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Cystatin C as a Predictor of Contrast-induced Nephropathy in Critically-ill Patients

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ABSTRACT

Background: Contrast-induced nephropathy (CIN) is a leading cause of acute kidney injury (AKI) in hospitalized patients and is associated with considerable morbidity and mortality. An increased serum creatinine level to define kidney injury is a poor marker. Although current evidence is conflicting, Cystatin C has been suggested to be a more sensitive early marker of AKI.

Objective: To evaluate Cystatin C as a marker of CIN in intensive care unit (ICU) patients administered with contrast media for diagnostic or therapeutic intervention.

Design: A prospective study.

Setting: Intensive Care Unit (ICU), King Abdul-Aziz University Hospital.

Method: A prospective study involving laboratory investigations: urea, creatinine, serum electrolytes, Cystatin-C and lactic acid were performed on 84 patients admitted to ICU from January 2010 to December 2011.

Result: During the 72 hour post-contrast follow-up period, 21 (25%) patients developed CIN; 14 (66.7%) on day one, 4 (19%) on day two and 3 (14.3%) on day three. Cystatin C levels pre-contrast administration were significantly higher in patients who developed CIN compared to those who did not (p=0.012). There were significant increases in Cystatin C and urea levels in CIN groups at 24-48 and 24-72 hours post-contrast. Creatinine levels in CIN group increased significantly at 72 hours post-contrast (p=0.009). Mortality rate was significantly high in CIN patients (p=0.038) irrespective of the lengths of hospital or ICU stay.

Conclusion: The incidence of CIN in ICU patients is fairly high and is associated with increased mortality. Cystatin C may represent a useful biomarker for prediction and early detection of CIN.

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INTRODUCTION

Despite progress in medical care, acute kidney injury (AKI) is associated with considerable morbidity and mortality[1-3]. AKI rate is approximately 5% for in-patients and 30-50% in intensive care units (ICU). In the United States, more than one million hospital in-patients are diagnosed with AKI each year. The risk of in-hospital death has been reported to range from 25% to 80%[4-6].

Due to the increased use of contrast-enhanced diagnostic and therapeutic procedures, contrast-induced neuropathy (CIN) has become one of the leading causes of AKI in

hospitalised patients[7-10]. CIN is a sudden deterioration of renal function after the intravenous or intra-arterial administration of iodinated contrast media in the absence of any other cause; it is defined as an increase in serum creatinine levels of more than 25% or an absolute rise of >44 mmol/L[11].

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Serum creatinine levels are used to define CIN and other forms of AKI; the levels can be influenced by a large number of non-renal factors, including body weight, race, age, gender, drugs and muscle metabolism; therefore, it is a poor marker of early renal dysfunction[12]. This is particularly true for an acute kidney insult, such as the administration of contrast since the unsteady state of the patient means that the serum creatinine level lags behind the actual renal injury. In many cases, serum creatinine levels remain low until up to 48-72 hours after the kidney injury occurs and in some cases can remain unchanged[12-15]. The difficulty in detecting AKI early may account for much of the morbidity and mortality associated with AKI, since treatments may be provided too late in the course of injury to be effective.

Due to the poor clinical utility of creatinine as a biomarker for the early detection of AKI, recent studies have focused on identifying reliable biomarkers for early detection of kidney injury[16,17]. Cystatin C is 13 kDa, non-glycosylated basic protein which acts as an endogenous inhibitor of cysteine proteases. It is produced by all nucleated cells of the body and released into the bloodstream at a constant rate; it is freely filtered by glomeruli due to its positive charge and relatively low molecular weight and is fully reabsorbed and catabolised in proximal tubular cells. It may therefore represent a useful marker of glomerular filtration.

Cystatin C levels can be easily measured and have been shown to be independent of age, sex, race, body mass and hydration levels. Patients at high risk of AKI, serum Cystatin C is able to detect AKI 1 or 2 days earlier than serum creatinine[18]. However, a study found that cystatin C levels did not rise earlier than creatinine levels in patients who developed AKI and demonstrated poor predictive ability for serum and urine Cystatin C, despite increased levels with increased RIFLE class[19].

The aim of this study is to evaluate Cystatin C as a marker of CIN in ICU patients administered with contrast media for diagnostic or therapeutic intervention.

METHOD

A prospective single-center study was performed involving 84 patients admitted to ICU. The patients had CT scan or non-coronary angiography with intravenous administration of iodinated contrast media between January 2010 and December 2011. Consent was obtained from all the participants prior to their inclusion in the study.

Patients included were aged 18-95 years admitted to the ICU. Patients who had heart failure, pregnant women, patients on dialysis, patients who had received intravenous contrast within 72 hours before the start of the study, patients known to have an allergy to contrast products,

those undergoing cardiac catheterization and those with end stage renal disease were excluded.

The following data were recorded: age, gender, admission diagnosis, co-morbidities, APACHE (Acute Physiology and Chronic Health Evaluation) II and Sepsis-related Organ Failure Assessment (SOFA) scores were recorded. APACHE II and SOFA scores were recalculated daily. ICU mortality, hospital and ICU stay and requirement for dialysis were recorded.

Risk, injury, failure, loss, end-stage kidney disease (RIFLE) criteria were determined before contrast and 24, 48 and 72 hours post contrast administration. Patients were classified based on the RIFLE and according to their worst creatinine and/or lowest urine output. The lowest creatinine level found within 3 months prior to ICU admission was used as baseline for the individual creatinine-based RIFLE classification. If no pre-admission creatinine level was determined, we considered the admission creatinine level as the individual baseline. Contrast-induced neuropathy (CIN) was defined as an increase in serum creatinine levels of more that 25% (or an absolute change of >44 mmol/L) from baseline.

Laboratory investigations, including urea, creatinine, serum electrolytes, cystatin-c and lactic acid were performed daily. Urine output was measured hourly. Blood sampling for cystatin C measurements were performed. Day 0 referred to samples taken before contrast, day 1 referred to samples taken 24 hours post contrast, day 2 referred to samples taken 48 hours post contrast, and day 3 referred to samples taken 72 hours post contrast. Cystatin C was measured with a nephelometric, a particle-enhanced immuno-nephelometric method on a Dimension Vista Analyzer (Siemens, Newark, DE19714, USA). Urea and creatinine levels were measured by standard clinical and chemical methods.

SPSSv19.0 was used for statistical analysis. CIN and non-CIN patients were compared for each of the four disease categories using the chi-square test for categorical variables and students' t-test for continuous variables. Significance was set at the 0.05 level.

RESULT

Eighty-four patients were included in the study between January 2010 and December 2011. Common diagnoses on admission to ICU included diabetes mellitus and hypertension (n=14; 16.7%) and cancer (n=13; 15.6%). Age ranged from 17-95 years, a mean age of 53.64 years (standard deviation 18.38). Forty-eight (57.1%) were males. The mean BMI of the group was 17.71 (SD 5.45).

During the 72 hour post-contrast follow-up period, 21 patients (25.0%) developed CIN. Of these, 14 (66.7%) developed CIN on day 1; 4 (19.0%) developed CIN on day 2; and 3 (14.3%) developed CIN on day 3. No difference in age, gender or BMI between the two groups was found, see table 1. The distribution of RIFLE classes was similar between the two groups prior to contrast administration, and both groups had similar APACHE II and SOFA scores suggesting that there were no significant differences in the severity of illness in patients who developed CIN compared to those that did not develop CIN.

Table 1: Characteristics of Patients Who Developed CIN and Those Who Did Not Develop CIN in the 72 Hours after Contrast Administration

	Developed CIN n = 21	No CIN n = 63	p
Age (mean ± s.d)	57.8 ± 16.4	52.3 ± 18.9	0.232
BMI (mean ± s.d)	26.5 ± 5.4	26.1 ± 5.5	0.730
Gender			
Female, n (%)	7 (33.3)	34 (54.0)	0.367
Male, n (%)	14 (66.7)	19 (30.1)	
RIFLE Classification			
Normal	16 (76.2)	46 (73.0)	0.328
Risk	3 (14.3)	12 (19.0)	
Injury	1 (4.8)	0 (0)	
Failure	1 (4.8)	5 (7.9)	
APACHE II (median [range])	20 (7-13)	17 (7-31)	-
SOFA (median [range])	6 (2-13)	6 (2-13)	-

We analyzed levels of creatinine, urea, cystatin C, sodium, potassium, lactate and urinary output in the two groups of patients. Cystatin C levels were significantly higher in patients who developed CIN compared to those who did not develop CIN (p = 0.012), see tables 2, 3, and 4.

Table 2: Serum and Urinary Markers

	Developed CIN n = 12	No CIN n = 30	p
Urea (mean ± s.d)	15.4 ± 11.3	12.3 ± 8.8	0.272
Creatinine (mean ± s.d)	166.1 ± 151.2	183.1 ± 261.0	0.779
Cystatin C (mean ± s.d)	1547.7 ± 1470.2	1705.6 ± 1108.1	0.012
Sodium (mean ± s.d)	140.9 ± 4.8	140.0 ± 8.4	0.541
Potassium (mean ± s.d)	4.0 ± 0.8	3.9 ± 0.85	0.398
Urinary Output (mean ± s.d)	1114.4 ± 620.7	1415.4 ± 918.1	0.097
Lactate (mean ± s.d)	2.3 ± 1.6	−1.4 ± 17.9	0.357

Table 3: Serum Markers according to CIN Diagnosis

	Developed CIN n = 12	No CIN n = 30	p
CIN -1			
Urea (mean ± s.d)	15.5 ± 11.4	11.8 ± 8.9	0.190
Creatinine (mean ± s.d)	169.9 ± 152.5	183.1 ± 261.0	0.827
Cystatin C (mean ± s.d)	2529.3 ± 1433.4	1706.0 ± 1072.5	0.008
CIN 0			
Urea (mean ± s.d)	20.2 ± 14.2	11.56 ± 7.6	0.011
Creatinine (mean ± s.d)	260.8 ± 215.0	156.8 ± 224.9	0.070
Cystatin C (mean ± s.d)	2620.7 ± 1640.9	1643.4 ± 1053.1	0.009

Table 4: Outcome of Patients

	Developed CIN n = 21	No CIN n = 63	p
Dialysis, n (%)	7 (33.3)	1 (1.6)	<0.001
Death, n (%)	15 (71.4)	29 (46.0)	0.038
Hospital length of stay (mean ± s.d)	26.2 ± 16.4	35.1 ± 30.5	0.207
ICU length of stay (mean ± s.d)	24.3 ± 17.7	28.5 ± 24.1	0.472
Maximum RIFLE classification			
Normal	2 (9.5)	43 (68.2)	p < 0.001
Risk	4 (19.0)	11 (17.5)	
Injury	11 (52.4)	1 (1.5)	
Failure	1 (4.8)	1 (1.5)	
Loss of function	2 (9.5)	7 (11.1)	
End-stage	1 (4.8)	0 (0)	
APACHE II at 72 hours (median [range])	22 (8-37)	19 (8-35)	-
SOFA at 72 hours (median [range])	7 (4-14)	6 (2-12)	-

Figure 1 shows changes in urea, creatinine and Cystatin C levels during the 72-hour post-contrast. Creatinine levels in the two groups cannot be separated at baseline. They began to diverge after 24 hours, with reducing creatinine levels in the control group and increasing levels in the CIN group. However, these differences failed to reach significance level until 72 hours after the administration of contrast (p=0.009). A similar pattern was also seen for urea, with very little difference between the two groups prior to the administration of contrast and diverging values from 24 hours. Unlike creatinine, the difference between urea levels in the two groups did reach significance level at 24 (p=0.035), 48 (p=0.014) and 72 hours (p=0.001). There were significant differences between the Cystatin C levels at baseline (p=0.035), and the difference was maintained at 24 (p=0.039) and 48 hours (p=0.034) post-contrast. The significance was lost at 72 hours.

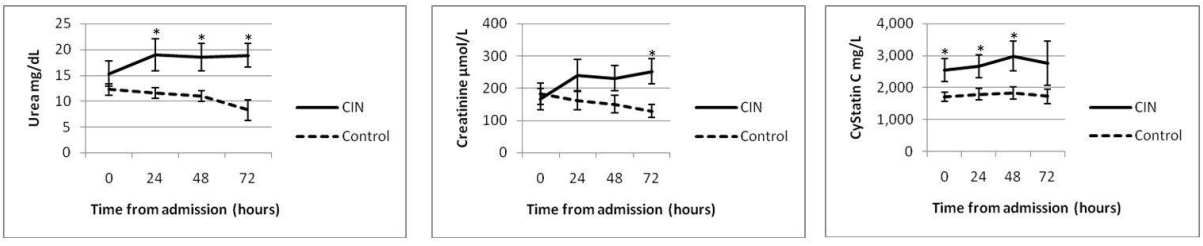

Figure 1: Creatinine, Urea and Cystatin C Levels in ICU Patients Grouped According CIN Development

Levels were significantly higher in the CIN group compared to the non-CIN group (p=0.008 and p=0.009, respectively). On the day of CIN detection, urea levels became significantly higher in the CIN group compared to the non-CIN group (p=0.011).

CIN patients were more likely to require dialysis during the 72-hour-period post-contrast administration than those who did not develop CIN (p<0.001). A significantly higher

mortality rate was observed in CIN patients (p=0.038); there were no differences in the hospital or ICU length of stay between the two groups. Whilst most non-CIN patients were graded as RIFLE classification (normal) throughout the study period (n=43; 68.2%), most CIN patients were classified as having kidney dysfunction, most common (injury) stage (n=11; 52.4%). APACHE II and SOFA scores remained relatively unchanged throughout the study period and did not substantially differ between the two groups.

DISCUSSION

One in five patients in our ICU population developed CIN following the administration of contrast media for diagnostic or therapeutic purposes. CIN was associated with worse outcomes, including higher incidence of mortality and poorer kidney function according to the RIFLE classification. Patients who developed CIN had higher pre-contrast levels of serum cystatin C.

The incidence of CIN in our study population was similar to some studies; other studies have reported lower incidences[20-26]. In our study, we defined CIN as an increase in creatinine of 25% from baseline; however, there are different definitions of CIN used; therefore, direct comparisons could be difficult. The severity of illness in our patients may have increased their risk of developing CIN compared to patients in standard in-patient wards.

Previous studies have suggested that age, may be risk factors for CIN; however, we found no significant differences between the two groups[26]. There were no differences in the severity of illness, according to APACHE I, SOFA scores and kidney dysfunction. Previous studies have found that patients with worse kidney function, lower urinary output and those who were more severely ill at time of admission were more likely to develop CIN[22].

One-third of our patients were treated with dialysis, which is similar to a previous study of CIN in ICU patients; other studies reported a lower rate of dialysis of 16%[22,27]. The rate of dialysis in our study is considerably higher than studies of non-ICU patients[28-30]. It is likely that the high incidence of dialysis in our population may be a result of the higher severity of underlying illness. The mortality rate in CIN patients in our study was extremely high (71%), and significantly higher than the mortality rate in patients who did not develop CIN. Two previous studies have reported mortality rates of 30% in ICU patients with CIN[26,27].

No significant difference between the APACHE II and SOFA scores of CIN and non-CIN patients in our study was found; therefore, the difference in mortality between the two groups cannot be attributed to the CIN group being more critically ill prior to contrast administration. No data on APACHE II and SOFA scores were available in previous studies of CIN in ICU patients.

A key finding in our study was the significantly increased level of cystatin C in patients who developed CIN. Notably, levels were not only raised after contrast-administration and before levels of creatinine and urea were altered, but also prior to contrast administration. These results suggested that not only Cystatin C is a sensitive early marker of CIN, but also Cystatin C levels may also be predictive of CIN development at least in the ICU setting. Our result was similar to a previous study which suggested that patients at high risk of AKI, serum cystatin C was able to detect AKI 1-2 days earlier than serum creatinine[18].

There were a number of limitations to our study. The study was only conducted in a single centre. Our study population only consisted of patients who received contrast-enhanced imaging. AKI in ICU patients is likely to be multifactorial due to the severity of the underlying illness; hence, it must be considered that the AKI may have been caused by the administration of contrast, by underlying disease (e.g. sepsis) or by both.

Future studies should investigate the incidence of AKI in patients not receiving CIN. The population in our study was relatively small and a number of important factors may influence kidney injury, such as the administration of nephrotoxic medication or the use of CIN preventative agents. We were unable to conduct a full risk analysis.

CONCLUSION

The incidence of CIN in ICU patients is fairly high and is associated with increased mortality. Cystatin C may represent a useful biomarker both for prediction and early detection of CIN.

To date, few strategies have been investigated to prevent CIN in ICU patients. Further studies to investigate CIN prevention strategies in critically ill ICU patients are of vital importance.

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