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Prophylactic Administration of Aminophylline to Prevent Renal Dysfunction in Asphyxiated Neonates

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Abstract

Background: Neonatal asphyxia is one of the most common neonatal problems. And kidney injuries are one of the most important complications of asphyxia in infants. Therefore, this study was designed to evaluate the effect of administering aminophylline on improving the renal function of asphyxiated preterm infants.

Methods: In this single-blind randomized clinical trial, forty term neonates with perinatal asphyxia were randomized to intervention (n=21) and control (n=19) groups, respectively, receiving a intravenously single dose of aminophylline (5 mg/kg) or an equal volume of placebo (5% dextrose in water) during the first 3 hours of life. Daily urine output, 24-hour fluid intake, weight and serum creatinine were recorded during the first 5 days of life.

Result: The incidence of severe kidney dysfunction was not significantly different between the two groups. (2 infants in the group of intervention with aminophylline and 3 in the control placebo group; p=0.23). Plasma creatinine (Pcr) levels were increased in both groups on the second day and reached the maximum in the third day. Then it gradually decreased during the fourth and fifth days of life. There was no significant difference in Pcr & GFR between the groups in these five days (p>0.05). However, urinary output/input ratio was higher in the aminophylline group in the first three days of life.

Conclusion: Prophylactic administration of aminophylline in asphyxiated neonates could not change the process of renal failure in the patients but could increase urinary output in the first days of life.

Key Words: Acute kidney injury, Aminophylline, Perinatal asphyxia, Renal function.

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1- INTRODUCTION

Perinatal asphyxia is among the most common problems in developing countries, and the incidence of this disorder is estimated at 1 to 10 per 1000 live births. It accounts for about 30% of neonatal mortality which leads to organ dysfunction (1, 2).

In 82% of asphyxiated infants, at least one organ is involved which results in permanent damages in 40% of the survivors (3, 4). The kidneys of the fetal are very vulnerable to perinatal asphyxia; they appear in the fifth week after fertilization and begin to urinate in the tenth week. (5) Early diagnosis and treatment of Acute Kidney Injury (AKI), also known as Acute Renal Failure (ARF), with low-dose dopamine still remains controversial (6). As in a systematic review, a failure was reported in demonstrating the usefulness of dopamine treatment on neonatal renal failure (5). Nonetheless, animal studies have shown that theophylline with its antagonistic effects on adenosine receptors in the kidney, and on phosphodiesterase, can theoretically increase diuresis, natriuresis, renal blood flow, and filtration.

Jeink et al. showed that the use of theophylline at a dose of 8 mg / kg in asphyxiated infants at the first hour of birth significantly reduced serum creatinine and B2M levels and increased glomerular filtration. Baker also treated 40 infants with asphyxia with 4 mg of theophylline per kilogram of body weight in the first hours of life in a randomized placebo-controlled study. In that study, a decreased serum creatinine, decreased urinary B2M secretion and severe renal impairment (serum creatinine greater than 1.5 mg / dl) were observed (7).

In another study, Bhet et al. measured the effect of higher doses of theophylline 8 mg / kg in the first hours of birth in infants with asphyxia. Follow-up of these neonates for at least one year showed that this treatment reduced the incidence of acute renal failure (creatinine more than 1.5 mg / dl per day) in these patients. However, there was no significant difference in serum creatinine levels between the two groups at one year of age (8) Methylxanthines through the inhibition of phosphodiesterase (PDE), which increases intracellular CAMP, activates protein kinase (PKA), inhibits leukotriene synthesis, and reduces inflammation. Also Methylxanthines have non-selective antagonism and have an impact on adenosine receptors justifying the cardiac and renal effects (9). Preliminary studies have shown that prophylactic treatment with a single dose of theophylline in rats increases renal blood flow and GFR during the ARF after 5 days (9). Therefore, this study was designed to evaluate the effect of administering aminophylline on improving the renal function of the asphyxiated preterm infants.

2- METHOD

The present study is a single- blind randomized clinical trial, conducted in Ghaem Hospital of Mashhad university of medical sciences, on 42 full-term neonates with asphyxia, who were randomly divided into intervention (n = 21) and control (n = 21) groups. In the intervention group, intravenous aminophylline at a single dose of 5 mg / kg was injected in the first 3 hours after birth and the control group received the same volume of placebo (5% dextrose).

Standard asphyxia treatment and supportive therapies were performed equally in both groups and Infant fluid intake was carefully adjusted. In the intervention group, aminophylline was injected intravenously after dissolving in 5% dextrose and increasing its volume to 1.5 ml per kg body weight. In the control group, the amount of 5% dextrose, 1.5 ml per kg of body weight was administered intravenously.

The newborns were divided into two groups using block randomization. In this study, blocks were considered 4 by 4. Then, the sample in each group consisted of 21 individuals and a total number of 42 considering a test power of 80 and a confidence level of 95%. Two participants from the control group were excluded from the study.

The infants' data were collected by trained individuals, using a researcher-made checklist. The researcher-made checklist was composed of two maternal and newborn demographic information sections (baby birth weight, week of pregnancy, gender, background disease, etc. and the patient clinical information section (kidney function, urinary output, etc.). Serum creatinine and GFR were measured every day until the fifth day, and urinary output and weight were measured daily and these values were compared as kidney function criteria in two groups. Also, changes in serum creatinine (and calculated GFR) during the first five days in each of the intervention and control groups were compared and each day this amount was compared between the two groups.

2-1. Inclusion and exclusion criteria

All born neonates who had at least 3 of the following 5 criteria were included in our study:

1) History of fetal distress (fetal bradycardia, late deceleration, meconium-aspiration syndrome)

2) Need to positive pressure ventilation after birth for more than 2 minutes

3) Apgar score less than or equal to 6 in the fifth minute of birth

4) Base deficit greater than or equal to 15 milliequivalents per liter in a blood sample taken, from the umbilical cord

5) PH less than 7.2 in the umbilical cord sample

Exclusion criteria were:

1) Maternal drug abuse during pregnancy

2) All conditions that are not related to asphyxia

3) Congenital Heart disease or Congenital malformations

4) Polycythemia, microcephaly, chromosomal disorders, positive culture and septicemia

2-2. Data Analysis

The data were entered into SPSS software version 19. To describe the quantitative variables, the mean and standard deviation and to describe the qualitative variables, frequency and percentage were used. Normality test was carried out using Kolmogorov–Smirnov test and if the data were normal, t-test and ANOVA were performed, otherwise the nonparametric ones including Mann-Whitney U and Kruskal-Wallis were used to assess the relations.

3- RESULTS

This study was performed on a total of 42 asphyxiated neonates who were divided into case (n=21) and control (n = 21) groups. Their clinical and demographic characteristics including birth weight, gestational age, and type of delivery (cesarean section or normal delivery) were similar in the two groups.

In the study, the amount of base excess in the control group was higher than the case group, but this difference was not significant (p=0/074), pH of arterial blood was similar in the two groups (**Table 1**).

During this study, only one death occurred in the control group due to sepsis. The difference in the ratio of output to intake between the two groups, in the first 3 days of life, was significant and the intervention group had a higher mean ratio of output volume to fluid intake compared to the placebo group (p=0.001, p<0.0001 and p=0.0001 for the first, second and third

day, respectively). Only one person in the case group became oligarchic (**Table 2**). There were significant differences between the two groups in plasma creatinine level, and severe renal impairment (cr. > 1.5 mg/dl for at least 2 days or raise of cr. more than 0.3 mg/dl) between the two groups (**Table 3**). Two patients in the case group (10.52%) and three patients in the control group (14.28%) had severe renal dysfunction, but this difference was not significant (P = 0.23). The differences in GFR were not significant between the groups (**Table 4**).

Table-1: Clinical and demographic characteristics of the neonates at the beginning of the study

variable	Intervention (19) mean ± SD or n (%)	Control (21) Mean±SD or n (%)	p-value
Birth weight (g)	32/280±2910	23/310±0/2820	0.34
Gestational age (weeks)	90/1±8/38	13/2±7/39	0.19
Cesarean delivery (%)	(9/57)11	(7/66)14	0.56
Meconium-stained amniotic fluid (%)	(8/36)7	8(1/38)	0.93
pH	15/0±04/7	18/0±06/7	0.70
(mEq/L) Base excess	90/1±2/17-	16/2±4/18-	0.074
Apgar score ≥ 6 (%)	12 (2/63)	(1/57)12	0.69
Need of resuscitation (%)	17 (5/89)	(7/85)18	0.55

Calculated by ANOVA and chi-square tests for quantitative and qualitative variables, respectively.

Table-2: Comparing the changes in the ratio of output volume to fluid intake between the groups

Time	Output/Input		p-value
	Intervention (19) Mean±SD	Control (21) Mean±SD	
After 24 hours	106/0±44/0	081/0±33/0	0.001
After 48 hours	037/0±76/0	053/0±48/0	<0.0001
After 72 hours	027/0±12/1	027/0±92/0	<0.0001
After 96 hours	038/0±13/1	043/0±17/1	0.092
After 120 hours	036/0±17/1	054/0±25/1	0.067

T-test was used to compare data.

Table-3: Comparing the changes in neonatal plasma creatinine level between the groups

Time	Output/Input		p-value
	Intervention (19) Mean±SD	Control (21) Mean±SD	
After 24 hours	31/0±12/1	27/0±08/1	0.65
After 48 hours	23/0±27/1	31/0±32/1	0.58
After 72 hours	28/0±34/1	25/0±24/1	0.39
After 96 hours	26/0±02/1	30/0±98/0	0.64
After 120 hours	25/0±81/0	31/0±92/0	0.22

T-test was used to compare data.

Table-4: Comparing the changes in GFR based on Schwartz formula between the groups

Time	Output/Input		p-value
	Intervention (19) Mean±SD	Control (21) Mean±SD	
After 24 hours	74/6±7/21	16/7±9/21	0.95
After 48 hours	99/3±3/18	84/6±0/17	0.85
After 72 hours	51/4±6/17	34/4±2/19	0.30
After 96 hours	26/9±0/24	29/11±3/25	0.69
After 120 hours	72/19±7/30	37/17±5/28	0.48

T-test was used to compare data.

4- DISCUSSION

The results indicated that early usage of a single dose of aminophylline can temporarily increase urinary output in term infants, but it has no significant effect on serum creatinine and glomerular filtration rate. In this study, the plasma creatinine (Pcr) in both groups increased on the first and second and third days and then decreased on the fourth and fifth days of life. Moreover, there was no significant difference in Pcr levels in the two groups in the first till the fifth days.

There was no significant difference between the two groups in the daily increase of Pcr more than 0.3 mg / dl defined in the serum creatinine level. Two patients in the case group (10.52%) and three patients in the control group (14.28%) had severe renal dysfunction, but this difference was not significant. In our study, prophylactic use of aminophylline could not change the Pcr.

Bhat et al. and Jenik et al. showed that a single dose of theophylline within the first hour of birth in asphyxiated term neonates significantly decreased the Pcr level and urinary excretion of beta2M, along with an increase in creatinine clearance (7, 8). Also Islami et al. indicated that Prophylactic theophylline, given early after birth, has beneficial effects on reducing kidney dysfunction in neonates with asphyxia (10). But in our study, creatinine levels on the fifth day of life were similar in the two groups. However, almost all studies suggest that serum creatinine decreases after the first days of life in infants with asphyxia, and this confirms the findings of our study. In the study of Islam et al, these values became similar in the fifth days of life (10).

Catarelli et al, Who compared Pcr levels between the two groups by eleventh day, observed a similar decrease in serum creatinine in both groups (11). GFR values in the mentioned studies were similar to Pcr changes. The results were similar in the studies by Bakr and Bhat, which used creatinine clearance instead of the Schwartz formula to calculate GFR (8, 12), unlike the five other studies, the reason for the lack of prophylactic use of aminophylline on GFR in the early days of life is unclear.

In the current study, we also evaluated the ratio of urinary output to the volume intake as an indicator of kidney function. This ratio was significantly higher in the aminophylline group than in the control group, at the end of the first to third days; but gradually disappeared with increasing urinary output in the control group on the fourth and fifth days. The results obtained in this study related to urinary output are very similar to other previous studies and methylxanthines have increased urinary output in almost all similar studies, but the duration and extent of its effect has been different, in different studies. In the study

of Bakr et al., Only on the first day of life, urinary output was higher in the theophylline group than in the sham group (12). Catrelli et al., and similarly Bhat et al., reported an increase in urinary output by day four (13). In other words, the results obtained in our study are largely justifiable. It appears that aminophylline in the present study increased urinary output by mechanisms other than the increase in GFR but did not alter serum creatinine levels by the glomerular filtration rate. In our study, the neonatal weight decreased on consecutive days in both groups. This reduction was greater in the aminophylline group; however, there was no significant difference between the neonates receiving the aminophylline and placebo on either day. The diuretic effect of aminophylline may cause weight changes in the case group, but due to the small sample size and existence of interfering factors, this effect was not found to be significant (14).

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6- CONFLICT OF INTEREST

None.

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