Risk prediction of acute kidney injury in cardiac surgery and prevention using aminophylline

A. R. Mahaldar[1,2], K. Sampathkumar[2], A. R. Raghuram[3], S. Kumar[4], M. Ramakrishnan[2], D. A. C. Mahaldar[4,5]

[1]Department of Nephrology, Manipal Hospital Goa, Dona Paula, Panjim, Goa, Departments of [2]Nephrology, [3]Cardiothoracic Surgery, and [4]Cardiac Anesthesiology, Meenakshi Mission Hospital and Research Centre, Madurai, [5]Department of Anesthesiology, Sree Chitra Tirunal Institute of Medical Science and Technology, Medical College PO, Trivandrum, India

ABSTRACT

The incidence of acute kidney injury (AKI) after cardiac surgery remains high. The nonspecific adenosine receptor antagonist aminophylline has been shown to confer benefit in experimental and clinical acute renal failure (ARF) due to ischemia, contrast media, and various nephrotoxic agents. We conducted a prospective open label trial to assess the effectiveness of aminophylline for prevention of renal impairment after cardiac surgery. One hundred and thirty-eight patients undergoing cardiac surgery were risk stratified as per Cleveland score to assess for prediction of AKI. Sixty-three patients received a bolus aminophylline of 5 mg/kg and a subsequent continuous infusion of 0.25 mg/kg/h for up to 72 h, while 75 patients received usual postoperative care. Serum creatinine concentrations were measured preoperatively and daily until day 5 after surgery and the glomerular filtration rate estimated using Cockcroft and Gault formula. Hourly urine output was recorded and patients assigned to respective RIFLE stage of AKI. Cleveland score ≥6 was associated with higher incidence of AKI: I and F (P<0.005). Number needed to treat, an insight into the clinical relevance of a specific treatment, is 8. These results suggest that the perioperative use of aminophylline infusion is associated with lower incidence of deterioration in renal function following cardiac surgery in high-risk patients.

Key words: Acute kidney injury, aminophylline, cardiac surgery

Introduction

The incidence of acute kidney injury (AKI) after cardiac surgery remains high despite improvements in surgical techniques and perioperative care, and is associated with an unacceptably high mortality. The accurate prediction of the patients who will develop AKI, application of measures to prevent the same, and early recognition of AKI are the goals for the nephrologists involved in the care of these patients.

Cleveland Clinic Foundation acute renal failure scoring system is shown to be valid and accurate in predicting AKI after open-heart surgery in Western population. However, the authors have suggested the model needs to be tested prospectively at multiple centers to substantiate its broad applicability.[1]

To optimize the approach to AKI, the application of RIFLE criteria (named by the severity of renal impairment: risk, injury, failure, loss, and end-stage kidney disease) have been validated and shown to be valuable method to evaluate AKI after cardiac surgery. The severity of RIFLE classification may be associated with increased 90-day mortality rate.[2]

The nonspecific adenosine receptor antagonist aminophylline has been shown to confer some benefit in experimental and clinical acute renal failure (ARF) due to ischemia, contrast media, and various nephrotoxic agents. Earlier attempts in using this drug to prevent AKI in coronary artery bypass graft (CABG) patients have provided inconsistent results.[3] The mechanism of action of aminophylline in preventing AKI needs consideration. Adenosine, in contrast to its general systemic effect as a vasodilator, is a renal arterial vasoconstrictor. This unique effect has been implicated as part of the tubuloglomerular feedback mechanism, which increases afferent arteriolar tone in response to increased distal tubular solute delivery. Adenosine

Address for correspondence:
Dr. Amol Ramesh Mahaldar, House No. 99/C, Xell Bastora, Bardez, Goa - 403 507, India. E-mail: dramolmahaldar@gmail.com

Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.98752

also acts synergistically with angiotensin II to constrict afferent arterioles. Adenosine via A-1 receptors has now been shown to be a possible mediator of the intrarenal hemodynamic changes that lead to acute tubular necrosis following radiocontrast administration.[4] Animal studies and clinical trials of using theophylline pretreatment have demonstrated attenuation of this intrarenal vasoconstriction and prevention of contrast-induced nephropathy.[4,5]

Our study takes advantage of these three strategies, viz. Cleveland Clinic scores for risk prediction, RIFLE criteria for early identification, and intravenous aminophylline for prevention of AKI in cardiac surgery.

Materials and Methods

This was a prospective open label, nonrandomized study approved by the Institutional Ethics Committee. One hundred and thirty-eight patients undergoing cardiac surgery at a tertiary care center were risk stratified as per Cleveland score as L (0-2), *I* (3-5) and H (≥6) groups. Sixty-three patients (A) received a bolus aminophylline of 5 mg/kg and a subsequent continuous infusion of 0.25 mg/kg/h for up to 72 h, while 75 patients (C) received usual postoperative care. Serum creatinine concentrations were measured preoperatively and daily until day 5 after surgery, and the glomerular filtration rate (GFR) estimated using Cockcroft and Gault formula (CG-GFR). Postoperative hourly urine output was recorded and patients assigned to respective RIFLE stage of AKI.

Results

The age, body mass index, Cleveland score, and use of cardiopulmonary bypass (CPB) were similar in group A and C ($P>0.01$) [Table 1].

The preoperative parameters were compared with postsurgery AKI outcomes and are summarized in Table 2. Age, HTN, and multiple grafts were not associated with worse outcomes, while female sex and cardiac surgery with CPB showed a higher incidence of postoperative AKI: I, F ($P<0.05$). Recent angiography within 7 days before surgery was associated with a higher incidence of AKI: I, F albeit not reaching statistical significance ($P=0.085$).

Hypokalemia was seen in 34 patients, 29.2% in study patients as against 20.5% control patients ($P>0.1$). Arrhythmia was recorded in 10 patients, 8.2% in control and 6.2% in study patients ($P>0.1$). Ventricular premature complexes noted in seven patients and sinus tachycardia in three patients did not require any treatment.

Table 1: Preoperative characteristics

	Aminophylline	Control (C)	*P* value
n=138	65	73	
Age (years)	57.69 ± 9.17	54.80 ± 9.69	0.382
Sex ratio F:M	3:62	14:59	0.009
BMI (kg/m^2)	24.26 ± 3.02	23.64 ± 3.26	0.252
HTN	31 (47.69)	31 (42.46)	0.538
Days <7 after angiogram	10 (15.38)	9 (12.32)	0.649
CPB	15 (23.07)	27 (36.98)	0.07
No. of grafts >1	55 (84.61)	62 (84.93)	0.687

F = Female; M = Male; BMI = Body mass index; HTN = Hypertension; CPB = Cardio pulmonary bypass. Figures in parentheses are percentages.

Table 2: Preoperative predictors of acute kidney injury

	N	AKI				*P* value
		O	R	I	F	
Cleveland score category						0.001
L	69	53 (76.8)	11 (15.9)	5 (7.3)	0 (0)	
I	63	46 (73)	13 (20.6)	2 (3.2)	2 (3.2)	
H	6	3 (50)	1 (16.67)	0 (0)	2 (33.33)	
Females	17	9 (52.9)	5 (29.4)	3 (17.6)	0 (0)	0.028
HTN	62	46 (74.2)	12 (19.4)	2 (3.2)	2 (3.2)	0.827
Age ≥50y	108	80 (74.1)	21 (19.4)	5 (4.6)	2 (1.8)	0.465
Multigrafts	117	91 (77.8)	18 (15.4)	5 (4.3)	3 (2.6)	0.481
Recent angiogram	19	14 (73.7)	3 (15.8)	0 (0)	2 (10.5)	0.085
CPB	42	23 (54.4)	12 (28.6)	4 (9.5)	3 (7.1)	0.005

AKI = Acute kidney injury; O = No injury by RIFLE criteria; R = Risk by RIFLE criteria; I = Injury by RIFLE criteria; F = Failure by RIFLE criteria. Cleveland score category: L = Cleveland score low risk 0-2; *I* = Cleveland score intermediate risk 3-5; H = Cleveland score high risk >6. Figures in parentheses are percentages.

Dialysis therapy in the form of continuous veno venous hemodiafiltration was instituted in three individuals (one in group A), while three patients succumbed during the same admission, all from control group (C).

Cleveland score ≥6 (H) was associated with higher incidence of AKI rifle criteria: I, F at 33.33% ($P<0.005$).

Effect of aminophylline

The outcomes in the study (A) and control (C) arms according to RIFLE stages were compared [Figure 1]. Incidence of AKI rifle criteria: I, F was significantly higher in group C compared with group A ($P=0.055$).

The difference was statistically more significant in the higher risk patients with Cleveland score ≥3 ($P=0.017$). Renoprotection was defined as prevention of incidence of AKI: I, F. Ten patients from control group C as against one from study group A developed AKI: I, F as shown in Figure 2 ($P=0.008$).

Number needed to treat

The effect associated to a specific treatment can be calculated in terms of absolute risk difference. The calculation is just the difference between the incidence proportion of a disease/event in the control group and the

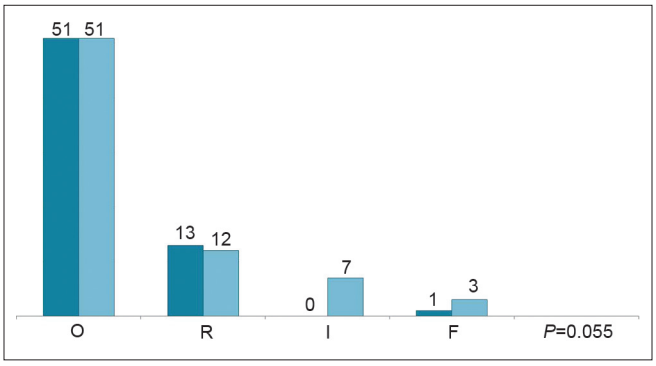

Figure 1: Incidence of acute kidney injury in study (A) and control (C) groups

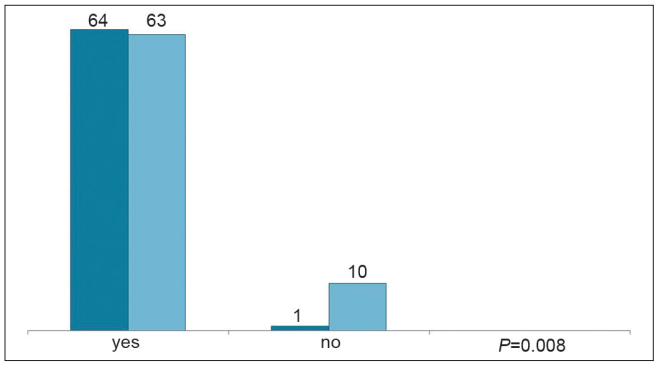

Figure 2: Renoprotection in study (A) and control (C) groups (O, R yes and I, F no)

incidence proportion of the same outcome in the treated group. On the basis of the risk difference, it is possible to calculate the NNT to prevent one adverse event as the inverse of the absolute risk difference (AR). The number must always be rounded up as it reflects the number of patients. In this study, the incidence proportions are 1.54% in study group A and 13.69% in control group C as shown in Table 3. AR is 12.15%. As shown in Table 3, the NNT is 8. Treating eight patients with the study drug aminophylline will prevent at least one AKI: I, F.

Table 3: Number needed to treat

	AKI: I, F	No AKI	Incidence (%)
Aminophylline	1	64	1.54
Control	10	63	13.69
Absolute risk difference = 13.69 – 1.54 = 12.15%			
NNT = 1/AR = 8.23 ~ 8			

NNT = Number needed to treat; AKI = I, F, injury and failure by RIFLE criteria; AR = Absolute risk reduction

Table 4: Cleveland clinic foundation acute renal failure scoring system

Risk factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG+valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to 2.1 mg/dl (reference <1.2)	2
Preoperative creatinine >2.1 (reference to <1.2)	5
Minimum score, 0; maximum score, 17	

IABP = Intra aortic baloon counterpulsation; COPD = Chronic obstructive pulmonary disease; CABG = Coronary artery bypass graft

Discussion

The incidence of AKI: I, F (7.97%) in our series is identical to that found by Conlon *et al*.[6] The incidence of acute renal failure requiring dialysis (ARF-D) was 4.41% in the high-risk group and is similar to that described by Abraham *et al*. and Grayson *et al*. (3.3 to 4.6%).[7,8]

The work of Thakar *et al*. provided Cleveland Clinic Foundation acute renal failure scoring system validated in American patients which predicts ARF after open-heart surgery. The score as shown in Table 4 enhances the accuracy of prediction of ARF and identifies patients who have a lower as well as a higher than average risk for ARF. This increases the clinical utility of the score in improving both individual patient care and by providing a vital tool in planning future clinical trials of early diagnosis and intervention in ARF.[1] We used the same score to stratify our patients undergoing cardiac surgery and found that there is a significant association with a score ≥6 and the occurrence of AKI: I, F (33.33% at P=0.001). This demonstrates the utility of Cleveland score in predicting AKI in Indian patients undergoing cardiac surgery.

The use of CPB in our series is associated with 16.16% AKI: I, F when compared with 4.16% in off pump coronary artery bypass (OPCAB) surgery, statistically significant with P=0.005. In an earlier report from our country, 46.66% and 20% patients developed renal dysfunction in on-pump and off-pump CABG, respectively. The same authors also described a negative correlation of creatinine clearance with age suggesting that increased age proves to be a risk factor.[9] This was, however, not the case in our data with no significant difference in AKI: I, F between patients less than 50 and >50 years (P=0.465). The lower incidence of AKI in our data may be due to a higher number of patients undergoing OPCAB (77.5%) especially in the high risk and elderly.

Time interval of less than 1 week from angiogram to cardiac surgery in our patients was associated with a marginally higher incidence (10.5%) of AKI: I, F, although not statistically significant (P=0.085). There are conflicting opinions on this with some studies suggesting delaying cardiac surgery beyond 24 hours of exposure to contrast agents, while others have demonstrated the

safety of same day angiography in cardiac surgery for valvular heart disease.[10,11] However, these studies were both retrospective analysis using serum creatinine alone for defining ARF. Consensus building on this issue will require further analysis with randomized controlled trials using larger patient database and consistent definition of AKI.

The measurement of GFR remains a contentious issue. As the use of recommended filtration markers is limited by cumbersome and costly techniques, renal function is typically estimated by using various specifically derived prediction equations. Most of these equations have been derived from Caucasian patients suffering from varying degrees of chronic kidney disease. A recent study from a healthy Indian population shows CG-GFR the least biased among the predictive equations.[12] The lack of early biomarkers has resulted in a delay in initiating therapies. Fortunately, the tools of modern science have revealed promising novel biomarkers for AKI, with potentially high sensitivity and specificity. These include a plasma panel (neutrophil gelatinase-associated lipocalin and cystatin C) and a urine panel (neutrophil gelatinase-associated lipocalin, interleukin 18, and kidney injury molecule-1).[13] A group of investigators from our country have attempted to evaluate plasma neutrophil gelatinase-associated lipocalin (NGAL) levels as a predictor of renal injury in patients undergoing CABG with CPB along with markers of oxidative stress. A. Prabhu *et al*. report that measurement of plasma NGAL in patients in the first few hours after CPB is predictive of AKI.[14]

There have been a number of studies from our country attempting to prevent AKI in patients undergoing cardiac surgery. A recent review on this subject by Maitra G *et al*. stressed that the most important preventive strategies are the identification of the preoperative risk factors and therefore the high-risk groups by developing clinical scoring systems.[15] This study suggests that risk stratification by Cleveland score may be used to identify high-risk cases. In a study alluded to above, Pramodh *et al*. conclude renal function is better preserved in patients undergoing OPCAB.[9] Prasad *et al*. studied the efficacy of *N*-acetylcysteine in preventing postoperative renal dysfunction following off-pump CABG. There was no significant difference in the incidence of renal dysfunction between patients in the *N*-acetylcysteine group (8.6%) and in the control group (11.4%, *P* value was 1.00). They concluded that *N*-acetylcysteine does not have any beneficial effect on renal function in high-risk patients undergoing OPCAB.[16]

Kapoor *et al*. prospectively assessed the role of oral theophylline in the prevention of contrast nephropathy (CN). They noted in the control group, 11/35 (31%) developed CN, while only 1 patient in the theophylline group (3%) had a decrease in GFR ($P=0.004$). The study noted that adenosine may play an important role in the pathogenesis of CN and concluded patients who received prophylactic oral theophylline had a significantly lower risk of CN than those who did not.[5] This study demonstrates that prophylactic treatment of well-balanced patients undergoing cardiac surgery with the nonselective adenosine receptor antagonist aminophylline has a renoprotective effect. Specifically, the incidence of AKI: I, F as defined by the RIFLE criteria is significantly lower 1.54% in patients receiving prophylactic aminophylline when compared with 13.71% in the control group ($P=0.055$). The prevention of AKI: I, F is remarkable in the higher risk patients with Cleveland score >3 ($P=0.017$).

Our study is in contrast to the study by Kramer *et al*., which demonstrated the lack of effect of theophylline in preventing ARF in CABG patients.[3] However, in this study, GFR was measured using ^{51}Cr EDTA clearance and percentage change in serum creatinine were compared. The accuracy of creatinine clearance is limited because as GFR decreases, creatinine secretion is increased, and thus the rise in plasma creatinine is less resulting in a potentially large overestimation of GFR. It has been suggested that the new recommendation for the definition of ARF takes account of both renal functions, the excretion of creatinine, and the production of urine and the association between postoperative ARF and thus mortality is strong.[2] By calculating the RIFLE level, in our study we could identify and consistently classify patients with increased risk of impairment in renal function after cardiac surgery.

Another issue is dose and duration of aminophylline administration. The i.v. bolus of aminophylline used in our study was slightly higher (5 vs 4 mg/kg body weight). Moreover, the patients ($n=56$) in the smaller series of Kramer *et al*. had a rather low risk of postoperative renal impairment, thus lowering the probability of being able to observe ARF and a potential treatment effect. The study did not have the statistical power to demonstrate moderate treatment effects of theophylline.[3]

Cardiac arrhythmias and serum potassium levels were not significantly different in the aminophylline and control group in our series, establishing the safety of such a strategy in this setting. This finding is consistent with earlier reports.[3]

NNT provides a good insight into the clinical relevance of the effect of a specific treatment and its calculation has been recently reviewed.[17] NNT for this study is 8, which implies that the use of the present strategy in eight patients is likely to prevent at least one episode of AKI postcardiac surgery.

This study demonstrates the safety and efficacy of using intravenous aminophylline in the prevention of AKI following cardiac surgery, especially among the high-risk patients. The limitations of this study include the open label, nonrandomized design and a higher number of males and CABG among operated patients. Future studies need to include a more homogenous and larger sample population.

References

1. Thakar CV, Arrigain S, Worley S, Yared JP, Paganini EP. A clinical score to predict acute renal failure after cardiac surgery. J Am Soc Nephrol 2005;16:162-8.
2. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V. Acute renal failure after cardiac surgery: Evaluation of the RIFLE classification. Ann Thorac Surg 2006;81:542-6.
3. Krämer BK, Preuner J, Ebenburger A, Kaiser M, Bergner U, Eilles C, *et al*. Lack of renoprotective effect of theophylline during aortocoronary bypass surgery. Nephrol Dial Transplant 2002;17:910-5.
4. Venkataraman R, Kellum JA. Prevention of acute renal failure. Chest 2007;131:300-8.
5. Kapoor A, Kumar S, Gulati S, Gambhir S, Sethi RS, Sinha N. The role of theophylline in contrast-induced nephropathy: A case-control study. Nephrol Dial Transplant 2002;17:1936-41.
6. Conlon PJ, Stafford-Smith M, White WD, Newman MF, King S, Winn MP, *et al*. Acute renal failure following cardiac surgery. Nephrol Dial Transplant 1999;14:1158-62.
7. Abraham VS, Swain JA. Cardiopulmonary bypass and the kidney. In: Gravlee GP, Davis RF, Kurusz M, Utley JR, editors. Cardiopulmonary Bypass: Principles and Practice. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 382-91.
8. Grayson AD, Khater M, Jackson M, Fox MA. Valvular heart operation is an independent risk factor for acute renal failure. Ann Thorac Surg 2003;75:1829-35.
9. Pramodh K, Vani, Muralidhar K. Renal function following CABG: Onpump vs offpump. Ind J Thorac Cardiovasc Surg 2003;19:169-73.
10. Ranucci M, Ballotta A, Kunkl A, De Benedetti D, Kandil H, Conti D, *et al*. Influence of the timing of cardiac catheterization and the amount of contrast media on acute renal failure after cardiac surgery. Am J Cardiol 2008;101:1112-8.
11. Brown ML, Holmes DR, Tajik AJ, Sarano ME, Schaff HV. Safety of same-day coronary angiography in patients undergoing elective valvular heart surgery. Mayo Clin Proc 2007;82:572-4.
12. Mahajan S, Mukhiya GK, Singh R, Tiwari SC, Kalra V, Bhowmik DM, *et al*. Assessing glomerular filtration rate in healthy Indian adults: A comparison of various prediction equations. J Nephrol 2005;18:257-61.
13. Parikh CR, Devarajan P. New biomarkers of acute kidney injury. Crit Care Med 2008;36(4Suppl):S159-65.
14. Prabhu A, Sujatha DI, Ninan B, Vijayalakshmi MA. Neutrophil gelatinase associated lipocalin as a biomarker for acute kidney injury in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Ann Vasc Surg 2010;24:525-31.
15. Maitra G, Ahmed A, Rudra A, Wankhede R, Sengupta S, Das T. Renal dysfunction after off-pump coronary artery bypass surgery- risk factors and preventive strategies. Indian J Anaesth 2009;53:401-7.
16. Prasad A, Banakal S, Muralidhar K. N-acetylcysteine does not prevent renal dysfunction after off-pump coronary artery bypass surgery. Eur J Anaesthesiol 2010;27:973-7.
17. Tripepi G, Jager KJ, Dekker FW, Wanner C, Zoccali C. Measures of effect: Relative risks, odds ratios, risk difference, and 'number needed to treat'. Kidney Int 2007;72:789-91.

How to cite this article: Mahaldar AR, Sampathkumar K, Raghuram AR, Kumar S, Ramakrishnan M, Mahaldar D. Risk prediction of acute kidney injury in cardiac surgery and prevention using aminophylline. Indian J Nephrol 2012;22:179-83.

Source of Support: Nil, **Conflict of Interest:** None declared.