

Impact of Blood Glucose Levels on Contrast Induced Nephropathy after Percutaneous Coronary Intervention in Patients not known to be Diabetic with Acute Coronary Syndrome.

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Abstract:

Key words:

Blood glucose,
Contrast
induced
nephropathy,
Acute coronary
syndrome, PCI.

Background: Contrast-Induced Nephropathy (CIN) is an iatrogenic disorder, resulting from exposure to contrast media. The association between pre-procedural blood glucose levels and CI-AKI risk (regardless of pre-existing diabetes) is unknown. The present study was conducted to evaluate the incidence of CI-AKI in patients with admission hyperglycemia in non-diabetic ACS patients.

Methods: This is Prospective, observational study done in the department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka. Considering inclusion and exclusion criteria, 50 patients were non diabetic with ACS with normal blood glucose ($d < 7.8$ mmol/l or $d < 140$ mg/dl) in (Group I) and 50 patients were non diabetic with ACS with high blood glucose (> 7.8 mmol/l or > 140 mg/dl) undergoing percutaneous coronary intervention in (Group II). On admission random blood glucose was measured. Non-ionic low osmolar contrast agents (Iopamidol) was used in all patients. Serum creatinine, serum electrolytes was measured and creatinine clearance rate was determined within 24 hours before PCI and day 1 and 2 after PCI.

Results: The incidence of CIN was 24% in high blood glucose group and 4% in normal blood glucose group ($p=0.004$). It was also observed that gradual incremental increase in risk of CIN associated with higher admission blood glucose level. There was positive correlation between s. creatinine and admission blood glucose but it showed negative correlation between CCr and admission blood glucose after PCI in ACS patients not known to be diabetic.

Conclusion: The present study reveals that index admission high blood glucose in acute coronary syndrome patients not known to be diabetic is associated with increased incidence of contrast induced nephropathy after percutaneous coronary intervention.

(*Cardiovasc. j.* 2013; 6(1): 23-30)

Introduction:

Contrast induced nephropathy is a complex syndrome of acute renal failure occurring after the administration of iodinated contrast media.¹ Contrast induced nephropathy is generally defined as an increase in serum creatinine concentration of > 0.5 mg/dl (> 44 μ mol/L) or 25% above baseline within 48 hours after contrast administration.² Most recently, the acute kidney injury network has defined contrast-induced acute kidney injury (CI-AKI) as a rise in the serum creatinine level ≥ 0.3 mg/dl or an increase in the serum creatinine level of $\geq 50\%$ or more from baseline that occurred within 48 hour after coronary angiography.³ The

use of iodinated contrast media has been described as the third most common cause of hospital acquired renal insufficiency. It commonly occurring after coronary angiography and/or angioplasty and computed tomography scans.⁴ It occurs within 24-48 hours of exposure, with creatinine level typically peaking 3-5 days after procedure and returning to baseline or near baseline value in 1-3 weeks.¹

Patients either with or without a prior history of diabetes mellitus (DM) may present with hyperglycemia during acute coronary syndrome. Among patients with no prior history of DM, hyperglycemia may reflect previously undiagnosed diabetes, pre-existing carbohydrate

intolerance, stress-related carbohydrate intolerance, or a combination of these.⁵ A higher percentage of the hyperglycemic non-diabetic suffered cardiac arrest before admission compared with hyperglycemic DM (15% and 2% respectively).⁶ A recent report showed that, these patients who had no known diabetes at the time of acute myocardial infarction (AMI) and whose admission blood glucose levels were less than 200 mg/dL (<11.1 mmol/L), up to 40% were diagnosed as having impaired glucose tolerance and 25% as having diabetes when tested 3 months after discharge.⁷

The incidence of radiographic contrast agent-induced acute renal failure is estimated to be as high as 5.7% to 29.4% among patients with diabetes mellitus and 14.8% to 55% in patients with chronic renal insufficiency, though the incidence is <2% in general population.⁸ Shaheen has shown that, the overall incidence of contrast induced nephropathy (CIN) is 10%. In subgroup analysis the incidence was 13.3%, 10% and 20% respectively in patients with pre existing renal impairment, diabetes and both. This study also found two other risk factors for namely age and contrast volume.⁹ There is a decrease in the incidence of CIN when low osmolar contrast media (LOCM) are used instead of high osmolar contrast media (HOCM).¹⁰ The incidence of nephrotoxicity is less in iso-osmolar non-ionic contrast medium (e.g Iodixanol) than in low-osmolar non-ionic contrast medium (e.g Iopamidol).¹¹ But one study by Hossain in Bangladesh has shown that no significant difference between iso-osmolar and low-osmolar contrast media in patients with chronic kidney disease (CKD).¹² The lowest rate of CIN occurring in patients receiving less than 100 to 140 ml of contrast media. Contrast volume in excess of 5 ml/kg strongly predict nephropathy requiring dialysis. A significantly increased risk of CIN has also been demonstrated among patients who received a second dose of contrast media within 48 hours.¹³ The most important risk marker for nephropathy after exposure to iodinated contrast media is pre-existing renal impairment and diabetes mellitus. Other markers associated with an increased risk of contrast induced nephropathy (CIN) include nephrotoxic drugs, anemia, age older than 70 years, pre-procedural

hemodynamic instability, volume depletion, congestive heart failure (CHF) and hypoalbuminaemia.¹⁴ Another study by Akhtaruzzaman has shown that, the incidence of contrast induced nephropathy in anemic patients is more (26%) after percutaneous coronary intervention (PCI), than with normal hemoglobin (8%).¹⁵ However, while diabetes is a well recognized risk factor for CI-AKI, the association between pre-procedural blood glucose levels and CI-AKI risk (regardless of pre-existing diabetes) is unknown. Thus, it is possible that a combination of admission hyperglycemia in non-diabetic ACS patients and contrast exposure during PCI could significantly increase the risk for CI-AKI.¹⁷

Methodology:

This is prospective, observational study done in the department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka from July, 2011 to May, 2012. The main objective of the study was to determine the relationship between level of admission blood glucose and contrast induced nephropathy after percutaneous coronary intervention in acute coronary syndrome patients not known to be diabetic. Considering inclusion and exclusion criteria, 50 patients were non diabetic with ACS with normal blood glucose (≤ 7.8 mmol/l or ≤ 140 mg/dl) undergoing percutaneous coronary intervention (Group I) and 50 patients were non diabetic with ACS with high blood glucose (> 7.8 mmol/l or > 140 mg/dl) undergoing percutaneous coronary intervention (Group II). ACS patients not known to be diabetic undergoing percutaneous coronary intervention with normal renal function were included in the study. Patients with known Diabetes Mellitus, Hb% <10 gm/dl, serum creatinine ≥ 1.5 mg/dl, history of intake of nephrotoxic drugs in previous 7 days, history of intravascular administration of an iodinated contrast medium in previous 7 days, severe concomitant diseases (e.g. chronic liver disease, known neoplastic disorder), hemodynamically unstable patients, patients with congestive heart failure (NYHA class III and IV) were excluded from the study.

Study procedure: Informed written consent was taken from each patient before enrollment.

Meticulous history was taken and clinical examination was performed. Demographic data such as age, sex, height (cm), weight (kg), BMI(kg/m²) were noted. Risk factors profiles including hypertension, dyslipidemia, family history of coronary artery disease and smoking were noted. Base line investigations, serum lipid profile, ECG, Echocardiography, and all other investigations required before percutaneous coronary intervention were done in all cases. Procedure was performed within index hospital admission with ACS. On admission random blood glucose was measured. Non-ionic low osmolar contrast agents (Iopamidol) was used in all patients. Volume of contrast medium (ml) was recorded. After percutaneous coronary intervention, every patient was followed up by clinical examination and investigation. 24 hours urine volume was measured at day 1 and day 2.

Serum creatinine, serum electrolytes was measured and creatinine clearance rate was determined within 24 hours before PCI and day 1 and 2 after PCI. In case of renal impairment (CIN) serum creatinine, serum electrolytes, and creatinine clearance rate were measured daily from 3rd day onward after PCI until recovery. Patients were observed and questioned regarding adverse events and were instructed to report any symptoms. All adverse events were recorded during the follow up period. All relevant data were collected in an approved data collection form.

Observation and Results:

Demographic profile of both groups were shown in the tables I & II which revealed there was no significant difference in term of age, sex, and risk factor profiles in both study group.

Table-I
Age distribution of the study subjects (n=100)

Age in years	Group I (n = 50)		Group II (n = 50)		p value
	Number	(%)	Number	(%)	
<40	4	(8.0)	8	(16.0)	
41 – 50	12	(24.0)	11	(22.0)	
51 – 60	25	(50.0)	18	(36.0)	
61 -70	7	(14.0)	9	(18.0)	
> 70	2	(4.0)	4	(8.0)	
Mean ± SDRange (min – max)	54.6±10.3(28 – 85)		53.5±11.5(30 - 80)		0.59 ^{ns}

ns = Not significant p value reached from unpaired t-test

Table-II
Distribution of clinical subsets of patients with ACS (n=100)

Types of ACS	Group I (n= 50)		Group II (n =50)		p value
	Number	(%)	Number	(%)	
UA	6	(12.0)	5	(10.0)	0.74 ^{ns}
NSTEMI	12	(24.0)	10	(20.0)	0.62 ^{ns}
STEMI	32	(64.0)	35	(70.0)	0.28 ^{ns}

ns = Not significant. Data were analyzed using Pearson Chi-Square (χ^2) test.

Table-III
Comparison of volume of contrast agent used between two groups (n=100)

Volume of contrast (ml)	Group I (n= 50)		Group II (n =50)		p value
	Number	(%)	Number	(%)	
d" 150	15	(30.0)	18	(36.0)	0.61 ^{ns}
> 150	35	(70.0)	32	(64.0)	

s = Significant. Data were analyzed using Pearson Chi-Square (χ^2) test.

The table II shows the clinical types of ACS between the study groups. ACS types demonstrates that 12% of patients in group I had UA, 24% NSTEMI, and 64% STEMI. In group II, 10% of the patients had UA, 20% NSTEMI and 70% STEMI. No significant difference was observed between the groups in terms of ACS types (p>0.05).

Table III shows that in group I , 30% of patients received d” 150 ml of contrast volume and 70% patients received >150 ml of contrast. But in group II, 36% of patients received ≤150 ml of contrast volume and 64% patients received >150 ml of contrast. The volume of contrast used had no significant difference between the groups (p>0.05).

Table-IV

Changes in serum creatinine between baseline and day 2 among patients of study group (n=100)

Group	Serum creatinine		p value
	Baseline Mean ± SD	Day 2 Mean ± SD	
Group I (n=50)	1.0±0.1	1.1±0.1	0.18 ^{ns}
Group II (n=50)	1.0±0.2	1.3±0.5	0.001 ^s

s = Significant. ns = Not significant. Data were analyzed using paired student t - test.

Table-V

Changes in creatinine clearance rate (CCr) between baseline and day 2 among patients of study group (n=100)

Group	CCr		p value
	Baseline Mean ± SD	Day 2 Mean ± SD	
Group I (n=50)	77.6±18.4	71.6±15.9	0.11 ^{ns}
Group II (n=50)	80.2±19.8	67.3±21.9	0.001 ^s

s = Significant. Data were analyzed using paired student t - test.

Table-VI

Incidence of contrast induced nephropathy among studied patients (n=100)

Group	CIN				p value
	Developed		Not developed		
	Number	(%)	Number	(%)	
Group I (n=50)	2	(4.0)	48	(96.0)	0.004 ^s
Group II (n=50)	12	(24.0)	38	(76.0)	

Data were analyzed using Pearson Chi-Square (χ²) test.

Table-VII

Changes in serum creatinine between baseline and day 2 among patients of CIN (n=14)

Group	Serum creatinine		p value
	Baseline Mean ± SD	Day 2 Mean ± SD	
Group I (n=2)	0.75±0.21	1.4±0.00	0.04 ^s
Group II (n=12)	0.96±0.25	1.9±0.77	0.001 ^s

ns= Not significant. s = Significant. Data were analyzed using paired students t - test.

The table IV shows the changes in the serum creatinine between baseline and day 2 among patients of study groups. The mean serum creatinine of group I was 1.0 mg/dl and 1.1 mg/dl at baseline and day 2 respectively, which was not statistically significant ($p=0.18$). But in group II the mean serum creatinine was 1.0 mg/dl and 1.3 mg/dl on baseline and day 2 respectively. This differences were statistically significant ($p=0.001$).

The table V shows the changes in the creatinine clearance rate among patients of study groups at different time interval. The mean CCr of group I was 77.6 ml/min and 71.6 ml/min at baseline and day 2 respectively and the change was statistically insignificant ($p=0.11$). It was also observed that the mean CCr in group II was 80.2 ml/min and 67.3 ml/min at baseline and day 2 respectively. This difference was statistically significant ($p=0.001$).

The table VI shows when the most common definition of contrast induce nephropathy (as an increase in serum creatinine concentration ≥ 0.5 mg/dl or $\geq 25\%$ increase of serum creatinine from baseline within 48 hours after exposure to contrast media) was used the it was observed that CIN was higher in group II (24%) than that of group I (4%) which was statistically significant ($p=0.004$).

The table VII shows the peak increase in the serum creatinine concentration among patients of CIN within 2 days of contrast administration, which was 0.65 mg/dl in group I as compared with 0.94 mg/dl in group II respectively. A statistically significant change in serum creatinine was observed on day 2 from baseline both in normal and high blood glucose group flowing PCI ($p<0.05$)

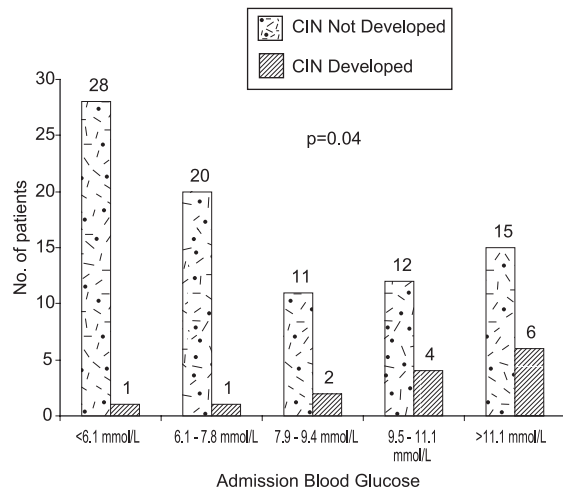


Fig.-1: Comparison between level of admission blood glucose and incidence of CIN among patients ($n=100$).

The figure 1 shows comparison between level of admission blood glucose and incidence of CIN among ACS patients undergoing PCI not known to be diabetic. It was observed that gradual incremental increase in risk of CIN associated with higher admission blood glucose levels.

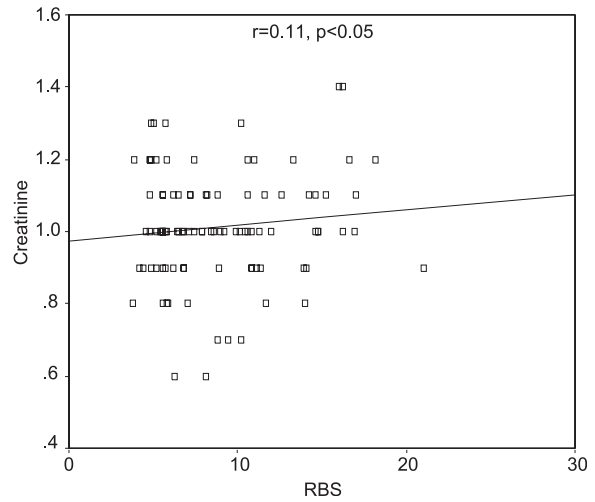


Fig.-2: Correlation between S. creatinine and admission blood glucose after PCI in ACS patients not known to be diabetic.

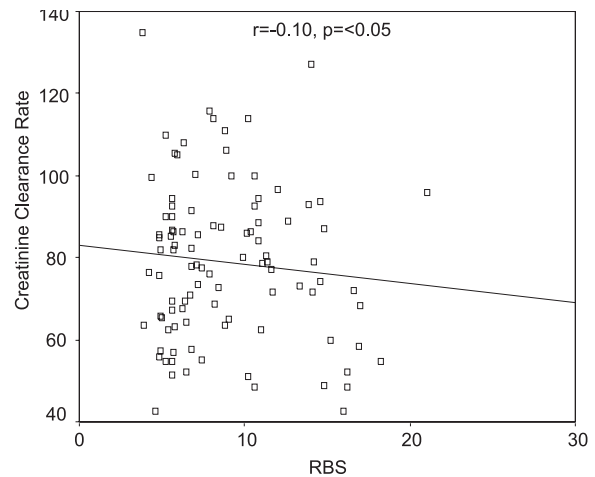


Fig.-3: Correlation between CCr and admission blood glucose after PCI in ACS patients not known to be diabetic.

Multiple regression analysis showed that of the 5 variables contrast induced nephropathy were found to be significantly associated with blood glucose (standardized coefficient ($\hat{\alpha}$) 1.580, 95% confidence interval 1.765-13.349, $p < 0.05$) and contrast volume (standardized coefficient ($\hat{\alpha}$) 0.357, 95% confidence interval 0.999-1.047, $p < 0.05$).

Discussion:

This was a prospective observational study conducted in the National Institute of Cardiovascular Diseases (NICVD), Dhaka for a period of July, 2011 to May, 2012. A total of one hundred patients, divided into two groups, were studied during the study period over one year. Group I (n= 50) Patients with normal blood glucose (≤ 7.8 mmol/l or ≤ 140 mg/dl) and group II (n=50) patients with high blood glucose (> 7.8 mmol/l or > 140 mg/dl). The mean age of patients in group-I was 54.6 ± 10.3 years, whereas in group-II it was 53.5 ± 11.5 years. The mean difference was not statistically significant ($p=0.59$). Among all study patients, highest number of patients was in the age group 51-60. That is similar to study conducted by Hossain.¹⁰ The mean age of the study patients was also within the range (40-60 years) found in one study conducted in Bangladesh.¹⁸ Hayder and Shaheen observed the mean age was a little lesser than the present study.^{9,19} However and have observed higher mean age which may be due to increased life expectancy in western country.^{20,21} The majority of patients were male 82% in group I and 88% in group II and remaining female, with a male to female ratio 5.66:1 in the whole study population. No significant ($p>0.05$) difference was found regarding sex distribution between two groups. Almost similar male female ratio (6.9:1) was observed in a study conducted by M Akhtaruzzaman in NICVD.¹⁵ The number of female patients were less in almost all previous studies like Hossain, and Hayder Solomon, et al and McCullough, et al also observed male patients predominant in their studies.^{12,14,19,22}

Among all ACS patients, Unstable angina was 12%, NSTEMI was 24% and STEMI was 64% in group I patients. Whereas in group II 10% patients had unstable angina 20% had NSTEMI and 70% patients had STEMI. No significant difference was observed regarding clinical diagnosis between the groups ($p=0.74$, $p=0.062$, $p=0.28$ respectively). Hossain also found less number of unstable angina patients than myocardial infarction in his study.¹² But Nikolsky, et al. found about half of the patients had unstable angina.²³ The volume of contrast administered (≤ 150 ml), in normal blood glucose group was 30% and high blood glucose group was

36% but >150 ml of contrast was administered 70% in normal blood glucose group and 64% in high blood glucose group. The difference in receiving contrast volume between two groups was not statistically significant ($P>0.05$). The results are consistent with Shaheen.⁹ But higher amount of contrast were used by Marenzi, et al and Nikolsky.^{24,25}

When the most common definition of contrast induced nephropathy (as an increase in the serum creatinine concentration ≥ 0.5 mg/dl or $\geq 25\%$ from baseline value at 48 hours after exposure to contrast media) was used the incidence of CIN was 24% in high blood glucose group and 4% in the normal blood glucose group that includes 12 patients in high blood glucose group and 2 patients in normal blood glucose group. The result was statistically significant ($p=0.004$). Stolker, et al also found development of CIN is more common among hyperglycemic non diabetic ACS patients in comparison to normoglycemic non diabetic ACS patients. (18,1% vs 51.6%).¹⁷ Shaheen and M Akhtaruzzaman also found increased incidence of CIN among patients with high blood glucose but they included both diabetic and non diabetic patients in study population.^{9,15} When all study patients in both groups were considered, 14 patients developed CIN i.e the overall incidence of CIN was found 14% in the present study. The finding of the present study were very close to those of other multiple studies on contrast nephropathy. Marenzi, et al. found overall 14.5% patient developed contrast induced nephropathy, among them CIN occurred in 27% patients with acute hyperglycemia.²⁴ Nikolsky, et al. found the incidence of CIN after percutaneous coronary intervention was 13.9%.²³ Shaheen found the incidence of CIN after coronary angiography and percutaneous coronary intervention was 10%.⁹ McCullough, et al. also stated that incidence of CIN can rise to 50% or more in patients with multiple risk markers.⁴

A significant change in serum creatinine was observed on day 2 from baseline both in normal and high blood glucose group following PCI ($p<0.04$ vs. <0.001). The peak increase in the serum creatinine concentration among patients of CIN within two days after administration of contrast

medium was 0.65 mg/dl in group-I as compared with 0.94 mg/dl in group-II. Our study found that, among patients with contrast induced nephropathy one patient had admission blood glucose <6.1 mmol/l, one patient had blood glucose within 6.1 to 7.8 mmol/l, two patients were within range of 7.9 to 9.4 mmol/l, 4 patients had blood glucose within 9.5 to 11.1 mmol/l and highest number of patients that is 4 patients had blood glucose above 11.1mmol/l. So, it was observed that gradual incremental increase in risk of CIN associated with higher admission blood glucose levels. In a study by Stolker, et al. reported that there was a strong association between level of blood glucose and incremental increase in contrast induced acute kidney injury risk in patients without diabetes (contrast induced acute kidney injury rates across their 5 glucose groups from lowest to highest were 8.2%, 9.9%, 12.4%, 14.9%, 24.3%; $p < 0.001$) which are compatible with the present study.¹⁷

A total of 2 variables revealed to be significantly associated with the development of CIN i.e blood glucose and contrast volume ($p < 0.05$). In multiple regression analyses of the 5 variables, blood glucose and contrast volume were found to be the independent predictors of CIN with ORs being 1.765 and 1.0 respectively. There was positive correlation between s. creatinine and admission blood glucose, but it showed negative correlation between creatinine clearance rate (CCr) and admission blood glucose after PCI in ACS patients not known to be diabetic.

Regarding outcome of the study patients, no patient died in the present study and no patient developed acute renal failure requiring dialysis. McCullough, et al. found the occurrence of acute renal failure requiring dialysis after coronary intervention is rare (<1%).⁴ The serum creatinine of 100% patients in both groups returned to base line within two weeks. In group-II 98% returned to base line within first week and 2% returned to base line on second week. But 100% patients of group-I serum creatinine returned to baseline within first week. The outcomes are consistent with most studies on CIN when it was reported that CIN usually recovered within two weeks.²⁵

Conclusion:

The present study reveals that index admission high blood glucose in acute coronary syndrome

patients not known to be diabetic is associated with increased incidence of contrast induced nephropathy after percutaneous coronary intervention. So, more attention should be paid to the blood glucose level of the patient before carrying out any coronary intervention.

Limitations of the Study:

Despite exercise of utmost caution through out the study, it has got some important limitation.

1) This was a prospective, observational study, not a randomized one. 2) The sample size was small, and it was a single centre based study. 3) Glycated hemoglobin estimation was not done as it is expensive, not so available and assays are not standard across laboratories. 4) Upto 2 weeks follow up was required to assess the renal status of the patients with CIN after PCI which was not done as most of the patients discharged on second or third post procedural day. 5) Creatinine clearance rate should be measured from 24 hours urinary output but here it is measured from Cockcroft Gault equation to reduce cost.

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