

Original Article



Effect of Aminophylline in Preventing Renal Dysfunction among Neonates with Prenatal Asphyxia: A Clinical Trial

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Abstract

Background: As there are different views on the effects of aminophylline on neonatal renal function, we intended to observe the effects of aminophylline on renal dysfunction in neonates with prenatal asphyxia.

Methods: This randomized trial was conducted in the Obstetrics and Gynecology Hospital, Tehran, Iran, from June 2016 to May 2017, in neonates with moderate to severe asphyxia during birth. Fifty-six neonates were divided randomly into two groups. The intervention group received one dose of 5mg/kg slow intravenous aminophylline injection and the placebo group received 2 mL/kg of intravenous 10% solution of dextrose saline during the first hour of life. They were monitored and compared for renal functional indices, electrolytes, and complications of asphyxia during the three days of life.

Results: The mean of Cr (37.9 ± 8.8 vs 38.5 ± 9.4 and 20.8 ± 4.8 vs 30.1 ± 5.2 $\mu\text{mol/L}$), GFR (21.55 ± 4.7 vs 20.25 ± 4.4 and 30.8 ± 7.1 vs 20.1 ± 6.5 mL/minute/1.73 m²), Na (135.1 ± 12.4 vs 134.5 ± 11.2 and 128.9 ± 11.5 vs 134.2 ± 10.9 mEq/L), and urine output (98.2 ± 25 vs 96.8 ± 23 and 148.7 ± 35 vs 108.8 ± 20 cc) were in the aminophylline treated and placebo group on the 1st and 3rd days, respectively. The mean difference of Cr (-9.3 (-8.9 ; -9.7) $\mu\text{mol/L}$); ($P = 0.02$), GFR (10.7 (10.1 ; 11.3) mL/minute/1.73 m²) ($P = 0.009$), Na (-5.3 (-5.9 ; -4.7) mEq/L) ($P = 0.002$), and urine volume (39.9 (24.9 ; 54.9) cc) ($P = 0.001$) presented statistically significant differences on the third day between the intervention and placebo group.

Conclusion: Aminophylline was effective in preventing renal dysfunction in neonates with asphyxia. Neonates who received aminophylline indicated a significant improvement in GFR and urine output on the first day of life.

Keywords: Asphyxia, Aminophylline, Renal Function

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Introduction

Perinatal asphyxia is a more prominent issue in developing countries, resulting from lack of prepartum care and advanced natal care with a prevalence reported up to 5%.¹ Neonates with perinatal asphyxia are 82% likely to have organ dysfunction in one or more of their organs, including the brain (72%), kidneys (42%) and lungs (26%).² Kidneys are the second most affected organs in perinatal asphyxia,³ with the incidence rates of acute kidney injury, functional renal failure, and intrinsic renal failure reported at 12%, 48.14%, and 51.85%, respectively.⁴

Perinatal asphyxia is perceived to be the primary cause of transient renal dysfunction or acute renal failure.⁵ Kidney malfunction manifests as oliguria and acute renal failure, which is caused by acute tubular necrosis.⁶

Furthermore, renal vein or artery thrombosis can occur along with severe perinatal asphyxia.⁷ The prognosis of

renal dysfunction is of utter importance in preventing complications like hyponatremia caused by increased fluid load and hyperkalemia.³

If asphyxia is severe, first peripheral tissues (like muscle tissue and the heart), and brain tissue will be deprived of oxygen, which in turn, will result in a shift towards anaerobic glycolysis.⁸ Anaerobic glycolysis will produce lactic acid, which causes metabolic acidosis and adenosine triphosphate hydrolysis. In addition, there will be an increase in adenosine.⁹ Adenosine acts as an inhibitory neuro-regulator in the central nervous system in pathways of respiratory neural inhibition during hypoxia.¹⁰ In the kidneys, in hypoxemic states, adenosine causes dilation of the efferent arteriole, therefore lowering the effective filtration pressure and glomerular filtration rate (GFR).¹¹

The major role of adenosine in mediating renal vasoconstriction in hypoxemia is supported by the fact

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that administering theophylline, which is a nonspecific antagonist of adenosine cell surface receptors, could prevent the hypoxemia-induced decrease in GFR.¹²

Although some studies do not support theophylline's positive effects on the renal function of neonates with perinatal asphyxia, many other studies suggest multiple beneficial effects of theophylline in this context, through clinical trials.¹³

As there are opposing views on this subject matter, and lack of as many studies done on aminophylline to prove its positive effects on complications of perinatal asphyxia, we intend to study the effects of aminophylline on renal function of neonates with severe perinatal asphyxia in comparison to newborns not receiving the medication, through a clinical trial.

Materials and Methods

Design and Patients

This is a double-blinded randomized clinical trial conducted in Shahid Akbarabadi hospital affiliated to Iran University of Medical Sciences, Tehran, Iran, from June 2016 to May 2017 to evaluate the effect of aminophylline injection in the first hours of life on renal function in neonates with perinatal asphyxia. A randomized blocking (block size of four) method was applied using a computer-generated random number list prepared by an investigator

with no clinical involvement in the trial. Sixty-two term neonates who were born with moderate to severe asphyxia during birth were assessed for eligibility. The severity of asphyxia was categorized as severe (Apgar score: 1–3) or moderate (Apgar score: 4–6). Eligible neonates were divided randomly using random blocks into two groups of twenty-eight. We excluded neonates if they had congenital anomalies, history of maternal drugs causing neonatal depression, blood culture-positive sepsis, or if the neonates required a mechanical mode of ventilation (Figure 1).

Blinding and Intervention

This study was conducted double-blinded: the patients (neonates) and the evaluator (analyzer) were not aware of the course of the intervention. The researcher and clinicians were informed of the allocation in the intervention group. The intervention group received one dose of 5 mg/kg (2 mL) slow intravenous aminophylline injection over 5 minutes during the first hour of life. The placebo group received 2 milliliters of intravenous 10% solution of dextrose saline as placebo under the same conditions as the intervention group.

Outcomes and Measurements

In this study renal function was defined as the primary outcome. To measure this criterion, blood urea nitrogen

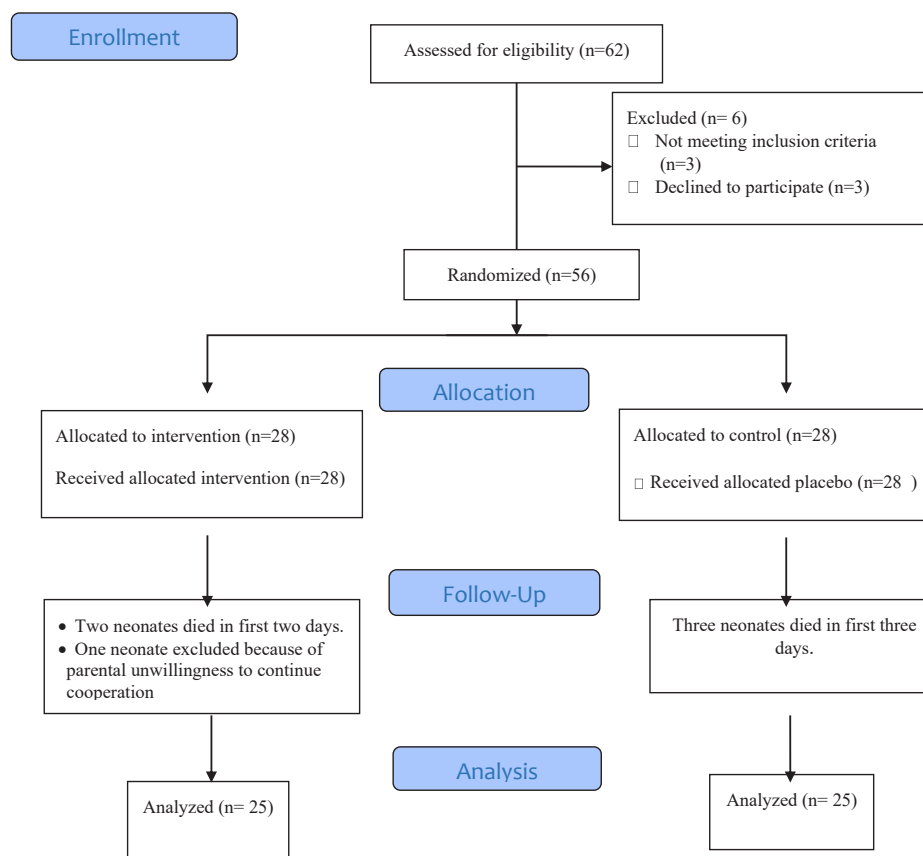


Figure 1. Follow-up Diagram of Patients (According to Consort Statement).

(BUN, mg/dL), creatinine (Cr, $\mu\text{mol/L}$), GFR [GFR was estimated on alternate days using Schwartz's formula: $\text{GFR (mL/min/1.73 m}^2) = 0.45 \times \text{length (cm)/plasma creatinine (mg/100 mL)}$], sodium (Na, mEq/L), potassium (K, mEq/L), calcium (Ca, mg/dL) and the neonates' fluid intake and urine output (cc) on 1st and 3rd days were monitored.

Secondary outcomes were comparison of renal function on 3rd day between severe and moderate asphyxia and complications of prenatal asphyxia between the aminophylline-treated and placebo groups.

Data Collection Methods

The data were collected by clinical observation, medical history, and laboratory findings; all were gathered in checklists and then recorded in the data bank.

Data Analysis

The sample size of the study was calculated at 28 for each group, based on an expected standardized mean difference of aminophylline effect on continuous subjective outcome of 1.1,¹⁴ and considering study power of 80% and two-sided alpha error of 0.05. The data was entered into the statistical analysis software, SPSS, version 16, and then statistically analyzed. Kolmogorov-Smirnov was used to assess the normality of data distribution. All descriptive data had normal distribution. Therefore, the results for the quantitative variables were reported in mean \pm SD format and the ordinal qualitative variables were reported in frequency and percentages. For comparing quantitative and qualitative variables, the Mann-Whitney U, Student's *t* test or chi-square test were used. *P* values <0.05 were considered statistically significant.

Results

A total number of 56 neonates met the inclusion criteria of perinatal asphyxia: these neonates were divided into two groups (aminophylline and placebo groups). Twenty-

eight neonates were enrolled in each group. Of 56 eligible neonates in the aminophylline and placebo groups, 3 neonates were excluded from each group. Ultimately, the analysis was done with 25 neonates in each group (Figure 1).

Each group received either aminophylline or an equal volume of placebo at similar chronological ages. The minimum, maximum and mean of gestational age were 37, 42 and 39.3 ± 4.8 weeks, respectively. The minimum, maximum and mean of birth weight was 1950, 4200 and 3105 ± 940 g. The mean values of first- and fifth-minute Apgar score were 2.24 ± 2.3 and 5.4 ± 2 , respectively and 54% of the neonates presented with moderate prenatal asphyxia. The demographic and clinical characteristics of the studied asphyxiated neonates are presented in Table 1. According to the results, differences in gender, gestational age, birth weight, mode of delivery (NVD, C/S), Apgar score, severe and moderate asphyxia were not significant between the two groups of aminophylline and placebo treatment (Table 1).

The comparison of BUN, Cr, GFR, Na, K, Ca, and urine output between aminophylline and placebo groups at baseline and third day is presented in Table 2. BUN, Cr, GFR, Na, and K did not follow the normal distribution pattern; therefore, Mann-Whitney U test was used for comparison. According to the results, both groups had similar daily estimated BUN, K, and Ca. There was no difference in the change in BUN, K, and Ca from baseline to 72 hours between the groups (*P* > 0.05).

Urine creatinine during the first three days of life showed a non-significant difference between the two groups. There was a significant difference in the change in creatinine from baseline to 72 hours between the groups (*P* = 0.022). GFR, as calculated using the Schwartz formula, showed a statistically non-significant difference between the two groups on the first day, which later became highly statistically significant (*P* < 0.009) between the aminophylline and placebo groups (30.8 ± 7.1 vs. 20.1

Table 1. Demographic and Clinical Characteristics of Aminophylline and Placebo Groups

Variable		Aminophylline Group (n = 25)	Placebo Group (n = 25)	P Value
Gender, No. (%)	Male	14 (56)	17 (68)	0.156*
	Female	11 (44)	8 (32)	
Gestational age, wk	Min-Max	37–42	38–41	0.085**
	Mean \pm SD	39.2 ± 3.2	39.4 ± 4.7	
Birth weight, g	Min-Max	2010–4200	1950–4170	0.452**
	Mean \pm SD	3050 ± 960	3160 ± 970	
Delivery mode, No. (%)	NVD	16 (64)	13 (52)	0.298*
	C/S	9 (36)	12 (48)	
Apgar score	$\frac{1}{5}$ minute	$\frac{2.2}{5.3}$	$\frac{2.28}{5.5}$	0.521**
Asphyxia	Moderate	13 (52)	14 (56)	0.652*
	Severe	12 (48)	11 (44)	

SD; standard deviation, NVD; normal vaginal delivery, C/S; cesarean section.

*Chi-square test; **Student's *t* test.

Table 2. Comparison of Renal Function between the aminophylline and Placebo Groups

Parameter		Groups		Diff	95% CI		P
		Aminophylline Group (n = 25)	Placebo Group (n = 25)		Lower	Upper	
		Mean ±SD	Mean ±SD				
BUN	First day	24.6 ± 4.0	25.1 ± 4.2	-0.5	-0.3	-0.7	0.308*
	Third day	23.4 ± 6.2	27.6 ± 5.8	-4.2	-4.6	-3.8	0.052*
Cr	First day	38.5 ± 9.4	37.9 ± 8.8	-0.6	-0.1	-1.2	0.652*
	Third day	20.8 ± 4.8	30.1 ± 5.2	-9.3	-8.9	-9.7	0.022*
GFR	First day	21.55 ± 4.7	20.25 ± 4.4	1.3	1	1.6	0.059*
	Third day	30.8 ± 7.1	20.1 ± 6.5	10.7	10.1	11.3	0.009*
Na	First day	135.1 ± 12.4	134.5 ± 11.2	0.6	-0.6	1.8	0.765*
	Third day	128.9 ± 11.5	134.2 ± 10.9	-5.3	-5.9	-4.7	0.002*
K	First day	4.9 ± 0.9	4.4 ± 2	0.5	1.8	-0.6	0.876*
	Third day	4.5 ± 1.6	4.8 ± 1.9	-0.3	0	-0.6	0.446*
Ca	First day	8.5 ± 1.8	8.9 ± 1.7	-0.4	-0.5	-0.3	0.562**
	Third day	8.7 ± 2.7	9.1 ± 2.2	-0.4	-0.9	0.1	0.438**
Urine output	First day	98.2 ± 25	96.8 ± 23	1.4	0.2	3.4	0.321**
	Third day	148.7 ± 35	108.8 ± 20	39.9	24.9	54.9	0.001**

* Mann-Whitney U test; **Student *t* test.

± 6.5 mL/min/1.73 m²) on the 3rd day. The level of Na showed a statistically non-significant difference between the two groups on the first day, which became statistically significant between the two groups on the 3rd day (*P* = 0.002). Both groups exhibited an increase in urine output on the 3rd day, which was significantly higher in the aminophylline group than the placebo group (*P* = 0.001).

Comparison of renal function between severe and moderate asphyxia in neonates was considered as one of the secondary outcomes in this study. According to the results, there was a significant difference in the value of Na between neonates with severe and moderate asphyxia (*P* = 0.042). Also, the mean third day urine volume in the aminophylline group significantly different between severe and moderate asphyxia (*P* = 0.035) (Table 3). Table 3 depicts the results of comparison of renal function on the 3rd day between severe and moderate asphyxia in neonates.

Five deaths occurred during the study period (two deaths in the aminophylline and three deaths in the placebo group) but the difference between the groups was not significant (*P* > 0.05). The occurrence of complications was reported in numbers and percentage. Complications

of prenatal asphyxia in this study consisted of pulmonary dysfunction, convulsion, cerebral hemorrhage, and death. According to the results, the complications of asphyxia were not significantly different between the two groups (Table 4, Figure 2).

Discussion

Given that asphyxia is the main cause for acute or transient kidney failure,¹⁵ this study was designed to assess the effects of aminophylline on renal dysfunction in neonates with prenatal asphyxia. The obtained results indicate that on the 3rd day, serum Cr, GFR levels, Na value and urine output of the neonates receiving aminophylline treatment was statistically different compared to the group receiving placebo. In contrast, no significant difference was observed between the two groups in all variables on the first day and BUN, K, Ca values on the third day.

Data from the aminophylline treated group revealed a significant decrease in serum creatinine levels on the 3rd day. The result of a study by Eslami et al showed that the level of serum creatinine was not significantly different between the theophylline and control groups on the first day. However, these levels significantly decreased in

Table 3. Comparison of Renal Function between Severe and Moderate Asphyxia in Neonates on the Third Day

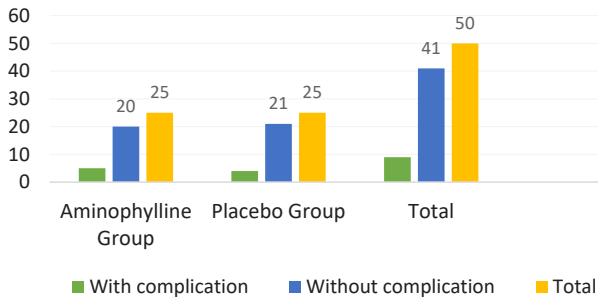
Parameter	Asphyxia		Diff	95% CI		P
	Moderate (n = 27)	Severe (n = 23)		Lower	Upper	
	Mean ± SD	Mean ± SD				
BUN	23.6 ± 6.4	27.6 ± 5.9	-4.03	-4.53	-3.4	0.340*
K	5.1 ± 2.7	4.4 ± 1.9	0.7	0	1.1	0.984*
Ca	8.8 ± 3.6	8.6 ± 2.4	0.2	-0.2	0.4	0.636**
Cr	23.7 ± 4.2	27.5 ± 6.9	-3.8	-4.6	-7.4	0.346*
GFR	27.6 ± 7.8	22.9 ± 5.1	4.7	2	7.4	0.255*
Na	135.7 ± 12.3	127 ± 11.5	8.7	6	9.5	0.042*
Urine output	141.1 ± 29	114.2 ± 26	26.9	23.9	29.9	0.035**

* Mann-Whitney U test; **Student *t* test.

Table 4. Comparison of Complications of Prenatal Asphyxia between the Aminophylline and Placebo Groups on the Third Day

Variables	Aminophylline Group (n = 25)	Placebo Group (n = 25)	P Value*
Pulmonary dysfunction, No. (%)	1(4)	1(4)	0.356
Convulsion, No. (%)	2(8)	1(4)	0.068
Cerebral hemorrhage, No. (%)	2(8)	2(8)	0.251

*Chi-square test.

**Figure 2.** Comparison of Complications between the Aminophylline and Placebo Groups.

the neonates of the theophylline group and significantly increased in the controls on the third day, which is similar to our findings.¹⁵

The estimated GFR increased significantly in the aminophylline treated group from 21.55 ± 4.7 on the 1st day to 30.8 ± 7.1 mL/min/1.73 m² on the 3rd day, indicating a significant difference compared to the control group. Studies by Youssef et al and Raina et al reported an increase in GFR in theophylline group compared to placebo group on the third day.^{16,17}

The findings of this study showed that neonates in the intervention group manifested a significant decrease in serum sodium levels after taking a loading dose of aminophylline. This effect of aminophylline has the potential to induce hyponatremia in critically ill neonates.¹⁸ The general mechanisms for hyponatremia (defined as serum sodium <130 mmol/L) include the inability to excrete a given water load leading to volume overload and dilution of serum sodium levels, excessive gastrointestinal or renal sodium losses, and inadequate sodium intake.^{18,19} The observation of the effect of aminophylline on serum sodium in asphyxiated neonates is in line with the findings of other authors.^{20,21} Pretzlaff et al found that an aminophylline bolus of 6 mg/kg given to eight children aged 1 month to 6 years already receiving a continuous infusion of furosemide increased urine output by over 80% and increased sodium excretion; these variables returned to baseline by 6 hours.²¹ These results suggest that neonates on aminophylline could actually benefit from supplements of sodium ions, and that close monitoring is still needed to prevent any side effects. Nevertheless, based on the result of studies, aminophylline is suggested to be used in neonates in developing countries due to either lack of availability or cost of others drugs.^{18,22-24}

The aminophylline group exhibited a significant increase in urine output during the first three days; there was a 0.68 mL/kg/h increase in urine output in the aminophylline group, and a 0.15.87 mL/kg/h increase in the placebo group. In line with our findings, in a study by Tamburro et al, the median urine output increased from 3.5 [IQR: 2.0, 5.0] at baseline to 4.2 [IQR: 2.7, 5.6] at 24-h with a median increase of 1.0 mL/kg/h ([IQR: -0.1, 1.5]) in the aminophylline group.¹⁴ Bell et al reported a small case series of 10 critically ill children who had a significant increase in urine output with theophylline administration.²⁵ Aminophylline has been used in various dosages for treatment or prevention of renal dysfunction or diuresis in neonates.^{13-18,21-25} These applications have been stimulated by a growing understanding of the role of adenosine in neonatal renal physiology,^{26,27} and supported by animal studies examining renal effects of theophylline and other methylxanthines.²⁸⁻³⁰ Experiments in laboratory animals show that adenosine could act as a vasoconstrictive metabolite in the kidneys. Adenosine is produced and released during hypoxia and ischemia from the kidneys, causing a drop in GFR and filtration fraction.^{31,32} The non-specific antagonist of an adenosine receptor, such as theophylline, can prevent the vasoconstriction caused by it.³³ It has been shown in animal models that adenosine antagonists can increase renal blood flow.³⁴ In some studies using different low-dose theophylline regimens to prevent renal dysfunction following perinatal asphyxia, a marked reduction was observed in renal involvement, typically from 55% to 60% of controls to 17% to 25% of theophylline-treated patients.³⁵⁻³⁷

In the present study, Na levels in neonates with severe asphyxia were significantly lower compared to the ones with the moderate form of the condition. In tandem with these findings, in a study by Thakur, a significant correlation was reported between serum sodium and Apgar score at 5 minutes.²⁰ Basu et al found increased severity of hyponatremia with increased severity of birth asphyxia.³⁸ Also, Gopal concluded that oliguria, hyponatremia and abnormal sonographic findings are prognostic factors for renal failure in neonates with prenatal asphyxia during birth.⁸ Hyponatremia may occur in neonates with perinatal asphyxia as there is increased secretion of anti-diuretic hormone in neonates which leads to increased water retention and hence, dilutional hyponatremia.²⁰ Another reason for hyponatremia is that the capacity of sodium reabsorption is limited and if the load of sodium reaching

the collecting tubules increases significantly, reabsorption does not occur proportionately and the sodium load is excreted in the urine.³⁹ Another factor contributing to hyponatremia is partial resistance to aldosterone.⁴⁰

Furthermore, the finding shows that the neonates' urine volume on the third day has a statistically significant negative association with the severity of prenatal asphyxia. It seems that urine measurements soon after birth may be a tool to identify severity of neonatal asphyxia.⁴¹

In summary, aminophylline prevented renal dysfunction in neonates with asphyxia. Neonates in the aminophylline group indicated a significant improvement in GFR and urine output on the first day of life. We suggest further studies on this topic, with larger sample sizes and longer, follow-up periods in our country so that the results would be qualitatively and quantitatively comparable to our study.

Authors' Contribution

MS, JB, ST, NK, MH, and SH conceptualized and designed the study, collaborated in data processing, collaborated in analysis. LA, ST, and NK wrote the manuscript, edited and critically reviewed manuscript. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

Authors had no conflict of interest to declare.

Ethical Statement

In all steps carried out in this study, the principles of the Declaration of Helsinki and the Ethics Committee of Iran University were followed. The study was approved by Iran University's Ethics Committee (IR.IUMS.REC.1395.8821215173) and has been registered at Iranian Registry of Clinical Trials (identifier: IRCT20181201041815N, <https://www.irct.ir/trial/36153>). The intervention substances were administered with informed consent from the newborns' parents before blinding. The medication was provided using the research's funding, as not to impose it on the patient. The neonate's caretaker was properly informed about enrolling in the study and their informed consent was taken. They were free to withdraw from the study in any step of the study and for any reason or for no reason at all. All patients' information was held confidential, was not made accessible to any person or organization and was reported only in aggregate.

Acknowledgements

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