ORIGINAL ARTICLE

The Role of Prophylactic Theophylline in Prevention of Acute Renal Failure in Neonates Exposed to Asphyxia

IFTIKHAR EJAZ, AFTAB ANWAR, ASMA MUSHTAQ, FATIMA ZEESHAN, IQRA WAHEED
Correspondence: Dr. Iftikhar Ejaz, Associate Professor Paediatrics & Paediatric Nephrologist, Children's Hospital & ICH, Ferozepur Road, Lahore. E-mail: driftikharijaz777@gmail.com, Cell: 0302-8420335

ABSTRACT

Background: Renal damage frequently complicates perinatal asphyxia. Renal vasoconstriction due to adenosine metabolite leads to a fall in glomerular filtration rate (GFR) and filtration fraction (FF). This might be inhibited by the nonspecific adenosine receptor antagonist, theophylline.

Objective: To determine the efficacy of prophylactic theophylline in prevention of acute renal failure in term neonates exposed to perinatal asphyxia.

Material and Methods: This descriptive case series was conducted at Department of Neonatology, The Children's Hospital, Lahore for 6 months. Total 75 asphyxiated term infants were included through non-probability purposive sampling technique. Children received 5 mg/kg single dose of IV theophylline during first 24 hours of life. Fluid intake, urine output, serum creatinine was recorded on proforma. The data was analyzed using SPSS version 20. The efficacy of theophylline was calculated as frequency and percentage.

Results: Mean age of presentation was 11.91±6.90 hours. Of the total 75 neonates, efficacy of theophylline i.e. prevented the neonates from developing AKI in 81.3% (n=61), while it had no effect in 18.7% (n=14). About 20% (n=15) patients died afterwards while 80% (n=60) patients were discharged home.

Conclusions: Prophylactic theophylline is effective in prevention of acute kidney failure in neonates exposed to perinatal asphyxia.

Key Words: Perinatal asphyxia, theophylline, acute renal failure.

INTRODUCTION

Perinatal asphyxia can result in multisystem organ damage in a neonate.[1, 2] Circulatory response to asphyxia results in redistribution of blood flow towards the brain, heart and adrenals, and away from kidney, skin and the gastrointestinal tract. It can cause damage to almost every tissue and organ of body and various target organs involved have been reported to be kidneys in 50%, followed by CNS in 28%, CVS in 25% and lungs in 23% cases.[3]

Fetal and neonatal asphyxia are the primary causes of transient renal or acute renal failure in neonates.[1, 3] All difficult deliveries requiring resuscitation at birth cause an initial episode of shock and renal ischemia, which triggers a transient ischemic state sensitive to oxygen deprivation neonates may develop vasomotor nephropathy or acute renal failure.[4, 5]

As kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 hours of a hypoxemic ischemic episode, which if prolonged, may even lead to irreversible cortical necrosis. Early recognition of acute renal failure is important in babies with hypoxic ischemic encephalopathy to facilitate appropriate fluid and electrolyte management as a stable chemical and biochemical melieu is vital. The kidney is one of the most frequently damaged organs in asphyxiated neonates.[6] Renal vascular resistance is greater while renal blood flow is lesser in newborn compared with adults, and renders the kidneys more susceptible to severe renal failure.[7]

OBJECTIVE

To determine the efficacy of prophylactic theophylline in prevention of acute renal failure in term neonates exposed to perinatal asphyxia.

MATERIAL AND METHODS

This descriptive case series was conducted at Department of Neonatology, the Children's hospital, Lahore for six months from 15-12-2010 to 15-06-2011. Sample size of 75 neonates born after completion of 37-42 weeks of gestation was calculated with 95% confidence level, 7.5% margin of error and taking expected percentage of efficacy of prophylactic theophylline i.e., 88.2%.[8] Informed

parental consent and demographic data were obtained. Intervention was done within first 24 hours of life (theophylline 5mg/kg). Serum electrolytes and renal functions were sent on 1st, 3rd and 5th days of life. Record of 24 hour fluid intake and urine output was maintained. All this information was recorded through a specially designed proforma. The data was entered and analyzed using SPSS version 20. The continuous variables like age have been demonstrated as mean and standard deviation. The qualitative variables like gender and efficacy of theophylline have been presented as frequency and percentage. Data has been stratified for stages of asphyxia (I, II, III) to address effect modifier. Perinatal asphyxia was labeled when any of the following (a) history of fetal distress available from record of referring hospital or health personnel, (b) need for immediate resuscitation, (c) history of delayed cry after birth available from record of referring hospital or health personnel (d) moaning after birth and (e) history of seizures after birth. Efficacy was labeled when any one of the following (a) serum creatinine level less than 1.5 mg/dl or rise in levels of serum creatinine less than 0.3mg/dl/day during first 5 days of life or (b) normal urine output defined as urine output 1-4ml/Kg/hour assessed for 5 days.

RESULTS

Mean age of presentation was 11.91±6.90 hours. There were 73.3% (n=55) male and 26.7% (n=20) female neonates. The mean weight of the babies was 2.68±0.48kg. About 57.3% (n=43) of the neonates had ANN I, 32% (n=24) had ANN II and 10.7% (n=8) had ANN III. Of the total 75 neonates, efficacy of theophylline i.e. prevented the neonates from developing AKI in 81.3% (n=61), while it had no effect in 18.7% (n=14). About 20% (n=15) patients died afterwards while 80% (n=60) patients were discharged home. Among died patients, 3 were those who achieved efficacy theophylline while 12 died neonates belonged to group in which efficacy was not achieved. This was significant difference and this showed that the risk of death is also low with theophylline (p=0.000).

Table I: Demographic characteristics of neonates at time of presentation

	Mean±SD / n (%)
Age(hours)	11.91±6.90
Sex	
Male	55 (73.3%)
Female	20 (26.7%)
Weight(Kg)	2.68±0.48
ANN I	43 (57.3%)
ANN II	24 (32.0%)
ANN III	8 (10.7%)

Table II: Outcome of Theophylline

		Frequency
Efficacy	Yes	61 (81.3%)
	No	14 (18.7%)
Outcome	Discharged	60 (80.0%)
	Death	15 (20.0%)
Total		75 (100%)

DISCUSSION

The kidney is the most damaged organ in asphyxiated full-term infants.[9] Acute hypoxemia is associated with an increase in renal vascular resistance and a decrease in GFR and FF(filtration fraction).[10] During oxygen deficit, when adenosine triphosphate hydrolysis prevails over adenosine triphosphate synthesis, adenosine (a direct degradative product of 59 adenosine monophosphate) increases and activates its receptors resulting in an increment of the renal vascular resistance (pre-glomerular vasoconstriction and post glomerular vasodilatation) thus decreasing GFR and FF.[11]

Hemodynamic renal changes produced by adenosine were observed during ischemic or hypoxemic experimental studies.[12] Moreover, adenosine administrated into the renal artery led to decrease GFR in humans.[13] Adenosine receptor antagonists like theophylline can inhibit renal vasoconstriction in response to exogenous and endogenous adenosine and have been successfully used to improve renal function after experimental ARF induced by glycerol,[14] endotoxin,[15] and radiocontrast administration in several animal models.[16]

It has been observed in rats that theophylline attenuates the extent of GFR reduction when it is administrated during maintenance phase of post-ischemic ARF.[17] Kemper demonstrated in anesthetized rats that administration of theophylline (8mg/kg), before adenosine infusion, prevents a sharp fall in glomerular filtration in comparison to adenosine alone.[18] Gouyon and Guignard demonstrated in newborn and adult animals that the fall in glomerular filtration induced by hypoxemia can be prevented by theophylline in low doses. These authors used rabbits as an

animal model that showed, in hypoxemia episodes, renal changes similar to those observed in human hypoxemic newborns.[19] Used commonly for apnea of prematurity, theophylline has also been shown to prevent both the reduction of GFR after contrast media application in humans and the renal insufficiency induced by hypoxemia in new-borns with respiratory distress syndrome.[20, 21]

Jenik and colleagues investigated theophylline effect in 60 perinatal asphyxiated infants.[22] Twenty-four patients received a single dose of 8 mg/kg IV theophylline, in the first hour of birth. Four infants (17%) suffered from severe kidney dysfunction compared to 15 infants (55%) in the control group. In our study although there was no control group but renal failure was present in 14 (18.7%) of the infants receiving theophylline. A study conducted by Jenick et al 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. Bakr investigated 40 severe asphyxiated infant in a similar study. Their selection criteria 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.[23]

In a similar study by Bhat and associates, 70 term neonates were divided into receivers of theophylline (n = 40) and placebo (n = 30). Renal dysfunction was present in 10 (25%) of the neonates as compared to 18 (60%) in the control group. 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.[24]

CONCLUSION

Thus theophylline is effective in prevention of acute kidney failure in term neonates exposed to perinatal asphyxia. Additional and larger studies will be necessary before the use of theophylline in asphyxiated new-borns can be considered for clinical practice. Prophylactic theophylline treatment, given early after birth, has beneficial effects in reducing the renal involvement in asphyxiated full-term infants, with no significant changes in CNS involvement.

REFERENCES

1. Martín-Ancel A, García-Alix A, Cabañas FGF, Burgueros M, Quero J. Multiple organ involvement in perinatal asphyxia. The J pediatr. 1995;127(5):786-93.
2. Mohan PV, Pai PM. Renal insult in asphyxia neonatorum. 2000.
3. Shankaran S, Woldt E, Koepke T, Bedard MP, Nandyal R. Acute neonatal morbidity and long-term central nervous system sequelae of perinatal asphyxia in term infants. Early human development. 1991;25(2):135-48.
4. NHMRC. Perinatal morbidity. Report of the health care committee expert panel on perinatal morbidity. Australia: National Health and Medical Research Council. Australian Govt. Publishing Service;1995.
5. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. Archives of neurology. 1976;33(10):696-705.
6. Perlman J, Tack E, Martin T, Shackelford G, Amon E. Acute systemic organ injury in term infants after asphyxia. Am J Dis of Children. 1989;143(5):617-20.
7. Gruskin AB, Edelmann CM, Yuan S. Maturational changes in renal blood flow in piglets. Pediatric research. 1970;4(1):7-13.
8. Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iranian journal of kidney diseases. 2009;3(4).
9. Willis F, Summers J, Minutillo C, Hewitt I. Indices of renal tubular function in perinatal asphyxia. Arch Dis Child-Fetal and Neonatal Edition. 1997;77(1):F57-F60.
10. Gouyon J-B, Vallotton M, Guignard J-P. The newborn rabbit: a model for studying hypoxemia-induced renal changes. Neonatology. 1987;52(2):115-20.
11. Hall JE, Granger JP, Hester RL. Interactions between adenosine and angiotensin II in controlling glomerular filtration. AJP-Renal Physiology. 1985;248(3):F340-F6.
12. Gouyon J-B, Guignard J-P. Functional renal insufficiency: role of adenosine. Neonatology. 1988;53(4):237-42.

13. Edlund A, Ohlsen H, Sollevi A. Renal effects of local infusion of adenosine in man. Clinical Science. 1994;87(Pt 2):143-9.
14. Bowmer C, Collis M, Yates M. Effect of the adenosine antagonist 8-phenyltheophylline on glycerol-induced acute renal failure in the rat. British j pharmacology. 1986;88(1):205-12.
15. Prada J, Churchill P, Bidani A, editors. Protective effect of theophylline in endotoxin-mediated acute-renal-failure (ARF) in rats. Kidney Int; 1986: Blackwell Science Inc 350, Main St, Malden, MA 02148.
16. Deray G, Martinez F, Cacoub P, Baumelou B, Baumelou A, Jacobs C. A role for adenosine calcium and ischemia in radiocontrast-induced intrarenal vasoconstriction. Am j nephrol. 1990;10(4):316-22.
17. Lin J-J, Churchill PC, Bidani AK. Theophylline in rats during maintenance phase of post-ischemic acute renal failure. Kidney int. 1988;33(1).
18. Kemper R. Die Antagonistischen Wirkungen von Adenosine und Theophyllin Auf Die Nierenfunktion der Rate. [English translation: The Antagonist Effects of Adenosine and Theophylline on the Renal Function of Rats]. Aachen, Germany1977.
19. Gouyon J-B, Guignard J-P. Theophylline prevents the hypoxemia-induced renal hemodynamic changes in rabbits. Kidney int. 1988;33(6).
20. Erley CM, Duda SH, Schlepckow S, Koehler J, Huppert PE, Strohmaier WL, et al. Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. Kid int. 1994;45(5).
21. Huet F, Semama D, Grimaldi M, Gouyon J-B, Guignard J-P. Effects of theophylline on renal insufficiency in neonates with respiratory distress syndrome. Intensive care medicine. 1995;21(6):511-4.
22. Jenik AG, Cernadas JMC, Gorenstein A, Ramirez JA, Vain N, Armadans M, et al. A randomized, double-blind, placebo-controlled trial of the effects of prophylactic theophylline on renal function in term neonates with perinatal asphyxia. Pediatrics. 2000;105(4):e45-e.
23. Bakr AF. Prophylactic theophylline to prevent renal dysfunction in newborns exposed to perinatal asphyxia—a study in a developing country. Pediatr Nephrol. 2005;20(9):1249-52.
24. Bhat MA, Shah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal function in term neonates with perinatal asphyxia: a randomized, placebo-controlled trial. The j pediatr. 2006;149(2):180-4.