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Original Article

Aminophylline Improves Urine Flow Rates but Not Survival in Childhood Oliguric/Anuric Acute Kidney Injury

Wasiu A. Olowu*, Olufemi Adefehinti

Pediatric Nephrology and Hypertension Unit, Obafemi Awolowo University Teaching Hospitals Complex,Ile-Ife, Osun State, Nigeria.

Abstract

Introduction: Acute kidney injury (AKI) morbidity and mortality rates remain high. Variable AKI outcomes have been reported in association with aminophylline treatment. This study evaluated AKI outcome in a group of Nigerian children treated with aminophylline.

Methods: This is a retrospective study of AKI in children treated with (N=9) and without (N=8) aminophylline. Studied outcome indices comprised urine flow rate (UFR), duration of oliguria/anuria, progression through AKI stages, number of patients requiring dialysis and mortality.

Results: Mean ages for the control and aminophylline arms were 4.6±2.7 and 4.9±2.1 years (P=0.7), respectively. All patients progressed to stage-3 AKI. Baseline median UFRs 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. Short duration of oliguria/anuria (≤ 6 days) was more frequently observed in aminophylline-treated patients compared to controls (77.8% Vs 25.0%; odds ratio 0.09; 95% CI: 0.01-0.89; P=0.04). Only the aminophylline group maintained steady serum creatinine levels. Four out of five patients in the control group were dialyzed compared to only one out of eight patients in the aminophylline group (odds ratio 0.16; 95% CI: 0.04-0.71; P=0.03). Mortality rates were similar in aminophylline-treated and control patients (33%Vs 25%; hazard ratio 0.8; 95% CI: 0.1-5.5; P=0.8).

Conclusion: Aminophylline therapy was beneficial for patients with AKI in terms of improved UFR and reduced need for dialysis, but failed to impact positively on survival.

* Correspondence author: Wasiu A. Olowu, Pediatric Nephrology and Hypertension Unit, ObafemiAwolowo University Teaching Hospitals Complex, PMB 5538, Ile-Ife, Osun State, Nigeria; E mail: yetundeolowu@yahoo.com

Keywords: Aminophylline; Dialysis; Survival; Urine Flow

Introduction

Acute kidney injury (AKI) is a sudden perturbation of kidney function that is frequently associated with high morbidity and mortality rates [1-3]. A diagnostic time limit of 48 hours was recently introduced to ensure early diagnosis, management and prevention of progression to irreversible renal function loss [4]. Furthermore, 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 [5,6]. In the injured kidney, adenosine is released endogenously from the macula densa causing vasoconstriction of the renal afferent arterioles via the adenosine A1receptor 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 [7]. One measure that has been tried with the objective of achieving better AKI outcome is the use of aminophylline (an ethylenediamine coupled theophylline) [7-11]. Aminophylline is converted to theophylline in the human 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 children are few [9-11, 13, 14], little is known about the efficacy and outcome of aminophylline therapy in childhood AKI. Children with AKI managed in our unit between January 2004 and December 2009 received different drug treatments aimed at improving outcome; one of such drugs was aminophylline. In this study we compared the outcome of aminophylline treated children to those who did not receive aminophylline treatment.

Table 1: Etiology of acute kidney injury in the aminophylline and control arms

Acute kidney injury etiology	Aminophylline arm (N=9)	Control arm (N=8)
P. falciparum malaria associated hemoglobinuria	5	3
Glucose 6-phosphate dehydrogenase enzyme deficiency associated hemoglobinuria	1	3
Septicemia	2	0
Gastroenteritis associated severe dehydration	0	1
Acute glomerulonephritis	0	1
Lupus nephritis	1	0

Methods

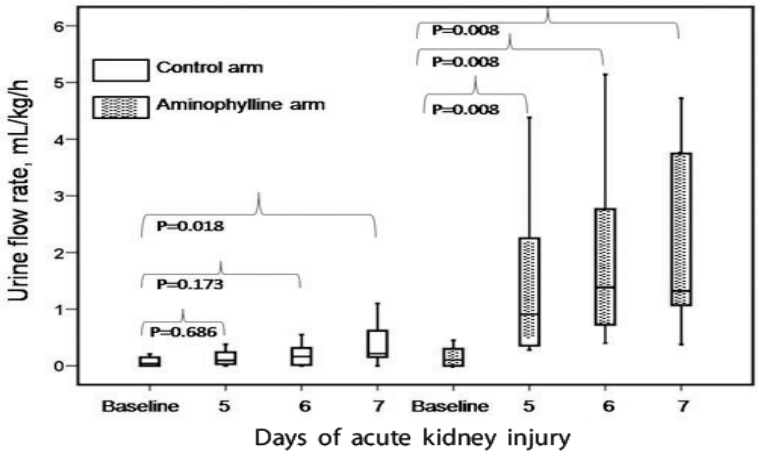
This retrospective case control study was conducted by reviewing the clinical charts of all AKI patients treated with or without aminophylline during the period between January 2004 and December 2009. Investigated outcome indices comprised urine flow rate (UFR), duration of oliguria/anuria, progression through AKI stages, need for dialysis and mortality. Inclusion criteria were AKI diagnosed within 48 hours of onset. Patients were included in the aminophylline group if they started a 72 hour aminophylline infusion within 72 hours of AKI onset. Exclusion criteria comprised non-oliguric AKI, insufficient serum creatinine (Scr) data, lack of daily urine volume records for at least one week, obstructive uropathy, bilateral congenital kidney anomaly or other forms of chronic kidney disease as well as administration of diuretics and/or calcium channel blockers. None of our patients received other drugs that can modify renal hemodynamics, such as dobutamine, dopamine and adrenaline. The clinical records revealed that the aminophylline arm received 5 mg/kg/24h (or 0.21 mg/kg/h) of the medication for 72 hours, usually 6 to 9 hours after oliguria/anuria onset. Serum theophylline level was not determined. No adverse effect of aminophylline was recorded for any of the patients. Aminophylline was delivered in 10% dextrose water infusion. The AKI network (AKIN) committee diagnostic and staging criteria were used [4]. Where baseline Scr was unknown, it was determined using the modification of diet in renal disease formula {estimated glomerular filtration rate (eGFR) =186 x [Scr] $^{-1.154}$ x Age $^{-0.203}$ x 0.742 (if female) x 1.210 (if black)} [12] by assuming a normal pre-morbid eGFR value of 100 ml/min/1.73m^2 in the patient as recommended by AKIN [4]. Pre-treatment and daily biochemical evaluations including Scr were performed in all patients. AKI was staged both at baseline and at the peak of kidney injury (highest recorded Scr before normalization or death) using the AKIN-Scr criterion. The baseline UFR was determined from at least a 6-hour urine output. UFR in the aminophylline and control arms for days 5, 6, and 7 were compared. Diuresis onset was regarded as early if UFR $\geq$ 0.5 ml/kg/h occurred within 6 days and late if it occurred after 6 days of AKI onset. The study was conducted at the Pediatric Nephrology and Hypertension Unit of the Obafemi Awolowo University Teaching Hospitals Complex, Osun State, Nigeria. The study conformed to the provisions of the revised Declaration of Helsinki, Edinburg, 2000. Our institutional ethics and research committee approved the study.

Data analyses were performed using the SPSS version 15.0 for Windows (2006 SPSS Inc.). Descriptive statistics comprised median, mean, standard deviation, percentages, and proportions. The comparative statistics used were Chi-square test, Fisher's exact test, Student's t-test, Wilcoxon signed ranks test for comparison of the medians and odds or hazard ratio where appropriate. Kaplan-Meier survival analysis and the log rank test were used to compare survival. A P value < 0.05 was considered statistically significant.

Results

Sixteen AKI cases were treated with aminophylline overall. Seven of the 16 patients were excluded because they had received in addition to aminophylline either furosemide or a calcium channel blocker or both. Overall, 17 patients satisfied the inclusion criteria with nine and eight patients in the aminophylline and control arms, respectively. The mean ages for the control and aminophylline arms were 4.6 ± 2.7 (1.5-10.0) and 4.9 ±2.1 (2.2-8.5) years, respectively (P=0.7). The aminophylline arm contained seven males and two females while the control arm contained four males and four females (P=0.2). Patients in the aminophylline arm received 50-125 (81 ± 25) mg of aminophylline per day. Etiologies of AKI in both groups of patients are summarized in Table-1. All patients progressed to the most severe form of AKI (stage 3). Four patients were anuric and four

Figure 1: Box plots comparing the median increase in urine flow rates from baseline to days 5, 6 and 7 in the aminophylline and control arms



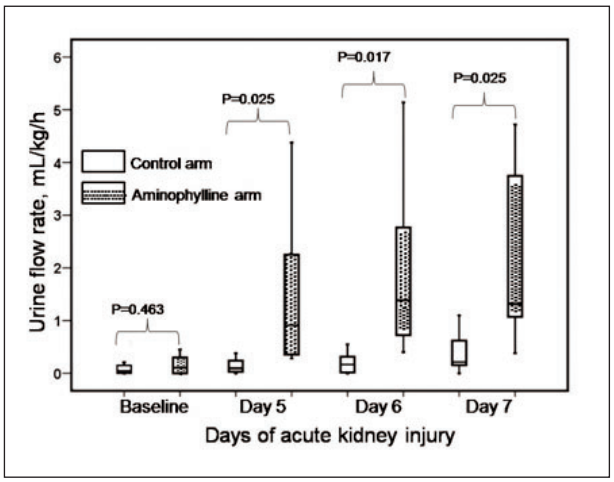
The lower and the upper arm of each box plot represent the 5th and 95th percentiles while the bottom and top of each box represents the 25th and 75th percentiles respectively.

were oliguric in the control arm while there were four and five anuric and oliguric patients in the aminophylline arm, respectively (P=1.0). While the UFRs for days 5, 6, and 7 increased significantly from the baseline in the aminophylline arm, this was not the case in the control group (Figure-1). Similarly, the UFRs for days 5, 6, and 7 were significantly higher in the aminophylline arm compared to controls (Figure-2). Seven out of nine aminophylline-treated patients had short duration of oliguria/anuria compared to two out of eight control patients (77.8% Vs 25.0%; odds ratio 0.09; 95% CI: 0.0-0.89; P=0.04). The median baseline and peak Scr for the control group were 4.9 (1.5-11.6) and 7.4 (5.6-15.4) mg/dl respectively (P=0.01). Similar measurements for the aminophylline arm were 2.0 (1.5-5.3) and 8.2 (6.0-11.0) mg/dl, respectively (P=0.01). Times to peak Scr in both the control and aminophylline arms were 6-12 days (median 8.0) and 4-12 days (median 8.0) respectively (P=0.6). The aminophylline arm maintained a relatively constant Scr level compared to controls that showed progressive and statistically significant increases in Scr level (Figure-3). Five out of eight control patients required dialysis while eight out of nine patients in the aminophylline arm required dialysis (P=0.08) at baseline. Four out of five patients who required dialysis in the control arm were dialyzed owing to clinical and laboratory deterioration. Only one out of eight patients in the aminophylline arm who required dialysis was dialyzed. Stable clinical and laboratory status as well as early diuresis onset following aminophylline treatment precluded dialysis in the remaining seven patients (odds ratio 0.16; 95% CI: 0.04-0.71; P=0.03). Two out of eight patients among the controls died while three out of nine patients in the aminophylline arm died (hazard ratio 0.77; 95% CI: 0.11-5.45; P=0.8). All patients were followed-up for 7-42 days (median 19 days).

Discussion

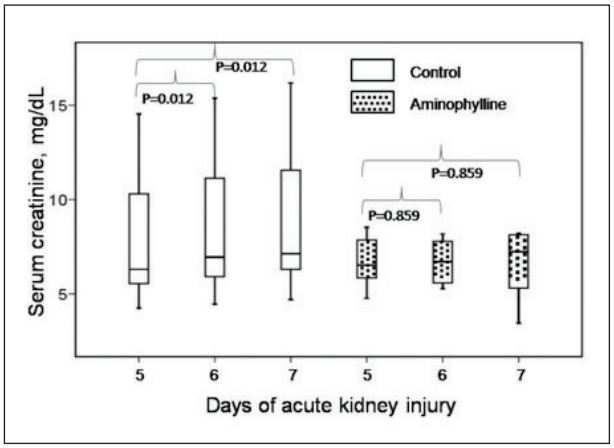
Emerging data on aminophylline treatment of AKI showed that the agent could be useful in improving outcome as demonstrated by improved urine flow rates [9-11, 13-15], steady state Scr [11, 15] and reversal of nephrotoxic oliguria [10]. In this study, aminophylline was significantly associated with improved outcome with regards to UFR, oliguria/anuria duration, number of patients dialyzed, and Scr level. This occurred despite both groups having similar age, gender, etiology and severity of kidney injury. Both groups had similar baseline Scr, time to peak Scr and prevalence of oliguria/anuria and all patients progressed to stage 3 AKI. The increase in UFRs from baselines for days 5, 6, and 7, was significantly higher for the aminophylline arm compared to controls. This is similar to findings in two other controlled studies in children [10, 11]. This study also showed aminophylline to be protective against prolonged oliguria/anuria. The relatively steady Scr levels found in the aminophylline arm suggest increased creatinine excretion following improved urine flow rates. This effect probably explains why patients treated with aminophylline were less likely to be dialyzed compared to controls. However, these positive impacts of aminophylline on the hemodynamic

Figure 2: Box plots comparing the median urine flow rates of the aminophylline and control arms



The lower and upper arm of each box plot represents the 5th and 95th percentile while the bottom and top of each box represents the 25th and 75th percentile respectively.

Figure 3: Box plots comparing day 5 with days 6 and 7 median serum creatinine in aminophylline and control arms



The lower and upper arm of each box plot represents the 5th and 95th percentile while the bottom and top of each box represents the 25th and the 75th percentile respectively.

events of the initiation and extension phases of AKI failed to translate to improved survival. Progression to stage 3 AKI which could not be prevented by aminophylline was probably a factor. Stage 3 AKI is especially associated with dismal prognosis [1, 16, 17]. As in other studies, small sample size was an important limitation of this study. A large prospective randomized controlled study is therefore warranted to further evaluate the effect of aminophylline treatment on childhood AKI survival. Notwithstanding this limitation, the study has revealed that with improved UFR and reduced number of dialyzed patients, aminophylline treatment could potentially reduce the treatment cost of AKI.

Conclusion

Although there was no improvement in patients' survival, the improved urine flow rates in the aminophylline treated group obviated the need for dialysis treatment in the majority of patients. This could impact positively on the overall AKI treatment cost.

Acknowledgement

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