Original Article

Prophylactic Theophyline Reduces Birth Asphyxia Related Renal Injury in Term Neonates

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Abstract

Introduction: Birth Asphyxia (Perinatal Asphyxia) in newborn is a condition caused by the inadequate supply of oxygen before, during, or just after birth. Kidney is the most damaged organ in asphyxiated full-term infants. Theophylline is considered to be effective as adenosine antagonist in reducing renal injury related to birth asphyxia

Objective: To determine mean serum creatinine and glomerular filtration rate in term neonates with perinatal asphyxia after prophylactic dose of theophylline as compared with that of control.

Materials and Methods: In this randomized controlled trial, a total of 60 neonates fulfilling inclusion criteria were included in study either born in the obstetric unit of the study centre (BBH) or referred from other local hospitals. After taking written informed consent, all neonates were randomized into either A (Theophylline group) or B (Placebo group). Theophylline group received single dose of intravenous aminophylline (5 mg/kg, 0.25 ml/kg) while 0.25 ml/kg of normal saline was administered to placebo group over five-minute period within the first hour of presentation. Each patient was evaluated using the predesigned proforma. The 24-hour fluid intake and the urine output were recorded during the first 5 days of life. To assess the infant's renal function, their serum creatinine, creatinine clearance (GFR) was determined on days one, three and five and compared between both groups.

Results: The mean age cases in Theophylline group was 10.73 ± 8.11 hours and in control group the mean age of cases was 14.33 ± 7.52 hours. In Theophylline group there were 17(56.67%) male and 13(43.33%) female cases while in control group there were 17(56.67%) male and 13(43.33%) female cases. The mean creatinine level in Theophylline group was 0.78 ± 0.29 and in control group was 1.15 ± 0.51 with statistically lower mean level in Theophylline group, p-value < 0.05. The mean Glomerular filtration rate in Theophylline group was 31.59 ± 6.35 and in control group was 21.17 ± 7.38 3with statistically higher mean Glomerular filtration rate in Theophylline group, p-value < 0.05.

Conclusion: Through the findings of this study, the therapeutic efficacy of theophylline is confirmed in terms of maintaining serum creatinine and glomerular filtration rate. So, in future renal function can be protected by introducing theophylline and by maintaining renal function we can reduce risk of mortality.

Keywords: Birth Asphyxia, Sarnat Grading System, Theophylline, Mean Glomerular Filtration Rate.

Introduction

Hypoxic ischemic encephalopathy (HIE) is a serious birth complication affecting full term infants; 40–60% of affected infants die by 2 years of age or have severe disabilities.(1) Globally, hypoxia of newborn infants is estimated to account for approximately 23% of the 4 million neonatal deaths and 26% of the 3.2 million stillbirths each year (2) . Acute kidney injury (AKI) is defined as rapid loss in kidney function (hours to days), resulting in derrangements in fluid balance, electrolytes and waste products. Perinatal asphyxia can result in multiorgan dysfunction due to redistribution of cardiac output. Perfusion to more vital organs such as the heart, brain and adrenals is maintained at the expense of the kidneys, gut and skin. As a consequence, kidney is one of the frequently injured organs in neonates who suffered severe birth asphyxia (3). Acute kidney injury (AKI) is a common consequence of perinatal asphyxia, occurring in up to 56% of these infants(4).Renal insufficiency is more frequent within 24 hours of a hypoxic ischemic episode (5)leading to irreversible cortical necrosis when prolonged(5,6) and permanent renal damage in 40% of survivors (7). Following hypoxia in the cerebral organ, anaerobic glycolysis provides lactic acidosis, adenosine tri phosphate hydrolysis resulting in increased levels of adenosine. Pre- and post glomerular vasoconstriction due to adenosine metabolites leads to a fall in glomerular filtration rate (GFR). This might be inhibited by the nonspecific adenosine receptor antagonist, theophylline. (8,9,10,12,13)

Several trials have been conducted across the globe to improve kidney dysfunction in asphyxic neonates. Alok Raina et al. showed that neonates in the theophylline group had lower serum creatinine levels (0.83 ± 0.35 versus 1.47 ±0.61; p = 0.00) and higher endogenous creatinine clearance or GFR (32.16 ±16.34 versus 17.73 ±7.92; p = 0.00) than the placebo group. (2)

A study by David Askenazi showed that treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates (12). Furthermore, Kidney Disease Improving Global Outcomes 2012 (KDIGO) guidelines suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI (14)

The rationale for this study is to evaluate renal function in term neonates with birth asphyxia after prophylactic dose of theophylline. Perinatal asphyxia is common in our settings and renal dysfunction is mostly managed by restricted fluid administration but no remedy is currently available to prevent renal dysfunction in asphyxic newborns. This can improve our management of newborns with birth asphyxia in future.

Materials and Methods

This study was conducted in neonatal intensive care unit (NICU) of Pediatric Department of Benazir Bhutto Hospital Rawalpindi. Duration of study was 6 Months from 5th September, 2018 to 5th March, 2019. It was a randomized control trial. For sample size. Level of significance=5, Power of test= 90%, Population standard deviation=48, Population variance=0.2304, Test value of population mean= 0.83, Anticipated population mean=1.47 (2.) Since minimum sample size is 30, sample size was 30 in both groups. Patients (n=60) were selected with non-probability consecutive sampling technique

Inclusion Criteria was all term neonates(Infants born after 37 0/7 to 41 6/7 weeks after first day of mother's last menstrual period.) either male or female with birth weight more than 2500g having birth asphyxia(a neonate with an Apgar score of up to three at 1 minute or up to five at 5 minutes after birth or severe acidosis (pH <6.7 with base deficit of >25 mmol/L or need for positive pressure ventilation at birth, seizures or severe hypotonia on clinical examination,Sarnat staging 2 and 3(provided in annexure). Exclusion criteria was Preterm , Small for gestation or low birth weight babies ; Neonates with congenital anomalies (cardiac or skeletal on clinical examination) ; neonates with maternal history of drugs known to cause foetal depression e.g. cocaine ; neonates requiring mechanical mode of ventilation ;Neonates with sepsis (positive blood culture, reluctance to feed, platelets <50,000.Neonates with birth asphyxia sarnat stage 1.(provided in annexure)

After taking written informed consent from a parent or guardian, selected neonates were randomized into either A (Theophylline group) or B (Placebo group). This randomization was performed by a person not directly related to the study. Theophylline group received single dose of intravenous aminophylline (5 mg/kg, 0.25 ml/kg) while 0.25 ml/kg of normal saline was administered to placebo group over a five-minute period within the first hour of presentation. Both the treatment and placebo preparations were provided in syringes with the same external appearance and administered to the subjects in the study and placebo

groups accordingly. All neonates with clinical features of hypoxic ischaemic encephalopathy were staged by the Sarnat grading system. Each patient was evaluated using the predesigned proforma. To assess the infant's renal function, their serum creatinine, creatinine clearance (GFR) was determined on days one, three and five and compared between both groups.

Data was entered and analysed by SPSS version 20. Descriptive statistics were used for qualitative and quantitative variables. Mean and standard deviation was calculated for quantitative variables like age, weight, serum creatinine levels and GFR.Qualitative variables like gender and asphyxia Sarnat stage was presented as frequency and percentage. Test of significance Independent sample t test was applied to compare between two groups. p -value ≤ 0.05 was considered significant.

Results

The mean age of cases in Theophylline group was 11.00 ± 8.55 hours and in control group the mean age of cases was 14.97 ± 8.35 hours.

In Theophylline group there were 17(56.67%) male and 13(43.33%) female cases while in control group there were 17(56.67%) male and 13(43.33%) female cases.

The mean gestational age at time of delivery in Theophyline group was 39.47 ± 1.31 weeks and in control group was 38.87 ± 1.41 weeks.

The mean birth weight in Theophylline group was 3188.29 ± 412.36 g and in control group was 3138.93 ± 395.23 g.

In Theophylline group there were 9(30%) neonates with Sarnat stage 2 and 12(40%) with stage 3 while in control group, 8(26.67%) had stage 2 and 15(50%) cases had stage 3.

The mean sodium levels in Theophylline group were 128.04 ± 1.64 and in control group was 135.47 ± 2.99, with statistically lower mean sodium in Theophylline group, p-value < 0.05.

The mean creatinine levels in Theophylline group was 0.78 ± 0.29 and in control group was 1.15 ± 0.51 with statistically lower mean level in Theophyline group, p-value < 0.05.

The mean Glomerular filtration rate in Theophylline group was 31.59 ± 6.35 and in control group was 21.17 ± 7.38 with statistically higher mean Glomerular filtration rate in Theophyline group, p-value < 0.05.

When data was stratified for birth weight and Sarnat staging, the mean Glomerular filtration rate in Theophylline group was statistically higher as compared to control group, p-value < 0.05, with higher GFR in neonates with sarnat 2 staging than 3.

Table 1: Comparison of Glumerular filtration rates in both study groups

	Study groups	*Mean*	*S.D*	*T-test*	*P-value*
Glomerular filtration rate	Theophylline (n=30)	31.60	6.35	5.861	<0.001**
	Control (n=30)	21.18	7.38		

****Highly Significant**

Table 2: Comparison of Creatinine and Glomerular filtration rate in both Study groups with respect to birth weight

Birth weight (g)		*Study groups*	*Mean*	*S.D*	*t-test*	*p-value*
2500 - 3000	Creatinine	Theophylline	0.71	0.28	-2.692	0.014*
		Control	1.20	0.51		
	Glomerular filtration rate	Theophylline	31.95	6.70	3.917	0.001*
		Control	20.33	7.11		
3000 - 4000	Creatinine	Theophylline	0.82	0.30	-2.331	0.025*
		Control	1.13	0.52		
	Glomerular filtration rate	Theophylline	31.42	6.34	4.244	<0.001**
		Control	21.74	7.71		

****Highly Significant**
***Significant**

Table 3: Comparison of Creatinine and Glomerular filtration rate in both Study groups with respect to Sarnat Staging

Sarnat Staging		*Study groups*	*Mean*	*S.D*	*t-test*	*p-value*
Stage 2	Creatinine	Theophylline	0.76	0.30	-.721	0.482
		Control	0.86	0.26		
	Glomerular	Theophylline	33.30	5.31	5.621	<0.001**

	filtration rate					
		Control	20.73	3.63		
Stage 3	Creatinine	Theophylline	0.76	0.31	-2.381	0.025*
		Control	1.18	0.55		
	Glomerular filtration rate	Theophylline	30.82	7.58	2.957	0.007*
		Control	21.52	8.52		

****Highly Significant**
***Significant**

Discussion

Perinatal asphyxia is an essential reason for neonatal mortality and neurological morbidity (15). Asphyxia can lead to multi organ dysfunction and redistribution of cardiac output to maintain cerebral, cardiac, and adrenal perfusion while potentially compromising renal, gastrointestinal, and skin perfusion as circulatory response (16). During acute hypoxemia, adenosine levels increase as ATP hydrolysis exceeds synthesis resulting in intra-renal vasoconstriction, decreased renal perfusion, and drop of glomerular filtration rate (GFR)(12). Compared to older children, newborns are more susceptible to acute kidney injury because they have low glomerular filtration rate, high renal vascular resistance, high plasma renin activity and decreased reabsorption of sodium in the proximal tubules (16). Despite our understanding of the impact of AKI on clinical outcomes, there are no FDA approved therapies to prevent or mitigate AKI (12). In the kidney, adenosine constricts the afferent arteriole and decreases glomerular blood flow; adenosine receptor blockade mitigates this vasoconstriction (17). The natriuresis caused by methylxanthines is predominantly the result of inhibition of tubular salt transport. Natriuresis without hemodynamic changes was also caused by methylxanthines in premature infants and newborn rabbits (18).

Bhat MA et al(10) conducted a study to see whether prophylactic theophylline can reduce the incidence and/or severity of renal failure in infants with asphyxia. Creatinine clearance was higher and excretion of beta 2 microglobulin (β2M) was lower in the theophylline 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. They concluded that A single dose of theophylline within the first hour of birth in 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(10).

In current study the mean creatinine levels in Theophyline group was 0.78 ± 0.29 and in control group was 1.15 ± 0.51 with statistically lower mean level in Theophyline group, p-value < 0.05. The mean Glumerular filtration rate in Theophyline group was 31.59 ± 6.35 and in control group was 21.17 ± 7.38 with statistically higher mean Glumerular filtration rate in Theophyline group, p-value < 0.05.

Jenik et al(21) designed a study to determine whether theophylline could ameliorate renal function in asphxic neonates. During the first day of life, the 24-hour fluid balance was significantly more positive in the infants receiving placebo compared with the infants receiving theophylline. Severe renal dysfunction was present in 4 of 24 (17%) infants of the theophylline group and in 15 of 27 (55%) infants of the control group (relative risk: .30; 95% confidence interval: .12–.78). Mean endogenous creatinine clearance of the theophylline group was significantly increased compared with the creatinine clearance in infants receiving placebo (21.84 ± 7.96 vs 6.42 ± 4.16). The GFR (estimated by Schwartz's formula) was markedly decreased in the placebo group. Urinary β2M concentrations were significantly reduced in the theophylline group (5.01 ± 2.3 mg/L vs 11.5 ± 7.1 mg/L). Moreover, 9 (33%) patients of the theophylline group versus 20 (63%) infants of the control group had urinary β2M above the normal limit (<.018). . Except for renal involvement, a similar frequency of multiorganic dysfunction, including neurologic impairment, was observed in both groups. These findings are similar to our study.

In a similar study done in Iran, 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 favoured 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(9). Bakr(8) et al

demonstrated that incidence of severe renal dysfunction was significantly higher in the control group. Serum creatinine values were less, and creatinine clearance and GFR were significantly higher in the theophylline group from the second day onwards.

Wassia et al [3] conducted meta-analysis involving 197 infants from four RCTs. Compared with placebo, prophylactic theophylline was associated with a significant reduction in the incidence of severe renal dysfunction (pooled relative risk) using fixed-effects model was 0.38 (95% confidence interval, 0.25 to 0.57; P<0.001)(3).

Alok Raina et al. showed that neonates in the theophylline group had lower serum creatinine levels (0.83 ± 0.35 versus 1.47 ±0.61; p = 0.00) and higher endogenous creatinine clearance or GFR (32.16 ±16.34 versus 17.73 ±7.92; p = 0.00) than the placebo group. Severe renal dysfunction, namely acute kidney injury, was present in 36 (15%) of the neonates in the theophylline group versus 117 (48%) in the placebo group (p < 0.01(2).

K Seo et al showed that aminophylline improved renal function and indices of renal inflammation.[22] Deirdre et al showed that prophylactic theophylline, given early after birth (within 1 h), has beneficial effects on reducing renal dysfunction in asphyxiated full-term infants.[23]

A study by David Askenazi showed that treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates.[12] Kiran P. Sathe showed that methylxanthines when used in hypoxic neonates seem to prevent oliguric renal failure.[24]

Another study supported 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).[11] Furthermore, Kidney Disease Improving Global Outcomes 2012 (KDIGO) guidelines suggest that a single dose of theophylline may be given in neonates with severe perinatal asphyxia, who are at high risk of AKI.[14]

Conclusion

Through the findings of this study, therapeutic efficacy of theophylline is confirmed in term of maintaining serum creatinine and glomerular filtration rate. So, in future renal function can be secured by introducing theophylline and by maintaining renal function we can reduce risk of mortality.

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