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Full Length Research Paper

n-Acetylcysteine for prevention of iodinated contrast-induced nephropathy in computed tomography angiography procedures in patients with chronic kidney disease

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N-Acetylcysteine (NAC) is used in the prevention of contrast-induced nephropathy (CIN) in our institution. The variation in clinical effects as a result of dosage differences between intravenous (IV) and oral administration warrants further investigation. This study primarily aimed to evaluate the incidence of CIN in patients with renal impairment, comparing those who received IV NAC with those receiving oral NAC. This was an observational, retrospective study conducted from 1st January, 2007 to 31st March, 2010. The study included 94 renally impaired patients (baseline glomerular filtration rate (eGFR) < 70 ml/min/1.73 m^2) who had undergone iodinated-contrast procedure, and received either IV NAC (150 mg/kg pre-procedure, then 50 mg/kg post-procedure) or oral NAC (600 mg twice daily for one day before the procedure, then for two days after the procedure). The changes in serum creatinine (SCr) over time: pre-procedure, post-procedure 24, 48 and 72 h for both regimens were recorded and analysed. The overall incidence of CIN was 22% in IV NAC group versus 28.0% in the oral group (P = 0.403). CIN was found to be significantly associated with unstable renal function but not route of NAC administration. In patients with stable renal function, the incidence of CIN was 8.3% in the IV group versus 11.9% in the oral group; P = 1.000. In patients with unstable renal function, the incidence of CIN was 46.2 and 42.9% in the IV and oral groups, respectively; P = 0.863. Diabetes mellitus (odds ratio (OR) = 10.704, P = 0.018) and unstable renal status (OR = 6.800, P = 0.015) were the independent predictors of CIN by multivariate analysis. Both IV and oral NAC had comparable effects on the incidence of CIN in patients with stable renal status. However, both routes of NAC administration were less effective in preventing CIN in patients with unstable renal status.

Key words: N-acetylcysteine, iodinated contrast-induced nephropathy, computed tomography angiography procedures, unstable renal function, renal impairment.

INTRODUCTION

The vast development in medical imaging has enabled various non-invasive diagnostic procedures to be carried out. In 2003, there were more than 80 million doses of iodinated intravascular contrast media administered world wide, equivalent to approximately 8 million litres (Katzberg and Haller, 2006).

The increase in radiologic procedures using iodinated contrast-media for both diagnostic and therapeutic purposes had raised the incidence of contrast-induced nephropathy (CIN). CIN is the third most common cause of hospital-acquired kidney injury (Nash et al., 2002; McCullough, 2008). It is associated with increased health-resource utilisation, prolonged hospital stay, increased mortality and exacerbation of chronic kidney disease (CKD) (Bartholomew et al., 2004; McCullough et

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al., 1997; Solomon et al., 2009). Recently, no study has been conducted to evaluate the effects of intravenous (IV) n-acetylcysteine (NAC) and oral NAC on the incidence of CIN in patients with renal impairment. Additionally, it would be important to establish the benefit of using high-dose IV NAC in comparison with lower-dose oral NAC. This study aimed to compare IV NAC and oral NAC with respect to CIN prevention in patients with renal impairment; to compare the post-procedure serum creatinine (SCr) changes in patients who received IV NAC with those receiving oral NAC; and to identify the risk factors associated with CIN. This study may also provide additional information relevant to practitioners in their effort to prevent CIN and provide data necessary to underpin their practice.

METHODOLOGY

Study design

This was a retrospective, observational study conducted from 1st January 2006 to 31st April 2011 in the Universiti Kebangsaan Malaysia Medical Centre. Patients were selected by screening through the computer system in the Pharmacy Department. Within the study period, the first 180 consecutive IV NAC records and the first 150 consecutive oral NAC records were selected from the computer system. All patient details were kept anonymous. In-patients with the following criteria were included in our study: aged 18 to 80 years old, underwent iodinated-contrast procedure of either computed tomography (CT) or CT angiography (CTA), and with baseline glomerular filtration rate (eGFR) ≤ 70 ml/min/1.73 m^2 but ≥ 5 ml/min/1.73 m^2; those diagnosed by the clinician as dehydrated, currently on regular renal replacement therapy (RRT) or with allergy to NAC or contrast media were excluded. Sample size was estimated using the Fleiss's method (Fleiss, 1981). The study protocol was approved by the local research ethics committee (reference no. UKM 1.5.3.5/244/NF-002-2011).

Patients were divided into two groups. The first group consisted of those who received IV NAC at 150 mg/kg in 500 ml 0.9% normal saline over 30 min before the procedure, then 50 mg/kg in 500 ml 0.9% normal saline for 4 h after the procedure. The second group comprised patients who received oral NAC of 600 mg twice daily given for one day before the procedure and continued for two days after the procedure. SCr and blood urea nitrogen values were recorded at 24, 48 and 72 h before the procedure and thereafter at the same time points. eGFR was estimated on the basis of SCr using the four-parameter modification of diet in renal disease (MDRD) equation (Levey et al., 2006). Contrast volume was determined by the type of procedure and the clinician who performed the procedure. Hydration was given as directed by the prescriber. The actual rate and duration of IV hydration were at the discretion of the clinician, who could modify the regimen based on the clinical status of the patient. CIN was defined as an increase in SCr of more than 25% from the baseline value within 48 h after administration of the contrast agent. Unstable renal function was defined as a change in SCr of more than 15% within the three days prior to iodinated-contrast procedure (Durham et al., 2002).

Data collection

Demographic information gathered included the weight, age, gender and race. Review of systems was done to identify those with a prior history of hypotension, diabetes mellitus (DM), advanced chronic heart failure, CKD, anaemia, sepsis and cancer. The time of performance of the contrast procedure was documented. NAC administration was detailed as follows: time of administration, dose and route. Renal profile was assessed at six time points, that is, 24, 48 and 72 h before as well as after the procedure.

Statistical analysis

All analyses were performed with SPSS software, version 18.0 (SPSS Inc., Chicago, Illinois, USA). All continuous data were tested for normality and were expressed as means ± standard deviation (SD). All statistical tests were two-sided and a P-value of less than 0.05 was considered significant.

Differences in the incidence of CIN between IV and oral NAC were analysed by Chi-square ($\chi 2$) test, which was further stratified by renal status, that is, patients with stable or unstable renal function. Repeated-measure analysis of variance (ANOVA) test was used to analyse the overall differences in SCr changes with respect to route of administration and renal status.

Univariate and multivariate analyses were used to predict the development of post-procedure CIN. A multivariable logistic regression model was applied to include all potential risk factors, such as hypotension, DM, age more than 75 years, CKD, chronic heart failure, sepsis, anaemia, underlying malignancy and exposure to contrast media in the preceding four weeks.

RESULTS

Subject characteristics

Ninety-four subjects were included in the final analysis. The clinical and baseline characteristics of the subjects were as shown in Table 1. The group who received IV NAC group had significantly greater number of patients with hypotension, DM, unstable renal function and sepsis when compared with the oral NAC group. There were no significant differences in other measured parameters.

The incidence of CIN in IV NAC and oral NAC groups

A total of 81 subjects, 25 from the IV NAC group and 56 from the oral NAC group, were included in this analysis. The overall incidence of CIN was 18 of 81 (22.2%). There was no significant difference in the incidence of CIN between IV NAC (7 of 25; 28.0%) versus oral NAC (11 of 56; 19.6%) groups (P = 0.403) (Figure 1).

There was a higher incidence of CIN among patients with unstable renal status (12 of 27; 44.4%) versus those with stable renal function (6 of 54; 11.1%), (P = 0.001) (Figure 2). A sub-group analysis was performed to determine the association between renal status, route of NAC administration and CIN. No significant differences were found in the incidence of CIN comparing stable renal patients who received IV NAC (1 of 12; 8.3%) or oral NAC (5 of 42 11.9%), (P = 0.862). Similar findings were reported for unstable renal patients in the IV NAC group (6 of 13; 46%) versus those in the oral NAC group (6

Table 1. Subjects' demographic data.

Parameter	IV NAC (n = 28)	Oral NAC (n = 66)	P-Value
Gender			
Male	19 (67.9)	43 (65.2)	0.800
Female	9 (32.1)	23 (34.8)	
Race			
Malay	16 (57.1)	29 (43.9)	0.241
Non-malay	12 (42.9)	37 (56.1)	
Age			
mean ± SD	57.6 ± 14.4	61.9 ± 11.7	0.164
Baseline serum creatinine (µmol/L)			
mean ± SD	170.5 ± 69.7	181.3 ± 95.2	0.590
Baseline urea (µmol/L)			
mean ± SD	12.75 ± 6.99	12.24 ± 7.41	0.748
Estimated glomerulus filtration rate (eGFR) ml/min/1.73 m^2			
mean ± SD	38.3 ± 13.3	37.7 ± 15.9	0.861
Renal status			
Stable renal function	14 (50.0%)	50 (75.8%)	0.014*
Unstable renal function	14 (50.0%)	16 (24.2%)	
Risk factors			
Hypotensive	8 (28.6)	6 (9.1)	0.035*
Diabetes mellitus	12 (42.9)	45 (68.2)	0.022*
Age > 75	2 (7.1)	6 (9.1)	0.924
Underlying chronic kidney disease	22 (78.6)	61 (92.4)	0.119
Congestive cardiac failure	3 (10.7)	8 (12.1)	0.874
Sepsis	21 (75.0)	23 (34.85)	<0.001*
Anaemia	21 (75.0)	46 (69.7)	0.603
Underlying malignancy	5 (17.9)	12 (18.2)	0.970
Exposure to contrast in the previous 4 weeks	7 (25.0)	12 (18.2)	0.452

*P < 0.05 denotes statistical significance. All data were presented in numbers (percentage) unless otherwise indicated.

of 14; 42.9%), (P = 0.863) (Figure 3). A total of 13 patients were excluded from this analysis as their CIN status could not be ascertained owing to a lack of renal profile results between 24 and 48 h after the procedure.

Post-procedure changes in SCr over 72 h in relation to renal status and route of NAC administration

Figure 4A demonstrated that post-procedure changes in SCr over 72 h did not differ significantly between IV and oral groups (F = 0.905; df = 1.490; P = 0.383). An increasing trend of SCr levels over time was noted in both groups (F = 5.071; df = 1.490; P = 0.016). SCr levels were subsequently stratified based on renal status. In patients with stable renal function, as shown in Figure 4B, those in the IV group had significantly higher baseline and post-procedure SCr levels than the oral group (F = 4.932; df = 1; P = 0.034). When the two groups were compared for their magnitudes of SCr changes over time, no significant difference was found (F = 0.902; df = 1.649; P = 0.395).

The three post-procedure time points (F = 1.535; df = 1; P = 0.223). Though, a similar increasing trend was

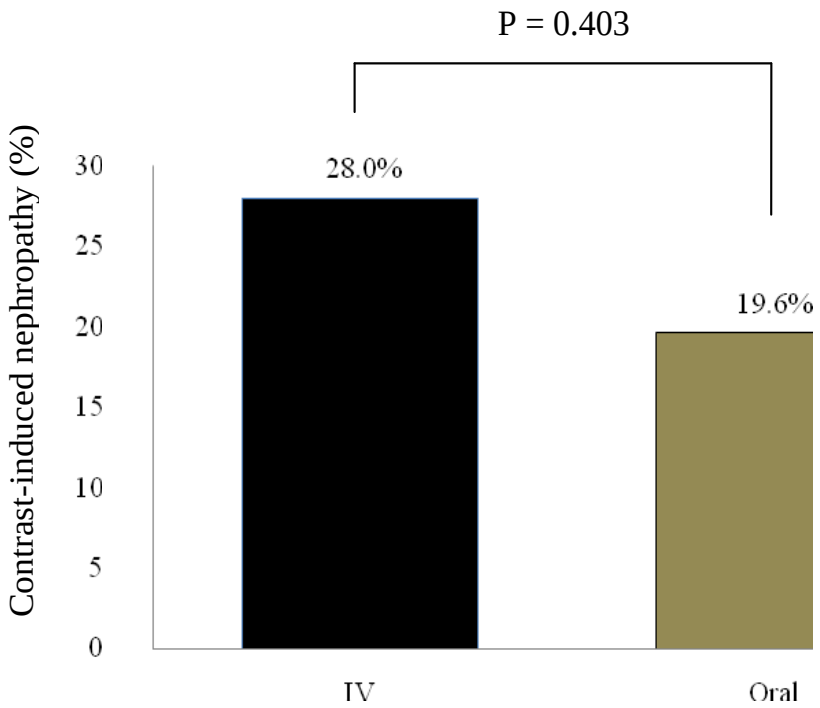

Figure 1. Incidence of CIN in patients given IV NAC (n = 25) or oral NAC (n = 56).

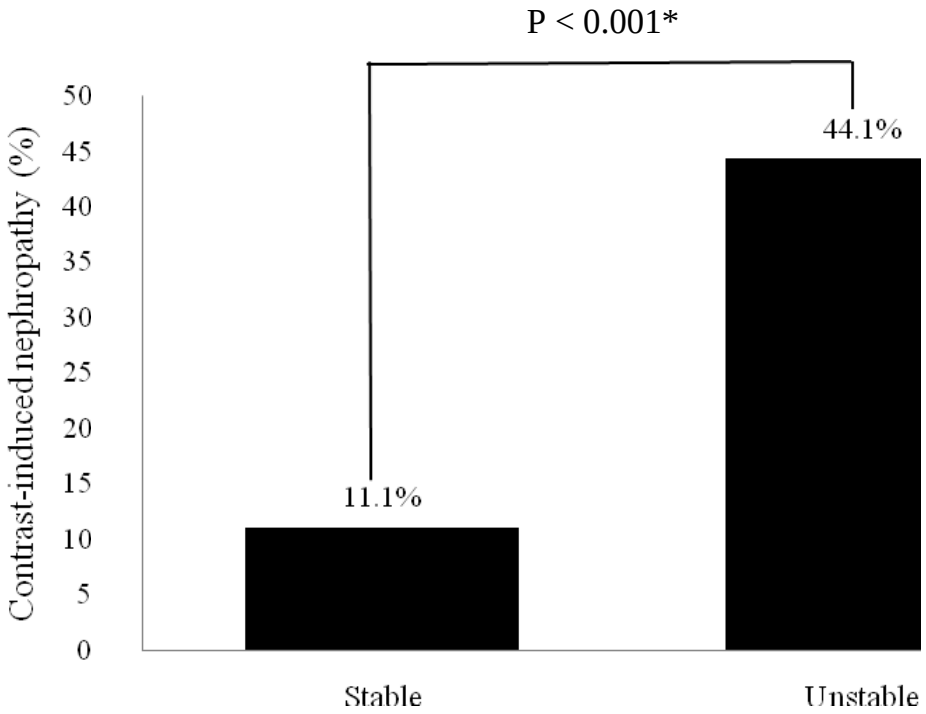

Figure 2. Incidence of CIN in patients with stable (n = 12) or unstable renal function (n = 42). *P < 0.05 denotes statistical significance. Stable renal function was defined as a change in SCr below or equal of 15% within the three days prior to iodinated-contrast procedure. Unstable renal function was defined as a change in SCr of more than 15% within the three days prior to iodinated-contrast procedure (Durham et al., 2002).

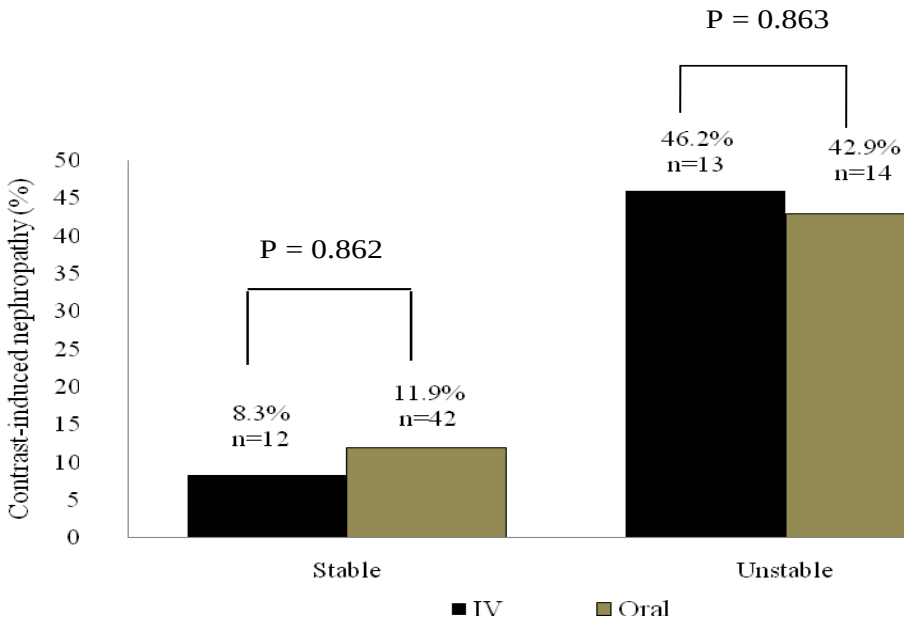

Figure 3. Incidence of CIN in patients with stable or unstable renal function, with reference to route of administration. Stable renal function was defined as a change in SCr below or equal of 15% within the three days prior to iodinated-contrast procedure. Unstable renal function was defined as a change in SCr of more than 15% within the three days prior to iodinated-contrast procedure (Durham et al., 2002).

observed for both groups (F = 0.338; df = 1.531; P = 0.027), the magnitude of SCr increases over time, but did not differ significantly between the two groups (F = 0.338, df = 1.531; P = 0.659).

Risk factors for CIN

By univariate analysis, predictors of the development of CIN were unstable renal function and DM (Table 3). Both DM (OR = 10.704, P = 0.018) and unstable renal status (OR = 6.800, P = 0.015) were the independent predictors of CIN by multivariate analysis.

DISCUSSION

The incidence of CIN in IV NAC and oral NAC groups

The major finding of this study is that the incidence of CIN was comparable in patients given IV or oral NAC. The underlying renal status was found to be associated with the occurrence of CIN. The incidence of CIN was consistently higher in patients with unstable renal function than those with stable renal function. Whether patients were treated with oral or IV NAC did not affect the outcome. We found an overall CIN incidence of 22.2%, which double that reported in two previous studies, that is, 11 and 12%, respectively (Katzberg and Haller, 2006; Hou et al., 1983). However, these studies recruited patients from the general population. In contrast, our study included subjects with unstable CKD. This group of patients are more susceptible to developing CIN (Mehran et al., 2004).

Furthermore, it was observed that the incidence of CIN was increased by four folds when patient renal function was unstable. This may be explained by higher rates of hypotension and sepsis in patients with unstable renal function (Table 2). Other possible causes of unstable renal function include reduced renal perfusion secondary to sepsis, reduced cardiac output or surgery. Pre-existing diseases of the respiratory or cardiovascular systems may also lead to deterioration of renal function (Pruchnicki and Dasta, 2002). It has been postulated that administration of contrast-media to renally unstable patients may cause further insult to the kidneys, thereby raising the incidence of CIN. However, we were unable to determine if our observation was a genuine reflection of CIN or the underlying disease progression.

Among patients with stable renal function, the incidence of CIN was found to be lower in the IV group when compared with the oral group, (8.3% versus 11.9%). This may be due to the higher number of diabetic patients in the oral group (Table 1). The incidence of CIN is also influenced by baseline SCr and osmolality of contrast media employed. A number of other studies, consistently reported a lower incidence of CIN where non-ionic, iso-osmolar contrast media were used, regardless of the route of NAC administration (Azmus et al., 2005; Baker et al., 2003). The association of such a

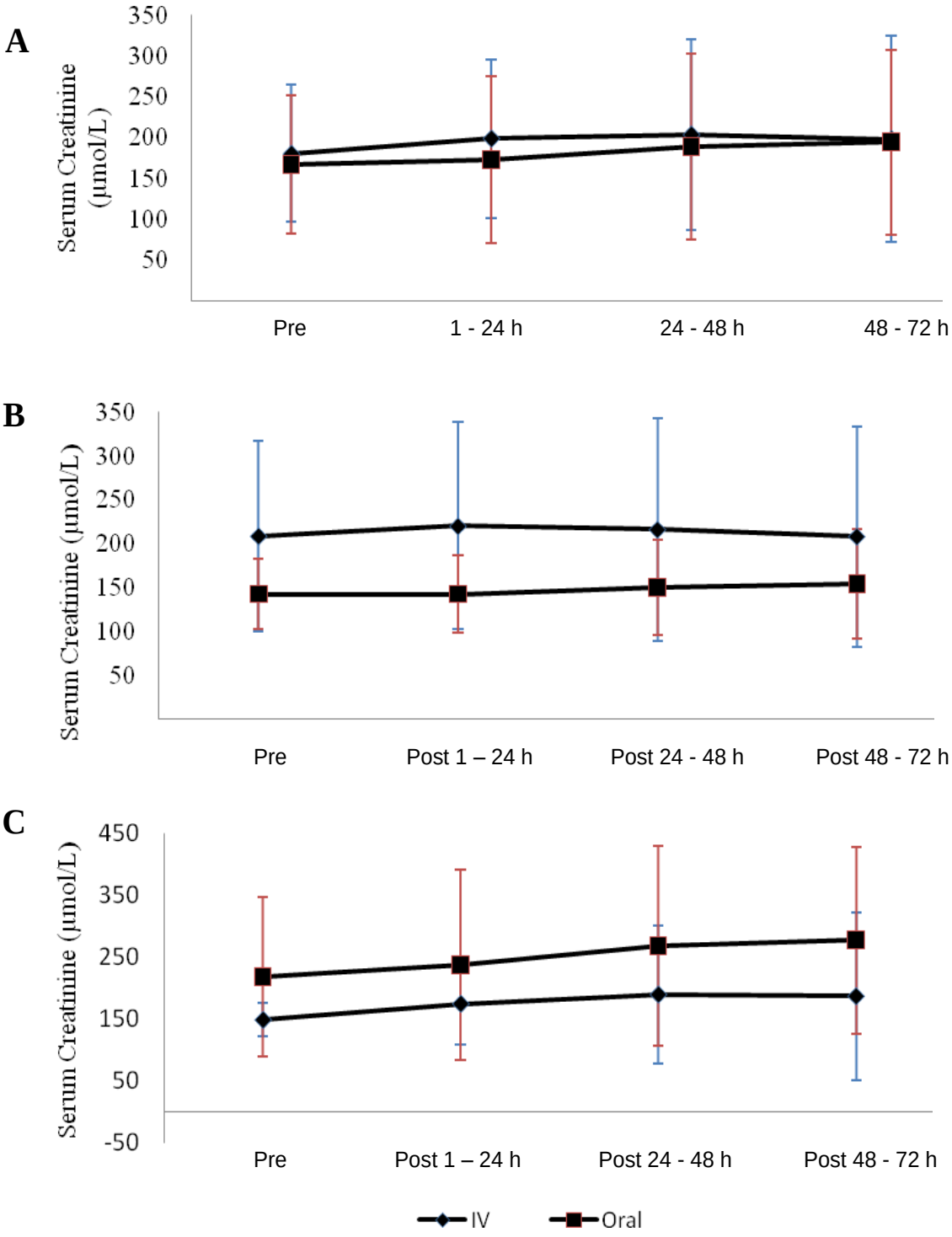

Figure 4. Changes in SCr over time: pre, post 1 - 24, 24 - 48 and 48 - 72 h, in relation to renal status and route of NAC administration. Panel A shows overall changes in SCr (IV versus Oral; n = 15 versus n = 34). Both routes reported an increasing trend (F = 5.071; df = 1.490; P = 0.016), but there were no differences in the magnitudes of changes between the routes over time (F = 0.902; df = 1.649; P = 0.395). Panel B shows the changes in SCr in subjects with stable renal status (IV versus Oral; n = 8 versus n = 23). SCr levels in the IV group were higher throughout (F = 4.932; df = 1; P = 0.034). There were no differences in the changes of SCr over time for both routes (F = 0.902; df = 1.649; P = 0.395). Panel C shows the changes in SCr in subjects with unstable renal status (IV versus oral; n = 7 versus n = 11). SCr levels were increased over time for both routes. However, the magnitude of increases in SCr over time did not differ between the two routes (F = 0.338, df = 1.531; P = 0.659).

Table 2. Risk factors stratified based on renal status.

	Stable renal function (n = 64)	Unstable renal function (n = 30)	P-value
Risk factors			
Hypotension	5 (78.0)	9 (30.0)	0.012*
Diabetes mellitus	42 (65.6)	15 (50.0)	0.148
Age > 75	4 (13.3)	4 (13.3)	0.453
Underlying chronic kidney disease	62 (96.9)	21 (70.0)	0.001
Chronic cardiac failure	8 (12.5)	3 (10.0)	0.994
Sepsis	22 (34.4)	23 (73.3)	0.000*
Anaemia	42 (65.6)	25 (83.3)	0.077
Underlying malignancy	8 (12.8)	9 (30.0)	0.040
Exposure to contrast in the previous 4 weeks	11 (17.2)	8 (26.7)	0.286

*P < 0.05 denotes statistical significance. All data were presented in numbers (percentage) unless otherwise indicated. Stable renal function was defined as a change in SCr below or equal of 15% within the three days prior to iodinated-contrast procedure. Unstable renal function was defined as a change in SCr of more than 15% within the three days prior to iodinated-contrast procedure (Durham et al., 2002).

Table 3. Risk factors for contrast-induced nephropathy (CIN).

	B	SE	Wald	df	P-value	OR	95% CI	
							Lower	Upper
Congestive heart failure	-0.195	1.097	0.032	1	0.859	0.823	0.096	7.060
Age > 75	-0.172	1.219	0.020	1	0.888	0.842	0.077	9.175
Cancer	0.924	0.868	1.133	1	0.287	2.520	0.459	13.822
Chronic kidney disease	-0.035	1.129	0.001	1	0.975	0.966	0.106	8.823
Diabetes mellitus	2.371	1.002	5.600	1	0.018*	10.704	1.503	76.250
Exposure to contrast within 4 weeks	-0.901	0.841	1.150	1	0.284	0.406	0.078	2.109
Hypotension	1.849	1.033	3.200	1	0.074	6.350	0.838,	48.129
Sepsis	0.740	0.758	0.952	1	0.329	2.095	0.474	9.261
Unstable renal function	1.917	0.787	5.938	1	0.015*	6.800	1.455	31.774
Constant	-3.996	1.560	6.562	1	0.010	0.018	-	-

Hosmer and Lemeshow Test, χ^2= 6.450, df = 8, P = 0.597. *P < 0.05 denotes statistical significance. SE: standard error, OR: odds ratio, CI: confidence interval.

contrast medium with reduced CIN incidence was well demonstrated (Hernandez et al., 2009; Soehardy, 2004). In contrast, the subjects used a low-osmolality contrast medium, iomeprol; this may also account for the higher incidence of CIN in our study.

Post-procedure changes in SCr over 72 h in relation to renal status and route of NAC administration

In patients with stable renal function, the baseline SCr in the IV group was higher when compared with the oral group. This may be explained by the fact that urgent contrast procedures are more likely to be performed in patients with a higher degree of co-morbidity. CIN had been shown to be strongly associated with increased baseline SCr. In a study, the incidence of CIN increased from 22.4 to 30.6% when baseline SCr increased from 177 to 265 µmol/L (Rihal et al., 2002). As a result, we had expected SCr in the IV group to increase to a greater extent than the oral group, mirroring raised CIN incidence. Surprisingly, SCr changes in the IV group remained stable throughout and were comparable with the oral group. In addition, previous studies using the same dose of IV NAC as that in our study had demonstrated that NAC was better than placebo at preventing CIN in patients with stable renal function (Baker et al., 2003; Soehardy, 2004). Our own findings, coupled with currently available evidence, had convinced us that NAC may have some protective effect against CIN in stable CKD patients. The major cause of CKD is inflammation, many of which are a direct result of the

oxidant effect of lead on tissues and cellular component, which may be mitigated by improving the cellular availability of antioxidant; example of such antioxidant includes NAC (Ishiaq et al., 2011). The present study reveals that decreased levels of glutathione reductase might be due to increased reactive oxygen species (ROS) generation in inflammatory condition. Administration of antioxidant protected the organs from the oxidative damage of tissues by reacting with ROS (Anuradha and Krishnamoorthy, 2011).

As previously discussed, our data had failed to show any significant benefit of IV NAC over oral NAC in patients with stable CKD. A few possible explanations exist. Firstly, there were more patients with sepsis and hypotension in the IV group. Secondly, there were more patients with DM in the oral group. DM and hypotension are recognised risk factors for CIN (Mehran et al., 2004; Dangas et al., 2005). A study suggested that diabetic patients have altered nitric-oxide-dependent vasodilatation and substantial reduction in outer medullary oxygen saturation in the kidneys making them more susceptible to CIN (Heyman et al., 2005). Sepsis may result in acute kidney injury by direct effect of toxins produced by bacteria, systemic hypotension that results in com-promised circulation or direct renal vasoconstriction due to the release of inflammatory agents (Gleeson and Bulugahapitiya, 2004).

In patients with unstable renal function, both IV and oral NAC groups reported increase in SCr over time. However, no significant difference was found in the magnitude of SCr changes. Baseline SCr was higher in the oral group than in the IV group (Figure 4C), probably because the decision to give IV or oral NAC in our institution is made based on the time of the procedure, instead of the underlying renal function. Besides that, SCr increases over time which indicates that it is independent of NAC route and dose. This suggests that higher NAC dose has no additional renoprotective effect in patients with unstable renal function. We thereby postulate that NAC may have a reduced protective effect against CIN in this high-risk patient group.

Most studies on NAC were conducted in patients with stable renal status, where NAC had been shown to be protective against CIN (Durham et al., 2002; Kay et al., 2003; Shyu et al., 2002). However, much care and consideration is warranted when translating the results of these studies into local practice because a handful of patients in our institution who require NAC are renally unstable. A study demonstrated that oral NAC (600 mg twice daily before and for 24 h after CT contrast procedure) has no protective effect in patients with unstable renal function (Jeong et al., 2007).

The inclusion of patients with unstable renal function is the unique feature of our study. The effectiveness of NAC in patients with unstable renal function is not well established (Jeong et al., 2007). Thus, it would be important to identify the benefits of NAC as a preventive measure for this group of patients. However, the effectiveness of NAC cannot be ascertained owing to the absence of a placebo group for comparison.

It was observed that there was a large difference in NAC dosage for IV and oral routes. Whether a higher dose of NAC confers additional benefits in protecting renally stable patients against CIN is still uncertain. Among the many studies conducted to evaluate the benefits of NAC, only two used a similar dose of IV NAC to that in our institution (Azmus et al., 2005; Hernandez et al., 2009). Both studies demonstrated positive results in comparison with placebo. Another study which used IV NAC of 500 mg prior to the procedure produced negative results (Webb et al., 2004). However, a study using higher-dose regimens reported positive results: IV NAC of 600 mg given as a bolus before the contrast procedure, followed by oral NAC 600 mg twice daily for 48 h after the procedure versus NAC administered in a similar manner, but with its dose doubled. Dose-dependent protection effect of NAC was demonstrated (Marenzi et al., 2004). Thus, it is likely that a higher dose of NAC may lead to additional renoprotective effects in patients with stable renal function.

In our study only DM and unstable renal function were found to be the predictors of the development of CIN. DM as an independent predictor for CIN had been shown in another study. The results from our findings suggest that CIN is about eleven-fold more likely in diabetic subjects. We did not find CKD a risk factor for CIN, though it has been regarded as having an important role in the development of CIN (McCullough et al., 2006). This may be due to the masking effect of NAC which had resulted in reduced CIN incidence among CKD patients in our study. Nevertheless, CIN is about seven-fold more likely to occur in subjects with unstable renal function.

There are several limitations to this study, such as the baseline characteristics in the two study arms were not well balanced. All IV NAC patients were included in the analysis, but in contrast only the first 70 oral NAC patients who appeared in the database were captured for analysis. This was because there were several hundred times more patients on oral NAC than those on IV NAC.

Conclusion

Both IV and oral NAC had comparable effects on the incidence of CIN in patients with stable renal status. However, both routes of NAC had reduced effectiveness in patients with unstable renal status. The use of iso-osmolar contrast should be highlighted. CIN prevention protocol may need to be restructured according to patient condition, particularly renal status.

SCr did not vary widely over time, regardless of the route of NAC administration, in patients with stable renal function. In patients with unstable renal function, SCr was in increasing trend for both oral and IV routes and the magnitude of changes was similar for both routes. DM and unstable renal function were the independent risk

factors for CIN.

REFERENCES

Anuradha R, Krishnamoorthy P (2011). Antioxidant activity of methanolic extract of Pongamia pinnata on lead acetate induced hepatic demage in rats. Afr. J. Biochem. Res., 5(12): 348-351.

Azmus AD, Gottschall C, Manica A, Manica J, Duro K, Frey M (2005). Effectiveness of acetylcysteine in prevention of contrast nephropathy. J. Invasive Cardiol., 17: 80-84.

Baker CS, Wragg A, Kumar S, De Palma R, Baker LR, Knight CJ (2003). A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. J. Am. Coll. Cardiol., 41: 2144-2148.

Bartholomew BA, Harjai KJ, Dukkipati S, Boura JA, Glazier S (2004). Impact of nephropathy after percutaneous coronary intervention and a method for risk stratification. Am. J. Cardiol., 93: 1515-1519.

Dangas G, Jakoyou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, Lansky AJ, Moussa I, Stone GW, Moses JW, Leon MB, Mehran R (2005). Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. Am J Cardiol., 95: 13-19.

Durham JD, Caputo C, Dokko J, Zaharakis T, Pahlavan M, Keltz J, Dutka P, Marzo K, Maesaka JK, Fishbane S (2002). A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. Kidney Int., 62: 2202-2207.

Fleiss JL (1981). Statistical methods for rates and proportions. 2nd ed. New York: John Wiley. p. 38-46.

Gleeson TG, Bulugahapitiya S (2004). Contrast-induced nephropathy. Am. J. Roentgenol., 183: 1673-1689.

Hernandez F, Mora L, García-Tejada J, Velázquez M, Gómez-Blázquez I, Bastante T, Albarrán A, Andreu J, Tasco J (2009). Comparison of iodixanol and ioversol for the prevention of contrast-Induced nephropathy in diabetic patients after coronary angiography or angioplasty. Rev. Esp. Cardiol., 62(12): 1373-1380.

Heyman SN, Rosenberger C, Rosen S (2005). Regional alterations in renal haemodynamics and oxygenation: a role in contrast medium induced nephropathy. Nephrol Dial. Transplant. Suppl., 20: 6-11.

Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT (1983). Hospital-acquired renal insufficiency: a prospective study. Am. J. Med., 74: 243-248.

Ishiaq O, Adeagbo AG, Nta H (2011). Effect of a natural antioxidant fruit-tomatoes (Lycoperscion esculentium) as a potent nephroprotective agent in lead induced nephrotoxicity in rats. J. Pharmacognosy Phytother., 3(5): 63-66.

Jeong KY, Suh GJ, Kim KS, Jo YH (2007). Is oral N-acetylcysteine effective on the prevention of radiocontrast-induced nephropathy in patients with acute renal failure? J. Korean Soc. Emerg. Med., 18(6): 570-576.

Katzberg RW, Haller C (2006). Contrast-induced nephrotoxicity: clinical landscape. Kidney Int., 69: S3-S7.

Kay J, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A (2003). Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomised controlled trial. JAMA. 289: 553-558.

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F (2006). Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann. Int. Med., 145(4): 247-254.

Marenzi G, Lauri G, Assanelli E, Campodonico J, Metrio MD, Marana I, Grazi M, Veglia F, Bartorelli AL (2004). Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infraction. J. Am. Coll. Cardiol., 44: 1780-1785.

McCullough PA (2008). Contrast-induced acute kidney injury. J. Am. Coll. Cardiol., 51: 1419-1428.

McCullough PA, Adam A, Becker CR, Davidson C, Lameire N, Stacul F, Tumlin J (2006). Risk prediction of contrast-induced nephropathy. Am. J. Cardiol., 98: 27K-36K.

McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW (1997). Acute renal failure after coronary intervention: incidence risk factors, and relationship to mortality. Am. J. Med., 103: 368-375.

Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G (2004). A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention. J. Am. Coll. Cardiol., 44: 1393-1399.

Nash K, Hafeez A, Hou S (2002). Hospital-acquired renal insufficiency. Am. J. Kidney Dis., 39: 930-989.

Pruchnicki MC, Dasta JF (2002). Acute renal failure in hospitalized patients: Part II. Ann. Pharmacother., 36: 1430-1442.

Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garatt KN, Holmes DR (2002). Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation, 105: 2259-2264.

Shyu KG, Cheng JJ, Kuan P (2002). Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. J. Am. Coll. Cardiol., 40: 1383-1388.

Soehardy Z (2004). A comparison if different treatment measures to prevent contrast-induced nephropathy in patients with underlying stable renal impairment undergoing coronary angiography. MMED Thesis, Nephrology Unit, UKMMC.

Solomon RJ, Mehran R, Natarajan MK, Doucet S, Katholi RE, Staniloae CS, Sharma KS, Labinaz M, Gelormini JL, Barrett BJ (2009). Contrast-induced nephropathy and long-term adverse events: cause and effect. Clin. J. Am. Soc. Nephrol., 4: 1162-1169.

Webb JG, Pate GE, Humphries KH, Buller CE, Shalansky S, Al shamari A (2004). A randomised controlled trial of intravenous N-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. Am. Heart J., 148: 422-429.