Original Article

Effects of Aminophyllinein Preventing Renal Failure in Premature Neonates with Asphyxia in Isfahan-Iran

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Abstract

Objectives: Considering the relation between prematurity andasphyxia and also renal failure in neonates, the aim of this study was to determine the effect of aminophyllinein urine and serum indices of renal failure and consequently its prevention, in Premature Infants with asphyxia in Esfahan-Iran.

Methods: In this descriptive clinical trial study, 22 preterm neonates diagnosed with perinatal asphyxia in neonatal ward of Shahid Beheshti hospital, during 2009.The participants were randomized in two intervention and placebo groups. They randomized to receive a single dose of aminophyiline (5 mg/kg) or placebo of 5% dextrose water for injection (5cc/kg) during the first hour of life.

Renal function was assessed by GFR, β2-microglobulin (β2M), N-acetyl-glucosaminidase (NAG) serum creatinine and electrolytes level measurement, during the 1st, 4th and 7th day of life, in two studied groups. The results compare between the two groups before and after intervention.

Results: Mean of urine output, was significantly higher in neonates who received aminophylline ($P<0.05$).Mean of β2M and NAG 24 hours after intervention was not significant in the two groups of asphyxiated preterm neonates ($P>0.05$).GFR was significantly higher in neonates who received aminophylline on 4th day of life ($P<0.05$) and it had trend to be significantly high on 7th day ($P=0.05$) and was not significantly high on 1st day ($P>0.05$) comparing with control group. The most common pathophysiology of renal failure was prerenal.

Conclusion: Aminophylline could prevent renal dysfunction in preterm neonates with asphyxia. Neonates who received aminophylin on the first day of life indicated a significant improvement in GFR and urine output.

Keywords: RenalFailure, Aminophylline, β2-Microglobulin, N-Acetyl-Glucosaminidase (JPMA 62: S-48; 2012).

Introduction

Perinatal asphyxia is one of the leading causes of neonatal morbidity and mortality worldwide. Its incidence is reported to be 5-8% in different neonatal centers, regarding the neonates' birth weight and gestational age.[1,2] It is more prevalent among preterm and low birth weight neonates. Perinatal asphyxia may lead to circulatory adaptive responses which consequently can cause damage to almost every tissue and organ of the body, predominantly kidneys.[3,4] It considered as the main leading cause of acute renal failure (ARF) in preterm neonates. The incidence of renal failure in asphyxiated neonates has reported to be 47%, commonly with non oliguric type.[5,6]

Many studies have performed to prevent the renal failure in at risk neonates. The findings of these studies specially those obtained from animal models have shown that pharmacological agents, such calcium channel blockers, methylxantines and atrial natriuretic peptide have a protective effect on renal adverse effects of hypoxemia.[7-10]

Adenosine has an important role in the reduction of glomerular filtration rate (GFR) and filtration fraction (FF) during hypoxemia or ischemia in asphyxianeonates. Therefore it seems that nonspecific adenosine receptor antagonists such as aminophylline could have a protective effect in preventing renal impairment in neonates with asphyxia by vasoconstriction inhibition.[11]

There are few studies on the effect of aminophylline on renal function in term neonates,[12,13] but there isn't any study in this field among preterm neonates. The aim of this study is to determine the effect of aminophylline on the prevention of renal dysfunction among the high risk group of preterm neonates with asphyxia.

Methods

In this descriptive clinical trial study, preterm neonates diagnosed with perinatal asphyxia in neonatal ward of Shahid Beheshti Hospital, during 2009, were enrolled.

The Medical Ethics Committee of the Esfahan University of Medical Sciences approved the study protocol, and all parents gave their written consent.

Maturation assessment of gestational age was determined using Ballard score.[14] Neonatal asphyxia manifested by: Apgar scores less than or equal to 6 at 5 minutes plus umbilical artery pH values less than 7.00,according to AAP guideline.[15]

Preterm neonates with major congenital malformations, chromosomal, or renal abnormalities, breech presentation and those with maternal gestational diabetes were excluded.

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

The loading infusion was administrated after admission to the neonatal intensive care unit within the first hour after birth at a rate of 60-65cc/kg/day, which increased by 10-15cc/kg daily.

The 24-hour fluid intake and the urine volumes were recorded during the first week of life.

Renal function was assessed by daily 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 studied groups.

Tubular performance was assessed by β2-microglobulin (?2M) and N-acetyl-glucosaminidase (NAG) measurement 24 hours after intervention, in studied groups. In cases with renal dysfunction during the first week of life, β2M and NAG were measured on the 7th day of life.

According to the findings of current study GFR<26cc/min, β2M>3.8mg/l and NAG >0.36mg/dl considered as renal tubular impairment and renal failure in preterm neonates.

The pathophysiology of renal failure asprerenal, renal, or postrenal failure was assessed on the 7th day of life. Renal ultrasonography was performed in studied neonates to exclude the anatomic kidney malformation and postrenal failure.

Obtained data from two groups of neonates before and after intervention recorded using a questionnaire.

Statistical Analysis:

Statistical analysis was performed using SPSS version 16(SPSS Inc., Chicago, IL, U.S.A.). Normality of data distribution was assessed with Kolmogrov-Smirnov. As all descriptive data had normal distribution, they expressed as mean ± standard deviation (SD). Quantitative data of the 2 groups was compared using the Students t-test or chi-square test. Pvalue <0.05was considered statistically significant.

Results

22 patients were studied in two intervention and placebo groups. There were no significant difference regarding gestational age, birth weight, sex and renal function indices between two groups of neonates before intervention (P>0.05). Mean of urine output, β2M and NAG 24 hours after intervention

Table-1: Mean of urine output, ?2-microglobulinandN-acetyl-glucosaminidase, 24 hours after intervention in the two groups of asphyxiated preterm neonates.

	Asphyxiated Aminophylline Group	Preterm Neonates Placebo Group	Pvalue
Urine output (cc/h/kg)	1.8±0.4	0.9±0.5	0.000
β2-Microglobulin (mg/L)	4.9±3.9	10.3±13.5	P>0.05
N-Acetyl-glucosaminidase (mg/L)	1.0±1.7	3.2±3.7	P>0.05

Table-2: Estimated Glomerular Filtration Rate (GFR) in1st, 4th and 7 days of life, in the two groups of asphyxiated preterm neonates.

GFR (ml/min/1.72 m^2)	Asphyxiated Aminophylline Group	Preterm Neonates Placebo Group	Pvalue
1st day	24.4±8.8	19.3±10.9	0.2
4th day	32.4±10.6	20.8±11.8	0.02
7th day	37.7±9.6	27.2±14.5	0.05

*P<0.05 for GFR between 1st, 4th and 7 days of life for both aminophyllineand placebo group.

Table-3: The pathophysiology of renal failure asPrerenaland renal, in1st, 4th and 7 days of life, in the two groups of asphyxiated preterm neonates.

	Asphyxiated Aminophylline Group N (%)	Preterm Neonates Placebo Group N (%)	P value
1st day			
-normal	6(55.5)	4(36.4)	
-Prerenal	5(45.5)	7(63.6)	0.6
-Renal	0	0	
4th day			
-Normal	9(81.8)	4(36.4)	
-Prerenal	2(18.2)	5(45.4)	0.007
-Renal	0	2(18.2)	
7th day			
-Normal	9(81.8)	6(54.5)	
-Prerenal	1(9.1)	4(36.4)	0.3
-Renal	1(9.1)	1(9.1)	

in the two groups of asphyxiated preterm neonates are presented in Table-1.

Two neonates (18.2%) from those who received aminophyl line had β2M >3.8 mg/l and also NAG >0.36mg/dl. These neonates diagnosed with renal failure during the 1st, 4th and 7th day of life.

Among asphyxiated preterm neonates who received 5% dextrose water, 5 neonates (45.5%) had β2M >3.8 mg/l and 6 ones (55.6%) had NAG >0.36mg/dl. Five neonates with high level of β2M and NAG diagnosed with renal failure.

Estimated Glomerular Filtration Rate (GFR) in1st, 4th and 7 days of life, in the two groups of asphyxiated preterm neonates are presented in Table-2.

Five neonates (45.5%) in the two groups of asphyxiated preterm neonates had GFR< 26cc/min in 1st day of life.2/5 neonates from those who received aminophyllineand4/5 neonates who received 5% dextrose water and had GFR< 26cc/min diagnosed with renal failure, after one week.

The pathophysiology of renal failure in1st, 4th and 7 days of life, in the two groups of asphyxiated preterm neonates are presented in Table-3.

Discussion

The findings of this study which investigated the effect of aminophyllineon the prevention of renal dysfunction in preterm neonates with asphyxia have indicated that aminophyline could be used for the mentioned purpose in this high risk group of neonates. As mentioned, there was no similar study in this field among preterm neonates with asphyxia, in literature review. But there were similar studies on the effect of aminophyllineon renal function of term neonates with asphyxia.

Jenik et al investigated the effect of theophylline on the prevention of renal dysfunction among term neonates with perinatal asphyxia and indicated that a prophylactic single dose of 8 mg/kg of theophylline within the first hour after birth could reduce the risk of renal dysfunction in this group of neonates.[12] Similar studies in India,[17] Egypt[13] and also in Iran[18] have reported the efficacy of theophylline, a nonspecific adenosine receptor antagonist, on preventing renal dysfunction among asphyxiated term neonates.

According to one study in China, aminophyl line protects the renal function in neonates with perinatal asphyxia.[19]

In a study in Italy, Cattarelli and colleagues investigated the effect of theophylline, another nonspecific adenosine receptor antagonist, on vasomotor nephropathy of preterm neonates with respiratory distress syndrome. They concluded that it could improve renal function inthese high risk neonates, during the first two days of life.[20]

Aminophylline had no significant effect on the level of β2-microglobulin (β2M) and

N-acetyl-glucosaminidase (NAG) as early tubular performance indices among our studied neonates.[21] The results of previous studies in this field were controversial.

Some studies have reported the relation between mentioned indices and neonatal asphyxia among term neonates, whereas others did not. Csáthy and colleagues reported that NAG is a sensitive indicator of the renal tubular damage in premature neonates.[22]

According to the study of Bhat et al in India which investigated the effect of prophylactic theophylline on the severity of renal failure in term infants with perinatal asphyxia,

β2-microglobulin reduced significantly after intervention in studied neonates.[17]

Jenik et al and Bakr reported similar results in this field.[12,13] The difference between our results and the mentioned study may be due to the studied population (preterm vs. term neonates), small sample size and differences in laboratory methods used for measuring these indices. However further studies are recommended.

Urine output increase significantly in the intervention group in our study. Though there was no similar report in this field in previous studies, butsome authors reported the similar effect of theophylline on urine output among preterm neonates with respiratory distress.[23]

Many studies in human neonates and animal models have demonstrated that aminophyllinecould prevent the

reduction in GFR among asphyxiated neonates.[12,13,18,24] GFR in the current study was significantly higher in neonates who received aminophyllineon 4th day of life and it had a trend to be significant on the 7th day and there was no significant difference between 1st day GFR in two studied group. It may be due to that the creatinine level inneonates on 1st day of life is predominantly related to its maternal level, so,considering the GFR formula, it could be explained.As reported by some studied,creatinine level increase during the first 2 days of life specially in preterm neonates.[25,26] Previous studies reported the relation in 5th day of life.[12,13]

Regarding the type of renal failure in this study the most common type was prerenal renal failure. There are different reports in this field, Karlowicz et al have reported that the most predominantly form of renal failure among asphyxiated full-term neonates was non oligurictype,[27] whereas Pejovic et al indicated that in term asphyxiated neonates the most predominant type of ARF was oliguric type.[28] More studies with larger sample size is needed for more accurate conclusion.

GFR estimation have indicated that in both two studied groups ,it increased during the 7 day period but the improvement was more significant for aminophylline received group. These findings suggest that aminophylline have a protective effect in preventing renal failure among preterm neonates with asphyxia.

In sum, aminophylline could prevent renal dysfunction in preterm neonates with asphyxia. Neonates who received aminophyline on the first day of life indicated a significant improvement in GFR and urine output.

Further studies with larger sample size are necessary to make an accurate conclusion in this field. However improvement in renal function, in this critically ill neonates, at any level, would be useful in the management of these patients.

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