients Undergoing Percutaneous Coronary Intervention. Am J Cardiol. 2008;101(3):279-285. doi:10.1016/j.amjcard.2007.08.030

30. Motulsky H. Intuitive Biostatistics : A Nonmathematical Guide to Statistical Thinking. (ed3). Oxford University Press; 2014.

31. Marusteri M, Bacarea V. Comparing groups for statistical differences: how to choose the right statistical test? Biochem Medica. 2010;20(1):15-32. doi:10.11613/BM.2010.004

32. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi Med J. 2012;24(3):69-71.

33. Greenland S, Senn SJ, Rothman KJ, *et al*. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. Eur J Epidemiol. 2016;31(4):337-350. doi:10.1007/s10654-016-0149-3

34. Azzalini L, Spagnoli V, Ly HQ. Contrast-Induced Nephropathy: From Pathophysiology to Preventive

Strategies. Can J Cardiol. 2016;32(2):247-255. doi:10.1016/j.cjca.2015.05.013

35. Su X, Xie X, Liu L, *et al*. Comparative Effectiveness of 12 Treatment Strategies for Preventing Contrast-Induced Acute Kidney Injury: A Systematic Review and Bayesian Network Meta-analysis. Am J Kidney Dis. 2017;69(1):69-77. doi:10.1053/j.ajkd.2016.07.033

36. Fan J, Sun H, Zhao X. Statins for prevention of contrast induced nephropathy after coronary angiography: A network meta-analysis. Int J Clin Exp Med. 2015;9(1):156-163.

37. Liu L-Y, Liu Y, Wu M-Y, *et al*. Efficacy of atorvastatin on the prevention of contrast-induced acute kidney injury: a meta-analysis. Drug Des Devel Ther. 2018;12:437-444. https://www.dovepress.com/efficacy-of-atorvastatin-on-the-prevention-of-contrast-induced-acute-k-peer-reviewed-article-DDDT. Accessed July 15, 2018.

38. Quintavalle C, Fiore D, De Micco F, *et al*. Impact of a high loading dose of atorvastatin on contrast-induced acute kidney injury. Circulation. 2012;126(25):3008-3016. doi:10.1161/CIRCULATIONAHA.112.103317

39. Molnar A, Parikh C, Coca S, *et al*. Association between preoperative statin use and acute kidney injury biomarkers in cardiac surgical procedures. Ann Thorac Surg. 2014;97(6):2081-2087. doi:10.1016/j.athoracsur.2014.02.033.Association

40. Akgüllü Ç, Hekim T, Eryılmaz U, *et al*. The usefulness of carvedilol and nebivolol in preventing contrast nephropathy in rats The usefulness of carvedilol and nebivolol in preventing contrast nephropathy in rats. Ren Fail. 2015;37(3):511-517. doi:10.3109/0886022X.2015.1006087

41. Coats A, Jain S. Protective effects of nebivolol from oxidative stress to prevent hypertension-related target organ damage. J Hum Hypertens. 2017;31(6):376-381. doi:10.1038/jhh.2017.8

42. Thamcharoen N, Thongprayoon C, Edmonds P, et al. Periprocedural nebivolol for the prevention of contrast-induced acute kidney injury: A systematic review and meta-analysis. N Am J Med Sci. 2015;7(10):446. doi:10.4103/1947-2714.168670

43. Akgüllü Ç, Eryılmaz U, Güngör H, *et al*. A clinical study about contrast nephropathy: Risk factors and the role of beta blockers. Anadolu Kardiyol Derg. 2015;15(3):232-240. doi:10.5152/akd.2014.5304

44. Fares H, Lavie CJ, Ventura HO. Vasodilating versus first-generation β-blockers for cardiovascular protection. Postgrad Med. 2012;124(2):7-15. doi:10.3810/pgm.2012.03.2532

45. Avci E, Yesil M, Bayata S, *et al*. The role of nebivolol in the prevention of contrast-induced nephropathy in patients with renal dysfunction. Anadolu Kardiyol Dergisi/The Anatol J Cardiol. 2011;11:613-617. doi:10.5152/akd.2011.164

46. Akindele AJ, Oludadepo GO, Amagon KI, Singh D, Osiagwu DD. Protective effect of carvedilol alone and coadministered with diltiazem and prednisolone on doxorubicin and 5-fluorouracil-induced hepatotoxicity and nephrotoxicity in rats. Pharmacol Res Perspect. 2018;6(1). doi:10.1002/prp2.381

47. Yasar A, Erdemir F, Parlaktas BS, *et al*. The effect of carvedilol on serum and tissue oxidative stress parameters in partial ureteral obstruction induced rat model. Kaohsiung J Med Sci. 2013;29(1):19-25. doi:10.1016/j.kjms.2012.08.003

48. Atwa A, Hegazy R, Shaffie N, Yassin N, Kenawy S. Protective effects of vasodilatory Beta-blockers carvedilol and nebivolol against glycerol model of rhabdomyolysis-induced acute renal failure in rats. Maced J Med Sci. 2016;4(3):329-341. doi:10.3889/oamjms.2016.082

49. Kertai MD, Boersma E, Westerhout CM, *et al*. A combination of satins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg. 2004;28(4):343-352. doi:10.1016/j.ejvs.2004.07.008

50. Gludağ S, Sbinç TB, Tali P, Ekyay ST, Cutlugon TA. Effects of Atorvastatin and Carvedilol on Chronic Cyclosporine Nephrotoxicity in Rats. J Clin Exp Nephrol. 2018;3(1):1. doi:10.21767/2472-5056.100052