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# Adverse Effects of Topiramate in Neonate with Moderate to Severe Perinatal Asphyxia: A Randomized Controlled Trial

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**Abstract** **Original Research Article**

***Introduction*:** A harmful pregnancy condition that harms both the mother and the fetus is perinatal asphyxia. It frequently happens as a result of challenges during labour, including protracted or challenging delivery, concerns with the umbilical cord, placental abnormalities, or maternal health conditions. Topiramate, an anticonvulsant, works through a variety of different methods. Topiramate looks to be effective as a neuroprotective agent as well as an anti-seizure medication in animal models of newborn brain injury. Angiogenesis, neurogenesis, and neuronal anti-apoptotic pathways are all stimulated and regulated by topiramate. In light of this, this observational study was conducted to ascertain Topiramate's negative consequences in kids with mild to moderate neonatal hypoxia. ***Methods*:** This observational case-control study was carried out in the Neonatal ward and ICU of Dhaka Shishu Hospital from April 2015 to March 2016. A total of 64 neonates were enrolled in this study and were assigned Group A -the interventional group (n=32) received topiramate and standard treatment protocol, and Group B or the control group (n=32) received only standard treatment protocol. The data were analyzed according to standard procedure. ***Results*:** Among the study neonates, based on sex in case and control groups, respectively, seventeen (17,53%) and twenty-one (21,66%) neonates were male, and fifteen (15,47%) and eleven (11,44%) neonates were female. Statistically, the sex distribution between groups was not significant (p=0.44). USG finding of the neonates after treatment was normal in 12 (48%) and 13(41%), and abnormal in 20(32%) and 19 (59%) neonates in the control and case groups, respectively. Out of 27 neonates in the control group, 11 (41%) were neurologically normal, and 16 (59%) had abnormal neurological findings. Out of 29 neonates in the case group, 24 (73%) were neurologically normal, and 5(17%) showed abnormal neurological findings. Statistically, significant variation was observed ($p<0.05$). There was a statistically significant difference ($p<0.005$). In impairment in different domains of development between case and control 1 month of age. There is a statistically significant difference in impairment in different domains of development between case and control at 3 months of age and the p-value is significant. ($p<0.005$). ***Conclusion*:** Initial topiramate administration showed significant efficacy in seizure control, improvement of ultrasonography (USG) findings, and the promotion of favourable neurodevelopmental outcomes at both 1 and 3 months of age in neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE) brought on by perinatal asphyxia. In these findings, topiramate improved the neurological outcome of asphyxiated neonates with moderate to severe hypoxic-ischemic encephalopathy.

**Keywords:** Pregnancy, Perinatal asphyxia, Topiramate, Newborn.



## INTRODUCTION

Perinatal asphyxia refers to a condition in which a baby experiences a lack of oxygen supply to their body and brain during the perinatal period, which includes the time immediately before, during, and after birth. It typically occurs due to complications during labour, such as prolonged or difficult delivery, umbilical cord problems, placental issues, or maternal health conditions [1]. Prematurity and problems connected to the intrapartum accounted for 45% of these newborn deaths, making them the most common causes of death [2]. In low-resource nations in particular, where the rate of asphyxia is ten times higher (10-20 per 1000 live births) than in high-resource countries, perinatal asphyxia still poses a serious

problem [3]. Neonatal fatalities make up almost half of all under-five deaths in Bangladesh, where the neonatal mortality rate is 41 per 1,000 live births [4]. One of the main preventable causes of newborn mortality in impoverished nations like Bangladesh is perinatal hypoxia. Globally, there are thought to be around 6.6 million perinatal deaths per year, predominantly in underdeveloped nations [5]. In Bangladesh, infant mortality is 33 per 1000 live births, while under-5, mortality is 41. This high IMR is mostly a result of the high newborn mortality rate, which is 24/1000 live births [6]. Prenatal asphyxia is an injury to the fetus or newborn caused by a lack of oxygen (hypoxia) and/or poor blood flow to various organs, and it will show up as trouble establishing spontaneous respiration, which is obvious by a delayed cry after birth that lasts at least one minute [7]. The two phases of hypoxic-ischemia injuries are the ischemic phase, which is dominated by necrotic processes, and the reperfusion phase, which is dominated by apoptotic processes that spread outside of the ischemic areas. This second phase occurs two to six hours after the H-I injury, and the latency period creates a valuable window during which therapeutic interventions can slow the progression of cerebral damage [8]. Anaerobic metabolism failure causes basic energy failure in phase 1 of hypoxia, however, shortly after reoxygenation, aerobic metabolism and cell activities are restored (phase 2). However, following this latent phase of 6–24 hours, a cascade of events causes mitochondrial energy generation to once more malfunction. Phase 2 follows a hypoxic event and lasts for 24-48 hours [9]. Limiting the secondary neuronal damage brought on by neonatal hypoxia may be possible with neuroprotective therapy that targets the latent phase. The increased understanding of cellular healing mechanisms can also open the door to therapeutic modalities that not only prevent further damage but also correct faults in the developing nervous system [10, 11]. Anticonvulsant topiramate has several different mechanisms of action. It prevents neuroexcitation, a fundamental energy failure in phase 1, by blocking sodium channels, high voltage triggered calcium current, boosting GABA-induced chloride influx, and inhibiting kinate/AMPA glutamate receptors [12]. In animal models of infant brain injury, topiramate appears to be useful as both an anti-seizure and a neuroprotective drug. Topiramate stimulates and modulates angiogenesis, neurogenesis, and neuronal anti-apoptotic pathways. In light of this, this observational study was done to determine the adverse effects of Topiramate in children with moderate to severe perinatal asphyxia.

## OBJECTIVES

To observe the adverse effects of Topiramate in children with moderate to severe perinatal asphyxia.

## METHODOLOGY

This observational case-control study was carried out in the Neonatal ward and ICU of Dhaka Shishu Hospital from April 2015 to March 2016. A total of 64 neonates were enrolled in this study and were assigned Group A -interventional group (n=32) received topiramate and standard treatment protocol, and Group B or control group (n=32) received only standard treatment protocol. Mild to severe hypoxia ischemic encephalopathy after oral topiramate treatment. The length of the hospital stay, the length of time it took to manage the seizure, and the neurological result at 1 and 3 months of age were all compared. Among the hospitalized neonates, those with gestational ages of less than 37 weeks, shorter than 24 hours, and sarnat and sarnat staging diagnoses of moderate to severe asphyxia were chosen and enrolled in the study after receiving informed written consent from the parents or guardians. Two groups of sample participants were chosen: Group A, the interventional group (n=32), which received topiramate as well as the standard treatment protocol, and Group B, the control group (n=32), which received only the usual treatment protocol. This division was carried out using a straightforward lottery system. which featured a numbered card.

**Inclusion Criteria:**

- Gestational age ≥37weeks.
- Age less than 24 hours.
- Moderate to severe asphyxia assessed by Sarnat & Sarnat staging.

**Exclusion criteria:**

- Baby born with congenital anomalies
- Haemodynamically unstable baby
- Gestational age less than 37 weeks
- Neonatal sepsis, and any gastrointestinal problem.

**Data analysis:**

The data were analyzed according to standard procedure. SPSS Win version 20 and Epi Info. (Version6) has been used for data analysis: Results of the findings was verified by doing standard test for significance like Unpaired student “t” test, Man-whitny test, Chi-Square (X2) tests, and finding out the p value.

## RESULT

Among the study neonates, based on sex in case and control groups, respectively, seventeen (17,53%) and twenty-one (21,66%) neonates were male, and fifteen (15,47%) and eleven (11,44%) neonates were female. Statistically, the sex distribution between groups was not significant ($p$=0.44). Status of perinatal asphyxia and HIE stage of perinatal asphyxia in case and control groups, respectively, found that

eighteen (18,56%) and around three-fifth of the neonates 20(62%) were in stage II, and fourteen (14,44%) and around two-fifth (12,38%) were in stage III. Statistical analysis showed no significant variation ($p$=0.79). The median age in the hour of the case was 5 hours and control was 5.5 hours. The median difference in age between the two groups was not statistically significant. ($p$=0.421). The mean (±SD) birth weight of the case and control group of neonates was 2890+223gm and 2912.5+196 gm, respectively. The mean difference in birth weight was not statistically significant ($p$=0.68). The Mean (±SD) of pH of the case and control group of neonates was 7.2±0.08 and 7.2 ±.007 respectively. Statistically, the mean difference between groups was not significant. ($p$=0.55). The mean (±SD) gestational age of the case and control groups was 38.97±0.86 and 39±1.02 weeks, respectively. The mean difference between groups was not statistically significant (P=0.89). Twenty-two mothers (22,69%) underwent vaginal delivery and nineteen (19,41%) underwent a Caesarean section in the case group and ten (10,31%) underwent vaginal delivery and thirteen (13,71%) in the control group, respectively. Statistical analysis showed no significant variation ($p$=0.6). Residence of study population shows that 18(56%), 15(47%) mother came from urban and 14(44%), 17(53%) came from rural in case and control respectively. There was no statistically significant difference ($p$=0.62). USG finding of the neonates after treatment was normal in 12 (48%) and 13(41%), and abnormal in 20(32%) and 19 (59%) neonates in the control and case groups, respectively. Statistical analysis did not show any significant variation ($p$=1.00) (**Table 1**). The median duration time taken to control neonatal seizure was 72 hours and 24 hours, respectively, in the control and case groups. The median difference was statistically significant ($p$<0.05). Feeding started by the neonates was 2.63+1.1 days and 4.5+1.3 days in the case and control groups, respectively. The duration was statistically significant ($p$<0.01). The mean (±SD) hospital stay was 6.3±1.7 days for the case group of neonates and 10.3±2.7 days for the control group of neonates. The mean difference in hospital stay was statistically significant (P<0.01). Case (topiramate) group required a short duration of hospital stay (**Table 2**). Out of 27 neonates in the control group, 11 (41%) were neurologically normal, and 16 (59%) had abnormal neurological findings. Out of 29 neonates in the case group, 24 (73%) were neurologically normal, and 5(17%) showed abnormal neurological findings. Statistically, significant variation was observed ($p$<0.05) (**Table 3**). Out of 26 neonates in the control group, 10 (38%) were neurologically normal. 16 (62 %) had abnormal neurological findings. Out of 28 neonates in the case group, 24 (85.7%) were neurologically normal 4(14.3%) showed abnormal neurological findings. Statistically, significant variation was observed ($p$<0.01). Out of 26 neonates in the control group, 10 (38%) were neurologically normal. 16 (62 %) had abnormal neurological findings. Out of 28 neonates in the case group, 24 (85.7%) were neurologically normal 4(14.3%) showed abnormal neurological findings. Statistically, significant variation was observed ($p$<0.01) (**Table 4**). There was a statistically significant difference (p<0.005). In impairment in different domains of development between case and control 1 month of age. There is a statistically significant difference in impairment in different domains of development between case and control at 3 months of age and the p-value is significant. ($p$<0.005) (**Table 5**).

**Table 1: Base line characteristic of study neonates and mothers of the neonates, (N=64)**

| **Characteristic** | **Case n=32(%)** | **Control n=32(%)** | ***p value*** |
|---|---|---|---|
| **Sex** | | | |
| Male | 17(53%) | 21(66%) | 0.44 (chi-square) |
| Female | 15(47%) | 11(44%) | |
| **Perinatal asphyxia with HIE** | | | |
| Stage II | 18(56%) | 20(62%) | 0.79 (chi-square) |
| Stage III | 14(44%) | 12(38%) | |
| **Age (hour)** | 5(3,7.75) | 5.5(4,7.75) | 0.421 (Man-whitny) |
| **Birth weight (gm)** | 2890±223 | 2912.5±196 | 0.68 ( t test) |
| **Arterial PH** | 7.2±0.08 | 7.2±0.07 | 0.55 ( t test) |
| **Gestation (weeks)** | 38.97±0.86 | 39±1.02 | 0.89 (t test) |
| **Mode of delivery** | | | |
| Vaginal | 22(69%) | 19(59%) | 0.6 (chi-square) |
| CS | 10(31%) | 13(41%) | |
| **Residence** | | | |
| Urban | 18(56%) | 15(47%) | 0.62 (chi-square) |
| Rural | 14(44%) | 17(53%) | |
| **USG findings of brain during hospital stay** | | | |
| Normal | 12(38%) | 13(41%) | 1.00(chi-square) |
| Abnormal | 20(62%) | 19(59%) | |

**Table 2: Distribution of the study population based on Immediate outcome (N=64)**

| **Immediate outcome** | **Case n=32(%)** | **Control n=32(%)** | ***p value*** |
|---|---|---|---|
| Duration of seizure control, Median | 24(19.536) | 72(48,72) | 0.00 |
| Initiation of oral feeding Mean±SD days | 2.63±1.1 | 4.5±1.3 | 0.00 |
| Duration of hospital stay Mean±SD, days | 6.3±1.7 | 10.3±2.7 | 0.00 |

**Table 3: USG findings at 1 month of age**

| **USG findings** | **Case n=30(%)** | **Control n=27(%)** | ***p value*** |
|---|---|---|---|
| Normal | 28(93%) | 14(52%) | 0.00 (Fisher exact) |
| Abnormal | 2(7%) | 13(48%) | |

**Table 4: Neurological outcome at 1 month and at 3 month**

| **Outcome** | **Case n=29(%)** | **Control n=27(%)** | ***p value*** |
|---|---|---|---|
| Normal | 24(73%) | 11(41%) | 0.002 (chi-square) |
| Abnormal | 5(17%) | 16(59%) | |
| **Outcome** | **Case n=28(%)** | **Control n=26(%)** | |
| Normal | 24(85.7%) | 10(38%) | 0.008 (Fisher-exact) |
| Abnormal | 4(14.3%) | 16(62%) | |

**Table 5: Impairment of different domain at 1 month & 3 months**

| **Characteristics** | | **Cases, n=29(%)** | **Control, n=27(%)** | ***p value*** |
|---|---|---|---|---|
| Gross motor | Abnormal | 5(17.3%) | 16(59.25%) | 0.004 |
| | Normal a | 24(82.7%) | 11(40.74%) | |
| Fine motor | Abnormal | 5(17.3%) | 16(59.25%) | 0.005 |
| | Normal | 24( 82.7) | 11(40.74%) | |
| Vision | Abnormal | 2(6.7%) | 13(48.14%) | 0.000 |
| | Normal | 27(93.3%) | 14(51.85%) | |
| Hearing | Abnormal | 2(6.7%) | 13(48.14%) | 0.000 |
| | Normal | 27(93.3%) | 14(51.85%) | |
| Speech | Abnormal | 1(3.44%) | 13(41.14%) | 0.000 |
| | Normal | 28(97.66%) | 14(51.85%) | |
| Cognition | Abnormal | 1(11.1%) | 13(41.14%) | 0.000 |
| | Normal | 28(89.9%) | 14(51.85%) | |
| **Characteristics** | | **Cases, n=28(%)** | **Controls, n=26(%)** | ***p value*** |
| Gross motor | Abnormal | 4(14.28%) | 16(61.5%) | 0.004 |
| | Normal a | 24(85.7%) | 10(38.5%) | |
| Fine motor | Abnormal | 4(14.28%) | 16(61.5%) | 0.005 |
| | Normal | 24( 85.7) | 10(38.5%) | |
| Vision | Abnormal | 2(7.6%) | 12(46.1%) | 0.000 |
| | Normal | 26(92.3%) | 14 (53.84%) | |
| Hearing | Abnormal | 2(7.6%) | 13(50%) | 0.000 |
| | Normal | 26(92.3%) | 13(50%) | |
| Speech | Abnormal | 1(3.5%) | 13(50%) | 0.000 |
| | Normal | 27(96.4%) | 13(50%) | |
| Cognition | Abnormal | 1(3.5%) | 13(50%) | 0.000 |
| | Normal | 27(96.4%) | 13(50% | |

## DISCUSSION

The first study project in Bangladesh examined the function of topiramate in neonatal hypoxia. This study showed that using topiramate for babies with HIE was both feasible and potentially effective. Topiramate administration was linked to positive neurodevelopment outcomes at 1 and 3 months of age, improved neuroimaging backgrounds, and prospective clinical changes.

The current treatment for hypoxic-ischemic encephalopathy (HIE) is predominantly supportive, to maintain physiologic parameters. If premature babies with moderate HIE underwent freezing within six hours, hypothermia improved the results [13].

64 neonates, all divided into two groups, among them, Group A (n=32) received only supportive care, but Group B (n=32) also received topiramate medication. 4 patients died during therapy, 3 in the control group and 1 in the case group. And three patients missed the follow-up appointment.

There were no significant differences between the two groups in terms of the baseline demographic variables (sex, gestational age, birth weight, place of residency), clinical variables (mode of delivery, onset of seizure, stages of perinatal hypoxia), or PH levels. This study showed significant improvement in the control of seizures, early initiation of feeding and hospital stay in the intervention group with topiramate. Another article found similar results in asphyxiated neonates [14].

This study also demonstrated topiramate's neuroprotective properties, which were reflected in the intervention group's lower rate of neonates with neurologic abnormalities. The results of the study population in the intervention and control groups indicated 24 (73%) normal at one month in the treatment group and 11 (41%), adverse neurological outcomes occurred 5 (17%) in the treatment group and 16 (59%) in the control group, and the findings are statistically significant (P 0.05). At 3 months, the neurological outcomes were normal in 24 (85.7%) of the treatment group, 10 (38%) of the control group, and 4 (14.3%), 16 (62%) of the control group. These results are statistically significant (P 0.01). Clinical developmental evaluation using the RNDA approach was used to evaluate improvements after three months. These outcomes supported earlier discoveries [15]. RNDA performed neurological assessments at 1 and 3 months. For newborns and very young infants, concurrent validity between the RNDA and traditional psychometric testing was good for the full range of functions, and integrate reliability was high [16].

There was no severe or moderate grade impairment among the 5 neurologically affected infants at a month in the case group; all are mildly impaired. One severely impaired neonate, 11 moderately impaired, and 4 mildly impaired neonates made comprised the control group's 16 impaired neonates. Patients in case group 4 at three months had modest impairments; no patients had significant or severe impairments. Among the 16 patients in the control group, 1 had a severe impairment, 12 had a moderate impairment, and 3 had a mild impairment. However, no statistically significant test was conducted. There has never been research done to grade the severity of hypoxia ischemic neonatal damage.

One of the most frequent causes of death and long-term neurologic abnormalities (cerebral palsy, mental retardation, learning disability, and epilepsy) in term and preterm newborns is perinatal asphyxia-induced brain injury [17].

The mortality rate was not impacted by topiramate, but the rate of impairment was, after three months, reduced from 62% to 14% (P =.008). This is comparable to the findings after head cooling, which markedly lowered the rate of impairment.

The topiramate group also experienced a marked reduction in clinical seizures. These results were in line with earlier trials that employed topiramate to treat neonates whose seizures were resistant to other anti-epileptic medication [18].

During the hospital stay, there is no discernible difference between the treatment and control groups' USG of the brain results. Among them, 12 (38%) in the therapy group and 13 (41%) in the control group had normal results. 19 (59%) of the treatment group had abnormal USG findings, compared to 20 (52%) of the control group. At 1 month, 2 (7% of cases) have aberrant USG results, compared to 13 (48%) in the control group and 14 (52%) in the case with normal USG findings. Statistics show that the difference is significant (p-value = 00). The outcomes was similar to other analysis [19].

In a relevant study carried out in Italy, the author measured topiramate levels in serum [20]. In this study, it was not done as it is not feasible in our country.

In our study, the case (topiramate) group had better outcomes than the control group in some of the cases.

## CONCLUSION

Early topiramate administration showed significant efficacy in seizure control, improvement of

ultrasonography (USG) findings, and the promotion of favorable neurodevelopmental outcomes at both 1 and 3 months of age in neonates with moderate to severe hypoxic-ischemic encephalopathy (HIE) brought on by perinatal asphyxia. If perinatal asphyxia is not properly treated, it can have significant effects, including harm to essential organs, particularly the brain, and long-term neurological problems or even death. In this findings, topiramate improved neurological outcome of asphyxiated neonate with moderate to severe hypoxic ischemic encephalopathy.

**Recommendations:** Large multicenter study should be done for further evaluation of these findings.

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**Conflict of interest:** None declared

**Ethical approval**: The study was approved by the Institutional Ethics Committee

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