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Original Article

The effect of prophylactic high dose N-acetylcysteine for the prevention of contrast induced AKI in patients with CKD (stage 3 and stage 4)

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Abstract

Background: Contrast induced acute kidney injury (CI-AKI) is a frequent cause of acute renal dysfunction following intravascular contrast administration. It is more frequent in chronic kidney disease population. High dose N-acetylcysteine (NAC) may provide better prophylaxis against CI-AKI than standard dose in CKD patient. Several measures are taken to prevent CI-AKI including to avoid use of nephrotoxic drugs, using non pharmacological (Iso -osmolar or low osmolar contrast media) and pharmacological (isotonic saline, iv sodium bicarbonate) agent etc.

Objective: To assess the effect of high dose N-acetylcysteine on prevention of contrast induced AKI in CKD patient in comparison to standard dose.

Method: Total 44 patients undergoing coronary angiogram (CAG) and /or percutaneous coronary intervention (PCI) were randomly selected into two groups. One group received single high dose NAC 1200mg IV bolus before procedure and 1200 mg orally twice daily for the 1st 48 hours after CAG. The Other group received single standard dose NAC 600mg iv bolus and 600 mg orally twice daily for 48 hours after intervention. All patients were hydrated with isotonic saline (0.9%Nacl) up to 500ml starting 3-4 hrs before and continuing after intervention.

Results: Contrast induced acute kidney injury (CI-AKI) occurred in 9 % of the total subjects. Four of the 23 patients in standard dose NAC group (17%) developed AKI whereas none is in high dose NAC group developed AKI. In the standard dose NAC group, pre procedure mean serum creatinine was 1.8± 0.6 mg/dl which increased to 1.9±0.7 mg/dl at 48 h post procedure (p=0.025). In high dose NAC group , pre procedure mean serum creatinine fall from 1.9±0.5mg/dl to 1.8±0.5 mg/dl at 48 h post procedure (p=0.015).

Conclusion: Administration of high dose N-acetylcysteine is more renoprotective using standard dose in reducing contrast induced acute kidney injury (CI-AKI) in patients with CKD (stage 3 and stage 4).

Keywords: NALC, Contrast Induced AKI, CKD.

Introduction:

At present, millions of doses of intravascular contrast media are being administered worldwide. The radio-contrast media is used in more than 10 million annual procedures in the USA (Sanaei et al., 2005).[1] Radiologic procedures such as coronary angiography (CAG) utilizing intravascular contrast media injections are being widely applied for diagnostic and therapeutic purposes. These led to a parallel increase in the incidence of contrast induced nephropathy (CIN).

Contrast-induced nephropathy (CIN), which is also called contrast induced acute kidney injury (CI-AKI), is an iatrogenic disease occurring after the intra venous or intra-arterial injections of iodine based contrast media(CM) during enhanced X-ray and computerized tomography (CT) imaging examinations or coronary artery interventions (Mehran et al., 2006).[2] Contrast induced nephropathy (CIN) was first described in a patient with multiple myeloma receiving intravenous pyelography (Bartels et al., 1954).[3]

CIN as the third leading cause of hospital-acquired acute kidney injury being responsible for 12% of all cases of AKI in hospital and is associated with significant morbidity and mortality 6% (Nash et al., 2002).[4] Contrast induced nephropathy (CIN) may be defined as an AKI that occurs within 24-72 hrs of

exposure to IV or intra-arterial iodinated contrast media that cannot be attributed to other cause. Among all procedures utilizing CM for diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary intervention (PCI) are associate with high rates of CIN (Mehran et al., 2006).[2]

The increasing use of contrast medium (CM), aging population and increase in chronic kidney disease (CKD) will result in an increased incidence of contrast induced nephropathy (CIN) unless effective preventive measures are used. The incidence of CIN is reported to be 0.6-2.3% in general population who not have any risk factor for CIN but the incidence can be increased to 90% in patients at high risk for CIN (Toprak et al.,2007).[5] The major risk factor for CIN is a GFR<60 ml/min/1.73m² being the most important particularly in-connection with diabetes mellitus. Others are neprhrotoxic medication (example-NSAID, ACE inhibitors, Loop hypotension, heart failure, severe anaemia, dehydration, organ transplant, Collagen vascular disease, AIDS, and age>70 years.

Chronic kidney disease is associated with decreased vasodilatory response which is important in developing CIN and in patients with renal insufficiency, the clearance of contrast medium(CM) is slower than in normal subjects. The causes of CI-AKI are vasoconstriction and direct tubulotoxicity due to reduction of antioxidant enzymes (Yoshioka et al., 1992).[6]

CIN occurs in upto 5% hospitalized patients who exhibit normal renal function prior to the injection of contrast medium(Curtis et al., 2007).[7] Thus CIN is uncommon in patients with normal preexisting renal function. CI-AKI can be prevented by identification of risk factors, prophylactic measures and the measures to reduce the offending drug.

In high-risk patients, it is reasonable not to use the high-osmolar and ionic CM to minimize the risk of CIN. Iso-osmolar CM iodixanol may be a better choice of high risk patients with chronic kidney disease requiring intra-arterial administration (Mccullough et al.,2011).[8] Intra-arterial contrast administration is a risk for CIN. This effect is thought to be due to the fact that the acute intra renal concentration of CM is much higher after intra arterial rather than intravenous injection. (Mehran et al.2004).[2]

Contrast induced nephropahy (CIN) develops due to the effect of oxygen free radicals and hyper osmolar stress on the renal medulla causing severe medullary hypoxia. Anti oxidant N-acetylcysteine, considering its double properties, as a free radical scavenger attenuate the cytotoxic effects of CM as well as a drug able to increase the vasodilating effect on the kidneys through an increase in the biologic effects of nitric oxide will prevents acute contrast nephrotoxicity in patients with impaired renal function. High dose intravenous N-acetylcysteine reduces oxidative stress and decreases the incidence of contrast-induced nephropathy. Hydration is the corner stone in preventing CIN. The free redicals hypothesis was evaluated by (Mehren et al., 2006)2 and their result suggested that bicarbonate as the anion in the hydration fluids causes alkalinization in the renal tubules diminishes renal damage significantly reduces contrast –induced nephropathy.

In a study (Trivedi et al., 2009)[9] which was conducted to evaluate the efficacy of high dose N-acetylcysteine administrated high-dose N-acetylcysteine daily dose greater than 1200 mg or a single peri-procedural dose (within 4 hours of contrast exposure) greater than 600 mg. Total sample size of 1677 subjects (842 assigned to high-dose N-acetylcysteine and 835 assigned to the control arm). On conclusion results suggest that high-dose N-acetylcysteine decreases the incidence of contrast-induced nephropathy more than low dose.

In another study (Marenzi et al., 2006)[10] which investigated the antioxidant N-acetylcysteine for the prevention of contrast-medium-induced nephropathy in patients undergoing primary angioplasty. They randomly assigned 354 consecutive patients undergoing primary angioplasty to one of three groups: to a standard dose of N-acetylcysteine (a 600-mg intravenous bolus before primary angioplasty and 600 mg orally twice daily for the 48 hours after angioplasty), to a double dose of N-acetylcysteine (a 1200-mg intravenous bolus and 1200 mg orally twice daily for the 48 hours after intervention), and to placebo .The result reveals serum creatinine concentration increased 25 percent or more from baseline after primary angioplasty in the control patients (33%), 15% of the patients receiving standard-dose N-acetylcysteine and 8% receiving high-dose N-acetylcysteine. Overall in-hospital mortality was higher in patients with contrast-medium-induced nephropathy than in those without such nephropathy (26 percent vs. 1 percent). On conclusion, results suggest that Intravenous and oral N-acetylcysteine may prevent contrast-medium -induced nephropathy with a dose-dependent effect in patients treated with primary angioplasty and may improve hospital outcome.

Many guidelines are intended as a practical approach to risk stratification and prevention of CIN. Those are as follows-Canadian Association of Radiologists Guideline (stated that an increase in serum creatinine (SCr) of >25% of baseline value or an absolute increase in serum creatinine by at least 44μmol/l occurring following the intravascular administration of CM without an alternative explanation. It is recommended eGFR ≥ 60 mL/min: very low risk for CIN-no specific prophylaxis necessary. eGFR < 45 mL/min mild to moderate risk of CIN that require IV hydration and eGFR <60 ml/min moderate to high risk of CIN that requires hydrate with IV Nacl or NaHCO3 , consider NAC , follow up SCr and eGFR in 48 to 72 hrs. (Adolph E at el.2008).[11]

UK Health care guidelines (Andew et al., 2014)[12] for contrast induced nephropathy prevention in adults stated as Low risk (0 risk factors) - no additional steps necessary. Moderate risk (1 risk factor)-hydration alone with saline or bicarbonate, High risk(>2 risk factors) or scr >2.0 and/ crcl<40 - Hydration with N-acetylcystiene is recommended.

According to KDIGO Guideline for contrast-induced AKI -2012 : AKI is defined as increase in SCr by ≥0.3 mg/dl (≥ 26.5 mmol/l) within 48 hours; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours. It recommend using either iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media in patients at increased risk of CI-AKI. and using i.v. volume expansion with either isotonic sodium chloride or sodium bicarbonate . It recommends not using oral fluids alone in patients at increased risk of CI-AKI. and suggest using oral NAC, together with i.v. isotonic crystalloids, in patients at increased risk of CI-AKI. (Barrett BJ et al.1993).[13]

Nationally there is little data about the incidence of CI-AKI after coronary intervention (CAG/PCI) specially in CKD patients. According to some guidelines CI-AKI can be prevented by administering N- acetylcysteine along with normal saline. This study was aimed at to implement prevention strategies by high dose N-acetylcysteine to reduce the development of CIN in CKD patients.

Materials and Methods

This prospective, randomized, open level, parallel group study was carried out in Mitford and United Hospital, Dhaka from July 2015 to June 2016. Total 44 patients known to have a history of chronic kidney disease was diagnosed by previous increased of serum creatinine for at least >3 months, by renal imaging which was revealed by bilateral small echogenic kidneys, diagnosed by eGFR(<60 to 15ml/min/1.73m², measured by MDRDformula) and also by ACR >30 mg/gm, associated with IHD, admitted for coronary angiogram (CAG) and / or percutaneous coronary intervention (PCI) were included in the study. No patients with acute kidney disease or end-stage renal disease on dialysis were included. Patients who had received a non steroidal anti- inflammatory agent (except aspirin 75 to 150mg) within 24 hrs of the study and those with a systolic blood pressure <90 mm of Hg or cardiac failure were excluded. The cause of renal insufficiency was diabetic nephropathy (diagnosed by long duration of diabetes for >10 years associated with retinopathy, ACR>30 mg/gm and also on anti diabetic treatment) in 22 patients, hypertensive nephropathy ((long duration of hypertension treated by at least one antihypertensive medication, associated with hypertensive retinopathy, protein was present in urine <1gm/day.) in 2 patients, obstructive nephropathy (presence of urinary symptoms, RBC in urine , features of obstruction in renal USG, ACR-nil) in 2 patients and unknown in 18 patients. The study was approved by the institutional ethical committees of the Mitford and United Hospital. After getting informed written consent, patients age, sex, body mass index, blood pressure, glycaemic status, hematocrict value, cholesterol level, pre-procedural serum creatinine and 48 hrs post-procedural serum creatinine were noted in predesigned data sheet.

Eligible patients were randomly (alternate pattern) assigned to received N-acetylcysteine at a standard dose (standard-dose group ie group A), N acetylcysteine at a double dose (high dose group ie group B). Patients in the high dose group received N-acetylcysteine 1200mg IV bolus before the procedure and 1200 mg orally twice daily at morning and evening for the 48 hours after CAG and patients in the standard dose group received N-acetylcysteine 600mg iv bolus before the procedure and 600 mg orally twice daily at morning and evening for the 48 hours after intervention. All patients were hydrated with 0.9% Nacl (upto 500ml) starting 3-4 hrs before and after intervention. Iso osmolar, non ionic radio-contrast agent iodixanol (visipaque) was used for CAG in all patients with an average of 100-200 ml usually. The anti ischemic, anti hypertensive, lipid lowering , platelet inhibitors and oral glycaemic agents were continued. No potential adverse drug reactions (itching, skin rash, flushing), worsening of renal function or needs of dialysis during

the study period. Serum creatinine level was estimated before the procedure (CAG or PCI), this pre-procedural serum creatinine was considered as basal serum creatinine. Serum creatinine level was again estimated at the end of 48 hours of contrast exposure. The rise of serum creatinine by ≥0.3 mg/dl within 48 hours or urine volume <0.5 ml/kg/hr for 6 hours of contrast administration was defined as contrast induced AKI. Both pre and 48 hours post procedure estimated GFR (eGFR) was measured by MDRD formula (4 variables) from the patients who developed CIN.

Data was collected through face –to-face interview. The interview was conducted anonymously as far possible.

Statistical analysis was performed by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-22). 95% confidence limit was taken.

Results

In this study, 44 patients were distributed into two groups. Group A (n=23) received standard dose N-acetylcysteine (NAC) 600mg & Group B (n=21) received high dose N-acetylcysteine (NAC) 1200mg

Clinical and laboratory characteristics of Group A (standard dose NAC) and Group B (high dose NAC)

Both Group A and Group B were matched for BMI, blood pressure, primary renal diseases and other laboratory parameters like Hb%, serum creatinine, eGFR, FBS, CKD stages. The cardiac function was also matched in both groups as measured by echocardiography. In group A , age range is 62±8years. In group B, age range is 63±7 years. Male was predominant in both groups and male female ratio were in Group A 3.6:1 and in Group B 4-25:1. The distribution was shown in Table I.

Table I: Baseline clinical and laboratory characteristics of Group A (standard dose NAC) and Group B (high dose NAC)

Variables	Group		
	Group A (n=23)	Group B (n=21)	p-value
Age (years)	62 ± 8	63 ± 7	0.743
Sex (Male:Female)	3.6:1	4.25:1	0.825
BMI(kg/m²)	26.4 ± 3	26.3 ± 4.4	0.934
SBP (mm of Hg)	133 ± 17	135 ± 13	0.783
DBP (mm of Hg)	78 ± 7	82 ± 8	0.075
Diabetic nephropathy	56%(13)	43%(9)	0.835
Obstructive nephropathy	4%(1)	5%(1)	
Hypertensive nephropathy	4% (1)	5%(1)	
Undetermined	35% (8)	47% (4)	
Hb (gm/dl)	12.1 ± 1.7	11.7 ± 1.6	0.462
S. Creatinine (mg/dl)	1.8 ± 0.6	1.9 ± 0.5	0.585
eGFR(ml/min/1.73m²)	39.6 ± 11	36.8 ± 10.7	0.391
FBS (mmol/L)	8.9 ± 3.4	11.5 ± 9.6	0.393
LV ejection fraction (%)	56.5 ± 7.4	57.9 ± 6.4	0.511
CKD stages			
3a	44% (10)	29% (6)	0.201
3b	26% (6)	52% (11)	
4	30% (7)	19% (4)	

Unpaired t test and Chi-square test was done to measure the level of significance (p<0.05)

Frequency of Primary renal disease types

Main primary disease was diabetic nephropathy in 50% cases . Hypertensive nephropathy and obstructive nephropathy was present in each 4.5% cases. Unknown etiology was present in 40.9% cases. In figure 1 showing frequency of primary renal diseases in all CKD patients in both study subjects.

Different stages of CKD in study groups

In group A, 44% (n=10) patients belongs to stage 3a, 26% (n=6) in stage 3b and 30% (n=7) in stage 4. In group B, 29% (n=6) patients in stage 3a, 52% (n=11) in stage 3b and in stage 4 19% (n=4). The distribution is shown in figure 2.

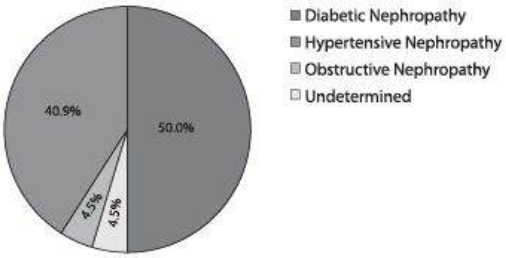

Figure 1: Pie chart showing primary diseases of all patients

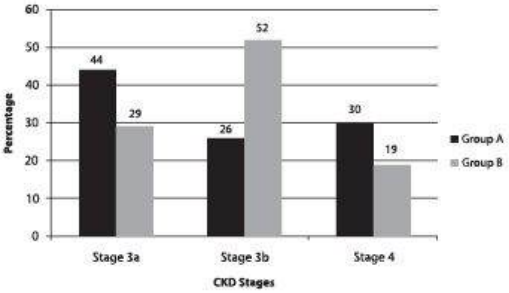

Figure 2: Bar chart showing different stages of CKD in study groups

Table II: Pattern of intervention (CAG / PCI) in Group A (standard dose NAC) and Group B (high dose NAC)

Procedure involved	Group		p-value
	Group A n (%)	Group B n (%)	
CAG	65% (15)	67% (14)	0.919
Both (CAG+PCI)	35% (8)	33% (7)	
Total	23	21	
Renal outcome after intervention in both Group A and Group B			
Contrast Nephropathy absent	83% (19)	100% (21)	0.045

Chi –square test and Fisher exact test was done to measure the level of significant (p<0.05)

Among 44 patients CI-AKI were developed in 9% (4) subjects. In group A, 17% cases developed contrast induced AKI which were four in number . In group B, none developed nephropathy. Regarding the procedure involved, CAG was done 65% (15) in Group A & PCI was done in 35% (8). In GroupB, 67% (14) cases underwent CAG and 33%(7) to PCI.

Table III: Comparison between those who developed nephropathy (CIN) and those who did not in group A (standard dose NAC)

Variables	CIN		p-value
	Present (n=4)	Absent (n=19)	
Age (years)	69 ± 9	61 ± 8	0.100
Sex (Male:Female)	3 :1	3.75:1	
Hb (gm/dl)	11.3 ± 2.1	12.3 ± 1.78	0.346
S. Creatinine (mg/dl)	2.7 ± 0.9	1.6 ± 0.3	0.001
eGFR (ml/min/1.73m²)	26.6 ± 13.6	42.4 ± 8.4	0.006
FBS (mmol/L)	12.2 ± 4.3	8.1 ± 2.8	0.050
LV ejection fraction (%)	50 ± 7.1	57.9 ± 6.8	0.048
CKD stages			
3a	1 (25%)	9 (47%)	0.609
3b	1 (25%)	5 (26%)	
4	2 (50%)	5 (26%)	
Primary diseases			
Diabetic nephropathy	2 (50.0)	11 (57.9)	0.163
Obstructive nephropathy	0 (0.0)	1 (5.3)	
Hypertensive nephropathy	1 (25.0)	0 (0.0)	
Undetermined	1 (25.0)	7 (36.8)	
Saline infusion at procedure (ml)	500 ± 0	515 ± 112	0.783
Urine output after 6 hrs (ml)	562 ± 242	658 ± 339	0.601

Unpaired t test and Chi-square test was done to measure the level of significance(p<0.05).

Both clinical and laboratory parameters were compared between CIN present and CIN absent gsubjects of groupA. Majority of parameters were matched between two groups. Those who developed CIN had significantly higher serum creatinine , lower eGFR, higher FBS and low LVEF%. Pattern of primary diseases and urine output after 6 hours were similar in both groups.

Table IV: Comparison of different clinical and laboratory parameters between stage 3 and stage 4 of Group A & Group B (n=44)

Variables	Group A		p-value	Group B		p-value
	Stage 3 (n=16)	Stage 4 (n=7)		Stage 3 (n=16)	Stage 4 (n=7)	
Age (years)	60 ± 8	68 ± 7	0.042	64 ± 73	59 ± 10	0.219
Sex (Male:Female)	3 :1	6:1		4.6:1	3 :1	
BMI (kg/m²)	26.6 ± 2.9	25.8 ± 3.3	0.577	26.2±3.8	26.6±7.2	0.867
SBP (mm of Hg)	129 ± 14	142 ± 20	0.079	134±14	135±13	0.969
DBP (mm of Hg)	79 ± 7	76 ± 8	0.404	82±7	83±9	0.753
Hb (gm/dl)	12.4 ± 1.8	11.6 ± 1.4	0.362	12.0 ± 1.4	10.8 ± 2.1	0.183
S. Creatinine (mg/dl)	1.7 ± 0.5	2.2 ± 0.7	0.063	1.7 ± 0.4	2.6 ± 0.2	0.001
eGFR(ml/mim/1.73m²)	42.6 ± 8.7	25.5±5.6	0.001	39.9 ± 9.4	23.8 ± 4.4	0.004
FBS (mmol/L)	8.2 ± 3.1	9.9 ± 3.8	0.316	7.1 ± 2.3	9.6 ± 5.9	0.300
LVEF (%)	56.1 ± 7.7	57.4 ± 6.9	0.720	57.2 ± 6.6	61.2 ± 4.4	0.263
Procedure involved						
CAG	56%(9)	86%(6)	0.345	59%(10)	4 (100)	0.255
Both (CAG+PCI)	44%(7)	14%(1)		41%(7)	0 (0.0)	

Unpaired t test and Chi-square test was done to measure the level of significance (p<0.05).

Different clinical and laboratory parameters of stage 3 and stage 4 CKD patients belonged to both Group A and Group B were compared and they were found matched in between and groups. The difference in S. creatinine and eGFR were due to selection criteria.

Table V: Comparison of pre and post procedure serum creatinine(mg/dl) concentration between Group A (standard dose NAC) and Group B (high dose NAC)

S. Creatinine	Group		p-value (between groups)
	Group A (n=23)	Group B (n=21)	
Pre procedure	1.8 ± 0.6	1.9 ± 0.5	0.585
Post procedure at 48 hours	1.9 ± 0.7	1.8 ± 0.5	0.696
Mean difference between pre & post	0.08 ± 0.2	-0.08 ± 0.14	
p-value (within group)	0.025	0.015	

Unpaired t test was done to measure the level of significance between groups

Paired t test was done to measure the level of significance within group

Comparison of serum creatinine before and 48 hours after procedure was done between Group A (standard dose NAC) and GroupB (high dose NAC). It was found that in Group A, serum creatinine increased significantly (P=0.025) whereas in Group B serum creatinine decreased significantly (P=0.015).

Table VI: Comparison of pre and post procedure estimated GFR(ml/min/1.73m² in Group A (standard dose NAC) and Group B (high dose NAC)

Estimated GFR	Group		p-value (between groups)
	Group A (n=23)	Group B (n=21)	
Pre procedure	39.6 ± 11.0	36.8 ± 10.7	0.391
Post procedure at 48 hours	38.7 ± 11.4	39.2 ± 11.5	0.887
Mean difference between pre & post	-0.8 ± 2.9	2.4 ± 4.3	
p-value (within group)	0.167	0.018	

Unpaired t test was done to measure the level of significance between group

Paired t test was done to measure the level of significance within group

Comparison of pre procedure eGFR and post procedure eGFR was done between Group A (single dose NAC) and Group B (double dose NAC). It was found that in Group A, eGFR was unaltered (P=NS) but in Group B, there was increased eGFR (P=0.018).

Discussion

This interventional study was carried out with the aim to asses the effect of high dose intravenous

N-acetylcysteine (1200 mg) on prevention of contrast induced AKI in CKD patient with moderate to severe renal failure in comparison to standard dose N-acetylcysteine (600mg). The definition in this study used for contrast induced AKI was elevation of serum creatinine by ≥0.3 mg/dl within 48 hours (KDIGO guideline for contrast induced AKI- 2012).

In this study it was observed that most of the patients were above 60 years of age in both Group A and Group B, (Ghani et al.,2009)[14] observed higher incidence of CI-AKI in above 60 years age group in their study patients. In present study incidence of CI-AKI was 9% which was similar to other study. So age was not a risk factor.

Males were predominant in both groups. The female percentage appeared less in present study possibly because of less incidence of ischaemic heart disease (IHD) among female (Tamam et al.,2015)[15] observed 7.9% men and 5.1%women have ischaemic heart disease in their study.

In the present study, it was observed that main primary renal disease diabetic nephropathy(DN) was present in 50% cases and higher FBS (12.2±4.3 mmol/l) was present in CIN patients. (Abe et al.,2009)[16] observed diabetic nephropathy was in 36.1% cases within which 5 .3% was CIN patients. (Ghani et al., 2009)14 observed higher diabetes mellitus (75.7%) in their study. So diabetes mellitus was an independent risk factor for developing CI-AKI. According to the US Renal Data System Annual Data Report, the leading cause of CKD in the United States was diabetes mellitus (Colins et al., 2009).[17]

In the present study, it was observed that 17% developed contrast induced AKI in standard dose group. Mauro (Maioli et al., 2006) also observed similar contrast induced nephropathy (CIN) occurred in 11.5% patients with renal dysfunction who were treated with standard dose NAC undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI).

In this study, serum creatinine was observed before and 48 hours after CAG/PCI and found that serum creatinine level was significantly increased after 48 hours of CAG/PCI in standard dose group though not all developed AKI level. On the other hand serum creatinine level before & after 48 hours of CAG/PCI in high dose group which decreased significantly. The fall in S.creatinine concentration in response to N-acetylcysteine seen in this study was also consistent with a previous study (Tepel et al.,2000).[21] The study suggested that the result of changes in glomerular filtration rate may underlie the observed changes in serum creatinine concentrations. (Drager et al.,2004)[18] found marked protective effects of N-acetylcysteine against contrast induced nephropathy in CKD patient are strongly associated with suppression of oxidant stress-mediated proximal tublar injury.

Two studies by Briguori et al., 2004[19] and Baker et al .,2003[3] support the hypothesis that a high dose of N-acetylcysteine reduce the contrast induced nephropathy. Baker et al., 2003[20] observed patients with CKD undergoing CAG/PCI received inravenous N-acetylcysteine at a dose of 150mg/kg before exposure to contrast medium and a dose of 50 mg/kg over the following four hour period. In a patient weighing 70 kg , this corresponds to cumulative dose of N–acetylcysteine of 14000mg, which was significantly higher than that used in the study by Tepel et al; (2400mg).[21]

In present study, CI-AKI developed 9% subjects. Briguori et al.,2004[19] found the rate of contrast induced nephropathy was lower in patients receiving the high dose N-acetylcysteine 4%. It could be due to lower serum creainine (1.56mg/dl) relatively high GFR (45±13ml/min/1.73m²) in their subjects. Baker et al .,2003[20] found a significantly lower incidence of contrast induced nephropathy in treated patients as compared with controls 5% versus 21%. Their observation suggests that high dose N-acetylcysteine not only prevents direct contrast medium induced nephrotoxicity but also exerts a broader kidney protective effect.

Marenzi et al.,2006[10] showed CI-AKI developed 15% of the patient received standard dose NAC and 8% received high dose NAC. The present study also showed similar incidence of nephropathy in standard dose NACgroup (17%). In agreement with these above observations, present study findings support a dose dependent protective effect of N-acetylcysteine in preventing CI-AKI.

Conclusions

- High dose N-acetylcysteine (1200mg) is more renoprotective than standard dose (600mg) in reducing contrast induced acute kidney injury (CI-AKI) in CKD patients (stage 3 and stage 4).
- High dose N-acetylcysteine should be considered prescribing in all patients of advanced CKD undergoing coronary angiogram (CAG) as a preventive measures against contrast induced nephropathy

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