Pak Heart J 2023:56(03)
ISSN: 0048-2706 (Print), ISSN: 2227-9199 (Online)

Prospective Assessment of the Effect of Aminophylline Infusion On Renal Function in Critically Ill Adults

M S Manoj[1], Vijay Anand Sivakumar[2], R Gnanasekaran[3], K S Anand[4]

[1]Physician and Intensivist, RIO Hospital Madurai, India. (Corresponding author)
[2]Associate Professor, Department of Emergency Medicine, Trichy SRM Medical College and Research Institute, India.
[3]Associate Professor, Department of Dermatology, Trichy SRM Medical College and Research Institute, India.
[4]Department of Critical Care Medicine, Meenakshi Mission Hospital and Research Institute, Tamilnadu, India.

Abstract

Background:AKI is a sudden decline of kidney function that is frequently associated with high morbidity and mortality rates. One drug that has been tried with the aim of achieving better AKI outcome is the use of aminophylline. Because studies involving adults are few, little is known about the efficacy and outcome of aminophylline therapy in AKI. However, the data that support the use of aminophylline in this patient population is not well established. So aim of this clinical trial is to assess the hypothesis that aminophylline improves renal function in critically ill adults. **Method:**This was 1000 bedded multispecialty hospital -based Prospective, open label, single arm study group conducted among 80 cases to the Department of Critical Care, in Meenakshi Mission Hospital and Research Centre, India, From March 2020 to February 2021 and after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.**Results:** In our study, all 80 cases had statistically significant increase in urine output in mean time of 8 hours. 81% of cases improved without RRT. 61% of the cases had more than 30% increase in eGFR from pre-treatment levels. Inotropes requirements stopped in 62.5% of the cases following aminophylline infusion. Cases requiring positive pressure ventilation requirement decreased from 75% to 13.8%. Only 6.3% cases required RRT. 5% of cases expired due to underlying disease. No adverse events noted. **Conclusion:**Based on the above results, it is evidenced that aminophylline improves renal function in critically ill patients. It may help in reducing the stay in ICU by early weaning from ventilator and inotropes as seen in our study. It helps in mitigating cost for the patient by reducing stay and avoiding RRT. There were no side effects associated with it when used in low dose as in our study. So that it can be safely used in resource limited setting. It helps in reducing mortality by reducing incidence of progression of AKI and other associated complications.

Keywords:AKI, Kidney, Aminophylline, Adults.

Introduction

AKI is a sudden decline of kidney function that is frequently associated with high morbidity and mortality rates. A diagnostic time limit of 48 hours was recently introduced to ensure early diagnosis, management and avoidance of progression to irreversible renal function loss. Further, early AKI biomarkers that can ensure prompt diagnosis have been identified. When these biomarkers become widely available to clinical practice, informed therapeutic interventions capable of aborting disease progression, morbidity and mortality multiplication can be applied. One drug that has been tried with the aim of achieving better AKI outcome is the use of aminophylline.

Aminophylline, the ethylenediamine salt of theophylline, is a well-established medication that promotes bronchodilatation by increasing the tissue concentrations of cAMP via phosphodiesteraseinhibition.

This pharmacological effect enables it to be useful in the treatment of a number of respiratory conditions including asthma.[1]Inspite of this well documented efficacy, with advent of other bronchodilators that are effective, less prone for toxicity, and ease to administer and monitor has resulted in a dramatic decline in its use for reactive airway disease. However, in addition to its impact on air flow, aminophylline has been demonstrated to have other effects that may be beneficial to the critically ill adults. It has been found in a variety of situation to be a useful diuretic and renoprotectiveagent.[2-5] Moreover, various laboratory, animal, and small clinical studies have reported aminophylline has potent anti-inflammatory properties.[6]Given these potential renal and anti-inflammatory benefits and its well-established benefit as bronchodilation, aminophylline may benefit a number of critically ill adults with a variety of conditions.

In the affected kidney, adenosine is released endogenously from the macula densa causing vasoconstriction of the renal afferent arterioles via the adenosine A1 receptor as well as vasodilatation of the renal efferent arterioles via the adenosine A2 receptor; thereby reducing the renal blood flow and glomerular perfusion pressure leading to ischemic kidney injury.

Aminophylline is converted to theophylline in our body, which in turn vasodilates the renal afferent arterioles through competitive inhibition of adenosine on the adenosine A1 receptor. Thereby, aminophylline improves renal blood flow and glomerular perfusion pressure and filtration.[7,8] Because studies involving adults are few, little is known about the efficacy and outcome of aminophylline therapy in AKI. AKI and impending AKI managed in our unit between March 2020 and February 2021 received different drug treatments aimed at improving outcome; one such drug is aminophylline.

However, the data that support the use of aminophylline in this patient population is not well established. We undertook a prospective, open-label, and single arm study of the physiologic effects of aminophylline in a tertiary centre critical care unit. So aim of this clinical trial is to assess the hypothesis that aminophylline improves renal function in critically ill adults.

Aims and Objectives

- To assess the hypothesis that aminophylline improves renal function in critically ill adults.
- To assess the hypothesis that aminophylline increases urine output and eGFR in critically ill adults.

Materials and Methods

his study was conducted after getting informed consent of 80 critically ill euvolemic patients more than 18 years old whose urine output less 0.5ml/kg/hr not on renal placement therapy or frusemide infusion and not a known case of seizure disorder and tachyarrythmias were included. These patients are started on aminophylline infusion in dose of 0.5 ml/kg/h for 24 hours not exceeding 24 hours. Hourly urine output and vitals before and after aminophylline infusion for first 24 hours were noted. Serial serum urea, serum creatine and eGFR were noted till discharge. Inotrope requirements and ventilator requirements were noted before and after aminophylline infusion. Outcome of the patient, renal outcome and adverse events were noted.

Inclusion Criteria

- Age more than 18 years admitted to ICU.
- Urine output less than 0.5 mg/kg/hr for 3 consecutive hours in the ICU in a euvolemic patient.

Exclusion Criteria

- Patient with history of seizures and tachyarrhythmias like ventricular tachycardia, ventricular fibrillation, atrial fibrillation, atrial flutter, AVRT, AVNRT and multifocal atrial tachycardia
- Dialysis requiring AKI or CKD
- Patient on frusemide infusion

Statistical Analysis

Statistical Analysis was done by using SPSS Version 26. All values were expressed as mean

(SD) for continuous variables and number (percentages) for categorical variables. Independent t tests for continuous variables and Chi- square test and fisher's exact test will be used to find out association between the categorical variables. P<0.05 will be considered as statistically significant.

Results

Total 80 cases were included in study.

In our study, maximum age was 82 years and minimum age was 25 years. Mean age of the subjects was 57.5 years. Maximum age group in our study was between 61-70 years. [Table 1]

Among 80 patients, 62 were males and 18 were females. Males forming 77.5% and females forming 22.5%. [Table 2]

Of 80 patients studied, patients with septic shock were 34 forming 42.5% followed by cardiogenic shock which was 26.25% formed by 21 patients. Patients underwent major surgeries were 16 forming 20%. Patients with haemorrhagic shock were 3 forming 3.75%. Patients with acute pulmonary edema were 2 in number forming 2.5%. Patient with ARDS, sepsis, pancreatitis and dengue shock syndrome 1 cases each forming 1.25% each. [Table 3]

Mean for the average systolic blood pressure before aminophylline infusion was 112.91 mmhg and mean for average systolic blood pressure after aminophylline infusion was 121.87 mmhg. So there was statistically significant increase in systolic blood pressure with P value of 0.001. Mean for the average diastolic blood pressure before aminophylline infusion was 67.59 mmhg and mean for average diastolic blood pressure was 69.68 mmhg after aminophylline infusion. So there was raise in diastolic blood pressure but it was not statistically significant. Based on the analysis, there is no statistically significant increase in heart before and after aminophylline infusion in first 24 hours. Mean of average heart rate before aminophylline infusion is 100.34 and mean of average heart rate after aminophylline infusion in first 24 is 100.48. [Table 4]

Following start of aminophylline infusion, all cases in our study had increase in hourly urine output more than 50%. [Table 5]

In our study, following start of aminophylline infusion, mean time taken for hourly urine output to increase more than 50 % is 8 hours. With minimum being 2 hours and maximum being 25 hours. [Table 6]

After aminophylline infusion, there was statistically significant increase in hourly urinary output with P value of 0.001. Mean of urine output in first hour of oliguria before aminophylline infusion was 26.65 ml/hr. Mean of urine output in second hour of oliguria before aminophylline infusion was 21.64 ml/hr. Mean of urine output in third hour of oliguria before aminophylline infusion was 20 ml/hr. Following aminophylline infusion, after a mean time of 8 hours urine output increased to more than 50% with mean urine output of 61.39 ml/hr followed by 67.11 ml/hr in next hour and then 72.87 ml/hr in third hour. [Table 7]

In our study, before aminophylline infusion mean of serum urea was 63.06 mg/dl. On discharge, after aminophylline infusion, mean of serum urea was decreased to 52.54mg/dl. This was statistically significant improvement in serum urea with P value of 0.011. Mean of serum creatinine before aminophylline infusion was 2.018 mg/dl. On discharge, after aminophylline infusion, mean of serum creatinine was decreased to 1.427 mg/dl. This was statistically significant improvement in serum creatinine with P value of 0.001. [Table 8]

Mean time taken for serum creatinine to reach baseline is 6 days. With minimum time taken was 1 day to maximum time taken was 45 days. [Table 9]

Of 80 cases, 49 cases forming 61.25%, had increase in eGFR more than 30% following aminophylline infusion not requiring RRT. [Table 10]

In our study, mean eGFR before aminophylline infusion was 40.216 ml/min/1.73m2. Mean eGFR on discharge was 65.53ml/min/1.73m2. This was statistically significant improvement with mean time of 6 days with P value of 0.001.

In our study, mean duration of ICU stay was 3 days, with minimum of 1 day to maximum of 18 days. Of 80 patients studied, 69 cases improved and survived till discharge which forms 86.3%. 7 cases went against medical advice, which forms around 8.8%. Out of 80 cases 4 casses

which forms around 5% of total cases expired during stay in hospital following aminophylline infusion due to underlying disease. Mean time taken to reach room air from mechanical ventilation and O2 support to room air after aminophylline infusion is 63.8 hours, with minimum of 18 hours to maximum of 336 hours. Before aminophylline infusion, 51 cases forming 65.1% were on assist controlled ventilation. After aminophylline infusion, cases with assist controlled ventilation requirements came down to 10 forming 12.5%. Before aminophylline infusion, 7 cases were on NIV forming 8.7%, after infusion cases with NIV requirement came down by 1 forming 1.3%. Of 2 patients CPAP/PSV, 1 patient was weaned to room air. Before aminophylline infusion, only 3 case were on room air forming 3.7%, after infusion cases on room air raised to 68 forming 85%. After aminophylline infusion, all patients on facemask O2 were weaned to room air. Mean time taken to wean of inotropes requirements after start of aminophylline infusion is 36 hours, with minimum time of 4 hours to maximum time of 96 hours. Before aminophylline infusion, 38 cases forming 47.5% were on single inotrope support, 11 cases were on dual inotropes forming 13.8%, 7 cases were on multiple inotropes forming 8.8%. Totally 56 cases forming 70.1 % were on inotrope support. After aminophylline infusion, 50 cases were weaned off from inotropes support which forms around 62.5%. 4 cases continued requiring inotrope support which forms 5% and inotropes were reduced in 3 cases which forms around 3.8%. 81.3% of the studied cases comprising of 65 cases improved well with aminophylline infusion not requiring RRT. 5% of studied case required hemodialysis. One case forming 1.3% underwent CRRT. 4 cases expired and rest AMA. Of 80 cases studied, none of the cases had any significant side effects following administration of aminophylline. [Table 11]

Table 1: Age Distribution in Study

Age	Cases	Percentage
20 – 30	5	6.3
31 – 40	6	7.5
41 – 50	11	13.8
51 – 60	18	22.5
61 – 70	30	37.5
> 70	10	12.5
Total	80	100.0
Mean	57 .5	
SD	13 .7	
Range	25	82

Table 2: Sex Distribution in Study

Parameter		Cases	Percentage
Sex	Male	62	77.5
	Female	18	22.5
	Total	80	100.0

Table 3: Case Distribution in Study

Parameter		Cases	Percentage
Diagnosis	Septic shock	34	42.5
	Cardiogenic shock	21	26.25
	Major surgeries	16	20
	Hemorrhagic shock	3	3.75
	Acute pulmonary edema	2	2.5
	ARDS	1	1.25

	Sepsis	1	1.25
	Pancreatitis	1	1.25
	Dengue Shock	1	1.25
Total		80	100.0

Table 4: Statistical Analysis on Avrerage Heart Rate Before and after Aminophylline Infusion in first 24 Hours

Parameter		Mean	SD	MeanDifference	P-Value
Average Systolic Blood Pressure (mmhg)	Before	112.91	16.263	8.962	0.001 Sig
	After (first 24 hours)	121.87	17.191		
Average Diastolic Blood Pressure (mmhg	Before	67.59	9.636	2.089	0.112 NS
	After (first 24 hours)	69.68	10.264		
Statistical Analysis on Average Systolic and Diastolic Blood Pressure Before and after Aminophylline Infusion in First 24 Hours					
Parameter		**Mean**	**SD**	**MeanDifference**	**P-Value**
Average Heart Rate (beats/min)	Before	100.34	14.968	0.139	0.939 NS
	After (first24 hours)	100.48	14.526		

Table 5: Analysis on Cases with More than 50% Increase in Hourly Urine Output Following Aminophylline Infusion

After Aminophylline Infusion	Number of Cases	Percentage of Cases
Cases With More Than		
50% Increase in Hourly Urine Output	80	100%
Cases With Less Than		
50% Increasese in Hourly Urine Output	NIL	NIL
Cases With No Change in		
Hourly Urine Output	NIL	NIL
TOTAL	80	100%

Table 6: Analysis On Time Taken for Hourly Urine Output to Increase More Than 50%

Parameter	Time Taken for Hourly UrineOutput >50%
Mean	7.8
Std. Deviation	5.3
Minimum	2
Maximum	25

Table 7: Statistical Analysis Between hourly Urine output before Aminophylline Infusion and Hourly Urine Output 50% increase after Aminophylline Infusion

Parameter	Mean	Std. Deviation
Before Aminophylline -1st hour oliguria (ml/hr)	26.65	9.894
Before Aminophylline –2nd hour oliguria (ml/hr)	21.64	9.215
Before Aminophylline- 3rd hour oliguria (ml/hr)	20.00	9.300
After Aminophylline, 50% increase- 1st hour(ml/hr)	61.39	18.379
After Aminophylline, 50% increase- 2nd hour (ml/hr)	67.11	19.549
After Aminophylline, 50% increase -3rd hour (ml/hr)	72.87	22.856

Table 8: Statistical Significance of Hourly Urine Output after Aminophylline Infusion

Parameter	Mean	SD	MeanDifference	P-Value
Before Aminophylline –				
1st hour oliguria	26.65	9.894		
			34.747	0.001 Sig
After Aminophylline,				
50% increase- 1st hour	61.39	18.379		
Before Aminophylline –				
2nd hour oliguria	21.64	9.215		
			45.461	0.001 Sig
After Aminophylline,				
50% increase -2nd hour	67.11	19.549		
Before Aminophylline-				
3rd hour oliguria	20.00	9.300		
			52.867	0.001 Sig
After Aminophylline,				
50% increase- 3rd hour	72.87	22.856		

Table 9: Statistical Analysis of Serum Urea and Serum Creatinine before Aminophylline Infusion and after Aminophylline Infusion on Discharge

Parameter		Mean	SD	Mean Difference	P-Value
Serum Urea (mg/dl)	Before Aminophylline infusion	63.06	34.634	10.519	0.011 Sig
	On Discharge	52.54	31.115		
Serum Creatinine (mg/dl)	Before Aminophylline infusion	2.018	.9679	0.59	0.001 Sig
	On Discharge	1.427	1.3171		

Table 10: Analysis on time taken for Serum Creatinine to reach Baseline after start of Aminophylline Infusion

Parameter	Time Taken For CreatinineTo reach baseline
Mean	6.00
Std. Deviation	7.848
Minimum	1
Maximum	45

Table 11: Percentage of Cases with Increase in Egfr more than 30% from base line on Discharge following Aminophylline Infusion

Increase in Egfrmore than 30%	Number of Cases	Percentage of Cases
Improved	49	61.25
Not improved	31	38.75
Total	80	100

Table 12: Statistical Analysis of Egfr before Aminophylline Infusion and after Aminophylline Infusion on Discharge

Parameter		Mean	SD	Mean Difference	P-Value
eGFR	Before Aminophylline infusion	40.216	18.5349	25.314	0.001 Sig
	On Discharge	65.530	25.8075		

Table 13: Analysis on time taken for the Case to Wean of Inotrope support after start of Aminophylline Infusion

Parameter	**Time Taken For eGFR To reach baseline**
Mean	6.00
Std. Deviation	7.848
Minimum	1
Maximum	45
Analysis on time Taken for eGFR *to reach Baseline after start of Aminophylline Infusion*	
Parameter	Duration of ICU stay
Mean	3.15
Std. Deviation	2.476
Minimum	1
Maximum	18
Analysis on Duration of Icu Stay after Aminophylline Infusion	
Parameter	Ventilator RequirementsHrs
Mean	63.8
Std. Deviation	48.1
Minimum	18
Maximum	336
Analysis on time taken for the Cases to Wean to room air following Mechanical Ventilation and O2 support after start f Aminophylline Infusion	
Parameter	Inotropes RequirementsHrs
Mean	36.3
Std. Deviation	20.2
Minimum	4
Maximum	96

Discussion

This study was undertaken to assess the hypothesis that aminophylline increase urine output in critically ill adults. Most of the previous studies done on aminophylline infusion for improvement of renal function were studied on pediatrics and neonates. Our study has total of 80 cases. This study has relatively larger sample size in comparison with previous study done by Robert F. Tamburro et al9, Bethany A. Lynch et al,[10] and Wasiu A. Olowu et al.[11] In this study, mean age of population studied was 58 years. With age ranging from 25 to 82 years. This in comparison with majority of previous studies done by Robert F. Tamburro et al, Bethany A. Lynch et al, Valerie Y Chock et al,[12] Lee, Joo Won et al and Wasiu A. Olowu comprised of mainly neonates and pediatric population. Our study population mainly comprised of males forming 77.5% and rest by females. This study was mainly done on

critically ill patients with various diagnosis like septic shock, cardiogenic shock, hemorrhagic shock, dengue shock syndrome, ARDS and immediate post major surgeries like CABG, Whipple's procedure etc. Majority of the cases comprised of septic shock. However, all the patients included studied were ensured euvolemic and normotensive with inotropes on start of aminophylline infusion. In our study, there was statistically significant increase in average systolic blood pressure with P value of 0.001 following use of aminophylline infusion. Previous studies don't have analyses on blood pressure. However, ShahrbanooShahbazi et al,[13] in his studies mentioned with use of this drug inotropic requirement decreased. However, in our study, there is not statistically significant increase in diastolic blood pressure after aminophylline infusion. In our study, there was not statistically significant increase in heart rate following aminophylline infusion. Previous studies done by Robert F. Tamburro et al and David M Axelrod et al,[14] didn't show significant side effects in their study. In our study, out of 80 cases all case had statistically significant increase in hourly urine output in a mean time of 8 hours following start of aminophylline infusion with minimum of 2 hours to maximum of12 hours. In previous study done by Valerie Y Chock noted increase in urine output by 2.6 ± 1.9 mL/kg/h after start of aminophylline infusion within 12 hours. He did it on neonates receiving therapeutic hypothermia for moderate /severe hypoxic ischemic encephalopathy. Study done by Robert F. Tamburro et found that urine output increased significantly with aminophylline use [median increase 0.5 mL/kg/h (Inter Quartile Range: −0.3, 1.3), p = 0.05]. Wasiu A. Olowu found baseline median urine output in the aminophylline and control arms were similar (0.13 vs. 0.04 ml/kg/hour respectively, P=0.5). The median UFR was significantly higher on day-5 (0.8 vs. 0.1; P=0.03), day-6 (1.0 Vs 0.2; P=0.02), and day-7 (1.2 vs. 0.2; P=0.03) in the aminophylline than the control arm, respectively. David M Axelrod found average daily urine output increased by 0.22 mL/kg/hr ($p < 0.001$), and fluid overload decreased on average by 0.42% per day in the 7-day study period ($p = 0.005$). SaadAlsaadoun et al,[15] did a meta-analysis of single-arm studies indicated no statistically significant difference in mean urine output (1.99 [−1.43–5.42]; P = 0.25) before and after aminophylline infusion. Even double arm study found that increase in urine output was statistically insignificant. This study demonstrated statistically significant improvement in serum urea with P value of 0.011 following administration of aminophylline infusion. Robert F. Tamburro found blood urea nitrogen remain unchanged following administration of aminophylline. SaadAlsaadounin his meta-analysis of single arm study found no statistical difference in mean blood urea nitrogen levels before and after aminophylline infusion. In our study, there statistically significant improvement of creatinine in a mean duration of 6 days following administration of aminophylline infusion. Lee, Joo Won in his systematic review and meta-analysis found that changes in serum creatinine level in the theophylline group were significantly higher than those in the placebo group from the first day of life to 3 and 5 days of age (weighted mean difference: -0.51, 95% CI: -0.62 to -0.40, $p < 0.001$, and weighted mean difference: -0.26, 95% CI: -0.34 to -0.18, $p < 0.001$, respectively). Girish Chandra Bhatt et al16 in his randomised clinical trials and quasi-randomised trials found decrease in serum creatinine over days 2–5 following administration of aminophylline. Valerie Y Chock found serum creatinine declined by 0.4 ± 0.2 mg/dL over first 4 days following administration of aminophylline. SaadAlsaadoun in his meta-analysis of double arm studies found significantly decreased serum creatinine in

aminophylline group. Robert F. Tamburro found serum creatinine remain unchanged following administration of aminophylline. Bethany A. Lynch, Pharm D in his retrospective review of chart found normalisation of serum creatinine found in 77% of his study population. Wasiu A. Olowu found only aminophylline group maintained steady creatinine whereas in control group required dialysis. David M Axelrod noted over the 7-day study period, serum creatinine decreased from a mean of 1.13 ± 0.91 to 0.87 ± 0.83 mg/dL (-0.05 mg/dL/d, $p < 0.001$) following aminophylline therapy. Out of 80 cases studied, 49 cases forming 61.25% had 30% increase in eGFR. There was statistically significant improvement in eGFR following administration of aminophylline in mean duration of 6 days. David M Axelrod in his retrospective cohort study found a concomitant increase was seen in estimated glomerular filtration rate from a mean of 50.0 ± 30.0 to 70.6 ± 58.1 mL/min/1.73 m (+3.66 mL/min/1.73 m/d, $p < 0.001$) following administration of aminophylline. Lee, Joo Won in his study found that improvement in glomerular filtration rate in the theophylline group were significantly higher than those in the placebo group from the first day of life to 3 days of age and the last day of follow-up (weighted mean difference: 12.30, 95% CI: 9.39-15.21, $p < 0.001$, and weighted mean difference: 9.35, 95% CI: 6.43-12.27, $p < 0.001$, respectively). In our study, 4 cases out of 80 critically ill patients expired due to underlying disease which forms around 5%. Bethany A. Lynch, PharmD in his study observed that observed mortality rates were similar in aminophylline-treated and control patients. SaadAlsaadoun in his metaanalysis of double arm studies noted mortality rates (RR = 0.79 [0.42–1.47], P = 0.45) were found to be statistically insignificant. Girish Chandra Bhatt concluded that a single dose of prophylactic theophylline helps in prevention of AKI/ severe renal dysfunction in term neonates with severe birth asphyxia (moderate quality evidence) without increasing the risk of complications and without affecting all-cause mortality (very low-quality evidence).4 out of 13 cases expired due to underlying disease which forms around 30%. Wasiu A. Olowu of 80 cases studied, 75% of the cases were on positive pressure ventilation, after aminophylline infusion only 13.8% required positive pressure ventilation, after mean duration of 63.8 hours. In our study, mean duration ICU stay following administration of aminophylline infusion is 3 days. Aminophylline is known and used as a bronchodilator so it also helps in improvement of lung function and assist in early weaning once underlying disease resolved. Moreover, aminophylline helps in improving the diaphragmatic function. Theophylline inhibits xanthine oxidase activity and therefore may protect the diaphragm against mechanical ventilation-induced oxidative stress and contractile dysfunction,[17]Furthermore, in studies of patients with chronic obstructive pulmonary disease, theophylline has been found to have a potent and long-lasting effect in terms of increasing the strength of and suppressing fatigue in the diaphragm. Thereby, reducing duration of ICU stay(18-20). Even low doses of theophylline resulting in a mean serum concentration of 4.6μg/ml improved diaphragmatic movements21. In our study, 70% of the cases were on inotrope support before start of aminophylline infusion. After infusion only 8,8% of cases were requiring continued inotrope support after mean duration of 36 hours. ShahrbanooShahbazi studied that the use of this drug may reduce the need for inotropic medication at the time of surgery. Of 80 cases studied, 81% of the cases improved without needing RRT. Only 6.3% of the cases required RRT. Wasiu A. Olowu observed in his study that aminophylline reduced the need for dialysis. Of 80 cases studied, none of the cases had life threatening arrhythmias or tachycardia, inspite our majority of cases on inotropes support.

Study done by Robert F. Tamburro, 20% were identified with side effects because dose used in this study was 3mg/kg loading followed by 1.5mg/kg every 8 hours as maintenance. They maintained through theophylline of 4-8 mcg/ml. David M Axelrod et al,[22] in his study noted no complications related to aminophylline administration. In his study dose of aminophylline used is 5 milligrams per kilogram intravenous (IV) load over 30 minutes, followed by 1.8 milligrams per kilogram IV every six hours, for 72 hours (total 13 doses). Trough level of 5-7 mcg/ml was maintained. SaadAlsaadoun in his meta-analysis found aminophylline administration in children with AKI reduces serum creatinine level without significant adverse effects.

Conclusions

Aminophylline infusion significantly improved renal fuction as evidenced in our study by increase in urine output and eGFR. Thereby reduced the need for RRT. It helps in progress of AKI after maintaining euvolemia and normotension. In critically ill patients, AKI is one of the majordeterminant of mortality and this simple intervention may obviate the need for RRT and associated complications.

References

1. Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane Database Syst Rev (2005) 2:CD001276. doi:10.1002/14651858.CD001276.pub2
2. Benoehr P, Krueth P, Bokemeyer C, Grenz A, Osswald H, Hartmann JT.
3. Nephroprotection by theophylline in patients with cisplatin chemotherapy: a randomized, single-blinded, placebo-controlled trial. J Am SocNephrol (2005) 16:452–8. doi:10.1681/ASN.2004030225
4. Bell M, Jackson E, Mi Z, McCombs J, Carcillo J. Low-dose theophylline increases urine output in diuretic-dependent critically ill children. Intensive Care Med (1998) 24:1099–105. doi:10.1007/s001340050723
5. Ng GY, Baker EH, Farrer KF. Aminophylline as an adjunct diuretic for neonates – a case series. PediatrNephrol (2005) 20:220–2. doi:10.1007/s00467- 004-1692-9
6. Kuan CJ, Branch RA, Jackson EK. Effect of an adenosine receptor antagonist on acute amphotericin B nephrotoxicity. Eur J Pharmacol (1990) 178:285–91. doi:10.1016/0014-2999(90)90107-H
7. McKinney GR. On the anti-inflammatory activity of aminophylline. ProcSocExpBiol Med (1964) 117:280–3. doi:10.3181/00379727-117-29557
8. Li L, Lai EY, Huang Y, Eisner C, Mizel D, Wilcox CS, et al. Renal afferent arteriolar and tubuloglomerular feedback reactivity in mice with conditional deletions of adenosine 1 receptors. Am J Physiol Renal Physiol (2012) 303:F1166–75. doi:10.1152/ajprenal.00222.2012.
9. Thomas NJ, Carcillo JA. Theophylline for acute renal vasoconstriction associated with tacrolimus: a new indication for an old therapeutic agent? PediatrCrit Care Med (2003) 4:392–3. doi: 10.1097/01.PCC.0000075322.56699.83
10. Tamburro RF, Thomas NJ, Ceneviva GD, Dettorre MD, Brummel GL and Lucking SE (2014) A prospective assessment of the effect of aminophylline therapy on urine output and inflammation in critically ill children. Front. Pediatr. 2:59. doi: 10.3389/fped.2014.00059
11. Lynch BA, Gal P, Ransom JL, Carlos RQ, Dimaguila MA, Smith MS, et al. Lowdose aminophylline for the treatment of neonatal non-oliguric renal failure – case series and review of the literature. J

PediatrPharmacolTher (2008) 13:80–7. doi:10.5863/1551-6776-13.2.80

12. Olowu WA, Adefehinti O. Aminophylline improves urine flow rates but not survival in childhood oliguric/anuric acute kidney injury. Arab J Nephrol Transplant (2012) 5:35–9
13. Chock VY, Cho SH, Frymoyer A. Aminophylline for renal protection in neonatal hypoxic-ischemic encephalopathy in the era of therapeutic hypothermia. Pediatr Res. 2021 Mar;89(4):974-980. doi: 10.1038/s41390-020-0999-y. Epub 2020 Jun 5. PMID: 32503030; PMCID: PMC7718287
14. Shahbazi S, Alishahi P, Asadpour E. Evaluation of the Effect of Aminophylline in Reducing the Incidence of Acute Kidney Injury After Cardiac Surgery. Anesth Pain Med. 2017;7(4):e21740. Published 2017 Aug 27. doi:10.5812/aapm.21740
15. Axelrod DM, Sutherland SM, Anglemyer A, Grimm PC, Roth SJ. A Double-Blinded, Randomized, Placebo-Controlled Clinical Trial of Aminophylline to Prevent Acute Kidney Injury in Children Following Congenital Heart Surgery with Cardiopulmonary Bypass. PediatrCrit Care Med. 2016;17(2):135-143. doi:10.1097/PCC.0000000000000612
16. Alsaadoun S, Rustom F, Hassan HA, Alkhurais H, Aloufi M, Alzahrani S, Bakhsh S, Dalbhi SA. Aminophylline for improving acute kidney injury in pediatric patients: A systematic review and meta-analysis. Int J Health Sci (Qassim). 2020 Nov-Dec;14(6):44-51. PMID: 33192231; PMCID: PMC7644458
17. Bhatt GC, Gogia P, Bitzan M, Das RR. Theophylline and aminophylline for prevention of acute kidney injury in neonates and children: a systematic review. Arch Dis Child. 2019 Jul;104(7):670-679. doi: 10.1136/archdischild-2018-315805. Epub 2019 Feb 23. PMID: 30798259
18. Whidden MA, McClung JM, Falk DJ, et al. Xanthine oxidase contributes to mechanical ventilation-induced diaphragmatic oxidative stress and contractile dysfunction. J ApplPhysiol 2009;106:385–94.
19. Yu TJ, Liu YC, Chu CM, Hu HC, Kao KC. Effects of theophylline therapy on respiratory muscle strength in patients with prolonged mechanical ventilation: A retrospective cohort study. Medicine (Baltimore). 2019;98(2):e13982. doi:10.1097/MD.0000000000013982
20. Kolbeck RC, Speir WA. Theophylline, fatigue, and diaphragm contractility: cellular levels of 45Ca and cAMP. J ApplPhysiol1991; 70:1933–7.
21. Janssens S, Derom E, Reid MB, et al. Effects of theophylline on canine diaphragmatic contractility and fatigue. Am Rev Respir Dis 1991; 144:1250–5.
22. Kim WY, Park SH, Kim WY, et al. Effect of theophylline on ventilator-induced diaphragmatic dysfunction. J Crit Care 2016; 33:145–50

.