



BIRTH ASPHYXIA; SHORT-TERM OUTCOME OF NEONATES TREATED WITH ALLOPURINOL

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ABSTRACT... Introduction: Out of 130 million births, about four million infants die in the first four weeks of their life. Birth asphyxia is a major cause of neonatal deaths in developing countries. Birth asphyxia is estimated to account for approximately 25% of neonatal mortality worldwide. Allopurinol is a cheap and freely available medicine whereas other management options are not widely used. **Objectives:** To analyze the short-term outcome between allopurinol-treated and non-allopurinol-treated asphyxiated neonates. **Study Design:** A randomized controlled study. **Setting:** Pediatric unit 2, Bahawal Victoria Hospital, Bahawalpur. **Duration of Study:** This study was conducted from March 2015 to September 2015. **Materials and Methods:** A total of 62 (31 in allopurinol and 31 in non allopurinol treated group) infants having admitted within 6 hours after birth with gestational age ≥ 36 weeks. All were suffering from stage-2 hypoxic ischemic encephalopathy, lethargy, hypotonia, flexion posture. All were having hyperactive tendon reflexes and poor moro reflex. All the admitted neonates were managed and followed up to 7 days of admission to note the need of anti-convulsants, conscious level and length of admission in intensive care unit (≤ 7 days or > 7 days). Neonates who died during the stay were noted and compared between both the groups. **Results:** Out of 62 infants, there were 34 (54.8%) males and 28 (45.2%) females. Mean gestational age was 37.90 weeks while mean weight of newborn infants was 2.75 kg. Overall Mortality was noted in 6 (9.68%) infants. When both groups were compared, no statistically significant difference was found between the two groups in terms of sex, gestational age, birth weight or mortality (p value > 0.05). **Conclusion:** Short-term outcome in terms of mortality between allopurinol-treated and conventional treatment asphyxiated neonates was found to be 6.5 vs 12.9%.

Key words: Birth asphyxia, cerebral palsy, neuro-developmental delay, allopurinol, mortality.

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INTRODUCTION

Birth Asphyxia is the inability of the newborn to initiate and sustain adequate respiration after delivery.¹ Birth asphyxia is responsible for approximately 25% of neonatal mortality around the world.^{2,3} About 4 to 9 million newborns face birth asphyxia every year.⁴ Birth asphyxia proves fatal for 1.2 million newborns annually and same number develop major complications like cerebral palsy, epilepsy and neuro-developmental delay.⁴

In Pakistan, nearly 65% of neonatal mortality is secondary to birth asphyxia which accounts for nearly 80000 deaths annually.^{5,6} Birth asphyxia was responsible for 35% of deaths in Lahore, 11% in KPK and 14% in Karachi while in urban

population, 26% deaths are noted be due to intra-partum asphyxia.^{7,8}

Supportive care to maintain appropriate temperature, perfusion, ventilation and normal metabolic state forms the pillar for management of neonatal asphyxia.^{5,9} For minimizing the complications, early detection by clinical and biochemical assessments plays an important role.⁹

Different management options are considered globally for successful management of neonatal asphyxia but hypothermia remains the only neuroprotective treatment to have been clinically tested in large randomized controlled trials that

has shown reduction in brain injury in asphyxiated term newborns.^{10,11} Being an Xanthine oxidase inhibitor, allopurinol is known to decrease free radical formation and lipid peroxidation after severe birth asphyxia in newborn.¹²

Allopurinol is a cheap and freely available medicine whereas other management options have not been widely tried and considered costly. Allopurinol seems efficient at reducing mortality¹³ (18% died with allopurinol vs. 55% controls) and morbidity¹⁴ (27% with allopurinol vs. 55% controls) in neonates with perinatal asphyxia.¹³ Beneficial effect of allopurinol treatment are on free radical formation, Cerebral blood volume (CBV), and electrical brain activity, and all these without toxic side effects.¹³ In previous studies intravenous (I.V) allopurinol was used, but in Pakistan, I.V formulation of allopurinol is not available. Oral formulation of allopurinol was used in this study through nasogastric tube and differences in short-term outcome between asphyxiated neonates on allopurinol treatment and neonates on conventional treatment will be analyzed. The results of this study are aimed to investigate allopurinol as an alternate strategy to treat infants with birth asphyxia as other recommended therapies like induced hypothermia are either not available or very costly.

MATERIAL & METHODS

This was a randomized controlled study, conducted in the Department of Paediatrics, Bahawal Victoria Hospital, Bahawalpur from March 2015 to September 2015. Protocol of the study was approved by the Institutional Ethical Committee. The sample size calculated was 62 (31 in each group) neonates with gestational age ≥ 36 weeks, determined by maternal dates and Ballard score, admission within 6 hours after birth and suffering from stage-2 hypoxic ischemic encephalopathy defined¹⁵ as neonate having respiratory distress (respiratory rate > 60 breath per minute), lethargy (sluggishness, inactivity), flexion posture (folding of arms and legs), hyperactive tendon reflexes (exaggerated response while performing tendon reflex or clonus), multifocal seizures and poor moro reflex

(sluggish response to loss of support). Neonates with congenital or syndromal malformations, delivered at home and who remain admitted in other hospitals for 48 hours, were excluded.

After explaining details and benefits / risks of the study, informed consent was taken from the parents / guardian. Variables recorded for each case included date, registration number, contact number, address, name, father's name, gender and gestational age at the time of admission. Randomization was done by opening numbered sealed envelopes containing cards indicating whether allopurinol treatment was performed or not. Oral allopurinol 40mg/kg per day, divided 12 hourly along with available symptomatic treatment was given to allopurinol group whereas conventional treatment group was offered only the available symptomatic treatment. General physical examination included vitals, anthropometric data and all systemic examination. Investigations included: complete blood count (CBC), serum glucose, serum calcium, renal function tests and x-ray chest. All the admitted neonates were managed and followed up to to 7 days of admission. Neonates who died during the stay were noted in both groups. All the data was entered on a pre-designed Performa for each patient (copy attached).

The collected data was analyzed by SPSS version 10. Quantitative variables like gestational age and weight were calculated by mean and standard deviation. Frequency and percentage were calculated for qualitative variables like deaths during the stay. Effect modifiers were controlled by stratification of gestational age, gender and weight. Chi square test was applied to compare the both groups and p value ≤ 0.05 was taken as statistically significant.

RESULTS

Out of 62 infants, there were 34 (54.8%) males and 28 (45.2%) females. Mean gestational age was found to be 37.90 weeks with standard deviation of 2.03. Mean weight of infants was 2.75kg with standard deviation of 0.19. Overall Mortality was noted in 6 (9.68%) infants. (Figure-1)

In Group A, there were 19 (61.3%) males and 12 (38.7%) females as compared to 15 (48.4%) males and 16 (51.6%) females in Group B with statistically insignificant p value of 0.307. (Table-I)

In Group A, there were 22 (71.0%) infants who were delivered with gestational age of \leq 38 weeks and 9 (29.0%) with $>$ 38 weeks as compared to 20 (64.5%) with \leq 38 weeks and 11 (35.5%) having $>$ 38 weeks in Group B with statistically insignificant p value of 0.587. (Table-II)

In Group A, there were 25 (80.6%) infants with gestational age of $<$ 3 kg and 6 (19.4%) with \geq 3 kg as compared to 23 (74.2%) with $<$ 3 kg and 8 (25.8%) having \geq 3 kg in Group B with statistically insignificant p value of 0.544. (Table-III)

As far as mortality was concerned, In Group A, there were 2 (6.5%) infants who died as compared to 4 (12.9%) in Group B with statistically insignificant p value of 0.390. (Table-IV)

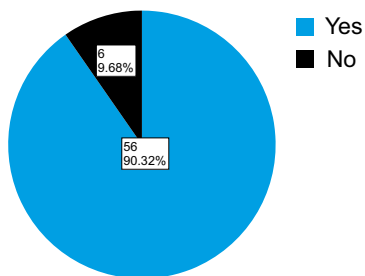


Figure-1. Overall Mortality amongst all the infants

Sex	Groups		Total
	A	B	
Male	19 (61.3%)	15 (48.4%)	34 (54.8%)
Female	12 (38.7%)	16 (51.6%)	28 (45.2%)
Totals	31	31	62

Table-I. Distribution of sex amongst both groups
P value = 0.307 (statistically insignificant)

Gestational Age (weeks)	Groups		Total
	A	B	
\leq 38	22 (71.0%)	20 (64.5%)	42 (67.7%)
$>$ 38	9 (29.0%)	11 (35.5%)	20 (32.3%)
Totals	31	31	62

Table-II. Distribution of gestational age amongst both groups
P value = 0.587 (statistically insignificant)

Birth Weight (kg)	Groups		Total
	A	B	
$<$ 3	25 (80.6%)	23 (74.2%)	48 (77.4%)
\geq 3	6 (19.4%)	8 (25.8%)	14 (22.6%)
Totals	31	31	62

Table-III. Distribution of birth weight amongst both groups
P value = 0.544 (statistically insignificant)

Mortality	Groups		Total
	A	B	
Yes	2 (6.5%)	4 (12.9%)	6 (9.7%)
No	29 (93.5%)	27 (87.1%)	56 (90.3%)
Totals	31	31	62

Table-IV. Distribution of mortality amongst both groups
P value = 0.390 (statistically insignificant)

DISCUSSION

Asphyxia can lead to severe hypoxic ischaemic organ damage in newborns followed by a fatal outcome or severe life-long manifestations. Birth asphyxia is not obvious all the times as the cause of perinatal and postnatal death but its marked influence for the mortality in newborns have been widely noted.¹⁶

In our findings, there were 34 (54.8%) males and 28 (45.2%) females infants. A local study from Isra University Hospital, Hyderabad found that 60% of the newborns were male.⁶ In another local study, more male babies (OR 2.3) were having hypoxic ischemic encephalopathy (HIE).¹⁷ Others have also found that male sex is a risk factor for HIE (OR 4.8).¹⁸ The significance of this finding remains unclear.

Mean gestational age was calculated to be 37.90 weeks. A study conducted in Nepal¹⁹ found similar numbers as 37.0 weeks. Gestational age of infants did not appear to be a significant risk factor in the present or past findings.¹⁷ Gestational age of \geq 36 weeks was considered for the current study so premature infants were not taken in this study. Premature infants are always on a risk to ischemic injuries of the white matter.²⁰ These newborns are also more prone to have some other potentially fatal problems compared to term infants.

No prior local study has been done to observe the effect of allopurinol on asphyxiated infants. This was a 1st local study which measured the short term outcome in infants treated with allopurinol. Allopurinol has been a new intervention for birth asphyxiated newborns. Several studies examined allopurinol and reported that its active metabolite oxypurinol offer protection against reperfusion induced brain injury by reducing free radical formation.²¹ The protective action of allopurinol is due to its xanthine oxidase-inhibiting property, but at high concentrations, it also scavenges free radicals such as hydroxyl and chelates transition metals like nonprotein-bound iron.²²

Overall Mortality 9.68% was noted in this study whereas when both treatment groups were compared (6.5% vs 12.9%), no statistical significance was found in both groups. Allopurinol has been compared previously which showed that allopurinol seemed more effective than placebo at reducing mortality in infants with perinatal asphyxia. Although the difference was not statistically significant, but Van Bel F et al¹⁴ noted fewer deaths in infants treated with allopurinol as compared with placebo (36% vs 64%). Another study²³ found similar mortality in infants using allopurinol as compared to placebo (10% vs 10%). A cochrane review²⁴ comprising multiple clinical trials found no significant difference between allopurinol and control group. No clear evidence of an effect on mortality, severe disability, neonatal seizure frequency, or the incidence of abnormalities on brain imaging during the neonatal period. As in the current study, more infants seem to survive with allopurinol treatment in asphyxiated newborns but the difference seems to be statistically insignificant as has been observed in the previously conducted trials. There are limited data available that assessed the effect of allopurinol in newborn infants with hypoxic-ischaemic encephalopathy. Previous studies have also not found significant evidence of beneficial effect of allopurinol on mortality, severe disability, neonatal seizure frequency, or brain imaging abnormalities during the neonatal period.²⁴

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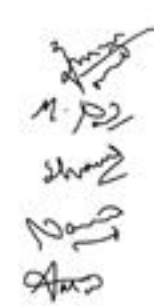
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PREVIOUS RELATED STUDY

Muhammad Azam, Fiaz Ahmad Malik, Pervaiz Akbar. BIRTH ASPHYXIA; RISK FACTORS (Original) *Prof Med Jour* 11(4) 416-422 Oct, Nov, Dec, 2004.

AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Dr. Muhammad Saleem	Drafting, Data Analysis	
3	Dr. Shamas-un-Nisa	Case selection, Discussion	
4	Dr. Malik M. Naeem	Drafting, Data Analysis, Literature Review, References	
5	Dr. Hafiz M. Anwar-ul-Haq	Data Collection, Literature Review, Drafting	