Impact of Low Hemoglobin on Contrast-Induced Nephropathy After Percutaneous Coronary Intervention

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Abstract:

Background: *Contrast-Induced Nephropathy (CIN) is an iatrogenic disorder, resulting from exposure to contrast media. The aim of this study was to assess whether anaemia is a predictor of contrast induced nephropathy after Percutaneous Coronary Intervention (PCI).*

Methods: *This was a prospective observational study. A total of one hundred patients fulfilling the inclusion and exclusion criteria who underwent (PCI) Percutaneous Transluminal Coronary Angioplasty with stenting, were studied during the study period of two years from January 2008 to December 2009. Patients were divided into two groups : Group-I (n=50), patients with low hemoglobin (male <13-10gm/dl, female < 12-10 gm/dl) and Group-II (n=50), patients with normal hemoglobin (male ≥13gm/dl, female ≥12gm/dl). Non-ionic low-osmolar contrast agents was used in all patients.Volume of contrast medium (ml) was recorded. Adequate hydration given intravenously (ml). Prior to procedure serum creatinine, serum electrolytes and Creatinine clearance rate were measured within 24 hrs before PCI and on days 1,2,3 after PCI. If there is renal impairment (CIN) serum creatinine, serum electrolytes and Creatinine clearance rate were measured daily from the 4th day onward after PCI until recovery.*

Results: *The mean serum creatinine level of low hemoglobin group and normal hemoglobin group were 0.9mg/dl and 1mg/dl respectively at base line. The low hemoglobin group experienced a considerable increase in serum creatinine up to 1.5mg/dl at day 3 compared to 1.3 mg/dl in normal hemoglobin group. When the most common definition of contrast induced nephropathy (as an increase in the serum creatinine concentration ≥0.5 mg/dl from baseline) was used the incidence of CIN was 26% in low hemoglobin group and 8% in the normal hemoglobin group.*

Conclusion: *preprocedural low hemoglobin is an independent determinant of increased incidence of contrast induced nephropathy after percutaneous coronary intervention.*

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Introduction:

Contrast-induced nephropathy (CIN) is a common and potentially serious complication that can follow the administration of iodinated contrast media to patients at risk of acute renal injury. The use of iodinated contrast media has been described as the third most common cause of hospital acquired renal insufficiency.[1] Contrast induced nephropathy (CIN) is typically defined as an increase in serum creatinine by either ≥0.5mg/dl or by ≥ 25% from baseline value at 48 to 72 hr after exposure to contrast media when alternative explanation for renal impairment has been excluded.[2,3,4] It occurs within 24-48 hr of the exposure, with creatinine level typically peaking 3-5 days after procedure and returning to baseline or near baseline value in 1-3 weeks.[5,6] The overall incidence of CIN in the general population is reported to be 1.2 to 1.6%.[2] But rates may vary from 0% to 90% depending on the presence of risk factors, most notably chronic renal insufficiency, diabetes mellitus and high contrast volume administration.[7,8] The most important risk marker for nephropathy after exposure to iodinated contrast media is preexisting renal impairment and diabetes mellitus. Other markers associated with an increased risk of contrast induced nephropathy (CIN) include nephrotoxic drugs, anaemia, age older than 70 years, preprocedural hemodynamic instability, volume depletion, congestive heart failure (CHF), contrast volume and hypoalbuminaemia.[1,9,10,11,12,13] Anaemia might be one of the factors contributing

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renal ischaemia. The partial oxygen pressure of the outer medulla in the kidney is very low during normal function and hence the combination of contrast induced vasoconstriction and anaemia may decrease oxygen delivery sufficiently to cause renal medullary hypoxia. Thus it is intuitive that anaemia may play a role in CIN risk.[14] Rates of contrast induced nephropathy steadily increased as baseline hemoglobin decreased.[15] Anaemia was found to be an independent predictor of mortality after PCI, and was associated with higher short term adverse procedural events.[16] Anaemia is common in our population. Chowdhury and Ali found the prevalence of anaemia to be 66.15% in the armed forces personnel.[17] It is one of the modifiable risk factor of CIN that can be corrected. If we can correct the anaemia before PCI incidence of CIN can be reduced. No such study has yet been carried out in our country. So we performed the present study to evaluate the nephrotoxic effects of contrast medium in anaemic patients after PCI.

Hypothesis:

Low hemoglobin is associated with contrast induced nephropathy after percutaneous coronary interventions (PCI).

Objectives:

General Objective

- To find out the incidence of contrast induced nephropathy in anaemic patients after percutaneous coronary intervention .

Specific Objective

- To determine the relationship between level of hemoglobin and contrast induced nephropathy after percutaneous coronary intervention.
- To see the relation of volume of contrast media and incidence of CIN.

Methodology: This is Prospective, observational study done in the department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Dhaka from January 2008 to December 2009.Considering inclusion and exclusion criteria, consecutive 50 patients with low hemoglobin (male <13-10gm/dl,female < 12-10 gm/dl), and 50 patients with normal hemoglobin (male ≥13gm/dl, femalee"12gm/dl),who underwent PCI (PTCA with stenting) were studied and the patients were divided into two groups. Group I= 50 patients with low hemoglobin, Group II = 50 patients with normal hemoglobin .

Inclusion criteria: All patients underwent PCI (PTCA with stenting) with normal renal function and hemoglobin ≥10gm/dl were included in the study.

Exclusion criteria: Following patients were excluded from the study: 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), patients with renal transplantation.

Study procedure: Informed written consent was taken from each patient. .Detailed history was taken and clinical examination performed. Initial evaluation of the patients was done by history, clinical examination and relevant investigations. Demographic data such as age, sex, height (cm), weight (kg), BMI (kg/m^2) were recorded. Risk factors profiles including hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease and smoking were noted. Hb% was measured within 24 hrs before PCI. Non-ionic low-osmolar contrast agents was used in all patients. Volume of contrast medium (ml) was recorded. Adequate hydration given intravenously (ml). Serum creatinine, serum electrolytes and Creatinine clearance rate were measured within 24 hrs before PCI and on days 1,2,3 after PCI. If there is renal impairment (CIN) serum creatinine, serum electrolytes and Creatinine clearance rate were measured daily from the 4^{th} day onward after PCI until recovery.24-hour total urine output were measured daily. 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.

Observations and Results :

Demographic profile of both groups were shown in the tables(I) and fig(1,2) 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 patients between two groups (n=100)

Age (years)	Group		p-value
	Group-I (n = 50)	Group-II (n = 50)	
≤40	7(14.0)	6(12.0)	
41 – 50	10(20.0)	15(30.0)	
51 – 60	25(50.0)	20(40.0)	
> 60	8(16.0)	9(18.0)	
Mean ± SD	53.6 ± 9.2	52.3 ± 9.6	0.464^{NS}

Data were analysed using Student's t-Test; NS = Not significant(p>0.05).

Figures in the parentheses denote corresponding %.

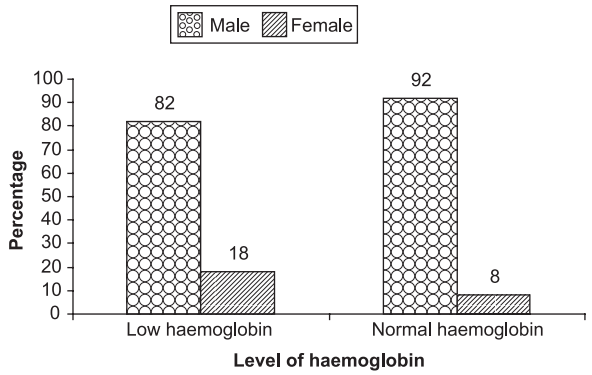

Fig.-1: *Distribution of patients by sex*

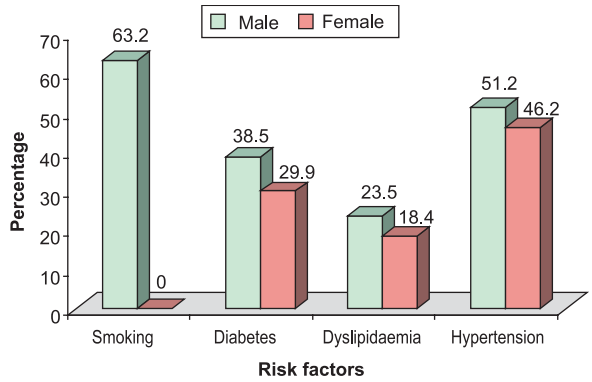

Fig.-2:*Sex-wise distribution of risk factors*

Sex-wise distribution of risk factors demonstrates that over 63% of the males was smoker as opposed to none in the female group (p < 0.001). Diabetes, dyslipidaemia and hypertension were also somewhat higher in male sex than those in the females (Fig. 2) .

Table II

Comparison of amount of contrast agent used between groups (n=100).

Volume of contrast (ml)	Group		p-value
	Group-I (n = 50)	Group-II (n = 50)	
d" 150	14(28.0)	17(34.0)	0.655^{NS}
>150	36(72.0)	33(66.0)	

Data were analysed using c^2 Test; Figures in the parentheses denote corresponding %. NS = Not significant(p>0.05).

Table II shows that in group-I, 28% of patients received ≤150ml of contrast volume and 72% patients received >150 ml of contrast. But in group-II, 34% of patients received ≤150ml of contrast volume and 66% patients received >150 ml of contrast. The volume of contrast were used almost identical between the both groups (p = 0.655).

Table-III

Distribution of patients by post-procedural complications (n=100).

Post-procedural complications	Group		p-value
	Group-I (n = 50)	Group-II (n = 50)	
Hypotension#	10(20.0)	2(4.0)	0.014^{S}
Arrhythmia¡	4(8.0)	1(2.0)	0.181^{NS}
Itching¡	3(6.0)	4(8.0)	0.663^{NS}
Anorexia/vomiting¡	3(6.0)	2(4.0)	0.500^{NS}
Local Haematoma¡	4(8.0)	1(2.0)	0.181 ^{NS}
Angina pectoris#	8(16.0)	2(4.0)	0.046^{NS}

Data were analysed using Chi-square (^{2}) Test. ¡ Data were analysed using Fisher Exact Test; S = Significant; NS = Not significant.
Figures in the parentheses denote corresponding percentage.

Table III illustrates the post-procedural complications encountered by the patients. Hypotension was significantly higher in the group-I (20%) than that in the group-II (4%) (p = 0.014). Angina pectoris was also considerably higher in the former group (16%) than that in the latter group (4%) (p = 0.046). Other complications like arrhythmia, itching, anorexia/vomiting and Local haematoma were almost identically distributed between groups.

Table IV

Serum creatinine level at different time interval(n=100).

Serum creatinine	Group		p-value
	Group-I (n = 50)	Group-II (n = 50)	
At baseline	0.9 ± 0.1	1.0 ± 0.1	
At day 1	1.2 ± 0.4	1.1 ± 0.3	
At day 2	1.3 ± 0.5	1.3 ± 0.2	
At day 3	1.5 ± 0.2	1.3 ± 0.3	0.629^{NS}
At day 4	1.2 ± 0.3	1.2 ± 0.2	
At day 5	1.1 ± 0.1	1.1 ± 0.2	
At day 6	1.0 ± 0.1	1.0 ± 0.2	
At day 7	0.9 ± 0.1	1.0 ± 0.1	

Repeated measure ANOVA statistics was employed to analyse the data and 'p' refers to overall differences between groups. NS = Not significant(p>0.05).

The table IV. shows the mean serum creatinine level of group-I and group-II were 0.9 mg/dl and 1 mg/dl respectively at baseline which experienced a sharp rise to 1.2 and 1.1 mg respectively at day 1. The group-I experienced a considerable increase in serum creatinine up to 1.5 mg/dl at day 3 compared to 1.3 mg/dl in group-II. Then it began to fall and reached to around 1 mg/dl by day 7. No significant difference was found between groups in terms of changes in serum creatinine level from baseline to day 7 (p = 0.629).

Table-V

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

Group	CIN		p-value
	Developed	Not developed	
Group-I (n = 50)	13(26.0)	37(74.0)	0.017^{S}
Group-II (n = 50)	4(8.0)	46(92.0)	

Data were analysed using Chi-square (c^2) Test; S = Significant(p<0.05).
Figures in the parentheses denote corresponding percentage.

Table V shows the when the most common definition of contrast induced nephropathy (as an increase in the serum creatinine concentration ≥0.5 mg /dl) was used the incidence of contrast induced nephropathy (CIN) was observed to be higher in the low hemoglobin group (26%) than the normal hemoglobin group (8%) (p = 0.017).

Table-VI

Factors associated with contrast induced nephropathy.

Factors	CIN		p-value
	Developed (n = 17)	Not developed (n = 83)	
Age (yrs)			
≤50>	4(23.5)	34(47.0)	0.177^{NS}
50	13(76.5)	49(53.0)	
Sex			
Male	15(88.2)	72(86.7)	0.616^{NS}
Female	2(11.8)	11(13.3)	
Diabetes mellitus			
Present	12(58.8)	40(46.4)	0.006^{S}
Absent	5(41.2)	43(53.6)	
Hypertension			
Present	13(76.5)	47(56.6)	0.170^{NS}
Absent	4(25.0)	36(43.4)	
Dyslipidaemia			
Present	4(23.5)	15(18.1)	0.855^{NS}
Absent	13(76.5)	68(81.9)	
Contrast volume exposure			
≤150 ml	2(11.8)	29(34.9)	0.043^{S}
>150 ml	15(88.2)	54(65.1)	

Data were analysed using Chi-square (c^2) Test; S = Significant. NS = Not significant. Figures in the parentheses denote corresponding percentage.

Table VI shows the analyses of factors associated with contrast induced nephropathy, patients having diabetes and contrast volume exposure > 150 ml were more frequently associated with contrast induced nephropathy than patients without diabetes and contrast volume exposure of ≤150 ml (p = 0.006 and p = 0.043 respectively).

Table VII

Independent predictors for contrast induced nephropathy (logistic regression analysis).

Variables of interest	Univariate analysis (p-value)	Multivariate analysis	
		Odds Ratio (95% CI of OR)	p-value
Low hemoglobin	0.017	3.12 (0.89-10.92)	0.047^{S}
Diabetes mellitus	0.006	3.82 (1.22 - 11.92)	0.021^{S}
Contrast volume exposure > 150 ml	0.043	2.28 (0.75-6.38)	0.048^{S}

S = Significant(p<0.05). NS = Not significant(p>0.05).

Multivariate analysis:
Table VII. demonstrates the 3 variables, low hemoglobin, diabetes and contrast volume >150 ml were found to be the independent predictors of CIN with ORs being 3.12, 3.82 and 2.28 respectively. These mean that patients subjected to PCI having low hemoglobin were at more than 3 times (95% CI of OR = 0.89 – 10.92) higher risk of developing CIN than the patients who did not have low hemoglobin (p = 0.047). Similarly patients with diabetes were 4 times (95% CI of OR = 1.22 – 11.92) as likely to acquire CIN following PCI than the patients without diabetes (p = 0.021). Also Contrast volume > 150 ml 2 times (95% CI of OR = 0.75 – 6.38) higher risk of developing CIN in low hemoglobin group than the normal hemoglobin group following PCI (p = 0.048).

Discussion:
Among all study patients, highest number of patients was in the age group 51-60. The majority of patient were male (87%).The mean BMI of group-I was 24.7±1.8 kg/m^2 and group-II was 25.6±4.3 kg/m^2.

Among the risk factors for ischemic heart disease smoking was the commonest (72%). This was followed by Hypertension (68%), Diabetes (50%), Dyslipidaemia (29%) and positive family history of coronary artery disease (22%) in a decreasing order of frequency. However, there was no statistically significant difference of incidence of these risk factors between the two groups (P>0.05).

These data were almost similar to those found in a study in Bangladesh. In his thesis khalequzzaman noted smoking was the commonest (72.8%) risk factor.[19] kar found equal incidence of smoking (50%) and Hypertension (50%).[20] Distributions of common risk factors between male and female was statistically not significant (p> 0.05) except smoking (p<0.001).

About post-procedural complications hypotension was significantly higher (20%) in low hemoglobin group than the normal hemoglobin group (4%). Nikolsky et all also found significant number of patients experience hypotension in lower base line hematocrit quintile (<36.8% hematocrit = 12.2 gm/dl Hb) was 13.4% and highest hematocrit quentile (44.8% =14.9 gm/dl Hb) the incidence of hypotension was 6.9%.[15] Angina pectoris was also considerably higher in the former group (16%) than that in the latter group (4%) (p=0.046). Other complications like arrhythmia, itching, anorexia/vomiting and haematoma were almost identically distributed between groups.

Less than 150ml contrast agent was administered in 28% patients of low hemoglobin group and 34% patients of normal hemoglobin group but more than 150ml of contrast was administered in72% in low hemoglobin group and 66% patients of normal hemoglobin group. The difference in receiving contrast volume between two group was not statistically significant (p>.05).

The mean serum creatinine level of low hemoglobin group and normal hemoglobin group were 0.9mg/dl and 1mg/dl respectively at base line. The low hemoglobin group experienced a considerable increase in serum creatinine up to 1.5mg/dl at day 3 compared to 1.3 mg/dl in normal hemoglobin group. Then it began to fall and reached to around 1mg/dl by day 7. The peak increase in the serum creatinine concentration within three days after administration of contrast medium was 0.6 mg/dl in group-I as compared with 0.3 mg/dl in group-II. No significant difference was found between groups in terms of changes in serum creatinine level from base line to day 7 (p=0.629).

The mean creatinine clearance rates at base line, were 78 ml/min and 69.7ml/min in group-I and group-II respectively which continued decreasing up to day 3 when it became 52.4 ml/min in low hemoglobin group and 57.3 ml/min in normal hemoglobin group. There after creatinine clearance began to increase both group and at day 7 reached to 69.6 ml/min and 68.7 ml/min in group-I and group-II respectively, but there was no statistically significant between the groups (p=0.292).

When the most common definition of contrast induced nephropathy (as an increase in the serum creatinine concentration e" 0.5 mg/dl from baseline) was used the incidence of CIN was 26% in low hemoglobin group and 8% in the normal hemoglobin group that i.e 13 patients in low hemoglobin group and 4 patients in normal hemoglobin group. The result was statistically significant (p=0.017). In a study by Nikolsky et al. reported that the incidence of CIN in lower baseline hematocrit quintile (<36.8% hematocrit = 12.2 gm/

dl Hb) was 23.3% and higher hematocrit quintile (e"44.8% hematocrit = 14.9 gm/dl Hb) was 10.3%.[15] When all study patients in both group were considered, 17 patients developed CIN i.e the overall incidence of CIN was found 17% in the present study. The finding of the present study were very close to those of other multiple studies on contrast nephropathy. Nikolsky et al. found the incidence of CIN after percutaneous coronary intervention was 13.9%.[15] McCullough et al also shows the incidence of CIN can rise to 50% or more in patients with multiple risk markers.[14] Shaheen found the incidence of CIN after coronary angiography and percutaneous coronary intervention was 10%.[21] The peak increase in the serum creatinine concentration among patients of CIN within three days after administration of contrast medium was 0.80 mg/dl in group-I as compared with 0.50 mg/dl in group-II. A significant change in serum creatinine was observed on day 3 from baseline both in low and normal hemoglobin group following PCI ($p < 0.001$). Analysis of factors associated with contrast induced nephropathy show that out of 17 patients, age < 50 years 4 patients developed CIN compared to 13 patients developed CIN when patients age > 50 years. The difference was not statistically significant (p=0.177).

Regarding diabetes mellitus, out of 17 patients who developed CIN, 12 patients with CIN was diabetic and 5 Patients was non diabetic. This difference was statistically significant (p=0.006). Patients with contrast volume exposure total 31 patients received £ 150ml of contrast and only 2 patients developed CIN. But 69 patients received > 150ml of contrast and 15 patients developed CIN. The difference was statistically significant (P= .043). The risk of CIN is minimal in patients receiving < 100 mL of contrast media .[2] Each 100ml of contrast medium administered was associated with a significant increase of 12% in the risk of nephropathy.[11] A total of 3 variables were significantly associated with the development of CIN in univariate and multivariate logistic regression analyses i.e low hemoglobin, diabetes mellitus and contrast volume > 150ml. All of these variable are considered as recognized risk factors on the basis of a number of international studies.[2] 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%).[1] The Serum creatinine of 100% patients in both group returned to base line within two weeks. In group-I 96% returned to base line within first weeks and 4% returned to base line on second weeks. But 100% of patient of group-II serum creatinine 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.[8]

Conclusion:

Contrast induced nephropathy is a common and important cause of iatrogenic acute renal dysfunction and carries significant risk for affected patients. The present study reveal, that preprocedural low hemoglobin is associated with increased incidence of contrast induced nephropathy after percutaneous coronary intervention. So more attention should be paid to the hemoglobin level of the patient before carrying out any coronary intervention.

Recommendations: Even small changes in renal function carry significant risk for the affected patients. The most effective strategy for the prevention of this complication is careful selection and assessment of patient. If possible anemia should be corrected before contrast administration. patients with non-correctable risk factor should received the minimal necessary dose of contrast.

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 .
3. Due to small sample volume we could not find out the precise relationship between the degree of anaemia and volume of contrast medium with CIN.

Conflict of Interest - None.

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