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ORIGINAL ARTICLE

Clinically Significant Contrast Induced Acute Kidney Injury after Non-Emergent Cardiac Catheterization - Risk Factors and Impact on Length of Hospital Stay

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ABSTRACT

Objective: To evaluate the frequency and risk factors associated with clinically significant contrast-induced nephropathy (CIN) in patients undergoing non-emergent coronary angiography.

Study Design: Descriptive study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from January 2005 to December 2007.

Methodology: Case records of patients who underwent coronary angiography with a serum creatinine of ≥ 1.5 mg/dl at the time of procedure were evaluated. Clinically significant contrast induced nephropathy (CSCIN) was defined as either doubling of serum creatinine from baseline value within a week following the procedure or need for emergency hemodialysis after the procedure.

Results: One hundred and sixteen patients met the inclusion criteria. Mean age was 64.0 ± 11.5 years, 72% were males. Overall prevalence of CIN was 17% (rise of serum creatinine by ≥ 0.5 mg/dl) while that of clinically significant CIN (CSCIN) was 9.5% (11 patients). Patients with CSCIN had significantly lower left ventricular ejection fraction (p = 0.03, OR: 0.24; 95% CI = 0.06 – 0.91) and higher prevalence of cerebrovascular disease (p < 0.001, OR: 14.66; 95% CI = 3.30 – 65.08). Mean baseline serum creatinine was significantly higher, 3.0 ± 1.5 vs. 2.0 ± 1.1 mg/dl (p = 0.03, OR: 1.47; 95% CI = 1.03 – 2.11) whereas mean GFR estimated by Cockcroft-Gault formula was significantly lower at 25 ± 7.4 vs. 41.0 ± 14.6 ml/minute (p = 0.001, OR = 0.89, 95% CI = 0.84 – 0.95) at the time of procedure in patients with CSCIN. Mean length of hospital stay was significantly higher in this group compared to those without CIN, 9.0 ± 5.1 vs. 3.0 ± 3.2 days (p = 0.001, OR = 1.31, 95% CI = 1.12 – 1.54). Multivariate analysis revealed low GFR (p = 0.001, OR = 0.88; 95% CI = 0.82 – 0.95) and low ejection fraction (p = 0.03, OR = 0.20; 95% CI = 0.04 – 0.91) to be independent factors associated with CSCIN. No significant differences were noted between the two groups in patients with hypertension, diabetes and heart failure.

Conclusion: CSCIN is a significant concern in high risk groups despite prophylaxis. Patients with lower EF, cerebrovascular disease and low GFR at the time of procedure are more likely to have CIN.

Key Words: *Acute kidney injury. Contrast induced nephropathy. Cardiac catheterization.*

INTRODUCTION

Acute Kidney Injury (AKI) caused by a radio-contrast dye or Contrast Induced Nephropathy (CIN) is a common complication of coronary angiography.[1] Despite advances in preventive measures, CIN is the third leading cause of AKI and is associated with higher rates of morbidity and mortality in hospitalized patients, with a more complicated and longer in-hospital stay.[2-4] The incidence of acute kidney injury in, otherwise healthy individuals undergoing coronary angiography has been reported to be as low as 2%. However, in high risk patients with inadequate prophylaxis, the frequency of developing CIN can be as high as 80%.[2,5]

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Chronic kidney disease (CKD) is the most significant risk factor for CIN and multiple studies have shown that it is an independent risk predictor for CIN.[3,4,6] Several prophylactic measures have been tested to prevent kidney injury after contrast exposure. The most studied ones are hydration, sodium bicarbonate infusion, anti-oxidants such as N-acetyl-cysteine and ascorbic acid, and lately statins.[7-10] Among these, peri-procedure hydration with normal saline has been proven to be most effective.[7]

Unfortunately, there is no definite definition of CIN. Most studies have used 0.3-0.5 mg/dl rise in creatinine as a cutoff for defining CIN.[11] Although studies have shown association of CIN with adverse patient outcomes,[1-3] data on actual incidence of 'clinically significant CIN' in patients undergoing non-emergent cardiac intervention and its impact on cost of health care is scarce, especially from this region of the world.

The aim of this study was to evaluate the frequency and associated risk factors for 'clinically significant' CIN in high risk patients undergoing non-emergent coronary

angiography, and its economic impact on patients at the Aga Khan University Hospital, Karachi, Pakistan.

METHODOLOGY

The case records of patients who underwent coronary angiography with or without intervention between January 2005 and December 2007 at the Aga Khan University Hospital, Karachi, Pakistan were retrospectively studied.

Patients who underwent non-emergent coronary angiography with or without intervention and had a serum creatinine level of 1.5 mg/dl or above at the time of procedure were included in the study. Serum level ≥ 1.5 mg/dl was chosen to select only patients with deranged renal function which are high risk with baseline impairment. Moreover, only patients who received non-ionic contrast were included for the purpose of consistency.

Those patients were excluded who underwent emergent coronary angiography or without adequate prophylaxis against CIN, those who received ionic contrast, patients with hemodynamic instability requiring vasopressor or ionotropic support, patients with stage-V chronic kidney disease (CKD), those who had repeat exposure to contrast within 72 hours, and those who underwent coronary artery by-pass surgery (CABG) within a week following angiography.

Contrast induced nephropathy (CIN) was defined as an absolute increase of 0.5 mg/dl or more in serum creatinine from baseline at 48 or 72 hours following exposure to contrast. “Clinically significant contrast induced nephropathy” (CSCIN) was defined according to the definition of the American College of Cardiology National Cardiovascular Data registry as either doubling of serum creatinine from baseline value within a week following the procedure or need for emergency hemodialysis after the procedure.[12] Patients who had CIN but did not meet the “clinically significant” definition or no CIN were classified as having “clinically insignificant contrast induced nephropathy” (CICIN). Mean glomerular filtration rate (GRF) was estimated by Cockcroft-Gault formula.[13]

The primary outcome measure was the frequency of clinically significant contrast induced nephropathy while the secondary outcome included evaluation of the risk factors and co-morbidities associated with CSCIN, its impact on length of stay and cost of hospitalization in these patients.

A descriptive analysis was done for demographic and clinical features and results are presented as mean ± standard deviation and median [range] for skewed variables for quantitative variables and number (percentage) for qualitative variables, respectively. In univariate analysis, association between clinically significant CIN and its risk factors were assessed by using the Chi-square test or Fisher exact test where appropriate. For comparison of continuous variables, independent sample t-test for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables was used to assess the difference of means.

To assess univariate associations between the outcomes and potential co-variates, odds ratios (ORs) and their 95% confidence intervals (CIs) were computed by logistic regression analysis. All significant factors on univariate analysis were considered for inclusion in the multivariable logistic model.

All analyses were conducted by using the Statistical Package for Social Sciences (SPSS) (release 19.0, standard version, copyright © SPSS; 1989-02). All p-values were two sided and considered as statistically significant if < 0.05.

The study was approved by Ethical Review Committee of the Aga Khan University Hospital, Karachi.

Table I: Demographic and clinical characteristics of the patients studied.

Patients' characteristics	n = 116
Age	64.0 ± 11.5
Gender	
Males	84 (72%)
Females	32 (28%)
Diabetes mellitus	79 (68%)
Hypertension	104 (90%)
Heart failure	33 (28%)
Ejection fraction	
< 30%	25 (22%)
30 – 55%	45 (39%)
> 55%	46 (39%)
Liver disease	2 (2%)
Cerebrovascular disease	10 (9%)
Peripheral vascular disease	5 (4%)
Use of medications at the time of procedure	
Non-steroid	5 (4%)
ACE	70 (60%)
Diuretic	66 (57%)
Procedure detail	
Diagnostic only	70 (60%)
Diagnostic plus PCI	46 (40%)
Type of contrast used	
Ionic	0 (0%)
Non-ionic	116 (100%)
Volume of contrast (ml)	
< 100	62 (53%)
> 100	54 (47%)
Creatinine after procedure	2.1 ± 1.2
Estimate GFR	38.7 ± 15
Creatinine 24 hours after procedure	2.0 ± 1.2
Creatinine 48 hours after procedure	2.2 ± 1.4
Peak serum creatinine	2.5 ± 1.5
Doubling of creatinine within week after procedure	10 (9%)
Need of hemodialysis	4 (3%)
Median length of stay (days)	2 (1-26)

Continuous variables are expressed as mean ± standard deviation and categorical variables are expressed in number of patients (%).

Table II: Univariate analysis for the factors predicting the risk of clinically significant contrast induced nephropathy (CIN) (*p-values and Odds ratio are calculated by comparing Groups 1 and 3).

Characteristics	Group 1: Clinically significant CIN. N = 11	Group 2: Clinically insignificant CIN. N = 12	Group 3: No CIN. N = 93	p-value*	Odds ratio (95% C.I.)
Age (in years)	68.4 ± 11.3	63.5 ± 11.8	63.6 ± 11.6	0.20	1.03 (0.98-1.09)
Gender					
Men	7 (64%)	7 (58%)	70 (75%)	0.41	1.0
Women	4 (36%)	5 (42%)	23 (25%)		1.73 (0.46-6.48)
Diabetes mellitus	8 (73%)	12 (100%)	59 (63%)	0.54	1.53 (0.38-6.18)
Hypertension	10 (91%)	11 (92%)	83 (89%)	0.86	1.20 (0.13-10.42)
Heart failure	4 (36%)	8 (67%)	21 (23%)	0.31	1.95 (0.52-7.34)
Cerebrovascular disease	5 (45.5%)	0	5 (5%)	< 0.001	14.66 (3.30-65.08)
Liver disease	0	0	2 (2%)	0.62	N.S.
Peripheral vascular disease	0	2 (17%)	3 (3%)	0.54	N.S.
Ejection fraction					
< 30%	5 (45.5%)	4 (33%)	16 (17%)	0.03	1.0
> 30%	6 (54.5%)	8 (67%)	77 (83%)		0.24 (0.06-0.91)
Estimate GFR (ml/min)	25.0 ± 7.4	32.0 ± 12.6	41.0 ± 14.6	0.001	0.89 (0.84-0.95)
Contrast volume					
< 100 ml	5 (45.5%)	9 (75%)	48 (52%)	0.70	1.0
> 100 ml	6 (54.5%)	3 (25%)	45 (48%)		1.28 (0.36-4.48)
Baseline creatinine (mg/dl)					
< 2.0	4 (36%)	5 (42%)	72 (77%)	0.008	1.0
> 2.0	7 (64%)	7 (58%)	21 (23%)		6 (1.60-22.48)
Mean baseline creatinine (mg/dl)	3.0 ± 1.5	2.5 ± 1.1	2.0 ± 1.1	0.03	1.47 (1.03-2.11)
Creatinine 24 hours after procedure (mg/dl)	3.0 ± 1.2	2.4 ± 1.0	1.9 ± 1.1	0.01	1.57 (1.07-2.30)
Creatinine 48 hours after procedure (mg/dl)	4.0 ± 2.0	3.1 ± 1.5	1.8 ± 1.1	0.002	2.10 (1.30-3.40)
Peak serum creatinine (mg/dl)	4.5 ± 1.8	3.7 ± 1.5	2.1 ± 1.2	< 0.001	1.95 (1.35-2.81)
Median length of hospital stay (days)	10 (2-16)	4 (1-13)	2 (1-26)	0.001	1.31(1.12-1.54)

N.S = Not significant.

Table III: Incidences of contrast induced nephropathy in Asian and Western countries.

Study	Location of study	Type of study	Definition of CIN	Number of patients	Incidence of CIN	Need for dialysis (Number of patients)	Mean length of hospital stay in days (CIN vs. no CIN)
Present study	Karachi, Pakistan	Retrospective	1. Rise in serum creatinine > 0.5 mg/dl 2. Doubling of creatinine or need of emergency hemodialysis	116	1. 17% 2. 9.5%	4 patients	9 vs. 3
Soofi 2006[19]	Karachi, Pakistan	Retrospective	Rise in serum creatinine > 0.5 mg/dl	200	8%	Not given	Not given
Uddin *et al.* 2005[18]	Karachi, Pakistan	Retrospective	Rise in serum creatinine > 0.5 mg/dl	115	9.65%	Not given	Not given
Rahman *et al.* 2010[20]	Dhaka, Bangladaesh	Prospective	Rise in serum creatinine ≥ 0.5 mg/dl or ≥ 25%	245	24.08%	Not given	Not given
Pakfetrat *et al.* 2010[6]	Shiraz, Iran	Prospective	RIFLE* criteria	290	15.5%	Not given	Not given
Senoo *et al.* 2010[21]	Osaka, Japan	Prospective	Rise in serum creatinine ≥ 0.5 mg/dl or ≥ 25%	335	28%	Not given	Not given
Chong *et al.* 2010[22]	Singapore	Retrospective	Rise in serum creatinine by ≥ 0.5 mg/dl or ≥ 25%	3036	7.3%	Not given	Not given
Ghani *et al.* 2009[23]	Kuwait	Prospective	Rise in serum creatinine concentration of ≥ 44.2 µmol/L within 48 hours after procedure	247	5.52%	Not given	Not given
Shema *et al.* 2009[3]	Nahariya, Israel	Retrospective	Rise in serum creatinine > 0.5 mg/dl	1111	4.6%	Not given	24 vs. 13
Marenzi *et al.* 2004[4]	Milan, Italy	Prospective	Rise in serum creatinine > 0.5 mg/dl	208	19%	Not given	13 vs. 8
Rihal *et al.* 2002[2]	Mayo clinic, USA	Retrospective	Rise in serum creatinine > 0.5 mg/dl	7586	3.3%	Not given	Not given

**RIFLE = Risk, injury, failure, loss, and end-stage criteria; CIN = Contrast induced nephropathy.*

RESULTS

A total of 116 patients were included in the final analysis. The mean age was 64 ± 12 years. Eighty four (72%) patients were male. Overall prevalence of CIN i.e. serum creatinine rise > 0.5 mg/dl was 17% (20 patients) while that of CSCIN was 9.5% (11 patients). Baseline clinical and procedural characteristics are given in Table I.

Comparison between the patients with CSCIN, CICIN and no CIN is shown in Table II. The patients were divided into three groups according to the ejection fraction: EF < 30%, between 30 – 55% and > 55%. More patients with low EF had CSCIN (45.5%) versus no CIN group (17%), p = 0.03. Out of 93 patients with no CSCIN, only 17% had EF < 30%, 34% between 30 – 55% and the majority (49%) had > 55%. Five (45.5%) out of 11 patients with CSCIN had a history of cerebrovascular disease compared to only 5% in the patients with no CSCIN, p = < 0.001. Seven (64%) out of 11 patients with CSCIN had a baseline serum creatinine level greater than 2.0 mg/dl (p = 0.01). Mean GFR was also found to be significantly lower at the time of procedure in patients with CSCIN at 25.0 ± 7.4 versus 41.0 ± 14.6 ml/minute (p = 0.001). Out of 11 patients in CSCIN group, 4 (36.4%) needed hemodialysis. The mean cost of hospital stay in patients with CSCIN was found to be Rs. 197,045 ± 156,955 as compared to Rs. 155,690 ± 160,545 in patients without CSCIN (p = 0.49) while the mean length of hospital stay was higher in patients with CSCIN (9.0 ± 5.1 days) as compared to their no CIN counterparts (3.0 ± 3.2 days; p = 0.001).

A univariate analysis carried out by comparing patients with CSCIN and no CIN revealed cerebrovascular disease (OR: 14.66; 95% CI = 3.30 – 65.08), ejection fraction < 30% (OR: 0.24; 95% CI = 0.06 – 0.91), mean GFR (OR: 0.89; 95% CI = 0.84 – 0.95), baseline creatinine > 2.0 mg/dl (OR: 6.0; 95% CI = 1.60 – 22.48), creatinine 24 hours after procedure (OR: 1.57, 95% CI = 1.07 – 2.30), creatinine 48 hours after procedure (OR = 2.10; 95% CI = 1.30 – 3.40), peak serum creatinine (OR = 1.95; 95% CI = 1.35 – 2.81) and length of hospital stay (OR = 1.31; 95% CI = 1.12 – 1.54) to be statistically significant (Table II).

Significant factors on univariate analysis were incorporated into multiple-logistic-regression model to evaluate independent risk factors associated with CSCIN. Low GFR (p = 0.001, OR = 0.88; 95% CI = 0.82 – 0.95) and low ejection fraction i.e. < 30% (p = 0.03, OR = 0.20; 95% CI = 0.04 – 0.91) were found to be the independent risk factors associated with CSCIN.

DISCUSSION

Cardiovascular disease has been known to be much more common in South Asian population, with a high burden of morbidity and mortality.[14] Risk factors such as obesity, hypertension, diabetes, dyslipidemia and sedentary lifestyle are highly prevalent in this part of the world.[15] Furthermore, reports of premature coronary artery disease from this region are of great concern.[16] With the rising incidence of coronary artery disease, rates of diagnostic and therapeutic coronary angiographies have also increased over the last few decades. However, coronary angiography is not devoid of complications, one of which is acute kidney injury or contrast induced nephropathy (CIN).

The pathogenesis of CIN remains unclear. However, it has been suggested to be multi-factorial, a combination of direct toxicity to renal tubular cells and renal ischaemia. Direct toxicity is attributed to generation of free oxygen radicals after exposure to the contrast media whereas ischaemia occurs due to vasoconstriction, leading to medullary hypoxia. Down regulation of vasodilators (nitric oxide and prostaglandins) along with generation of vasoactive substances (adenosine and endothelin) have also been implicated.[17]

To the best of authors' knowledge, only two studies have been reported from Pakistan assessing the frequency of CIN in patients undergoing coronary angiography.[18,19] The criterion used to define CIN in these studies was a rise in serum creatinine of > 0.5 mg/dl from baseline. Using this definition, the percentage of patients with CIN was much higher in this study; 17% compared to 9.6% and 8% reported in the prior two studies, respectively. These studies also did not evaluate risk factors such as reduced left ventricular ejection fraction, prior history of cerebrovascular accidents, peripheral vascular disease and liver disease which might be associated with CIN.

Among the 116 CKD patients studied, 9.5% developed 'clinically significant' CIN, which was defined as doubling of serum creatinine or need for hemodialysis within 7 days of coronary angiogram. Contrasting incidence has been reported in the past.[2-4,6] Table III compares the recently published regional and international data on incidence of contrast induced nephropathy in patients undergoing coronary angiograms.[18-23] The variability is most likely multi-factorial; due to different definitions being used, variable cohort size, diverse patient populations, single centre vs. multicentre studies etc.

Multiple risk factors for CIN have been identified and thoroughly looked into in the past. Of these, reduced GFR and low ejection fraction are the two important ones. In this study, low ventricular ejection fraction (EF) was found to be associated with clinically significant CIN, which has been reported previously.[4,22,24] A lower EF leads to hypo-perfusion of the organs including kidneys, leading to ischaemic damage which subsequently results in the formation of free oxygen radicals, vasoconstriction and endothelial activation that directly damages the kidney.[22] A study reported EF < 40% in 50% of the patients with CIN relative to 11% without

CIN (p = < 0.0001).[4] Another survey from Mayo Clinic showed decreased mean LVEF in patients with acute kidney injury who died during the course of their stay in the hospital.[2] This was further confirmed by Chong *et al*. who reported that abnormal LVEF resulted in high mortality rate in patients, 6.4% vs. 2.0%.[24]

Presence of underlying reduced GFR is by far the most important risk factor for development of CIN.[6,24] Serum creatinine levels solely are extensively used to estimate the renal function. However, several studies have found deranged GFR values even in patients with normal creatinine levels.[25] This is due to the fact that reduction in muscle mass leads to reduced serum creatinine level and though it is within normal limits, GFR might be decreased significantly. Chong *et al*. found a rise from 7.4% to 34.0% in the incidence of CIN with a decrease in GFR from 30 – 60 to < 30, respectively. Moreover, patients with GFR < 30 were resistant to prophylactic treatment.[24] The present results are compatible with the literature which showed that patients with CIN had almost doubled mean creatinine levels and 1.5 folds reduced GFR indicating severe baseline renal insufficiency.

CIN is associated with a longer duration of hospital stay due to its more complicated clinical course. In one study, a 1.5 fold increase in hospital stay was noted while other reported twice the increase in duration.[3,4] The presently reported patients with clinically significant CIN had a three folds increase in the hospital stay compared to those without CIN. Moreover, an increasing trend in the cost of hospital stay was also observed which, however, was not significant. This could be due to several confounding factors such as admission to high definition units vs. wards vs. private rooms.

There are several limitations of the study which need to be addressed. Being a retrospective analysis has its engraved bias. This study cohort formed a small population which might underestimate the risk factors. Since it is a single centre study, it cannot be representative of the general population. The study was conducted at a private institute which mainly caters to middle to higher socioeconomic class and hence, results may not be generalized to poor socioeconomic classes. Prospective analysis with a control group would help to limit these shortcomings.

CONCLUSION

Clinically significant contrast induced nephropathy is a major concern for increase in morbidity in this high risk population despite adequate prophylaxis. Patients with poor EF, cerebrovascular disease and reduced GFR at the time of angiography are more likely to develop clinically significant CIN.

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