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Theophylline for Prevention of Kidney Dysfunction in Neonates With Severe Asphyxia

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Original Paper

Introduction. Recent studies have suggested theophylline for prevention of kidney dysfunction in asphyxia. This study was designed to determine whether theophylline could prevent or ameliorate kidney dysfunction in term neonates with perinatal asphyxia.

Materials and Methods. We assigned 36 severely asphyxiated term infants (Apgar score ≤ 5) into 2 groups to receive intravenously a single dose of either theophylline (5mg/kg; n =17) or placebo (n =19) during their first 60 minutes of life. The 24-hour fluid intake and the urine volumes were recorded during the 1st, 3rd, and 5th days of life. Severe kidney dysfunction was defined as a serum creatinine level elevated up to more than 1.50 mg/dL for at least 2 consecutive days after a fluid challenge, or 0.3-mg/dL/d rising levels of serum creatinine.

Results. On the 1st day, the 24-hour fluid balance was more positive in infants receiving placebo compared to infants receiving theophylline. Over the next few days, the change in fluid balance favored the theophylline group. Significantly higher serum creatinine values were recorded in the placebo group on the 3rd day. Severe kidney dysfunction was present in 2 infants of the theophylline group (11.7. %) and in 8 (42.1%) of the controls. The glomerular filtration rate was markedly increased in the theophylline group. There was no difference in the severity of the asphyxia between the infants of the theophylline and control groups.

Conclusions. Prophylactic theophylline, given early after birth, has beneficial effects on reducing kidney dysfunction in neonates with asphyxia.

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INTRODUCTION

Perinatal asphyxia is a prevalent complication along with child birth. It has been estimated that nearly 5% to 8% of newly born infants suffer different degrees of perinatal asphyxia in the primary hours of birth that lead to admission to the neonatal intensive care unit (NICU).[1-4] Asphyxia is an important cause of acute kidney failure (AKF) and transient kidney impairment with adverse effects, especially in 5 days of birth.[5,6] In asphyxia, we encounter gas distribution disorder which leads to progressive hypoxia and hypercapnea. If severe, it affects primarily the muscles and heart, and then, the cerebral organ. Following hypoxia in the cerebral organ, anaerobic glycolyse provides lactic acid, metabolic acidosis, adenosine three phosphate hydrolysis, and increase of adenosine. Pre- and postglomerular vasoconstriction due to adenosine metabolites leads to a fall in glomerular filtration rate (GFR). This might be inhibited by

the nonspecific adenosine receptor antagonist-like Theophylline.[7]

Several studies have reported the effectiveness of theophylline, calcium channel blockers, and thyroxin to treat asphyxia.[5,8-12] Results of a study by Bakr to determine the effectiveness of theophylline to prevent kidney dysfunction in term neonates with perinatal asphyxia confirmed the prophylactic impact of theophylline administered early after birth, with beneficial effects in reducing the renal involvement in asphyxiated full-term infants.[8] We conducted this interventional clinical trial to compare improved kidney dysfunction with theophylline administration in term infants with severe asphyxia admitted during their 5 first days of life to the NICU of Shahid Sadoughi Hospital.

MATERIALS AND METHODS

We conducted a double-blind controlled trial from January 2007 to April 2008 to study on term and postterm infants (pregnancy week ≥ 37) who admitted to the NICU. We selected severely asphyxiated infants with a birth weight of 2500 g or greater. Severe asphyxia was defined as an Apgar score of 3 or less in the first minute, an Apgar score of 6 or less in the fifth minute, base deficit higher than 15 mEq/L in cord or arterial blood sample, or the need for severe resuscitation. The exclusion criteria were preterm delivery, small for gestational age, congenital anomalies (congenital kidney disorders, disorders with no asphyxia relation, and chromosomal disorders), the need for treatment with drugs affecting kidney function, hypotension (mean arterial pressure ≤ 40 mm Hg), requirement of ventilator, seizure, cerebral attacks, severe kidney dysfunction (creatinine ≥ 1.5 mg/dL in 2 days), and oliguria (urine output ≤ 1 mL/h/kg for 24 hours).

We enrolled 41 infants, but 5 were excluded from study (2 because of chromosomal and kidney anomalies, 3 due to refusal of the parents). We randomly assigned 17 infants into the theophylline group and 19 into the control group based on a random number table. The infants of the theophylline group received a single intravenous dose of theophylline, 5 mg/kg, slowly. The infants of the control group received 2 mL of placebo (10% dextrose solution). The infusions were administered in the first 5 minutes after NICU admission during the first hour after birth. Asphyxia treatment for the two groups was administered equally.

We recorded fluid intake in 24 hours, urinary volume (by bag title or catheter), urinary and serum creatinine levels, serum electrolytes levels (sodium, potassium, and calcium), and urinary sodium excretion in the 1st, 3rd, and 5th days after birth. We defined acute kidney failure as an increase in serum creatinine level equal to or greater than 0.3 mg/dL or a serum creatinine level higher than 1.5 mg/dL for at least 2 consecutive days. We estimated the GFR using the Schwartz formula (0.45 × length /plasma creatinine level). Hematuria was investigated by standard dipstick or urinalysis. Complete blood count was recorded in the 1st day and in the 5 first days if blood transfusion was done. In addition, further information provided by the parents was collected.

The collected data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA). Continuous variables were demonstrated as mean ± standard deviation. The chi-square test, Fisher exact test, and the t test were used for comparisons between the two groups. *P* values less than .05 were considered significant.

RESULTS

All of 36 the asphyxiated term infants were included in the study analyses. The two groups were not significantly different in terms of birth weight ($P = .44$), gestational age ($P = .43$), sex ($P = .50$), vaginal or cesarean delivery ($P = .27$), arterial blood pH ($P = .08$), base deficit ($P = .69$), inotrope agent ($P = .72$), Apgar score in 1 minutes ($P = .09$) and 5 minute ($P = .61$), resuscitation maneuvers ($P = .36$), and adrenalin ($P = .55$).

Serum creatinine levels were not significantly different between the theophylline and control groups on the 1st day ($P = .87$); however, these levels significantly decreased in the infants of the theophylline group and significantly increased in the controls on the 3rd day ($P < .001$). On the 5th day, serum creatinine levels decreased in both groups (Table 1). On the 3rd day, an increasing trend in urinary creatinine levels in was found in the infants of the theophylline group (from 27.4 ± 19.0 mg/dL to 33.6 ± 10.0 mg/dL), while a decrease was documented in control group on the 3rd and 5th days (Table 1). The estimated GFRs were not significantly different between the two

Table 1. Serum and Urinary Creatinine Levels During the First Five Days of Life in Two Groups of Asphyxiated Neonates

Creatinine Measurements	Infants		*P*
	Theophylline Group	Placebo Group	
Serum creatinine, mg/dL			
1st day	0.92 ± 0.22	0.86 ± 0.20	.87
3rd day	0.63 ± 0.22	1.06 ± 0.47	< .001
5th day	0.56 ± 0.14	0.73 ± 0.14	.03
Urinary creatinine, mg/dL			
1st day	27.4 ± 19.0	24.1 ± 18.0	.02
3rd day	33.6 ± 10.0	19.7 ± 9.7	.97
5th day	26.4 ± 13.0	19.2 ± 11.0	.54

groups on the 1st day; however, they significantly increased in the theophylline group on the 3rd day (P = .23). On the 5th day, although GFRs increased in the control group, they remained lower than those in the theophylline group (Table 2). Due to the natriuresis effect of theophylline, urinary sodium excretion on the 1st day was significantly higher in the theophylline group than in the control group (P = .02; Table 3).

Severe kidney dysfunction was detected in 2 patients of the theophylline group (11.8%) and 8 of the control group (42.1%) during the first 5 days after birth (P = .04). The other diagnosed complications of asphyxia are listed in Table 4. The causes of death were multi-organ failure and persistent pulmonary hypertension following meconium aspiration in 2 patients.

DISCUSSION

Asphyxia, especially its nonoliguric form, is the main cause for acute or transient kidney failure.[1,13,14] The preventive role of theophylline to reduce nephrotoxicity of contrast imaging studies of angiography or computed tomography has

Table 2. Estimated Glomerular Filtration Rate (GFR) During the First Five Days of Life in Two Groups of Asphyxiated Neonates

GFR, mL/min/1.72 m^2	Infants		*P*
	Theophylline Group	Placebo Group	
1st day	25.4 ± 7.3	28.2 ± 12.8	.87
3rd day	42.4 ± 19.1	27.5 ± 10.7	.02
5th day	42.3 ± 12.5	37.5 ± 6.5	.10

Table 3. Urinary Sodium Excretion During the First Five Days of Life in Two Groups of Asphyxiated Neonates

Urinary Sodium, mg/dL	Infants		*P*
	Theophylline Group	Placebo Group	
1st day	53.5 ± 28.0	30.1 ± 16.0	.18
3rd day	44.3 ± 23.0	41.6 ± 23.0	.54
5th day	48.5 ± 30.0	98.0 ± 44.0	.54

Table 4. Complications During the First Five Days of Life in Two Groups of Asphyxiated Neonates*

Complication	Infants		*P*
	Theophylline Group	Placebo Group	
Severe kidney dysfunction	2 (11.8)	8 (42.1)	.04
Need for ventilation	2 (11.8)	7 (36.8)	.08
Seizure	2 (11.8)	6 (31.6)	.38
Cerebral hemorrhage	0	1 (5.3)	.08
Death	1 (5.8)	1 (5.3)	.70
Hematuria	7 (41.2)	13 (68.4)	.07
Blood transfusion	2 (11.8)	3 (15.8)	.56

*Values in parentheses are percents.

been reported.[15] In another clinical trial, the use of theophylline, calcium antagonists, thyroxin, and some cytokines were shown to improve kidney dysfunction resulted from perinatal asphyxia.[11,12]

Jenik and colleagues investigated theophylline effect in 60 perinatal asphyxiated infants.[10] Twenty-four patients received a single dose of theophylline, 8 mg/kg, intravenously in the first hour of birth. Four infants suffered from severe kidney dysfunction compared to 15 infants in the control group. In our study, 2 infants (11.8%) with theophylline and 8 in the control group (42.1%) developed kidney dysfunction. In Jenik and colleagues' study,[10] the GFR was higher in infants on theophylline than in controls (21.84 ± 7.96 mL/min/1.72 m^2 versus 6.42 ± 4.16 mL/min/1.72 m^2). This was similar to our results (25.39 ± 7.32 mL/min/1.72 m^2 versus 42.36 ± 19.10 mL/min/1.72 m^2). Also, the severity of asphyxia and multi-organ involvement were similar between the two groups in these two studies. The Jenik and colleagues' study results showed prophylaxic prescription of theophylline as a single dose of 8 mg/kg could decrease serum creatinine and urinary β2-microglubolin and increase creatinine clearance. We used a dose of 5 mg/kg instead of 8 mg/kg and we did not estimate urinary β2-microglubolin in our study.

Bakr investigated 40 severe asphyxiated infant in a similar study.[8] Their selection criteria, matching, and intravenous infusion of a single dose of 5 mg/kg of theophylline were similar to ours. Severe kidney dysfunction was detected in 25% and 60% of the case and control groups, respectively. Although the serum creatinine was not different between the two groups on the first day of birth, on the next days, it significantly elevated in the control group. This was similar to the elevation of serum creatinine in our control group after the first day of birth. The estimated GFR significantly decreased in the control group. We also recorded a significant decrease of the GFR in the control group. Urinary sodium excretion was 45 ± 55 mEq/L in the theophylline group versus 49 ± 57 mEq/L in the control group. In our theophylline group, the randomly estimated urinary sodium excretion showed significant increase on the first day (2.2 mEq/L; P = .001) and decreased on the third and fifth days compared to its decrease on the first day and increase on the next days in the control group. In Bakr's study,[8] creatinine clearance and urinary β2-microglubolin were significantly higher and lower in the case than the control group, respectively. In their study, death occurred following persistent pulmonary hypertension and sepsis complications in 2 infants in each group. Seizure and the need for respiratory ventilation were seen in 70% and 37.5%, respectively.

In a similar study by Bhat and associates, 70 term neonates were divided into receivers of theophylline (n = 40) and placebo (n = 30).[12] The increase of serum creatinine level in the placebo receivers was reported during the second to fifth days, while creatinine clearance increased in the theophylline receiver group. No significant different in urine sodium excretion was reported between the two groups.

The asphyxia complications, especially the highly frequent central nervous system involvement, were seen in the two groups with no significance in frequency differences.

CONCLUSIONS

According to our results, prophylactic theophylline, given early after birth, has beneficial effects on reducing kidney dysfunction in neonatal asphyxia. Further studies are needed to confirm its usage in NICUs.

CONFLICT OF INTEREST

None declared.

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