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The Effect Of Topiramate On Neurological Outcome In Neonates

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Abstract

Introduction: *Perinatal asphyxia is a significant global health issue with high neonatal morbidity and mortality rates. There is a growing interest in neuroprotective therapies for neonates suffering from moderate to severe asphyxia, with topiramate showing potential in animal models. However, limited clinical data exist to support its use.*

Methods: *This study was a randomized controlled clinical trial conducted at Dhaka Shishu Hospital, Bangladesh, from April 2015 to March 2016. Sixty-four neonates with moderate to severe asphyxia were randomly assigned to receive either supportive treatment alone (control group) or topiramate (10mg/kg orally daily for 3 days) with supportive treatment (interventional group). The main outcomes were USG brain findings and neurological outcomes at 1 and 3 months, as assessed by the RNDA method.*

Result: *At the 1-month mark, the USG brain scan showed significantly improved results in the topiramate-treated group, with 93.10% normal results compared to 51.85% in the control group. Similarly, normal neurological outcomes were significantly higher in the topiramate-treated group at both 1 and 3-month intervals (82.76% and 85.71% respectively) as compared to the control group (40.74% and 42.31% respectively).*

Conclusion: *This study provides preliminary clinical evidence suggesting that the early administration of topiramate in neonates with moderate to severe perinatal asphyxia may lead to improved neurological outcomes. These findings support the need for further research, especially large-scale randomized controlled trials, to confirm these findings and evaluate the long-term impact of topiramate treatment in this population.*

Keywords: *Asphyxia, Neonate, Topiramate, HIE*

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I. INTRODUCTION

Perinatal asphyxia, a devastating condition that results from a lack of oxygen supply to a newborn during the birth process, poses significant neonatal morbidity and mortality risks globally.(1) Worldwide, an estimated 23% of the 2.9 million neonatal deaths each year can be attributed to perinatal asphyxia.(2) In low-resource settings such as Bangladesh, the scenario is direr, with the neonatal mortality rate standing at 17.5 per 1000 live births in 2020, of which perinatal asphyxia contributes a significant proportion.(3) Perinatal asphyxia often leads to Hypoxic-Ischemic Encephalopathy (HIE), a neonatal encephalopathy characterized by clinical and laboratory evidence of acute or subacute brain injury.(4) HIE is further classified into mild, moderate, and severe stages, each associated with increasing neurological injury, mortality rates, and long-term neurodevelopmental consequences.(5) Factors contributing to perinatal asphyxia range from conditions affecting the maternal-fetal unit, such as preeclampsia, gestational diabetes, intrauterine growth restriction, and placental insufficiency, to intrapartum events such as prolonged labor, abnormal fetal positioning, or umbilical cord accidents.(6–8) The prevention and management of these risk factors, coupled with improved prenatal care and obstetric practices, can

reduce the incidence of perinatal asphyxia. Despite advancements, HIE from perinatal asphyxia still results in significant long-term morbidity, including neurodevelopmental disabilities like cognitive impairment, cerebral palsy, epilepsy, and a range of learning disabilities and behavioral disorders.(9) Therapeutic hypothermia is currently the standard of care for newborns with moderate to severe HIE. This involves cooling the baby's body temperature for a few days after birth, which can help reduce brain damage. However, its effectiveness can be limited by various factors, including the timing of initiation and severity of asphyxia.(10) Furthermore, in resource-limited settings such as Bangladesh, logistical constraints can limit the accessibility of therapeutic hypothermia, highlighting the need for feasible and effective alternative treatment options. In this context, Topiramate, an antiepileptic drug, comes into focus. It works by modulating the activity of certain neurotransmitters and blocking specific channels in neurons, thereby preventing excessive electrical activity.(11) In various preclinical studies, topiramate has shown promising neuroprotective capabilities, mainly due to its ability to enhance GABA-mediated inhibition, antagonize AMPA/kainate receptors, and inhibit carbonic anhydrase.(12) In animal models of hypoxia-ischemia, topiramate was observed to reduce neuronal injury and improve neurological outcomes, suggesting potential applicability in neonates with HIE.(13) Some clinical studies involving adults have indicated topiramate's neuroprotective potential in conditions like stroke and traumatic brain injury.(14) However, its role as a neuroprotective agent in neonates with HIE remains under-investigated, especially in developing countries like Bangladesh, where the burden of perinatal asphyxia is particularly high. This study aimed to fill this knowledge gap by conducting a randomized controlled trial exploring the effects of topiramate on neurological outcomes in neonates with moderate to severe perinatal asphyxia in Bangladesh. If found to be effective, the integration of topiramate into the current treatment protocols could provide a cost-effective, accessible, and beneficial solution to the significant health burden imposed by perinatal asphyxia.

II. METHODS

This randomized controlled clinical trial study was conducted at the Special Care Baby Unit (SCABU) and other wards of Dhaka Shishu Hospital, Dhaka, Bangladesh. The study duration was 1 year, from April 2015 to March 2016. During this period a total of 64 neonates were included in the study following the inclusion and exclusion criteria, and were divided into two equal groups of 32 patients each. Group-1, or the interventional group, received topiramate 10 mg/kg orally daily for 3 days with supportive treatment within 24 hours of birth. Group-2, or the control group were given supportive treatment e.g. oxygen, volume expanders, inotropes, diuretics, anticonvulsants, antibiotics alone. Inclusion criteria were full-term newborns (Gestational age ≥37weeks), age <24 hours, and presenting with moderate to severe asphyxia assessed by Sarnat & Sarnat staging.(15) However, neonates with congenital anomalies, neonatal sepsis, gastrointestinal problems, hemodynamically unstable babies and preterm babies were excluded from the study. Informed consent was obtained from the ethical review committee of the study hospital. APGAR Score was used to assess the condition of neonates. During therapy Serum electrolytes, RBS, ABG, Serum calcium, Blood grouping and USG of brain were done before and after intervention. Complete physical and neurological examination was done at 1 month and 3 months. Neurological assessment was done by RNDA method. Renal function test, Liver function test were done if required. A pre-tested questionnaire was administered by the investigator for data collection, and standard clinical procedures were performed as necessary.

III. RESULTS

Table 1: Distribution of participants by baseline characteristics (N=64)

Baseline Characteristics	**Group-1 (n=32)**		**Group-2 (n=32)**		**P-value**
	n	**%**	**n**	**%**	
Sex					
Male	17	53.13%	21	65.63%	>0.05
Female	15	46.88%	11	34.38%	
Perinatal Asphyxia Stage					
Stage II	18	56.25%	20	62.50%	>0.05
Stage III	14	43.75%	12	37.50%	
Age					
Median	5		5.5		>0.05
Interquartile Range	3-7.75		4-7.75		
Birth Weight					

Mean ± SD	2890±223	2912.5±196	>0.05
Arterial PH			
Mean ± SD	7.2±0.08	7.2±0.07	>0.05

Table 1 presents the baseline characteristics of the 64 participants distributed equally across Group-1 and Group-2 (n=32 each). Gender representation was almost balanced in both groups, with male neonates constituting 53.13% and 65.63% in Group-1 and Group-2, respectively. Female neonates represented 46.88% of Group-1 and 34.38% of Group-2. The distribution of perinatal asphyxia stages was also similar across both groups; Stage II asphyxia was found in 56.25% of neonates in Group-1 and 62.50% in Group-2, whereas Stage III asphyxia was noted in 43.75% and 37.50% of neonates in Group-1 and Group-2, respectively. The median age of neonates in both groups was similar (5 for Group-1 and 5.5 for Group-2), with interquartile ranges of 3-7.75 for Group-1 and 4-7.75 for Group-2. The mean birth weight was marginally higher in Group-2 (2912.5±196 g) compared to Group-1 (2890±223 g), and both groups had a similar mean arterial pH of 7.2±0.08 for Group-1 and 7.2±0.07 for Group-2. Notably, none of these differences were statistically significant, with all P-values exceeding 0.05, indicating a homogenous sample at baseline across both groups.

Table 2: Distribution of participants by baseline maternal characteristics (N=64)

Maternal Characteristics	**Group-1 (n=32)**		**Group-2 (n=32)**		**P-value**
	n	**%**	**n**	**%**	
Mode of Delivery					
Vaginal Delivery	22	68.75%	19	59.38%	>0.05
Cesarean Section	10	31.25%	13	40.63%	
Residence					
Urban	18	56.25%	15	46.88%	>0.05
Rural	14	43.75%	17	53.13%	
Gestational Age					
Mean	38.97±0.86		39±1.02		>0.05

Table 2 illustrates the maternal characteristics of participants in both groups. In Group-1, 68.75% of deliveries were vaginal, whereas 59.38% of Group-2 mothers had vaginal deliveries. Cesarean sections comprised 31.25% and 40.63% of deliveries in Group-1 and Group-2, respectively. The place of residence was fairly balanced between urban and rural areas in both groups. 56.25% of Group-1 and 46.88% of Group-2 mothers resided in urban areas, while 43.75% of Group-1 and 53.13% of Group-2 mothers lived in rural locations. The mean gestational age was essentially the same for both groups, with Group-1 mothers having a mean gestational age of 38.97±0.86 weeks, and Group-2 mothers showing a slightly higher mean gestational age of 39±1.02 weeks. Notably, all these differences were not statistically significant, as the P-values exceeded 0.05 for each category, indicating a comparable sample of mothers across both groups.

Table 3: USG findings of brain during hospital stay (N=64)

USG finding	**Group-1 (n=32)**		**Group-2 (n=32)**		**Odds Ratio (95% CI)**	**P-value**
	n	**%**	**n**	**%**		
Normal	12	37.50%	13	40.63%	0.88 (0.32-2.39)	>0.05
Abnormal	20	62.50%	19	59.38%		

Table 3 displays the ultrasound (USG) findings of the brain for the neonates during their hospital stay. In Group-1, 37.50% (n=12) of the scans were found to be normal while in Group-2, slightly more, 40.63% (n=13), were deemed normal. Conversely, abnormal USG findings were noted in a greater percentage of the neonates, with 62.50% (n=20) in Group-1 and 59.38% (n=19) in Group-2. The odds ratio of having normal USG findings in Group-1 compared to Group-2 was 0.88 (95% confidence interval 0.32 to 2.39), indicating no significant difference between the two groups. This is further confirmed by the p-value > 0.05, suggesting the differences observed could be due to chance.

Table 4: USG findings of brain at 1 month (N=56)

USG finding	Group-1 (n=29)		Group-2 (n=27)		Odds Ratio (95% CI)	P-value
	n	%	n	%		
Normal	27	93.10%	14	51.85%	0.08 (0.02-0.39)	<**0.01**
Abnormal	2	6.90%	13	48.15%		

Table 4 reveals the ultrasound (USG) findings of the brain at 1-month follow-up for the neonates in both groups. The total number of neonates at this point was 56, with 29 in Group-1 and 27 in Group-2. In Group-1, a significant 93.10% (n=27) of the scans were normal compared to just 51.85% (n=14) in Group-2. Abnormal findings were considerably higher in Group-2, affecting 48.15% (n=13) of the neonates, as opposed to a mere 6.90% (n=2) in Group-1. The odds of having a normal USG result in Group-1 as compared to Group-2 was significantly lower at 0.08 (95% confidence interval 0.02 to 0.39). The p-value of less than 0.01 confirms the statistical significance of this disparity, suggesting a possible beneficial impact of the intervention in Group-1 on brain health at the 1-month mark.

Table 5: Neurological outcome at 1 month (N=56)

Neurological Outcome	Group-1 (n=29)		Group-2 (n=27)		Odds Ratio (95% CI)	P-value
	n	%	n	%		
Normal	24	82.76%	11	40.74%	0.14 (0.04-0.49)	<**0.05**
Abnormal	5	17.24%	16	59.26%		

Table 5 details the neurological outcomes at the 1-month evaluation for the neonates in the study, with 29 in Group-1 and 27 in Group-2. A substantial 82.76% (n=24) of Group-1 neonates exhibited normal neurological outcomes, a stark contrast to Group-2 where only 40.74% (n=11) had normal outcomes. The prevalence of abnormal neurological outcomes was significantly higher in Group-2, affecting 59.26% (n=16) of neonates, compared to only 17.24% (n=5) in Group-1. The odds ratio of 0.14 (95% confidence interval 0.04 to 0.49) suggests a markedly lower probability of a normal neurological outcome in Group-1 when compared to Group-2. The p-value of less than 0.05 further affirms the statistical significance of these results, potentially reflecting the beneficial effect of the intervention employed in Group-1 on the neurological outcomes of the neonates at the 1-month mark.

Table 6: Neurological outcome at 3 months (N=54)

Neurological Outcome	Group-1 (n=28)		Group-2 (n=26)		Odds Ratio (95% CI)	P-value
	n	%	n	%		
Normal	24	85.71%	11	42.31%	0.14 (0.04-0.49)	<**0.05**
Abnormal	5	17.86%	16	61.54%		

Table 6 presents the neurological outcomes at the 3-month evaluation for the neonates in Group-1 (n=28) and Group-2 (n=26). A striking 85.71% (n=24) of neonates in Group-1 were found to have normal neurological outcomes, while only 42.31% (n=11) of neonates in Group-2 presented with normal outcomes. The incidence of abnormal neurological outcomes was significantly higher in Group-2, with 61.54% (n=16) affected, compared to only 17.86% (n=5) in Group-1. The odds ratio of 0.14 (95% confidence interval 0.04 to 0.49) indicates a significantly lower likelihood of a normal neurological outcome in Group-1 compared to Group-2. This difference is statistically significant with a p-value of less than 0.05, which may reflect the continued potential beneficial effect of the intervention in Group-1 on the neurological outcomes of the neonates at the 3-month mark.

IV. DISCUSSION

In the realm of neonatal health, perinatal asphyxia remains a significant challenge and carries high morbidity and mortality rates, both globally and in Bangladesh.(16) This study endeavored to investigate the potential role of topiramate, a well-known antiepileptic drug, in improving neurological outcomes for neonates with moderate to severe perinatal asphyxia. Our initial examination revolved around the uniformity of the two groups, where a total of 64 neonates were randomly distributed into two groups with 32 neonates in each. Baseline characteristics such as gender, perinatal asphyxia stage, age, birth weight, arterial pH, and maternal characteristics were analogous in both groups. Such homogeneity allowed for a minimization of confounding factors, adding

credibility to the subsequent analysis of the impact of topiramate.(17) Regarding the USG brain findings during the initial hospital stay, no statistically significant difference was observed between the two groups. However, a clear divergence was noticed at the 1-month interval. Group-1, treated with topiramate, demonstrated significantly improved USG findings with 93.10% normal results compared to 51.85% in Group-2. This finding indicated a substantial drop in abnormal brain findings in Group-1 by nearly 55.65%. This lends credence to existing research stating the neuroprotective potential of topiramate. Particularly, its role in modulating glutamatergic and GABAergic systems and curtailing neuronal excitability.(11,12)

In terms of neurological outcomes, a consistent pattern mirroring the USG findings was noticed. At both the 1-month and 3-month intervals, Group-1 demonstrated a significant superiority, presenting normal neurological outcomes in 82.76% and 85.71% of neonates respectively, compared to only 40.74% and 42.31% in Group-2. This underscores a nearly 42% improvement in neurological outcomes for neonates treated with topiramate. The congruence of improved neurological outcomes and USG findings further substantiates the structural and functional benefits of topiramate.(18) However, it's important to keep in perspective that the present study does not extrapolate these short-term benefits into the long-term developmental trajectory of these neonates, which is likely influenced by multiple variables such as the severity of the initial injury, co-existing conditions, and efficacy of interventions.(19) Thus, the precise implications of topiramate need to be further explored. This study is limited by its relatively small sample size, and therefore recommends larger multi-center randomized controlled trials to consolidate the effectiveness of topiramate in perinatal asphyxia and solidify its inclusion in clinical practice.

V. Limitations of The Study

This study, while enlightening, is limited by its relatively small sample size. As such, further research, especially larger multi-center randomized controlled trials, are necessary to consolidate the evidence regarding the effectiveness of topiramate in perinatal asphyxia and its potential inclusion in routine clinical practice.

VI. CONCLUSION

In conclusion, this study provides initial empirical evidence suggesting that the administration of topiramate within the first 24 hours of birth to full-term neonates with moderate to severe perinatal asphyxia may be associated with enhanced neurological outcomes. If corroborated by larger studies, topiramate may emerge as a key component in the treatment of neonatal perinatal asphyxia.

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