Incidence and Progression of Cardiac Surgery-associated Acute Kidney Injury and its Relationship with Bypass and Cross Clamp Time

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Abstract

Introduction: Cardiac surgery-associated kidney injury (CSA-AKI) is common but relatively less is known about its progression. The present study is aimed at evaluating the incidence and course of CSA-AKI and its relationship with the different durations of cardiopulmonary bypass (CPB) and cross clamp times. **Materials and Methods:** Occurrences of CSA-AKI are evaluated as per the Akin Kidney Injury Network (AKIN) criteria over the course of 5 postoperative day (POD) in 100 patients. The relationship of different durations of CPB and aortic cross clamp time with CSA-AKI is analyzed by Chi-squared test for trend and other appropriate tests using INSTAT software. **Results:** One hundred (43 male, 57 female; mean age of 37.01 ± 12.28 years, and baseline mean serum creatinine 0.99 ± 0.20 mg %) patients undergone mostly valve replacement, and congenital heart disease correction was evaluated. Nearly 49% suffered CSA-AKI (81.63% AKIN Class I) with maximum numbers on 2nd POD. Serum creatinine followed a falling trend 3rd POD onward except in 8.16% cases of CSA-AKI. Oliguria was absent even in AKIN Class II. The CPB time >70 min and cross clamp time >60 min increase CSA-AKI risk by an OR of 4.76 and 2.84, respectively ($P < 0.05$). **Conclusion:** CSA-AKI is very prevalent; mostly of AKIN Class I and increases with increasing CPB and cross clamp time. Urine output is not a reliable indicator of CSA-AKI. The AKIN Class II on the very 1st POD or increasing trend of serum creatinine beyond 3rd POD should alert for early intervention.

Keywords: *Aortic cross clamp, Cardiac surgery-associated kidney injury, Cardio pulmonary bypass*

Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequent happening affecting nearly 30% of the cases undergoing cardiac surgery.[1] This is associated with increased hospital length of stay and mortality.[2,3] Despite being known for decades, there is relative lack of effective therapeutic approaches to address this major problem till date. Therefore, risk modification appears to be an important strategy to reduce the incidence of CSA-AKI. The cardiopulmonary bypass (CPB) and aortic cross clamp time are few of the modifiable risk factors.[3-5] However, relatively less is known about the relationship of different durations of CPB and cross clamp time with CSA-AKI and its natural course over the next few postoperative days (PODs). The current study is aimed to evaluate the relations which, in turn, will facilitate our knowledge on the course of CSA-AKI, help in risk stratification, and give a basis for detecting the potential worsening case to initiate early intervention for improved outcome.

Materials and Methods

After the Institutes' Research Board approval, the present retrospective evaluation of prospectively collected data was conducted on patients who underwent cardiac surgeries on CPB with aortic cross clamp during 2012–2014. The study was planned with an 1-alfa 95, 1-beta 80, unexposed to exposed ratio of 0.5, and expected incidence in unexposed and exposed at 20% and 50%, respectively; which gave a sample of 95 total by Kelsey method, but 100 patients' data were included (calculated using http://www.openepi.com/SampleSize/SSCohort.htm). Demographic parameters, baseline preoperative serum creatinine, and blood urea were noted. Patients having preoperative serum creatinine >2 mg/dl and known cases of chronic renal failure and/or on hemodialysis (HD) were excluded from

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the present analysis. Estimated glomerular filtration rate (eGFR) has been calculated using the Cockcroft and Gault equation.[6] Perioperative care was given by the same team of surgeon, anesthesiologist, intensivist, perfusionist, and nursing team. All cases were done through median sternotomy incision. Hemodynamics was targeted within ±20% of baseline during prebypass period, and a mean arterial pressure (MAP) of 55–65 mmHg was maintained during CPB. During nonpulsatile CPB, a flow of 2.4 L/min/m^2 body surface area (BSA) was maintained. Vasopressor, vasodilator, and/or ionotropic supports were given as needed while coming out of bypass and postoperatively to maintain minimum of 65–70 mmHg MAP and effective left ventricular contraction. Serum creatinine and blood urea level were obtained and urine output (UO) was recorded daily from POD 1–5. CSA-AKI incidence and severity were determined using the Akin Kidney Injury Network criteria (AKIN)[7] and expressed in absolute number and percentage scale. The serum creatinine, blood urea, and UO of different PODs and levels among the CSA-AKI positive and negative cases were also analyzed to know the trend and course of the CSA-AKI. The cohort is further stratified based on the different durations of CPB and cross clamp time (i.e., <70, 71–140, >140 min and <60, 61–120, and >120 min, respectively), and relationship with CSA-AKI is evaluated by Chi-squared test for trend. The INSTAT software (Graphpad software, Inc, La Zolla, CA, USA) was used for analyzing statistical significance, and $P < 0.05$ was considered significant.

Results

Data of 100 patients in the age group of 17–74 years (43 male and 57 female; mean ± standard deviation [SD] age, weight, and height of 37.01 ± 12.28 years, 49.4 ± 6.67 kg and 158.76 ± 6.78 cm, respectively) were evaluated. The mean ± SD preoperative blood urea and serum creatinine were 31.73 ± 17.80, 0.99 ± 0.20 mg%, and eGFR was 67.72 ± 18.89 ml/1.73 m^2 BSA. Intraoperative UO was well above 1 ml/kg/h with mean ± SD of 6.11 ± 1.22. The mean ± SD duration of CPB was 94.57 ± 43.26 (95% confidence interval [CI]: 85.97–103.17) min while aortic cross clamp duration was 72.80 ± 36.82 (95% CI: 65.48–80.11) min. The predominant surgeries performed were valve replacement (65%), of which 58.46% developed CSA-AKI [Table 1].

Forty nine (49%) patients developed CSA-AKI during the 5 PODs. The mean ± SD serum creatinine level and the point incidence of CSA-AKI were highest on 2nd POD (i.e., 1.22 ± 0.38 mg% and 36 cases, respectively) [Table 2]. The mean serum creatinine level followed a decreasing trend from 3rd POD onward even in the CSA-AKI positive cases [Table 3]. The mean serum creatinine level increased from the baseline by 42.79% on the 1st POD which further increased reaching peak on POD 2 in CSA-AKI positive cases as compared to 3.84% rise on the 1st POD which become equal to baseline on the 2nd POD in CSA-AKI negative cases. The demographic, baseline creatinine, CPB, cross clamp time, etc., of CSA-AKI positive and negative cases are shown in Table 3. The incidence of CSA-AKI increased along with the increase in the CPB and cross clamp time significantly. The CPB time >70 min increased the CSA-AKI risk by an odds ratio (OR) 4.76 as compared to 71–140 min and by an OR 6.30 for >140 min ($P < 0.01$) while for the aortic cross clamp time >60 min increased the CSA-AKI risk by an OR of 2.84 as compared to 61–120 min and by an OR 3.64 for >120 min ($P = 0.01$) [Table 4].

Table 1: Surgical procedures performed and respective cardiac surgery-associated acute kidney injury expressed in absolute number and percentage scale

Surgery performed	*n*=100	CSA-AKI, *n* (%)
Simple congenital heart disease repair (atrial septal defect, ventricular septal defect, patent ductus arteriosus closure, pulmonary vulvotomy)	27	6 (22.22)
Valve replacements (aortic, mitral, and double valve replacement±tricuspid annuloplasty±atrial septal defect repair±LA clot removal)	65	38 (58.46)
Double outlet right ventricle, rupture aneurysm repair and LA myxoma excision	5	3 (60.0)
Coronary artery bypass graft + valve replacement	1	1 (100)
Coronary artery bypass graft (triple vessel)	2	1 (50.0)

CSA-AKI: Cardiac surgery-associated acute kidney injury, LA: Left atrial

Discussion

In the present observational cohort study, it was tried to evaluate the incidence of CSA-AKI and its course during the 1st 5 PODs with an intention to get more insight so that more appropriate risk stratification and informed decision-making for timely intervention can be done in perioperative and postoperative period. In the present study, 49% of the patients met the definition of CSA-AKI which is relatively higher as compared to the findings of other studies and reviews.[1,2] This is probably and partly because of the criteria used (i.e., AKIN) in the present study which categorizes even 0.3 mg% absolute rise of serum creatinine as Class I acute kidney injury (AKI). The AKIN criteria have shown to diagnose significantly more patients as having AKI as compared to risk, injury, failure, loss of kidney function, and end-stage renal failure.[8] The present study finding is showing slightly higher incidence as

Table 2: Point incidence of cardiac surgery-associated acute kidney injury and comparisons of postoperative day 1-5 serum creatinine, blood urea and urine output using paired *t*-test

Time	Serum creatinine (mg%)		Two-tailed	Blood urea (mg%)		Two-tailed	UO (ml/kg/h)		Two-tailed	CSA-AKI (*n*), *n*=100
	Mean±SD	95 % CI	(*P*)	Mean±SD	95 % CI	(*P*)	Mean±SD	95% CI	(*P*)	
Baseline	0.99±0.20	0.94-1.03	Reference	31.73±17.80	27.76-34.83	Reference	Data NA	Data NA		-
POD 1	1.20±0.31	1.13-1.26	<0.0001	41.00±14.19	38.18-43.82	<0.0001	1.13±0.22	1.09-1.18	Reference	35
POD 2	1.22±0.38	1.14-1.29	<0.0001	43.31±14.63	40.40-46.21	<0.0001	1.12±0.21	1.08-1.17	0.5138	36
POD 3	1.17±0.43	1.09-1.26	<0.0001	43.36±16.73	40.03-46.68	<0.0001	1.15±0.23	1.10-1.19	0.4794	34
POD 4	1.12±0.37	1.04-1.19	0.0013	40.68±16.35	37.42-43.93	<0.0001	1.16±0.24	1.11-1.21	0.1557	29
POD 5	1.05±0.32	0.99-1.12	0.0590	37.77±15.50	34.69-40.85	0.0003	1.16±0.21	1.12-1.20	0.1768	19

POD: Postoperative day, SD: Standard deviation, CI: Confidence intervals, CSA-AKI: Cardiac surgery-associated acute kidney injury, NA: Not available, UO: Urine output

compared to a recent retrospective analysis using Kidney Disease; Improving Global Outcome (KDIGO) criteria for AKI (49% vs. 42%).[3] This is probably because both the AKIN and KDIGO classifies >0.3 mg% absolute rise of serum creatinine as Class I AKI.[7,9] The predominant surgery performed in the present study was valve replacement surgeries (66%) which is also an independent risk factor for postoperative acute renal failure.[10]

The mean serum creatinine level increased up to 51.39% from baseline on the 2nd POD and then started falling from the 3rd POD onward among the cases who suffered from CSA-AKI except in 4 (8.16%) cases. Out of these 4 cases, serum creatinine remained >220% of baseline in 3 patients till the 5th POD. One (2.04%) patient who met the criteria of AKIN Class II on the very 1st POD showed persistent increasing trend beyond 5th POD and progressed from AKI Class II to Class III requiring HD and ultimately succumbed to death on 36th POD. Patients with CSA-AKI progressing to renal failure requiring HD varies from 1% to 3%.[2,9,11] A multicenter retrospective study suggests that early renal replacement therapy (RRT) (<3 days after cardiac surgery) is associated with decreased length of hospital stay as well as mortality.[12] The observation of the present study probably give us a basis for identification of the at risk patient for HD and probably can be used to supplement the decision-making on early initiation of RRT on this type of patients.

The mean intraoperative UO was not different in CSA-AKI positive and negative cases. Moreover, it is observed that UO was not low during CPB also. It is probably because mannitol was used in CPB priming solution. This can also be explained by the maintenance of adequate renal blood flow due to relatively low regional vascular resistance during CPB.[13] UO in AKI in postoperative period is usually expected to fall. However, in the present study, the mean postoperative UO was above 1 ml/kg/h even among the patients who developed CSA-AKI in all the 5 PODs evaluated, and the UO was not different (i.e., less) than the non-CSA-AKI cases. Interestingly, the oliguria (i.e., UO <0.5 ml/kg/h) was not present in the patients who suffered from CSA-AKI Class II during the 5 PODs and not even in the patient who later on landed up on HD. This finding suggests that UO is not correlated with the development of CSA-AKI.

CSA-AKI is independently associated with increased mortality, and even minimal increase in serum creatinine postoperatively can have an impact on 30 day's mortality.[1,3,14] The deleterious effect of CPB and cross clamp on renal function is multifactorial and well known and they are regarded as potential modifiable risk factors.[2,15] Offpump coronary artery bypass graft has shown to be associated with lower need of RRT postoperatively[16] and therefore, emphasis has been given to avoid CPB and aortic cross clamp during cardiac surgeries. However, this is not

Table 3: Comparisons of the cardiac surgery-associated acute kidney injury positive and negative cases using unpaired t-test

Parameters	CSA-AKI present (*n*=49)		CSA-AKI absent (*n*=51)		Two-tailed *(P)*
	Mean±SD	95% CI	Mean±SD	95% CI	
Age (years)	38.53±13.25	34.71-42.34	35.54±11.20	32.39-38.70	0.2268
Weight (kg)	49.59±6.72	47.66-51.52	49.21±6.69	47.33-51.10	0.7798
eGFR (ml/1.73 m^2)	68.97±18.73	63.53-74.42	66.56±19.15	61.22-71.90	0.5261
CPB time (min)	103.83±37.6	93.02-114.65	85.66±46.74	72.50-98.82	0.0351
X-clamp (min)	81.44±30.99	72.53-90.35	64.49±40.24	53.16-75.82	0.0206
Intraoperative UO (ml/kg/h)	5.89±1.25	5.53-6.25	6.32±1.17	5.99-6.65	0.0775
POD 1 UO	1.12±0.20	1.06-1.18	1.15±0.23	1.09-1.22	0.3928
POD 2 UO	1.11±0.21	1.065-1.17	1.14±0.22	1.07-1.20	0.5348
POD 3 UO	1.12±0.19	1.07-1.18	1.17±0.25	1.10-1.25	0.2728
POD 4 UO	1.16±0.21	1.10-1.22	1.17±0.27	1.09-1.25	0.8555
POD 5 UO	1.16±0.22	1.10-1.23	1.16±0.20	1.10-1.22	0.9956
Serum creatinine (mg%)					
Preoperative	0.93±0.20	0.87-0.99	1.04±0.19	0.99-1.10	0.0044
POD 1	1.32±0.36	1.22-1.43	1.08±0.19	1.02-1.13	<0.0001
POD 2	1.40±0.44	1.28-1.53	1.04±0.21	0.98-1.10	<0.0001
POD 3	1.40±0.49	1.26-1.54	0.96±0.20	0.90-1.01	<0.0001
POD 4	1.31±0.39	1.20-1.43	0.93±0.24	0.86-1.00	<0.0001
POD 5	1.21±0.38	1.10-1.32	0.90±0.16	0.86-0.95	<0.0001
Blood urea (mg%)					
Preoperative baseline	31.28±16.47	26.54-36.02	31.31±19.15	25.92-36.70	0.9938
POD 1	44.75±13.79	40.78-48.72	37.39±13.79	33.52-41.26	0.0088
POD 2	49.59±13.53	45.70-53.48	37.27±13.13	33.57-40.97	<0.0001
POD 3	51.89±15.38	47.47-56.32	35.15±13.69	31.30-39.01	<0.0001
POD 4	48.10±17.10	43.18-53.02	33.54±11.96	30.18-36.91	<0.0001
POD 5	42.75±17.61	37.69-47.82	32.98±11.40	29.77-36.19	0.0013

eGFR: Estimated glomerular filtration rate, UO: Urine output, CPB: Cardiopulmonary bypass, X-clamp: Aortic cross clamp, SD: Standard deviation, CI: Confidence intervals, POD: Postoperative day, CSA-AKI: Cardiac surgery-associated acute kidney injury

always possible, especially in valve replacement surgeries. Therefore, CPB management has been also targeted for research in relation to CSA-AKI. Patients with normal preoperative renal function who developed postoperative acute renal failure have shown to had longer CPB durations, lower CPB perfusion flow, and longer periods on CPB at pressures <60 mmHg.[17] In the present study cohort, BSA-based fixed CPB flow is expected to have an equal impact, if any, on all patients. The finding of significantly increased CSA-AKI numbers (P = 0.0028) with increasing trend of CPB durations suggest that longer CPB duration increases CSA-AKI. The cross clamp time has also shown similar and significant impact on CSA-AKI (P = 0.0159). The present study has also shown that the CPB duration of 71–140 min and >140 min increases the risk of CSA-AKI by an OR of 4.76 and 6.30, respectively.

One of the motives behind knowing the trend or progression of serum creatinine and CSA-AKI was to early suspect and detect the cases. Recently, different biomarkers have been investigated to do the same. CPB is associated with tubular damage which increases the production of kidney-specific proteins such as neutrophils gelatinase-associated lipocalin (NGAL), cystatin C, and kidney injury molecule 1, which have been noted within 2–6 h of surgery and correlate to the extent and duration of AKI as a biomarker.[18-20] Point of care NGAL has been in use recently for the purpose, and although its early appearance is independent of GFR, it is generally predictive of a subsequent decline in GFR.[20] Urinary NGAL has shown to be effective as an earlier marker of AKI than serum creatinine but lacks high sensitivity and specificity.[21] It also lacks the features of ideal biomarker, and serum creatinine remains still a valuable and only reliable tool for AKI.[22]

The present finding is however limited with the fact that it is a single-center, retrospective study. The sample size is also relatively lower although postanalysis power calculation of the present study taking the minimum difference between two CPB duration-based groups (22.2% in 27 patients and 57.6% in 59 patients) gave a power of 87.69% in normal approximation while with continuity correction it became 81.66% (calculated using http://www.openepi.com/Power/PowerCohort.htm); which appears to be acceptable. Prospective study with larger sample is likely to give more insight. Multivariate analysis to establish independent association is not done as the objective of the study was limited to know the relation (i.e., trend) of CSA-AKI with the different durations of CPB and cross clamp time.

Table 4: Incidence and relation of cardiac surgery-associated acute kidney injury with different durations of cardiopulmonary bypass and aortic cross clamp time analyzed using ANOVA

Parameters	CPB time, mean±SD			*P*	X-clamp time, mean±SD			*P*
	≤70 min	71-140 min	>140 min		≤60 min	91-120 min	>120 min	
Age (years)	31.66±10.30	39.57±12.48	36.5±12.30	0.0196	32.0±11.15	40.48±11.91	37.45±12.90	0.0048
Weight (kg)	49.03±7.23	49.18±6.20	51.00±7.72	0.6282	48.13±6.56	49.65±6.48	52.45±7.43	0.1571
Height (cm)	156.88±5.99	158.94±6.18	161.57±9.62	0.1048	157.18±5.48	158.82±6.82	163.72±9.51	0.0179
Base serum creatinine (mg%)	0.95±0.15	1.01±0.21	0.97±0.26	0.4350	0.92±0.16	1.03±0.22	0.98±0.19	0.0468
Baseline eGFR (ml/1.73 m^2)	72.35±19.09	65.08±18.30	69.89±20.32	0.2299	72.98±18.95	64.10±18.60	67.12±17.48	0.0901
Baseline blood urea (mg%)	28.33±12.14	33.61±20.83	27.28±11.08	0.2959	27.70±12.59	34.55±21.22	28.00±12.44	0.1634
Intraoperative UO (ml/kg/h)	7.00±0.62	5.97±1.11	4.98±1.41	<0.0001	6.75±0.76	5.94±1.15	4.74±1.47	<0.0001
CSA-AKI, *n* (%)	6 (22.22)	34 (57.62)	9 (64.28)	0.0028*	12 (32.43)	30 (57.69)	7 (63.66)	0.0159*
OR#	Reference	4.76	6.30		Reference	2.84	3.64	
95% CI of OR#		1.67-13.52	1.52-26.09			1.17-6.85	0.89-14.91	

*Chi-squared test of independence and #Fisher's exact test. eGFR: Estimated glomerular filtration rate, UO: Urine output, SD: Standard deviation, CSA-AKI: Cardiac surgery-associated acute kidney injury, OR: Odds ratio, CPB: Cardiopulmonary bypass, X-clamp: Aortic cross clamp, CI: Confidence interval

Conclusion

CSA-AKI is very prevalent; mostly of AKIN Class I and increases with increasing CPB and cross clamp time. UO is not a reliable indicator of CSA-AKI. The AKIN Class II on the very 1st POD or increasing trend of serum creatinine beyond 3rd POD should alert for early intervention.

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Conflicts of interest

There are no conflicts of interest.

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