Incidence and Risk Factors of Contrast Induced Nephropathy among Sudanese Patients Undergoing Cardiac Catheterization

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Note:

The three authors have the same degree of contribution to the research

Abstract

Objectives:

to gather information regarding the incidence and risk factors for development of contrast induced nephropathy among Sudanese patients undergoing cardiac catheterization in Khartoum State, Sudan.

Method:

A pretested questionnaire of incidence and risk factors for development of contrast induced nephropathy among patients undergoing cardiac catheterization, 78 questionnaires were completed during the study period of two months in two hospitals, a convenience sampling/ Total coverage was selected conforming to various inclusion and exclusion criteria of the study were considered as the sample frame. The data was subjected to descriptive statistics analysis including frequencies, percentages, counts and associations using (Chi-square test) for the increase in the creatinine clearance reading after 48hrs with congestive heart failure, baseline creatinine reading, systolic blood pressure and risk score.

Results:

Completed questionnaires were 78 during the period of two months. Most of the investigated patients were elderly. This study confirmed that the risk factors for the development of CIN are many including the pre-existence of diabetes mellitus and kidney failure, also more elderly patients are more suspected to develop CIN. Nevertheless, the more the contrast volume used during the procedure the higher the risk for development of CIN. Finally the higher the *Mehran et al*. Risk score value calculated for a patient; is associated with a higher risk of contrast-induced nephropathy.

Conclusion: This study confirmed the risk factors stated in the previous published literature, of pre-existence of diabetes mellitus, kidney failure, elderly patients are at higher risk, more volume of contrast could add on risk to patients and finally the higher the risk score value the higher the risk of contrast induced nephropathy.

Key Words Contrast Induced Nephropathy. Cardiac Catheterization. Incidence. Risk Factors. Sudan

Introduction

The incidence of CIN in the general population has been calculated to be <2%. While in high-risk patients i.e. patients with chronic renal impairment, diabetes mellitus, congestive heart failure, and older age, the incidence has been calculated to be >20% to 30%.[1]

In most cases, the serum creatinine level peaks between 2 and 5 days after contrast exposure and returns to normal within 14 days. Registry data report the incidence of contrast-induced nephropathy requiring dialysis treatment to be approximately 0.4%.[4] Irrespective of cause, preexisting impairment of renal function appears to be the most important risk factor.[2-13] Diabetes mellitus with associated renal insufficiency has been identified as an independent risk factor for contrast nephropathy, with as many as 56% of those who develop the condition progressing to irreversible renal failure.[14,15]

Reduction of effective intravascular volume (due to congestive heart failure, liver cirrhosis, or abnormal fluid losses), prolonged hypotension (especially when induced by intensive antihypertensive treatment combined with angiotensin-converting enzyme inhibitors and diuretics, most notably furosemide), and dehydration have been reported as contributing to prerenal reduction in renal perfusion, thus enhancing the ischemic insult of contrast media.[16,17,18,19,20]

Multiple myeloma has been reported as a risk factor for contrast-induced nephropathy. It has been argued that high amounts of protein in the tubular lumen with concomitant contrast material load may cause an obstructive nephropathy, a mechanism that is thought to be central to the development of renal insufficiency in patients with nephrotic-range proteinuria secondary to multiple myeloma.[21,22,23] However, given that acute renal failure rarely occurs after contrast administration if dehydration is avoided[24] and that a review of seven retrospective studies showed an incidence of contrast-induced nephropathy of only0.6–1.25%

In patients with myeloma, it seems unlikely that multiple myeloma in the absence of other risk factors confers excessive risk of development of contrast-induced nephropathy.[16,17,24,25] however, the importance of hypercalcemia, hyperuricemia, and proteinuria per se as independent risk factors is not clear.[20, 26]

Volume, timing and the route of contrast administration also affects the incidence of contrast induced nephropathy i.e. Large doses and multiple injections of contrast media within 72 hour increase the risk of the patient's developing contrast-induced nephropathy.[6, 20-31]

Similarly, the osmolarity of the contrast media plays an important role with large clinical studies and meta-analyses indicating that the use of a low osmolarity contrast media substantially reduces the risk of nephropathy in high-risk patients compared with the use of high osmolarity contrast media. [32-37] Advanced age is reported to predispose patients to renal sodium and water wasting due to reduction in renal mass, function, and perfusion.[6, 20] Sepsis, through direct damage by bacterial toxins to renal tubules and impairment of circulation, has also been reported as a risk factor, as have hypertension, peripheral vascular disease, and atopic allergy.[6, 15, 38]

Mehran et al have reported a risk score for prediction of CIN after percutaneous coronary intervention. That risk score includes hypotension (5 points, if systolic blood pressure <80 mm Hg for at least 1 hour requiring inotropic support), use of intra-aortic balloon pump (5 points), congestive heart failure (5 points, if class III/IV by New York Heart Association classification or history of pulmonary edema), age (4 points, if >75 years), anemia (3 points, if hematocrit <39% for men and <36% for women), diabetes mellitus (3 points), contrast media volume (1 point per 100 mL), estimated glomerular filtration rate (GFR; GFR in mL/min per 1.73 m^2; 2 points, if GFR 60 to 40; 4 points, if GFR 40 to 20; 6 points, if GFR <20). A risk score of <6, 6 to 10, 11 to 16, and >16 indicates a risk for CIN of 7.5%, 14%, 26%, and 57%, respectively. It should be emphasized that higher contrast volume is an important risk factor for CIN. Although no definite proof has been obtained yet, the risk of non-steroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors to exacerbate CIN has been reported because of their effects on renal perfusion or tubulotoxicity. It is thus clear that CIN is a potentially harmful condition. The reason that problems seem to be increasing is that the number of angiographies and CT examinations in clinical practice is increasing, and today higher doses are administered to sicker and older patients.[1, 39]

The mechanism by which contrast agents produce nephrotoxicity is poorly understood but probably includes a reduction in renal perfusion resulting in regional hypoxia, as well as direct tubular toxicity. Therapies studied to date have targeted renal vasoconstriction and hypoxia-induced oxidative stress with limited success. Of the studied therapies are, antioxidants (Acetylcysteine and ascorpic acid), Peri-procedural Hydration, vasodilators **(**Dopamine/Fenoldopam), Theophylline, calcium channel blockers and extracorporeal removal of contrast **[1,4,12,13,40-43]**

Aim of the study

This study sought to gather information reporting the incidence of contrast induced nephropathy and to identify the risk factors leading to development of CIN among Sudanese patients undergoing cardiac catheterization in Khartoum State, Sudan. Nonetheless, to formulate recommendations that will lead to better practice.

Methods

An observational case finding hospital based study, using pre-piloted questionnaire. This study was conducted in two hospitals. Convenience Sampling / Total Coverage was selected, i.e. all the patients during the study period including those presented for emergency or elective catheterization. Moreover, patients who participated at the piloting phase of the study and patients who refused to take part of this study were excluded. The questionnaire used during this study was generated from previously navigated studies, which ensures that it is valid and pre-tested, it was reviewed by an expert panel which consisted of two consultant cardiologists for content and face validity, and a statistician for content validity. A pilot study was carried out for face and content validity and ease of use of the data collection tool. A random sample of 10 patients was interviewed to complete the questionnaire. Thus any ambiguity in the questions had been addressed and amended as required.

Data entry and statistical analysis were performed using SPSS for Windows version 20. Missing data was excluded from the analysis. The data was subjective to descriptive statistics analysis including: percentages, frequencies, counts and co-relations. Co-relations were investigated using Chi-square test association.

Results

Through the study period of two months and after applying various inclusion and exclusion criteria, the average number of patients underwent cardiac catheterization in the two targeted hospitals were 1 to 3 patients per day, and the operation itself (cardiac catheterization) was performed 6 days a week. Thus, a total of 78 patients were covered during the study period.

The participated patients' demographic characteristics are listed in table (1). The proportions of males and females took part in the study were: 66.7% (n=52) males and 33.3% (n=26).

The majority of the investigated patients who underwent cardiac catheterization were within the age groups (66-70) and (71-75) years old. The percentage and number of patients within the two age groups were: 24.4% (n=19) for each age group. This data in details is listed in Table (2).

The frequency of the risk factors for development of CIN was quantified. The results showed that the presence of diabetes mellitus within the investigated patients was 42.3% (n=33). Also it has been found that chronic renal failure is present in 10.3% (n=8) of the participated patients. For congestive heart failure and haematocrit they were present in 14.1% (n=11) and 84.6% (n=66) of the reported patients respectively. These results are listed in Table (3).

Most of patients under study 47.4% (n=37) who had undergone cardiac catheterization had received a volume of contrast within the range of (151-200) ml. See Table (4)

Baseline creatinine was reported in ranges in all the patients under study, it was found that 48.7% (n=38) of the patients fall within the range of 1-1.5 mg/dl. Listed in Table (5)

Also it was found that 71.8% (n=56) of the patients under study has a systolic blood pressure of > 80 mmhg. See table (6)

When a comparison between two gender groups was done, it was found that creatinine results were increased in males by ≥ 0.5 mg/dl more than the females, as there were 72.7% (n=8) males and 27.3% (n=3) Females had an increase in creatinine reading after 48hrs by ≥ 0.5 mg/dl. See Table (7)

According to the collected data it was found that two age groups of (71-75) Years and > 75 Years the number of patients who had an increase in the reading of creatinine after 48hrs by ≥ 0.5mg/dl were equal which was found to be (n=4) patients within each age group. Listed in Table (8)

Results showed that of the 11 patients who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl, 6 patients of them have diabetes mellitus. In the other hand 5 of them (who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl) they did not have DM which is arisk factor for developing CIN in cardiac catheteriazation operation , these results are presented in table (9)

For the renal failure risk factor it was found that the number of patients who had an increase in their creatinine reading after 48hrs by ≥ 0.5 mg/dl was 4 patients of the 11 patients who had an increase in their baseline creatinine. See Table (10) Nevertheless, it was found that the least risk factor present among the investigated patients was the presence of congestive heart failure, only one patients had an increase in the creatinine reading after 48hrs by ≥ 0.5 mg/dl and had congestive heart failure. Presented in Table (11) Also the results showed that all the patients (n=11) who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl, all of them had an increase in their haematocrit i.e. (n=11).

Presented in Table (12) Most of the patients who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl, the volume of contrast that had been administered to them during the operation of cardiac catheterization had fallen within the range of (151-200)ml of contrast i.e. (n=6) patients. Rest of the investigated patients (n= 5) had received (100-150) ml of contrast volume. See Table (13)

Results showed that (n=6) of the investigated patients who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl, their baseline creatinine reading was within the range of (1.6-2) mg/dl. And (n=5) patients of them had baseline creatinine reading of (1-1.5) mg/dl. Presented in Table (14)

The last risk factor investigated in this study was the measurement of systolic blood pressure. Number of patients who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl and their systolic blood pressure reading <80mmhg was found to be (n=6) patients. And (n=5) patients for those whose their systolic blood pressure reading >80mmhg and their creatinine readings increased after 48hrs by ≥ 0.5 mg/dl. See Table (15)

Finally, risk score was calculated for each of the participants in this study. This on the basis of findings in each investigated single case, this by giving points to each risk factor using the Mehran et al.[39] risk scale. In the scale the points were calculated as follows:

-Hypotension systolic blood pressure <80mmhg ..... 5 points
-Intra-aortic balloon pump..... 5 points
-Presence of congestive heart failure..... 5 points
-Age > 70 Years..... 4 points
-Anaemia haematocrit < 39% for males and < 36% for females..... 3 points
-Presence of diabetes mellitus..... 3 points
-Contrast media volume..... 1 point/100ml
-GFR 60-40 ml/min..... 2 points
-GFR 40-20 ml/min..... 4 points
-GFR < 20 ml/min..... 6 points

According to this risk scale findings showed that among the investigated patients, all of the ones who did suffered an increase in their creatinine reading after 48hrs by ≥ 0.5 mg/dl i.e. developed contrast induced nephropathy, were within the range of > 16 points risk score. See Table (16)

There was significant association between the increase in their creatinine reading after 48hrs by ≥ 0.5 mg/dl and presence of chronic renal failure, high baseline creatinine reading, hypotensive systolic blood pressure and high risk score. The P-values were (0.002), (0.047), (0.036) and (0.000) respectively. Significant association considered where (p values < 0.05) and not significant where p values (Chi-square test) > 0.05.

Discussion

Contrast induced nephropathy has gained increased attention in the clinical setting, particularly during cardiac intervention but also in many other radiological procedures in which iodinated contrast media are used. The invasive/interventional cardiologist uses radio-graphic contrast media (RCM) on a daily basis and must strive to minimize the risks associated with these agents. Contrast induced nephropathy is the third leading cause of hospital-acquired acute renal failure, accounting for 12% of cases.[2] Nevertheless, contrast-induced nephropathy is associated with significant consequences, including prolonged hospitalization, increase costs, the requirement for dialysis, and an increased risk of death. Clinical outcomes associated with acute renal failure following cardiac catheterization can be catastrophic, with an in-hospital mortality rate of 20% in unselected patients and a 1-year mortality rate of up to 66% in patients with acute myocardial infarction and preexisting renal dysfunction.[3] As a result this study aimed to quantify the incidence and to assess the risk factors of contrast induced nephropathy among Sudanese patients undergoing cardiac catheterization. This study, as mentioned was conducted in two private hospitals: Al-zaytona Specialized Hospital and Al-Mawada Private Hospital which are located in Khartoum State, Sudan. Method of this study comprised quantitative parameters. According to findings, the majority of the investigated patients who underwent cardiac catheterization were elderly i.e. within the age groups (66-70) and (71-75) years old. The percentage and number of patients within the two age groups were: 24.4% (n=19) for each age group. From a cultural point of view, people of Sudan in general, are a modest and polite people, they always try to answer requests of help from others, and I think according to that the response rate was high, only two patients refused to participate in this study; as a result they were excluded from the results. According to the results, it was found that the majority of respondents were elderly. This finding is sharply corresponds to Barriet et al. and Birck et al. studies as they found that advancing age is reported to predispose patients to renal sodium and water wasting due to reduction in renal mass, function, and perfusion.[6, 20] Moreover, the cardiac catheterization procedure itself mainly done in elderly patients, as a result the study population was elderly. The incidence of contrast

induced nephropathy in the patients under study was calculated to be 14.1% of the studied patients. This finding corresponds with another study conducted by Tepel et al. In which the incidence of contrast induced nephropathy in general population has been calculated to be <2%. While in high risk patients i.e. patients with chronic renal impairment, diabetes mellitus, congestive heart failure, and older age, the incidence has been calculated to be >20% to 30%.[1] When a comparison between the two gender groups was done, it was found that creatinine results were increased in males by ≥ 0.5 mg/dl more than the females, as there were 72.7% (n=8) males and 27.3% (n=3) Females had an increase in creatinine reading after 48hrs by ≥ 0.5 mg/dl. This is sharply corresponds to navigated data in which accounted that males usually underwent cardiac interventions and treatment strategies i.e. Acute coronary heart disease and ischaemic stroke events appeared approximately 10 years earlier in men than in women, and these rates remained higher in men than in women in all age groups. The gender difference was more marked for coronary heart disease than for ischaemic stroke. This may be taken into account when developing interventions and treatment strategies. Hyvärinen et al. [44] According to the result there is a significant association between the increase in their creatinine reading after 48hrs by ≥ 0.5 mg/dl and increase in the calculated risk score value. The P-value was (0.000). Significant association considered where (P-values < 0.05) and not significant where p-values (Chi-square test) > 0.05. This finding corresponds to the risk score for prediction of CIN after percutaneous coronary intervention that has been reported by Mehran et al. [39] Our data showed that the CIN risk increases proportionally to the doses of contrast media. Intuitively, the less contrast media administered, the lower the risk for CIN, in fact volume of contrast remains the primary modifiable risk factor. Most of the patients who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl, the volume of contrast that had been administered to them during the operation of cardiac catheterization had fallen within the range of (151-200)ml of contrast i.e. (n=6) patients. Rest of the investigated patients (n= 5) had received (100-150) ml of contrast volume. Many studies have documented a clear correlation between volume of contrast and risk of CIN. Kane et al. demonstrated a significant rise in incidence of CIN with increase of volume of contrast. [45] Although the pathogenesis of this condition is not fully understood, it is most likely the result of the prolonged vasoconstriction, for alterations in nitric oxide metabolism that lead to renal vasoconstriction, and impaired auto regulation induced by contrast media pre-dispose to medullary hypoxia, in combination with direct cytotoxicity to the renal tubular epithelium. This may be further influenced by contributions from several systemic factors; in fact the damage may be mediated by formation of free radicals in the acidic tubular environment.[46] There was significant association between the increase in their creatinine

reading after 48hrs by ≥ 0.5 mg/dl and presence of chronic renal failure and high baseline creatinine reading. The P-values were (0.002) and (0.047). Significant association considered where (P-values < 0.05) and not significant where P-values (Chi-square test) > 0.05. This is sharply corresponds to findings of Moore et al.,[13] who found a highly significant relationship ($p < 0.001$) between an increasing baseline level of serum creatinine and the frequency of nephrotoxicity. Results showed that of the 11 patients who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl, 6 patients of them have diabetes mellitus. In the other hand 5 of them (who had an increase in their creatinine readings after 48hrs by ≥ 0.5 mg/dl) they did not have diabetes mellitus which is a risk factor for developing contrast induced nephropathy in cardiac catheterization. Also these results corresponds to Parfrey et al.,[8]

showed that none of 85 patients with diabetes and normal renal function developed clinically significant renal impairment (defined as an increase of > 50% in serum creatinine levels). However, given that those with diabetes alone in
a prospective trial of patients with diabetes, were
found to be at slightly higher risk of renal failure than the general population, it seems prudent to include diabetes in a pre-procedural risk assessment.

Strengths and Limitations

Our study has some limitations: the study included a small population, admitted to two centres in Khartoum State. Also due to limitation in resources the principal investigator was one of the data collectors, this may be a cause of some bias. Finally, due to limited availability of data fields; we could not consider periprocedural hydration volume, proteinuria, urine output, intra-aortic balloon pump in our multivariate analysis. One of the major strengths is that it was possible in the two hospitals to conclude both emergency and elective patients who underwent cardiac catheterization. This excluded any sort of selection bias. Moreover, the results in this study could be generalized for all hospitals that do this kind of procedures.

Conclusion

The findings of this study on one hand, according to literature data, provides further epidemiological evidence that the risk factors for the development of CIN are many including the pre-existence of diabetes mellitus and kidney failure, also more elderly patients are more suspected to develop CIN. Nevertheless, the more the contrast volume used during the procedure the higher the risk for development

of CIN. Finally the higher the Mehran et al. Risk score value calculated for a patient; is associated with a higher risk of contrast-induced nephropathy.

In summary, contrast-induced nephropathy is a common condition that is associated with adverse outcomes and substantial resource use. Despite the clinical importance of contrast-induced nephropathy, much remains to be known about how best to prevent it. Well-designed and adequately powered randomized trials are urgently needed to study fundamental issues such as the optimal type, route, volume, and timing of hydration, as well as the role of other commonly advocated prophylaxis strategies such as N-acetylcysteine and feno

Table 1 : Patients Gender

Gender	N(%)
Male	(52) 66.7
Female	(26) 33.3

Table 2: Patient Age (Years)

N= number of patients

Patient Age Group	N (%)
(55-60) Years	(16) 20.5
(61-65) Years	(8)10.3
(71-75) Years	(19) 24.4
>75 Years	(16) 20.5
Total	(78) 100

Table 3: Risk factors Present within the studied patients

Risk Factor	N (%)
Presence of DM	33 (42.3)
Presence of chronic renal failure	8 (10.3)
Presence of congestive heart failure	11 (14.1)
Haematocrit	66 (84.6)

Table 4: Contrast Volume

Contrast Volume (ml)	N (%)
(100-150) ml	24 (30.8)
(151-200) ml	37 (47.4)
>200 ml	17 (21.8)
Total	78 (100)

Table 5: Baseline creatinine

Baseline Creatinine	N (%)
<1mg/dl	18 (23.1)
1-1.5mg/dl	38 (48.7)
1.6-2mg/dl	22 (28.2)
Total	78 (100)

Table 6 : Systolic Blood Pressure

Systolic Blood Pressure	N (%)
<80mmhg	22 (28.2)
>80mmhg	56 (71.8)
Total	78 (100)

Table 7: Increase of Creatinine after 48hrs by ≥ 0.5 mg/dl * Patient Gender (M or F)

It was found that the creatinine was raised by ≥ 0.5 mg/dl in 14.1% (n=11) of the population under study.

		Patient Gender (M or F)		Total (N)
		Male (N)	Female (N)	
Increase of Cr after 48hrs by ≥ 0.5 mg/dl	Yes (N)	8	3	11
	No (N)	44	23	67
Total (N)		52	26	78

Table 8: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Patient Age (years)

		Patient Age (years)					Total (N)
		55-60 (N)	61-65 (N)	66-70 (N)	71-75 (N)	>7 (N)	
Increase of Cr after 48hrs by ≥ 0.5 mg/dl	Yes (N)	2	0	1	4	4	11
	No (N)	14	8	18	15	12	67
Total (N)		16	8	19	19	16	78

Table 9: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Presence of Diabetes Mellitus

		Presence of Diabetes Mellitus		Total (N)
		Yes (N)	No (N)	
Increase of Cr after 48hrs by ≥ 0.5 mg/dl	Yes (N)	6	5	11
	No (N)	27	40	67
Total (N)		33	45	78

Table 10: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Presence of Chronic Renal Failure

		Presence of Chronic Renal Failure		Total (N)
		Yes (N)	No (N)	
Increase of Cr after 48hrs by > 0.5	Yes (N)	4	7	11
	No (N)	4	63	67
Total (N)		8	70	78

Table 11: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Presence of Congestive Heart Failure

		Presence of Congestive Heart Failure		Total (N)
		Yes (N)	No (N)	
Increase of Cr after 48hrs by > 0.5	Yes (N)	1	10	11
	No (N)	10	57	67
Total (N)		11	67	78

Table 12: Increase of Cr after 48hrs by ≥ 0.5mg/dl * Haematocrit

		Haematocrit		Total (N)
		Yes (N)	No (N)	
Increase of Cr after 48hrs by > 0.5	Yes (N)	11	0	11
	No (N)	55	12	67
Total (N)		66	12	78

Table 13: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Contrast Volume

		Contrast Volume			Total (N)
		100-150ml	151-200ml	>200ml	
Increase of Cr after 48hrs by > 0.5	Yes (N)	5	6	0	11
	No (N)	19	31	17	67
Total (N)		24	37	17	78

Table 14: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Baseline Creatinine

		Baseline Creatinine			Total (N)
		<1mg/dl	1-1.5mg/dl	1.6-2mg/dl	
Increase of Cr after 48hrs by > 0.5	Yes (N)	0	5	6	11
	No (N)	18	33	16	67
Total (N)		18	38	22	78

Table 11: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Systolic Blood Pressure

		Systolic Blood Pressure		Total (N)
		<80mmhg	>80mmhg	
Increase of Cr after 48hrs by > 0.5	Yes (N)	6	5	11
	No (N)	16	51	67
Total (N)		22	56	78

Table 12: Increase of Cr after 48hrs by ≥ 0.5 mg/dl * Risk Score

		Risk Score				Total (N)
		<6 points	6-10 points	11-16 points	>16 points	
Increase of Cr after 48hrs by > 0.5	Yes(N)	0	0	0	11	11
	No (N)	5	40	22	0	67
Total (N)		5	40	22	11	78

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