Acute Kidney Injury Associated with Cardiopulmonary Bypass Surgery

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Acute kidney injury (AKI) is a highly prevalent and important complication of cardiac surgery. By most estimates, up to 30% of cardiac surgery patients develop clinically relevant kidney injury. When the injury is severe enough to necessitate dialysis, which is the case for approximately 1% to 2% of patients, it confers an 8-fold increase in the odds of death. Even when the injury is relatively modest, it is independently associated with markedly increased morbidity and mortality. This is a prospective observational study designed to determine the incidence of acute kidney injury following cardiopulmonary bypass surgery and to assess the risk factors of AKI, done in nephrology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March 2009 to February 2010. Adult patients (age more than 18 years) who underwent cardiopulmonary bypass surgery at the department of cardiac surgery, BSMMU, were selected. Base line serum creatinine was estimated before operation. Post operative serum creatinine was estimated 1st , 3rd and 5th post operative day. All vital signs were checked at regular interval on 1st three post operative day. The anti-hypertensive, anti-ishchaemic, lipid lowering, oral hypoglycaemic drugs and insulin were continued. Before discharge during hospital stay, patients were followed up regularly. Out of 120 patients 34 patients developed AKI. Out of 34 AKI patients 4 patients required dialysis (AKI-D). 4 patients expired among those who developed AKI and 2 patients expired who did not develop AKI. 3 patients expired out of 4 patients who required dialysis and 1 patient expired out of 30 patients who did not require dialysis. This study revealed that increased age, overweight, smoking, diabetes, COPD, congestive heart failure (CHF), stroke, peripheral arterial disease, carotid bruit and cardiopulmonary bypass (CPB) time >110 minutes are significant risk factors for the development of AKI. Sex and type of surgery are not significant risk factors for the development of AKI.

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Key words: Acute kidney injury (AKI), Cardiopulmonary bypass surgery

Introduction

Acute kidney injury (AKI) is a highly prevalent and important complication of cardiac surgery. By most estimates, up to 30% of cardiac surgery patients develop clinically relevant kidney injury.[1] When the injury is severe enough to necessitate dialysis, which is the case for approximately 1% to 2% of patients, it confers an 8- fold increase in the odds of death.[2] Even when the injury is relatively modest, it is independently associated with markedly increased morbidity and mortality.[3] Furthermore, the majority of the patients who develop AKI that requires

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dialysis (AKI-D) remains dialysis dependent, leading to long term morbidity and mortality.[4] Despite advances in bypass technique, intensive care and delivery of haemodialysis, morbidity and mortality associated with AKI have not markedly changed in the last decade.[5] The aetiology of renal insufficiency following cardiac surgery is poorly understood, but it is believed that ischaemic injury of the kidney, resulting from inadequate perfusion, is a major factor, although renal injury by endotoxins (e.g antibiotics, anaesthetic agents, contrast media, diuretics) and exotoxins (e.g myoglobins) may also be involved.[6] Although the overall incidence of AKI is relatively low, approximately 75000 cases of AKI would have been expected to have developed over a decade, with a significant number of patients dying in the hospital, given the increasing frequency of cardiac surgery procedures (1.9 million from 1993-2002 in the U.S).[7] Another study described a cohort of patients who underwent cardiopulmonary bypass (CPB), AKI (defined as a rise in serum creatinine >1mg/dl above baseline) occurred in 7.9% of patients, and AKI-D occurred in 0.7%.[8] Other studies that used a definition of AKI as a 50% or greater rise in serum creatinine from baseline demonstrated a rate as high as 30%.[9] The incidence of AKI is dependent on the particular type of CPB surgery . Typical coronary artery bypass grafting has the lowest incidence of AKI (approximately 2.5%) and AKI-D (approximately 1%), followed by valvular surgery with an incidence of AKI of 2.8% and AKI-D 1.7%.[10] The highest risk group includes combined coronary artery bypass grafting/valvular surgery with an incidence of AKI 4.6% and AKI-D of 3.3%.[11] Mortality associated with the development AKI is as high as 60% in some studies but likely averages 15 to 30%, depending on the definition of AKI and the postoperative period studied (hospital discharge or 30-D mortality). In patients who require dialysis, mortality is as high as 60 to 70%.[12] It is interesting that even a small rises in serum creatinine are associated with significant mortality. Chertow et al. in a multivariate analysis that adjusted for comorbid factors identified the occurrence of AKI-D as an independent determinant of risk of death with an odds ratio of 7.9. Lassnigg et al. demonstrated that the 30-D mortality of patients who developed a 0- to 0.5 mg/dl and >0.5-mg/dl rise in serum creatinine was 2.77 and 18.64 fold higher respectively, than patients without a change in serum creatinine. Patients who develop AKI-D often remain dialysis dependent. Leacche et al. 2004, studied patients who underwent CPB procedures. Of patients who developed AKI-D, 64% required permanent dialysis and 1 year survival was only 10%. The link between the development of AKI and mortality likely involves numerous factors, including those directly related hemodialysis (hemodynamic instability, catheter-related infections, ventricular ectopy and visceral ischemia); immune dysregulation associated with AKI; platelet dysfunction; and other less defined associations. Registry data from Liano et al. demonstrated that in patients with AKI, infection was cause of death in 40%.[13] In patients who underwent CPB, Thakar et al. also demonstrated a high risk of infections.[14] The patients with AKI-D, the incidence of serious infections, including sepsis, was 58.5% as compared with 3.3% in all patients who underwent CPB. Because Acute kidney injury (AKI) is a potentially serious adverse event have higher rates of mortality and resource utilization with the worst values even in dialyzed patients, emphasis needs to be directed at the preventive measures, the first step of which is to estimate the patients risk for acute kidney injury. The number of patients with risk factors for AKI is

increasing, the prevalence of certain risk factors such as advancing age, diabetes and chronic kidney disease is increasing. During the last few years, the number of cardiac surgery performed has grown enormously in Bangladesh. But there is no data regarding the incidence of AKI after such procedure. The result of the study will be helpful to find out the risk factors of AKI in cardiopulmonary bypass surgery and take appropriate initiative for prevention of AKI.

Methods

This is a prospective observational study done in Bangabandhu Sheikh Mujib Medical University (BSMMU) for 1 year during the period of March 2009 to February 2010. A total 120 adult patients (more than 18 years) who underwent cardiopulmonary bypass surgery at the department of cardiac surgery, BSMMU was included in this study. Patients with preexisting renal dysfunction (serum creatinine > 1.3 mg/dl) were excluded from our study. Informed consent was obtained from each patient. A detailed history was taken from each patient. Sociodemographic variables as age, sex and smoking, anthropometric variables as weight, clinical variables as blood pressure, COPD, congestive cardiac failure, stroke, peripheral vascular disease, carotid bruit and left ventricular ejection fraction, biochemical variables as serum creatinine and blood sugar were studied. Procedural factors as type of surgery and cardiopulmonary bypass time were also studied. Demographic profile, clinical examination and relevant investigation reports and procedural factors of all patients were recorded in pre-designed data collection sheet. The anti-hypertensive, anti-ischaemic, lipid lowering, oral hypoglycaemic drugs and insulin were continued. Base line serum creatinine was estimated before operation. Postoperative serum creatinine was estimated 1st, 3rd and 5th postoperative day. For estimation of serum creatinine 3cc blood sample was collected and sent immediately to laboratory. Sample was analyzed by automated clinical chemistry analyzer ABX pentra 400 of HORIBA ABX, France. All vital signs were checked at regular interval on 1st three postoperative day. Before discharge during hospital stay, patients were followed up regularly. Study population was divided into two groups. Group-A who developed AKI and group-B who did not develop AKI. Analysis was done to find out whether there is relationship between incidence of AKI with age, sex, smoking, HTN, diabetes, congestive heart failure, type of surgery, ejection fraction, peripheral arterial disease and CPB time. Data were collected by using structured questionnaire. In order to collect data and sample, we went to cardiac surgery department on most of the working days. After an elaborative discussion regarding the implication of the study, age, name recorded as per participant's statement at the time of interview. Weight was taken with light cloths and without shoes by an approximately calibrated weight measuring scale placed on a flat surface. Blood pressure was recorded at least after 5 minutes rest being relaxed on a chair with a support on the back keeping bared arm on a table at heart level. Systolic BP was recorded based on 1st korotkoff sound and diastolic BP was recorded based on 5th korotkoff sound. The average of the two readings were taken separated by at least 2 minutes. For estimation of serum creatinine, venous blood samples were collected by sterile disposable syringe with strict aseptic precaution. Samples were immediately sent to department of Biochemistry, BSMMU. Statistical analysis was conducted using SPSS (Statistical package for social science) version 13.0 for windows software. The tests statistics used to analyze the data were descriptive statistics, Chi-squire test, student's t-test. Multivariable logistic regression models were applied including all the confounding variables. Level

of significance for all analytical test were set at 0.05 and p value <0.05 was considered significant.

Results

A total of one hundred and twenty patients who fulfilled the inclusion criteria were studied during the study period. Patients were divided into two groups. Group A (n=34) those developed acute kidney injury (AKI) and group B (n=86) who did not develop acute kidney injury.

Age distribution shows a significant variation between the two groups (P<0.001). Mean (± SD) age of Group A patients (62.00 ± 8.20 years) was significantly higher than Group B patients (46.56 ± 9.58 years). In group A, most of the patients belonged to age group 51-70 years (76.5%), followed by >70 years (14.7%), 31-50 years (8.8%) and none in age group ≤30 years, while in group B, most of the patients belonged to age group 31-50 years (59.3%), followed by 51-70 years (31.4%), ≤30 years (9.3%) and none in age group >70 years.

Mean (± SD) weight of group A patients (65.26 ± 7.56 kg) was significantly higher (P<0.001) than group B patients (52.99 ± 9.44 kg). However, mean (± SD) ejection fraction was significantly higher (P<0.001) in group B patients (64.03 ± 8.44%) than group A patients (51.74±7.79%).

Table II shows univariate analysis of risk factors associated with development of postoperative AKI. Sex showed no significant effect on development of AKI (P= 0.126, OR= 2.066, 95% CI 0.805-5.301). Smoking habit showed a significant association (P<0.01, OR 0.243, 95% CI 0.104-0.567). History of diabetes mellitus showed a highly significant association (P<0.001, OR 5.402, 95% CI 2.287-12.755). History of hypertension showed a highly significant association (P<0.001, OR 9.474, 95% CI 3.070-29.232), history of Chronic obstructive pulmonary diseases (COPD) showed highly significant association (P<0.001, OR 6.754, 95%), CI 20568-17.763). History of congestive heart failure (CHF) showed a highly significant association (P<0.001, OR 9.148, 95% CI 3.717-22.515). History of stroke showed a highly significant association (P<0.001, OR 7.748, 95% CI 2.2443-24.570). History of Peripheral arterial disease showed a highly significantly association (P<0.001, OR 6.756, 95% CI 2.632-17.336). History of Carotid bruit showed a highly significant association (P<0.001, OR 8.667, 95% CI 3.216-23.357). CPB time (≤110 and >110 minutes) showed a highly significant association (P<0.001, OR 0.048, 95% CI 0.017-0.137).

Table III shows type of cardiopulmonary bypass (CPB) surgery done. In group A and group B, patients, respectively, CABG was done in 22 (64.7%) and 61 (70.9), valvular in 9 (26.5%) and 23 (26.7%) and CABG plus valvular in 3 (8.8%) and 2 (2.3%). Type of surgery showed no significant association with development of AKI after surgery.

Mean (±SD) operative time was significantly higher (P<0.001) in group A patients compared to group B (122.35±16.11 vs 89.09±15.94 minutes). In group A, equal number of patients (47.1%) required 91-120 and 121-150 minutes, In group B, most patients (62.8%) required 61-90 minutes, followed by 91-120 minutes (29.1%), 121-150 minutes (7%), ≤ 60 minutes (1.2%)and none 151-180 minutes (Table-IV)

In group A, out of 34 patients, 12 (35.5%) required up to 110 minutes and 22 (64.7%) required more than 110 minutes, while in group B, out of 86 patients, 79 (91.9%) required up to 110 minutes and 7 (8.1%) required more than 110 minutes.

Table V shows that out of 34 patients who developed AKI, significantly (P<0.001) low number of patients required postoperative dialysis (11.8%).

Significantly high death rate was observed among group A (11.8%) than group B (2.3%) patients (P<0.05, OR 5.600, 95% CI 0.975-32.156) (Table-VI).

Death was significantly higher among patients AKI patients who required dialysis (75% out of 4) (P<0.001, OR 87.00, 95% CI 4.263-1775-511) (Table VII).

Table VIII shows preoperative and postoperative status of serum creatinine level in group A and group B patients. Comparison of preoperative mean (±SD) serum creatinine level between group A (0.97±0.21 mg/dl) and group B (0.93±0.18 mg/dl) patients showed no significant variation. However, postoperatively, mean (±SD) serum creatinine level in group A patients (3.42±1.79 mg/dl) compared to group B (1.05±0.20 mg/dl) was significantly high (P<0.0001). Percentage rise was 269.89%) in group A, while the rise was only 13.25% in group B.

Table IX shows logistic regression analysis. Except age (P<0.001), weight (P<0.05), and CPB time >110 minutes (P<0.01) none showed any significant risk in the development of postoperative AKI.

Table I: Basic data of the study patients

Parameters	Group A (n=34)	Group B (n=86)	P value
Age (years)means ± SD	62.00 ± 8.20	46.56 ± 9.85	0.0001***
≤ 30	0(0%)	8(9.3%)	
31-50	3(8.8%)	51(59.3%)	0.0001***
51-70	26(76.5%)	27(31.4%)	
>70	5(14.7%)	0(%)	
Weight (kg) Mean ± SD	65.26 ± 7.56	52.99 ± 8.08	0.0001***
EF%, Mean ± SD	51.74 ± 7.79	64.03 ± 8.44	0.0001***

Chi-square/Unpaired Student's `t' test
*** = Significant (P<0.001)

Table II: Risk factors for development of postoperative AKI

Parameters	Group A (n=34)		Group B (n=86)		P Value	Odds ratio	95% CI
	No	(%)	No	(%)			
Sex					0.126^{ns}	2.066	0.805-5.301
Male	27	(79.6)	56	(65.1)			
Female	7	(20.6)	30	(34.9)			
Smoking Habit					0.001**	0.243	0.104-0.567
Nonsmoker	11	(32.4)	57	(66.3)			
Smoker	23	(67.6)	29	(33.7)			
Diabetes					0.0001***	5.402	2.287-12.755
Present	23	(67.6)	24	(27.9)			
Absent	11	(32.4)	62	(72.1)			
Hypertension					0.0001***	9.474	3.070-29.232
Present	30	(88.2)	38	(44.2)			
Absent	4	(11.8)	48	(55.8)			
COPD					0.0001***	6.754	2.568-17.763
Present	15	(44.1)	9	(10.5)			
Absent	19	(55.9)	77	(89.5)			
CHF					0.0001***	9.148	3.717-22.515
Present	23	(67.6)	16	(18.6)			
Absent	11	(32.4)	70	(81.4)			
Stroke					0.0001***	7.748	2.443-24.570
Present	11	(67.6)	5	(5.8)			
Absent	23	(32.4)	81	(94.2)			
Peripheral arterial disease					0.0001***	6.756	2.632-17.336
Present	16	(47.1)	10	(11.6)			
Absent	18	(52.9)	76	(88.4)			
Carotid bruit					0.0001***	8.667	3.216-23.357
Present	16	(47.1)	8	(9.3)			
Absent	18	(52.9)	78	(90.7)			
CPB time (min)					0.0001***	0.048	0.017-0.137
≤110	12	(35.3)	79	(91.9)			
≥110	22	(64.7)	7	(8.1)			

Univariate analysis (Chi-square test), ns = Not significant; ** = Significant (P<0.01), *** = Significant (P<0.001)

Table III: Type of surgery required

Surgery	Group A (n=34)		Group B (n=86)		P value
	No.	(%)	No.	(%)	
CABG	22	(64.7)	61	70.9	
Valvular	9	(26.5)	23	26.7	0.272^{ns}
CABG + Valvular	3	(8.8)	2	2.3	

Chi- square; ns = Not significant

Table IV: CPB surgery time required

Time (minutes)	Group A (n=34)		Group B (n=86)		P value
Mean±SD	122.35±16.11		89.09±15.94		0.0001***
	No.	(%)	No.	(%)	
≤60	0		1	(1.2)	
61-90	1	(2.9)	54	(62.8)	
91-120	16	(47.1)	25	(29.1)	0.0001***
121-150	16	(47.1)	6	(7.0)	
151-180	1	(2.9)	0		

Chi-square/Unpaired Student's 't' test
*** = Significant (P<0.001)

Table V: Dialysis required for patients with postoperative AKI (n=34)

Dialysis	No.	%	P value
Required	4	11.8	
Not required	30	88.2	0.0001***

Z-test
*** = Significant (P<0.001)

Table VI: Outcome of patients who underwent CPB surgery.

Status	Group A (n=34)		Group B (n=86)		P value	Odds ratio	95% CI
	No.	%	No.	%			
Expired	4	11.8	2	2.3	0.033*	5.600	0.975-32.156
Survived	30	88.2	84	97.7			

Univariate analysis (Chi-square test)
* = Significant (P<0.05)

Table VII: Outcome of AKI patients

Status	Dialysis required (n=4) No.	%	Dialysis not required (n=30) No.	%	P value	Odds ratio	95% CI
Expired	3	75.0	1	3.3	0.0001***	87.000	4.263-1775.511
Survived	1	25.0	29	96.7			

Univariate analysis (Chi-square test)
*** = Significant (P<0.001)

Table VIII: Pre- and postoperative serum creatinine level

Serum (creatinine)	Group A (n=34) Mean±SD	Group B (n= 86)	P value
Preoperative	0.97±0.21	0.93±0.18	0.197
postoperative	3.42±1.79	1.05±0.20	0.0001***
Percent change from preoperative to postoperative.	+269.89	+13.25	

Unpaired Student's 't' test
ns=Not significant
***= Significant (P<0.001)

Table IX: Results of logistic regression

Parameters	Coefficient	SE	Wald	Sig	Odds ratio	95% CI for odds ratio	
						Lower	Upper
Age[a]	-4.1478	1.2012	11.9231	0.000	0.1058	0.0015	0.1664
Weight[a]	-2.1338	1.4480	4.1459	0.042	0.1184	0.0152	0.9233
Diabetes	-1.7477	1.2182	2.0581	0.151	0.1742	0.0160	1.8965
COPD	-1.4502	1.4995	0.9353	0.334	0.2345	0.0124	4.4317
CHF	1.9293	1.3959	1.9104	0.167	6.8849	0.4464	106.1866
PAD	-0.1753	1.3225	0.4169	0.519	0.4257	0.0319	506865
EF[a]	-1.9320	0.7331	0.0572	0.811	0.8392	0.1995	3.5309
Carotid bruit	-6.3210	1.3243	9.5404	0.145	0.1449	0.0108	1.9417
CPB time >110 min	-6.3210	2.0464	9.5404	0.002	0.0018	0.0000	0.0993
Constant	44.3654	13.3276	11.0812	0.000			

COPD = Chronic obstructive pulmonary disease, CHF = Congestive heart failure, PAD = Peripheral arterial disease, EF = Ejection fraction.
[a]Odds ratio expressed for a 10 unit change
Logistic regression analysis
0.000 = P<0.001
0.002 = P<0.01
0.042 = P<0.05

Discussion

Acute Kidney injury (AKI) is a prevalent and prognostically important complication of cardiac surgery. When the injury is severe enough to necessitate dialysis, it may confer a pronounced increase in the odds of death, even less severe injury may be associated with marked increased morbidity and mortality.[15] The definition we used for acute kidney injury was 50% rise in base line serum creatinine or 0.5 mg/dl increase in serum creatinine up to 5th day post operatively.In this study we divided the patients in two groups. Group-A patients were who developed AKI and group B patients who did not develop AKI. In our study the mean age of group A patients was 62±8.2 years where as in group B it was 46.56±9.58 years. In group A most of the patients belonged to age group 51-70 years (76.5%) while in group B most of the patients belonged to 31-50 years (39.3%) the age difference between the two groups

was statistically significant (p=0.0001). A total 83 patients were male (69.1%) and 37 patients were female (30.9%). In group A out of 34 patients 27(79.4%) were male and 7(20.6%) were female. In group B out of 86 patients 56(65.1%) were male and 30(34.9%) patients were female. The sex variation did not show significant effect on the development of AKI (p=0.126). In this study smoking, diabetes, hypertension, congestive heart failure, history of stroke, peripheral arterial disease, carotid bruit, cardiopulmonary bypass time showed significant association with the development of AKI but type of surgery did not show any significant association with development of AKI. In our study in group A out of 34 patients 4 patients (11.8%) required dialysis (AKI-D). This shows that significant low number of patients required dialysis. In group A 4 patients expired (11.8%) and 2 (2.3%) expired in group B. Significantly low death rate was observed in both groups. 3 patients (75%) expired out of 4 patients who required dialysis and 1 patients (3.3%) expired out of 30 patients who did not require dialysis. Death was significantly higher (p=0.001) among patients who required dialysis. In group A and group B preoperative serum creatinine was 0.97±0.21 mg/dl and 0.93±0.18 mg/dl respectively. Comparison of mean (±SD) serum creatinine level between two groups showed no significant variation. However postoperative mean (±SD) serum creatinine level in group A patients (3.42±1.79) compared to group B (1.05±0.20) was significantly high (o<.001). Percentage rise was 269.89% in group A while the rise was only 13.25% in group B. Different studies throughout the world showed a variable range of incidence of AKI associated with cardiopulmonary bypass surgery and a number of risk factors for the development of AKI. Without preexisting renal dysfunction up to 30% patients develop AKI.[1] With preexisting renal dysfunction postoperative AKI may occur upto 50% patients undergoing cardiopulmonary bypass operation.[16] In our study we excluded patients with preexisting renal dysfunction. In a study of 74 patients who underwent cardiopulmonary bypass operation showed incidence of AKI 24.32%, 1 patient (1.35%) required dialysis and died. Death rate was 100% among AKI-D.[17] In a prospective study of 186 patients, incidence of AKI was 30.6%. Among AKI patients 7% required dialysis. Mortality rate with or without AKI was 8.8% and 0.8% respectively. But it reached 50% in dialysis patients.[18] Different studies throughout the world by univariate analysis and logistic regression study showed different risk factors for the development of AKI. In a prospective study of 223 patients who underwent cardiac surgery with extracorporeal circulation showed the incidence of AKI 16.1% and AKI-D 4.9%. Risk factors associated with AKI in the univariate analysis were age, duration of CPB time >90 minutes, preoperative serum creatininie >1.2 mg/dl. In the multivariate analysis independent factors associated with AKI were age, preoperative serum creatinine >1.2 mg/dl. Mortality in the patients with AKI was 25% compared with 1.1% in those without AKI and 63.6% in those who required dialysis. In this study factors those not significantly associated with the development of AKI were sex, diabetes mellitus and history of stroke.[18]

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