THEOPHYLLINE FOR RENAL FUNCTION IN TERM NEONATES WITH PERINATAL ASPHYXIA: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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Objective To study whether prophylactic theophylline can reduce the incidence and/or severity of renal failure in term infants with perinatal asphyxia.

Study design Term neonates with severe perinatal asphyxia were randomized to receive a single dose of either theophylline (study group, n = 40) or placebo (control group, n = 30) during the first hour of life. Daily weight, output/input ratio, 24-hour fluid intake, and urine volumes were recorded during the first 5 days of life. Those infants with asphyxial renal failure were followed up for 1 year.

Results The incidence of severe renal dysfunction was increased in the control group. Creatinine clearance was higher and excretion of beta 2 microglobulin (β2M) was lower in the theophylline group. Conversely, the glomerular filtration rate was lower in the control group. In infants with renal failure, serum creatinine and creatinine clearance returned to normal in the neonatal period, and the increased β2M excretion normalized by age 6 weeks.

Conclusions A single dose of theophylline within the first hour of birth in term neonates with perinatal asphyxia results in a significant decrease in serum creatinine level and urinary excretion of β2M, along with an increase in creatinine clearance. *(J Pediatr 2006;149:180-4)*

The kidney is one of the most frequently damaged organs in asphyxiated full-term neonates.[1-3] These asphyxiated neonates may develop vasomotor nephropathy (prerenal) or acute renal failure (ARF). Gunn et al[4] reported that all infants with hypoxic-ischemic encephalopathy in their study developed signs of ARF. Renal adenosine along with angiotensin II causes afferent arteriolar vasoconstriction and efferent arteriolar dilatation after hypoxia or ischemia,[5-7] contributing to the decreased glomerular filtration rate (GFR) and filtration fraction.[8] Afferent arteriolar vasoconstriction and efferent arteriolar vasodilatation produced by adenosine can be inhibited by the nonspecific adenosine receptor antagonist theophylline.[9]

Data regarding the role of theophylline in the prevention of postasphyxial renal injury in term neonates is very limited and to date, only 1 study has demonstrated beneficial effects.[10] We used a randomized controlled trial to test whether prophylactic administration of theophylline can decrease the incidence and/or severity of renal failure in infants with perinatal asphyxia. Furthermore, we followed those infants with postasphyxial renal failure until normalization of renal and tubular function, which may take up to 1 year according to the literature.[11]

METHODS

The study was conducted in the neonatal intensive care unit of the Sheri Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, India. The infants enrolled in the study were born in the obstetric department of SKIMS, Lalded Women's Hospital, and 2 maternity homes located near SKIMS. All infants were enrolled after parental consent, and the study was approved by the SKIMS Ethics Committee.

Inclusion Criteria

Neonates eligible for the study were of term or postterm gestation and had severe perinatal asphyxia manifested by any 3 of the following criteria:

1. History of fetal distress (fetal bradycardia, late deceleration, decreased fetal heart rate variability, meconium-stained amniotic fluid)
2. Need for immediate neonatal ventilation with a bag and mask or through endotracheal intubation for $>$ 2 minutes after delivery
3. A 5-minute Apgar score of $\leq$ 6

ARF	Acute renal failure	GFR	Glomerular filtration rate
β2M	Beta 2 microglobulin		

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4. Base deficit ≥ 15 mEq/L in cord blood or admission arterial blood or cord blood pH < 7.

Exclusion Criteria

Infants with the following characteristics were excluded: drug use by the mother that may modify renal hemodynamics and renal function, any condition unrelated to asphyxia, cardiovascular disease unrelated to asphyxia, congenital malformation of the kidneys or urogenital tract, polycythemia, microcephaly and chromosomal disorders, or severe intrauterine growth retardation.

The neonates were randomized to receive a single dose of either theophylline (8 mg/kg; 0.3 mL/kg) or an equal volume of placebo (5% dextrose in water) intravenously. The theophylline dose was based on studies by Jenik et al [10] and Kelly and Shannon.[12] The loading dose was administered within the first hour of birth. Investigators and caregivers were blinded to the assignment of the patients.

The severity of asphyxia was quantitated using Portman's score, and the prevalence of multiorgan dysfunction was compared.[13] The asphyxia score is based on fetal heart rate, 5-minute Apgar score, and base deficit in the first hour of life and ranges from 0 to 9. The score for severe asphyxia is > 6, and that for moderate asphyxia is < 5.

The infants were nursed in an intensive care unit on servo controlled open care beds with skin temperature maintained at 36.5°C. They received fluids at a rate of 60 mL/kg of 10% dextrose on day 1 of life. Fluid and electrolyte intake was subsequently adjusted as indicated by clinical status. Fluid restriction was instituted in those infants with oliguric renal failure. The 24-hour fluid intake and urine volume were recorded for the first 5 days of life. Urine samples were collected either by attaching a bag to the perineum or using a urine catheter. All medications, transfusions, and fluid infusions were recorded. Daily water output/input ratio and weight were measured and recorded. Hypotension was defined as mean blood pressure < 45 mm Hg.[14]

Renal function was assessed by daily estimation of electrolyte and serum creatinine levels during the first 5 days of life (Autoanalyzer; Hitachi, San Jose, Calif). The samples were obtained at 24, 48, 72, 96, and 120 hours of life. The 24-hour urine collections were obtained on days 2 and 3 of life to evaluate urinary sodium and creatinine levels. The GFR was evaluated on days 2 and 3 of life by endogenous creatinine clearance (mL/min/1.73 m^2).

Criteria for postasphyxial severe renal dysfunction[14] were serum creatinine level > 1.5 mg/dL for 2 consecutive days and rising serum creatinine level (0.3 mg/kg/day). Both of these criteria were used in all patients with renal failure. Oliguria was defined as urine output < 1 mL/kg/h for at least 24 hours. Hematuria was assessed using standard dipstick reagent strips (Multistix; Bayer Diagnostics, Tarrytown, NY).

Tubular injury was assessed by excretion of β2M determined by enzyme immunoassay on the first voided urine 12 hours after theophylline administration. All urine samples were collected before administration of the first dose of aminoglycoside antibiotics. The upper level of normal (mean ± 2× standard deviation) for β2M excretion was 3.9 mg/L. These values are in accordance with those reported in the literature[15] and also correspond to the ± 2× standard deviation over mean standard value that we obtained from 30 healthy neonates born at gestational age > 37 weeks (unpublished data). The infants with renal dysfunction were followed every 2 weeks during the first 2 months of life and then monthly up to age 1 year.

The Student *t*-test, χ^2 test, and 2-way analysis of variance with repeated measure of a single factor were used for statistical analysis. The data are presented as mean ± standard deviation.

RESULTS

Over a period of 36 months (January 2001 to December 2003), 70 neonates fulfilled the entry criteria and were enrolled into the study. Forty neonates were randomized for the theophylline group and 30 for the control group. There were no significant differences in birth weight, sex, gestational age, mode of delivery, presence of meconium-stained amniotic fluid, individual components of asphyxia morbidity score (fetal heart rate, 5-minute Apgar score, base excess), arterial blood pH, and blood pressure between the theophylline and control groups (Table I). Each group received either theophylline or an equal volume of placebo at similar chronological ages (36 ± 7 min vs 37 ± 5 min).

Seven of these critically ill infants died. Of the 5 infants who died in the theophylline group, 4 died in the neonatal period (2 from multiorgan failure, 1 from sepsis, 1 from persistent pulmonary hypertension of the newborn), and 1 was readmitted after discharge with sclerema and died at age 6 weeks. Two infants in the control group died due to multiorgan failure in the neonatal period. Respiratory support was given to all of the asphyxiated neonates. Involvement of 1 or more systems occurred in 82% of the infants (Figure 1). Central nervous system involvement (eg, seizures, hypoxic ischemic encephalopathy, pseudobulbar palsy, abnormal tone) occurred in 80% (n = 56); pulmonary involvement (eg, persistent pulmonary hypertension, meconium aspiration, asphyxial lung disease) occurred in 37% (n = 26); cardiac involvement, in the form of clinical and echocardiographic appearance of tricuspid or mitral regurgitation or myocardial dyskinesia, occurred in 24% (n = 17); and gastrointestinal involvement (manifested by bloody stools, necrotizing enterocolitis, or gastrointestinal aspirate) occurred in 14% (n = 10). No difference in central nervous system, pulmonary, cardiac, or gastrointestinal involvement was found between the 2 groups; however, severe renal dysfunction was present in 10 (25%) of the neonates in the theophylline group versus 18 (60%) in the control group (relative risk = .41, CI 0.22-0.76; $P = < .001$). No side effects occurred in the infants receiving theophylline.

On the first day of life, plasma creatinine values were similar in the 2 groups; however, on day 2 to day 5 of life, plasma creatinine values were higher in the control group

Table I. Clinical characteristics of control and theophylline-treated asphyxiated neonates on the first day of life

	Theophylline group (n = 40)	Control group (n = 30)	*P* value
Birth weight (g)	2770 ± 400	2780 ± 230	.9*
Gestational age (wk)	38.2 ± 0.79	38.1 ± 0.88	.6*
Caesarean section (%)	12 (30%)	8 (26%)	.5†
Inborn	24 (60%)	17 (56%)	.1†
Meconium-stained amniotic fluid (%)	16 (40%)	12 (40%)	.5†
Initial arterial blood gases			
PH	7.0 ± 0.09	7.0 ± 0.04	.2*
Base excess (mEq\L)	−18.0 ± 1.8	−17.0 ± 2.01	.4*
Asphyxia score >6 (%)	30 (75%)	22 (77%)	.9†
Age at loading infusion of theophylline or placebo (min)	36 ± 6.01	37 ± 5.05	.3*
Ionotropic agents infused (%)	16 (40%)	15 (50%)	.5†
Mean blood pressure (mm Hg; 12 hr of life measured at hourly intervals)	45 ± 3.2	45 ± 2.6	.4*

Values expressed as mean ± standard deviation.
*Student's *t*-test.
†χ^2 analysis.

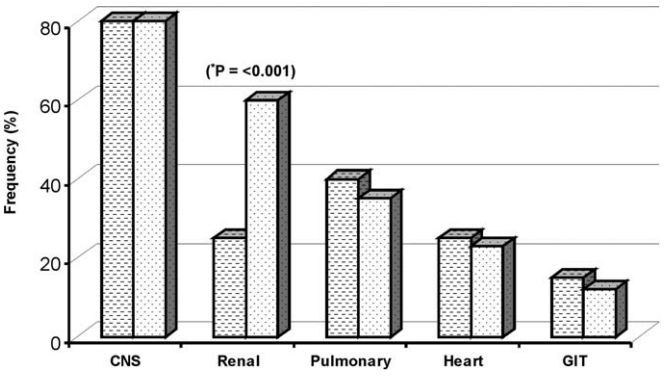

Figure 1. Percentage of organ involvement in the control and theophylline-treated asphyxiated infants. Note that kidney involvement is significantly less in the theophylline group ($P < .001$). ▩ Theophylline group ▨ Control group

Table II. Plasma creatinine in control and theophylline-treated groups of asphyxiated babies during the first 5 days of life

	Plasma creatinine (mg/dL)	
Day of life	Theophylline group (n=40)	Control group (n=30)
1	1.18 ± 0.69	1.50 ± 0.68
2	0.92 ± 0.65	1.56 ± 0.92
3	0.95 ± 0.50	1.59 ± 0.92
4	0.94 ± 0.45	1.62 ± 1.03
5	0.82 ± 0.47	1.57 ± 0.90

Values expressed as mean ± standard deviation.
P value < .004 using 2-factor ANOVA with repeated measure of a single factor.

than in the theophylline group (Table II). From day 2 to day 3 of life, endogenous creatinine clearance (mL/min/1.73 m^2) was higher in the theophylline group than the control group (20.54 ± 7.96 vs 7.36 ± 3.52; $P = < .001$). Although 24-hour urinary sodium excretion on days 2 and 3 of life was higher in the theophylline group, the difference between the 2 groups was not statistically significant (45 ± 29 mEq/L vs 38 ± 32 mEq/L; $P = > .1$). Urinary β2M excretion was significantly lower in the theophylline group (6.7 ± 2.4 mg/L vs 15.2 ± 5.6 mg/L; $P = < .001$). The output/input ratio was more in the theophylline group (Table III). Similarly, urine output was also significantly greater in the theophylline group (Figure 2). Weight loss during the first 5 days of life was greater in the theophylline group (Table IV). Dipstick testing for hematuria over first the 3 days of life demonstrated blood on at least 1 occasion in 18 of the 40 infants in the theophylline group, compared with 13 of the 30 infants in the control group ($P = > .1$). Although 4 infants (10%) in the theophylline group died in the neonatal period, compared with 2 (6%) in the control group, this difference was not statistically significant ($P = > .1$).

The infants with postasphyxial renal failure were followed up every 2 weeks up to age 2 months and then monthly up to age 1 year. Serum creatinine level and creatinine clearance normalized in the immediate neonatal period in all but 2 infants, in whom normalization did not occur until age 6 weeks. Increased β2M excretion normalized by age 6 weeks in all of the infants. At age 1 year, serum creatinine level (mg/dL) and creatinine clearance (mL/min/1.73 m^2) were similar in the 2 groups (0.6 ± 0.2 vs 0.7 ± 0.2 and 78 ± 21 vs 75 ± 22, respectively). Similarly, β2M excretion was similar in the 2 groups.

Table III. Output/input ratio between control and theophylline-treated groups of asphyxiated neonates in the first 5 days of life

Day of life	Output/input ratio	
	Theophylline group (n = 40)	Control group (n = 30)
1	0.34 ± 0.18	0.32 ± 0.16
2	0.55 ± 0.32	0.39 ± 0.21
3	0.63 ± 0.29	0.44 ± 0.22
4	0.81 ± 0.19	0.49 ± 0.24
5	0.88 ± 0.15	0.52 ± 0.22

Values expressed as mean ± standard deviation.
P value < .001 using 2-factor ANOVA with repeated measure of a single factor.

Table IV. Comparison of weight between control and theophylline-treated groups of asphyxiated neonates in the first 5 days of life

Day of life	Weight (g)	
	Theophylline group (n = 40)	Control group (n = 30)
1	2730 ± 410	2900 ± 250
2	2680 ± 420	2870 ± 240
3	2640 ± 410	2830 ± 230
4	2610 ± 410	2800 ± 250
5	2560 ± 430	2740 ± 210

Values expressed as mean ± standard deviation.
P value < .001 using 2-factor ANOVA with repeated measure of a single factor.

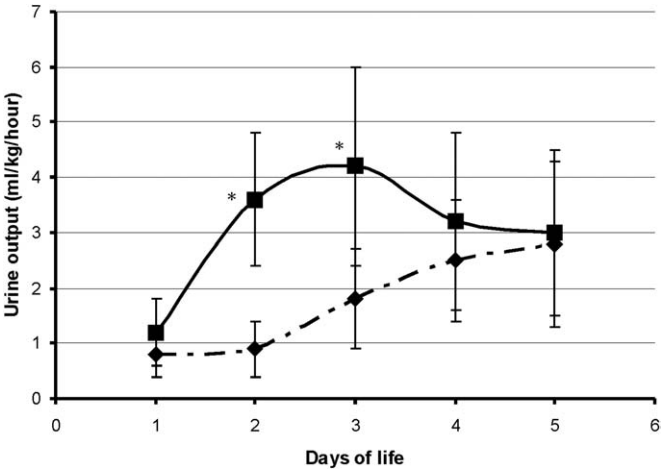

Figure 2. Urine output (mL/kg/h) in the control and theophylline-treated asphyxiated infants during the first 5 days of life. Note that the output from day 2 to day 4 is greater in the theophylline group.
*Significant using 2-factor analysis of variance with repeated measures of a single factor. —■— Theophylline group - —◆— - Control group

DISCUSSION

Our findings strengthen the conclusion that treatment with a single dose of theophylline (8 mg/kg) within the first hour of life in term neonates with perinatal asphyxia results in a significant decrease in serum creatinine level and β2M excretion and a significant increase in creatinine clearance. The kidney is the first organ to be affected by perinatal asphyxia. Acute hypoxia increases adenosine excretion, which activates its receptors, resulting in an increased renal vascular resistance and decreased GFR and filtration fraction. The nonspecific adenosine receptor antagonist theophylline inhibits renal vasoconstriction and has been successfully used to improve renal function after experimental ARF induced by glycerol,[16] radiocontrast medium,[17] and endotoxin[18] in animal models. Gouyon and Guignard[19] reported that the drop in GFR induced by hypoxemia can be prevented by low-dose theophylline administration in rabbits. The hypoxemia-induced changes in the kidneys of these animals were similar to changes noted in hypoxic human newborns. Kemper[20] demonstrated that in anesthetized rats, administration of theophylline before adenosine infusion prevented a sharp drop in GFR in comparison to adenosine alone. Theophylline has also been found to prevent a drop in GFR after contrast media administration in humans and renal insufficiency induced by hypoxemia in newborns with respiratory distress syndrome.[21,22]

The incidence of glomerular and proximal tubular dysfunction indicated by high serum creatinine and urinary β2M levels in our study were considerably lower in the theophylline group. GFR, estimated by endogenous creatinine clearance, was considerably higher in the theophylline group. The mechanism by which administration of theophylline results in lower plasma creatinine levels and improved urine output can be explained by an increase in GFR due to adenosine blockade.[23]

Although mortality was 10% (4/40) in the theophylline group, compared with 6% (2/30) in the control group, this difference was not statistically significant ($P = > .1$). The number of patients was too small to enable evaluation of a significant effect of theophylline on survival.

We followed up patients with postasphyxial renal failure until normalization of renal and tubular function occurred. Renal function improved in the neonatal period in all but 2 infants, in whom it normalized at age 6 weeks. The increased excretion of β2M normalized by age 6 weeks in all infants. Our infants demonstrated earlier normalization of both renal and tubular function than was found in the study by Di Petro et al,[11] in which tubular abnormalities persisted until age 1 year; however, a similar age of normalization of tubular function in asphyxiated term infants was reported by Willis et al.[24]

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