ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

ROLE OF AMINOPHYLLINE IN PREVENTING RENAL DYSFUNCTION IN NEONATES WITH PERINATAL ASPHYXIA

Dr. Sonal Mehta[1], Dr. Manmeet Kaur Sodhi[2], Dr. Vipul[3], Dr. Navjot Kaur[4], Dr. Kirandeep kaur[5]

[1,5]Junior Resident, [2] Professor, [3,4]Senior Resident; Department of Pediatrics, Government Medical College, Amritsar, Punjab, India,

Corresponding author:Dr. Sonal Mehta

Article History: **Received:** 13.05.2023 **Revised:**07.06.2023 **Accepted:** 15.06.2023

ABSTRACT

Background: Perinatal asphyxia is a common neonatal problem that contributes significantly to neonatal morbidity and mortality. Perinatal asphyxia is perceived to be the primary cause of transient renal dysfunction or acute renal failure. Adenosine plays an important role in tubuloglomerular feedback. Aminophylline is an adenosine receptor inhibitor, thus promotes renal perfusion and decreases solute load.

Objectives: To study the role of aminophylline in preventing renal dysfunction in neonates with perinatal asphyxia.

Methods: It is a prospective study with randomized control trials with cases and control group conducted over a period of one year in Department of Paediatrics, Govt. Medical College, Amritsar in collaboration with Department of Biochemistry. Renal functions were assessed on the basis of urine output, GFR and S. creatinine values on day1, 4 and 7.

Results: Two comparable groups of cases and controls showed that there was a significant difference in urine output between the two groups on day 1(p=0.0003) and day4(p=0.000007). However, no such difference was found on day 7. Statically, no significant difference was found in values of glomerular filtration rate and S. creatinine values.

Conclusion: Prophylactic use of aminophylline in neonates with perinatal asphyxia does not have significant impact in preventing AKI as there was no significant difference in S. creatinine values and GFR. There was no reduction in mortality rates in aminophylline treated group as compared to control group.

INTRODUCTION

Perinatal asphyxia is a common neonatal problem and contributes significantly to neonatal morbidity and mortality[1]. According to the World Health Organization, perinatal asphyxia is one of the three common causes of under-five child mortality (11%) following preterm birth (17%) and pneumonia (15%). Perinatal asphyxia is a common reason for admission to a neonatal intensive care unit and is frequently associated with encephalopathy and multi-organ dysfunction[2]. Perinatal asphyxia is a lack of blood flow or gas exchange to or from the fetus in the period immediately before, during, or after the birth process. The World Health Organization (WHO) defines birth asphyxia as inadequate oxygen perfusion to vital organs, generally, caused by a failure to initiate and sustain breathing at birth. Additionally, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics expand on the definition of neonatal asphyxia if the following conditions are fulfilled: umbilical cord arterial pH <7; APGAR score of 0–3 for longer than 5 min; neurological manifestations such as seizures, hypercapnia, metabolic acidosis and hypoxic-ischemic encephalopathy[5].

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

Perinatal asphyxia can result in profound systemic and neurologic sequelae due to decreased blood flow and/or oxygen to a fetus or infant during the peripartum period. Neonatal hypoxic-ischemic encephalopathy refers specifically to the neurologic sequelae of perinatal asphyxia[3].

Of those infants affected, 15-20% die in the neonatal period, and up to 25% of survivors are left with permanent neurologic deficits[6].Using the Sarnat staging for encephalopathy can be useful.

Brain injury stages consists of primary and secondary neuronal injury. Primary brain injury occurs due to interruption of oxygen supply and glucose to brain. This causes inactivation of the sodium potassium pump leading to intracellular accumulation of sodium which in turn causes water accumulation and cell lysis. This is followed by a latent period of 6-12 hours after which secondary neuronal damage occurs due to reperfusion to damaged areas, spreading neurotransmitters and increasing the affected brain area.

Perinatal asphyxia is the primary cause of transient renal dysfunction or acute renal failure. Kidney malfunction presents as oliguria and acute renal failure, which is caused by acute tubular necrosis. Furthermore, renal vein or artery thrombosis can occur along with severe perinatal asphyxia. The prognosis of renal dysfunction is of utter importance in preventing complications like hyponatremia caused by increased fluid load and hyperkalemia[7].

Hemodynamic renal changes produced by adenosine were observed during ischemic or hypoxemic experimental studies. Adenosine administrated into the renal artery led to decreased GFR in humans. 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[8].

It is important to maintain renal function in asphyxiated neonates during reperfusion or reoxygenation to minimize damage and improve outcome. A significant improvement of renal perfusion improves clinical care on fluid balance and drug clearance and lead to favourable long-term renal and neurodevelopmental outcome. Prophylactic aminophylline, given early after birth, has beneficial effects on reducing kidney dysfunction in neonates with asphyxia[9] Adenosine plays an important role in tubuloglomerular feedback. With increasing solute load in the renal tubules, energy depletion occurs, accompanied by the release of adenosine. The secreted adenosine stimulates pre-glomerular vasoconstriction leading to a reduction in solute flow.. The mechanisms of action of aminophylline in lowering serum creatinine clearance and improving renal perfusion could be explained by adenosine receptor inhibition at minimal doses and type IV phosphodiesterase blockade at increased doses. Aminophylline-induced phosphodiesterase inhibition lowers the breakdown of cAMP, which promotes renal vasodilation and renal perfusion[10]. With this background, the present study is undertaken to know the role of aminophylline in perinatal asphyxia.

MATERIALS AND METHODS

This prospective study with randomized control trial was conducted in nursery ward and NICU of paediatrics department of Bebe Nanki Hospital, GMC, Amritsar in collaboration with department of pharmacology and biochemistry of same institute. Study population was the neonates being admitted to baby nursery with predisposing factors for perinatal asphyxia.The study was conducted after taking permission from the ethics committee, Government Medical College, Amritsar and informed consent was taken from parents/guardians.

The participants were randomized into cases(50) and control(50) groups. The intervention was aminophylline 5mg/day. They were randomized to receive a single dose of aminophylline (5 mg/kg) or placebo of 5% dextrose water for injection (5ml/kg) during the first hour of life.

The 24-hour fluid intake and the urine volumes were recorded during the first week of life. Renal function was assessed by daily urine output, serum creatinine and electrolytes level measurement, during the first and 4thday of life. The GFR was estimated before and after the intervention (24 hours after intervention and during the 4th and 7th day of life) using Schwartz's formula, in two studygroups.. Obtained data from two groups of neonates before and after intervention recorded using a questionnaire. The obtained data was compared using the t test and p value was calculated to find any statistically significant difference between the two groups.

RESULTS

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

The 2 groups of 50(intervention) and 50 (controls) were comparable in terms of gender distribution, gestational age and weight.

TABLE 1: COMPARISON OF URINE OUTPUT IN INTERVENTION AND PLACEBO GROUP

URINE OUTPUT	INTERVENTION	PLACEBO	P VALUE
DAY 1	1.02±0.24	0.877±0.15	0.000345
DAY 4	1.309±0.25	1.08± 0.23	0.000007
DAY 7	1.489±0.29	1.41±0.27	0.089

The difference in the mean values in urine output between two groups, on
First and fourth day of post natal life was significant. The intervention group
Had a higher mean of urine output as compared to control group with significant p value. Although no significant difference in urine output was measured on day 7 of life.

TABLE 2: COMPARISON OF S. CREATININE VALUES BETWEEN INTERVENTION AND PLACEBO GROUP

S. CREATININE	INTERVENTION	PLACEBO	P- VALUE
DAY1	0.878±0.27	0.845±0.17	0.244
DAY4	0.702±0.28	0.702±0.15	0.5

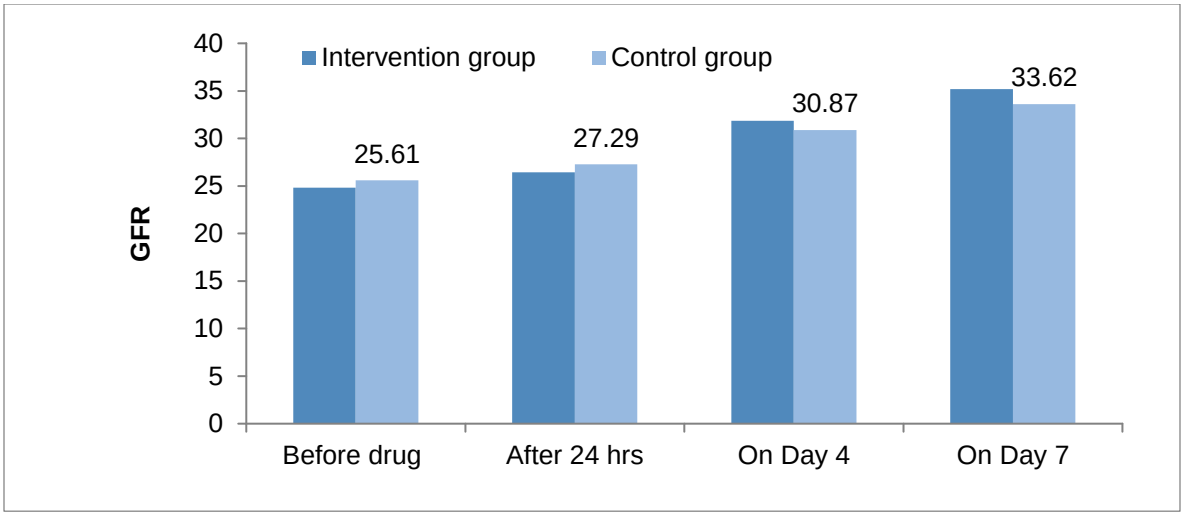
In this study, S. creatinine values were measured on day 1 and day 4 of life and compared using t-test. Nostatistically significant difference was found in mean serum creatinine values on day 1 and day 4 of life**.**

TABLE 3 and GRAPH 1: COMPARISON OF GFR BETWEEN INTERVENTION AND PLACEBO GROUP

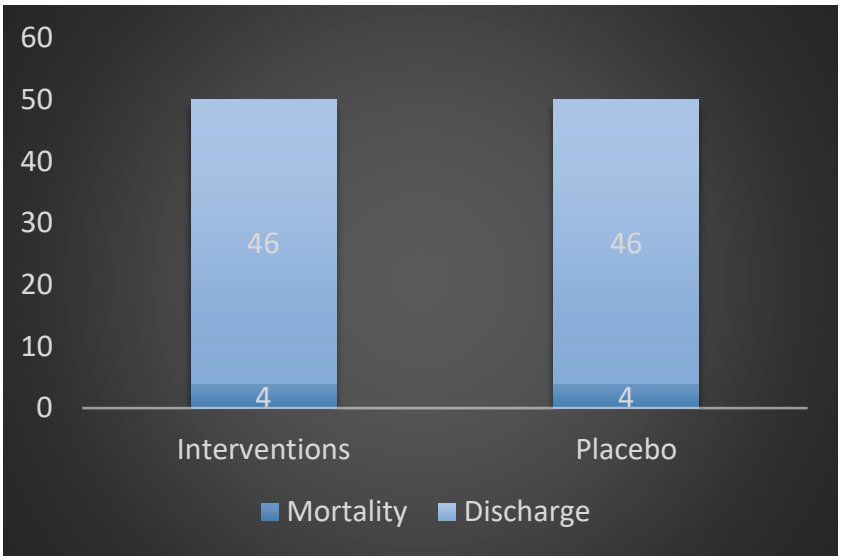
The collected data of GFR was calculated using Schwartz formula, was analysed and mean values of GFR were compared using t-test revealed a non-significant difference statistically between both groups. Also statistically, no significant difference was found between mean GFR compared in aminophylline treated group and control group after 24 hours, on day4 and on day 7.

GFR	INTERVENTION	PLACEBO	P-VALUE
BEFORE DRUG	24.83±8.41	25.616±5.84	0.3452
AFTER 24 HOURS	26.42±9.78	27.29±6.07	0.296
DAY 4	31.86±13.86	30.87±7.66	0.330
DAY7	35.19±13.85	33.622±7.67	0.241

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023



GRAPH 2: COMPARISON OF MORTALITY RATES BETWEEN INTERVENTION AND PLACEBO GROUP



In the study, it was found that 4 deaths occurred in intervention and 4 deaths were reported in placebo groups wherein the additional risk.

DISCUSSION

In the present study, mean gestational age (in weeks) of male and female neonates in intervention group was 37.11 ± 1.75 and 36.75 ±1.29 respectively. Similarly, mean gestational age of male and female neonates in Control group was 37.18 ± 0.84 and 37.23 ± 1.09 respectively. Data of both groups was compared by using t-test and p-value found to be insignificant (p> 0.05). Our study is similar to study conducted by Bhat MA et al (2009)[11] which showed that there were no significant differences in gestation age between the groups receiving theophylline vs. the control (38.2±0.79 vs. 38.1±0.88).

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

In present study, APGAR score was recorded to determine the severity of birth asphyxia. In the intervention group, APGAR score of less than three at one minute of life after birth was recorded in 32 (64%) neonates, while in Control group, it was recorded in 21(42%) neonates. Similarly in intervention group, APGAR score of less than six at five minutes of life after birth was recorded in 27 (54%) neonates, while in Control group, it was recorded in 22(44%) neonates. P-value was 0.589 which was statistically insignificant (p>0.05).

The other risk factors for perinatal asphyxia like eclampsia, preeclampsia, gestational hypertension and fetal bradycardia were found to be insignificant in both studied groups.

In the present study, urine output was measured on day 1, 4 and 7 of life. Mean value of Urine output in aminophylline treated vs. Control group on day 1 in males was 1.02±0.25 (ml/kg/hr) and in female was 0.86±0.16 with significant p-values 0.000345 and 0.00059 respectively. The difference in the mean values of ratio of urine output to intake between the two groups, on 1st and 4th day of post natal life was significant with significant p-values 0.000007and 0.000086respectively. No significant difference in the volume of urine output was calculated on day 7 of life in both studied groups in males and females with p-values 0.072 and 0.089 respectively (p> 0.05).This was similar to studies conducted by Saeidi et al (2022)[12]who assessed at the urine output to volume intake ratio. At the end of the first to third days, this ratio was significantly greater in the aminophylline group than in the control group; however, on the fourth and fifth days, it gradually decreased in the control group due to an increase in urine production which was similar to our study which showed increase in urine output on day 1 and 4 of post natal life.

Similar studies by da Silva PSL et al (2011)[13] in their study demonstrated that, low doses of aminophylline (3 mg/kg) administration prompted a 275% rise in urine production. Study BakrAF (2005)[14]demonstrated that urine output was higher in the theophylline group than in the control group only on the first day of life. Catarelli et al (2006)[15]and Bhat GC et al (2019)[16]also reported an increase in urinary output by 4th day.

In the present study, serum creatinine (mg/dl) levels were measured on day 1 and day 4 of life. Mean value of serum creatinine was measured and compared by using t-test. No statistically significant difference was found in mean serum creatinine values in both the groups on both day 1 and day 4 with p-value 0.244 and 0.5 respectively (p>0.05).Similar observations were made by Saeidi et al (2022)[12,] who observed aminophylline enhanced urine output but no effect on serum creatinine levels.

This was in contrast to studies by Jenik AG et al (2000) wherein the mean creatinine of the theophylline group was significantly lower (0.71±0.2 vs. 1.36±0.39) as compared to control group.Eslami Z et al (2009)[20]observed that at the third and fifth days (when theophylline group was compared to the control group), serum creatinine levels were significantly lower in both group and Bhat MA et al (2006)[21]reported that when given to term neonates with perinatal hypoxia within the first hour of delivery, theophylline significantly lowers serum creatinine levels than controls do at day five.The obtained data of GFR (ml/min/1.73 m^2) was calculated using Schwartz formula. No significant difference in the mean value of GFR was found in both studied groups before aminophylline administration (p-value 0.3.452). Similarly GFR was measured in both aminophylline treated and Control groups after 24 hours of drug administration, then on day 4 and day 7 of life. Mean values of GFR were analysed using T-test and statistically no significant difference was found in values of GFR with p-values 0.296, 0.330 and 0.241 respectively (p>0.05).This is in accordance to study by Saeidi R et al (2022)[12]who also observed that no apparent difference in plasma creatine and GFR was found during first five days, which is similar to our study findings. Similarly, Merrikhi AR et al (2011)[22]also reported that no significant rise in GFR during the first day of life (p >0.05).Ruo-lin Z et al (2018)[23]observed that GFR did not change between groups on the first day following perinatal asphyxia (WMD=1.68, 95% CI (-1.05, 4.41), P=0.230 00), but it was considerably higher in the intervention group than in the control group on the third and fifth days following perinatal asphyxia.

In contrast to our study, study conducted by Merrikh AR et al (2012)[24]concluded that aminophylline could prevent renal dysfunction in preterm neonates with asphyxia.

In the present study, 04 (4%) neonates expired during treatment in both aminophylline treated and Control group. Data was analysed to compare the mortality rates and found to be insignificant among

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

male and female in both studied groups with insignificant p-values 0.0617 and 0.508 respectively. The result in the present study was correlating with similar study done by Ruo-lin Z et al (2018)[23]where authors observed that fatality rate did not significantly differ between both the groups.

Higher percent of deaths were reported by Ejaz I et al (2013)[26] in their study, where authors reported that following treatment with theophylline, about 20% of patients (n=15) died, while 80% of patients (n=60) were sent home. The study also reported that use of theophylline leads low risk of death, as seen by this substantial difference (p=0.000).

CONCLUSION

Perinatal asphyxia is common in developing nations and severe perinatal asphyxia can lead to encephalopathy and acute kidney injury. Increase urine output was measured on day 1 and 4 of aminophylline treated group, but no difference in urine output was noted on day7 of life. Aminophylline has no effect on estimated GFR, serum creatinine and serum electrolyte levels in intervention group as compared to control group. There was no reduction in mortality rates in aminophylline treated group as compared to control group. So overall our study concluded that aminophylline has no effective role in preventing acute kidney injury due to perinatal asphyxia. It is recommended that further more studies will be required to see the effect of aminophylline in preventing renal dysfunction due to perinatal asphyxia.

REFERENCES:

1. Raina A, Pandita A, Harish R, Yachha M, Jamwal A. Treating perinatal asphyxia with theophylline at birth helps to reduce the severity of renal dysfunction in term neonates. Acta Paediatr. 2016;105(10):e448-51.
2. .Martin RJ, FanaroffA, Walsh M. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the fetus and infant.9th ed. Philadelphia: Elsevier Science Health Science Division.2010.
3. .AveryGB, MacDonald MG, Mullett MD. Avery's Neonatology: Pathophysiology &management of the newborn.6th ed. Philadelphia: Lippincott Williams & Wilkins. 2005.
4. .Askenazi D. Should neonates with perinatal asphyxia receive a single dose of IV theophylline to prevent acute kidney injury? Acta paediatrica (Oslo, Norway: 1992). 2016;105(10):1125.
5. .Haycock GB.Management of acute and chronic renal failure in the newborn. Semin Neonatol. 2003;8(4):325-34.
6. .Martín-Ancel A, García-Alix A, Gaya F, Cabanas F. Multiple organ involvement in perinatal asphyxia. J Pediatr. 1995;127(5):786-93.
7. .Bennet L, Booth L, Malpas SC, Quaedackers JS, Jensen E, Dean J. Acute systemic complications in the preterm fetus after asphyxia: Role of cardiovascular and blood flow responses. Clin Pharmacol Physiol. 2006;33(4):291
8. .Goldenberg RL, Harrison MS, McClure EM. Stillbirths: The hidden birth asphyxia—US and global perspectives. Clin Perinatol.2016;43(3):439–53.
9. .Woday A, Muluneh A, St Denis C. Birth asphyxia and its associated factors among newborns in public hospital, Northeast Amhara, Ethiopia. PLoS One. 2019;14(12):e0226891.
10. .Tasew H, Zemicheal M, Teklay G, Mariye T, Ayele E. Risk factors of birth asphyxia among newborns in public hospitals of Central Zone, Tigray, Ethiopia 2018. BMC Research Notes. 2018;11(1).
11. .Bhat MA, Charoo BA, Bhat JI, Ahmed SM, Ali SW, Mufti MH. Magnesium sulfate in severe peri-natal asphyxia‖: A Randomized, placebo-controlled trial pediatr. 2009; 123: 764-9.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023

12. Saeidi R, Fatahi S, Yaghoobi M, Maamouri G, Hajipour M. Prophylactic administration of aminophylline to prevent renal dysfunction in asphyxiated neonates. Int J Pediatr. 2022;10(4):15772-78.
13. .da Silva PSL, de Aguiar VE, Fonseca MCM. Additive diuretic response of concurrent aminophylline and furosemide in children: a case series and a brief literature review. J Anesthesia. 2011;26(1):118–23.
14. 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.
15. .Cattarelli D, Spandrio M, Gasparoni A, Bottino R. A randomized, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory
16. .Bell M, Jackson E, Mi Z, McCombs J, Carcillo J. Low-dosetheophylline increases urine output in diuretic-dependent critically ill children. J Intensive Care Med. 1998;24:1099–105.
17. .Pretzlaff RK, Vardis RJ, Pollack MM. Aminophylline in the treatment of fluid overload. Crit Care Med. 1999;27(12):2782–5.
18. .Jenik AG, Cernadas JMC, Gorenstein A, RamirezJA, 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. Pediatr. 2000;105(4):e45–5.
19. .Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis . 2009;3(4):222-6.
20. .Bhat MA, Shah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal function in term neonates with perinatal asphyxia: a randomized, placebo-controlled trial. J Pediatr. 2006;149(2):180-4.
21. .Merrikhi AR, Ghasemi S, Gheissari A, Shokrani M, Madihi Y. Effects of aminophylline in preventing renal failure in premature neonates with asphyxia in Isfahan, Iran. Iran J Kidney Dis. 2011;5(Suppl 1):18–9.
22. .Ruo-lin Z, Jun-ha Z, Ying W, Lan-junS, Xiao-yanLI, Qing-nan HE. Prophylactic use of theophylline on the prevention of renal dysfunction in after perinatal asphyxia neonates：A meta-analysis. Chin Gen Prac J. 2018;21(14):1713-18.
23. .Merrikhi AR, Ghaemi S, Gheissari A, Shokrani M, Madihi Y, Mousavinasab F. Effects of aminophyllinein preventing renal failure in premature neonates with asphyxia in Isfahan-Iran. J Pak Med Assoc. 2012;62(3):S48-51.
24. .Al-Wassia H, Alshaikh B, Sauve R. ―Prophylactic theophylline for the prevention of severe renal dysfunction in term and post-term neonates with perinatal asphyxia: a systematic review and meta-analysis of randomized controlled trials‖. J Perinatol. 2013 ;33(4):271-7.
25. .Ejaz I, Anwar A, Mushtaq A, Zeeshan F, Waheed I. The Role of Prophylactic Theophylline in Prevention of Acute Renal Failure in Neonates Exposed to Asphyxia. JFJMC. 2013;7(3):34-7.
26. .Khurshid G, Khurshid S, Mehmood H, Afshan S. Efficacy of Theophylline for prevention of kidney dysfunction in neonates with severe birth asphyxia. Pakistan J. Medical Health Sci. 2017;11(4):1346-48.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 07, 2023