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ORIGINAL ARTICLE

Role of Topiramete in Moderate to Severe Perinatal Asphyxia - A Randomized Controlled Clinical Trial

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Abstract

Background: *Topiramate is an anticonvulsant drugs that has multiple mode of mechanism of action. Topiramate appears to be effective as both an anti-seizure and neuroprotective agent in animal models of newborn brain injury.*

Objectives: *To determine the neurological outcome of oral topiramate with moderate to severe hypoxic ischemic encephalopathy.*

Methods: *This one year randomized controlled trial was carried out in the Neonatal ward and ICU of a tertiary care specialized hospital. A total of 64 neonate were enrolled in this study and were randomly assigned intervention group (Group-A, n=32) and control group (Group B=32). In case group oral topiramate 10mg/kg was given for 3 consecutive days along with standard treatment protocol. And control was given only standard protocol. Finally outcomes are compared.*

Results: *Baseline clinical characteristics, age, sex, mode of delivery, arterial pH, residence, basic status of HIE cases were matched in both groups. This study has shown significant reduction of neurological impairment in all domain (gross motor, fine motor, vision hearing, speech) at 1 and 3 months in case than control. There is also early seizure control, early initiation of feeding, short duration of hospital stay in case (treatment) than control without any side effects.*

Conclusion: *Early administration of topiramate to infants with moderate and severe HIE in perinatal asphyxia was very effective in controlling seizures, improving USG findings, and producing favorable neurodevelopmental outcomes at1 and 3 months of age.*

Key words*: Topiramete, moderate to severe perinatal asphyxia, early seizure control.*

Introduction

Perinatal asphyxia is the most important cause of preventable cerebral injury occurring in the neonatal period.[1] It is a major preventable causes of mortality among newborn in the developing countries like Bangladesh. It is estimated that about 6.6 million perinatal death occur each year globally, mostly developing countries.[2] In Bangladesh 39% of neonatal death caused by perinatal asphyxia.[3] An epidemiological survey in childhood impairments disabilities around 5 medical colleges in Bangladesh" done by Sishu Bikas Kendro found that mean prevalence of cerebral palsy is 63 per thousands.[4]

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Prenatal asphyxia is an insult to the fetus or newborn due to lack of oxygen (hypoxia) and or lack of perfusion to various organ which will manifest as difficulty in establishing spontaneous respiration evident by delayed cry after birth at least after 1 minute. Hypoxic-ischemic injuries develop in two phases. Neuroprotective treatment targeting the latent phase may limit the secondary neuronal damage due to perinatal asphyxia. The new knowledge about cellular repair mechanism can also pave the way for types of treatment that not merely limit damage, but can also repair the defects of immature nervous system.[5]

Topiramate is an anticonvulsant drugs that has multiple mode of mechanism of action. Topiramate appears to be effective as both an anti-seizure and neuroprotective agent in animal models of newborn brain injury. Neuronal anti apoptotic mechanisms, angiogenesis and neurogenesis are stimulated andmodulated by the topiramate.[6] Topiramate is safe, easily available, andcan administered orally.

Therefore with this idea study was conducted to determine the neurological outcome of oral topiramate with moderate to severe hypoxic ischemic encephalopathy.

Materials and Methods

This one year randomized control clinical trial was conducted in SCABU and other ward at Dhaka Shishu Hospital from 2015 to 2016. Total 64 babies were selected as sample. 32were in case group and 32 in control group. Outcome of oral topiramate with moderate to severe hypoxic ischemic encephalopathy were studied.

Comparison was done by time taken to control seizure,time of the initiation oral feeding,duration of hospital stay,neurological outcome at 1 month and 3 month of age.

Among the admitted neonates, gestational age ≥37 weeks, age less than 24 hours and by sarnat and sarnat staging diagnosed as moderate to severe asphyxia were selected and obtaining an informed written consent from the parents or guardian for enrolment in the study. Sample subjects were assigned into two groups, 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. This division was done by simple randomization (lottery method). In which a numbered card was picked by the attending nurse from a box for each of the neonates. If the card had an odd number then the neonate was assigned to control group and if the card had an even number then the neonate was assigned to case group. The picked cards were not put back into the box so the sampling was without replacement. Baby who had selection criteria but born with congenital anomalies, hemodynamically unstable, neonatal sepsis were excluded from the study. The treatment group were given topiramate 10 mg/kg orally daily for 3 days with supportive treatment e.g. oxygen, volume expanders, inotropes, diuretics, anticonvulsants, antibioticswithin 24 hours of birth.

The control group were given supportive treatment only. 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. Gross motor, fine motor, vision hearing, speech were assessed at one and three months by RNDA method. Renal function test, Liver function test were done if required.

The data were analyzed according to standard procedure. SPSS Win version 20 and Epi Info. (Version 6) 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 (χ^2) tests, and finding out the p value.

Results

During the study period total 110 neonates were assessed for eligibility. Out of them 35 were excluded according to exclusion criteria and 75 eligible neonates were assessed and randomized in two groups, 37 in case and 38 in control Group. After enrolment, 5 patients in case and 6 in control group had lost. Finally, 64 neonates completed the study 32 neonates in control group and 32 in intervention group. Baseline characteristics of case and control groups are described in Table I & II, it is noted that except topiramete use, all other characteristics were symmetrically distributed between both groups.

We matched with hospital stay of both case and control groups also, details in Table III. It was also statistically similar.

It was argued that there were significant difference in case and control considering immediate outcome like duration of seizure control, initiation of feeding etc (Table IV).

After 1 month and 3 month follow up there was significant difference in both neurological and brain USG findings (Table V, VI, VII).

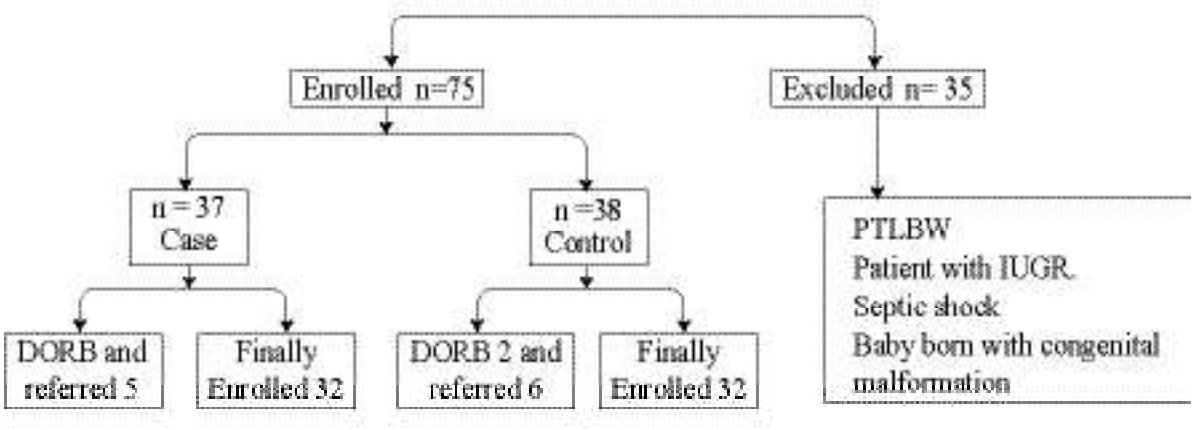

Fig 1 *Flow chart of patients enrollment*

Tabl I
Base line characteristic of study neonate

Parameters		Case(32) n (%)	Control (32) n (%)	p value
Gender	Male	17(53)	21(66)	0.44
	Female	15(47)	11(44)	
Perinatal asphyxia with HIE	Stage II	18(56)	20(62)	0.79
	Stage III	14(44)	12(38)	
Age (hour), Median, IQR	5(3,7.75)	5.5(4,7.75)	0.421	
Birth weight (gm), mean±SD	2890±223	2912.5±196	0.68	
Arterial pH	7.2±0.08	7.2±0.07	0.55	

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test, Man-whitney test, t test considering significant level p<0.05 at 95% CI.

Table II
Base line characteristic mothers of study neonate

Parameters		Case(32) n (%)	Control (32) n (%)	OR,95% CI	p value
Gestation (weeks)		38.97±0.86	39±1.02	1.5(0.52-4.2)	0.89
Mode of delivery	Vaginal	22(69)	19(59)	0.6	
	CS	10(31)	13(41)		
Residence	Urban	18(56)	15(47)	1.46(0.54-3.90)	0.62
	Rural	14(44)	17(53)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test, t test considering significant level p<0.05 at 95% CI.

Table III
USG findings of brain during hospital stay

USG findings	Case (n=32) n(%)	Control (n=32) n(%)	OR, 95% CI	p value
Normal	12(38)	13(41)	0.88(0.32-2.39)	1.00
Abnormal	20(62)	19(59)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test considering significant level p<0.05 at 95% CI.

Table IV
Immediate outcome

Duration of seizure control	Case (n=32) n(%)	Control (n=32) n(%)	p value
Median, IQR	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 V
USG findings at 1 month of age

USG findings	Case (n=30) n (%)	Control (n=27) n (%)	OR, 95% CI	p value
Normal	28(93)	14(52%)	0.08(0.02-0.39)	0.00
Abnormal	2(7)	13(48)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by Fisher exact test considering significant level p<0.05 at 95% CI.

Table VI
Neurological outcome at 1 month

Outcome	Case (n=29) n(%)	Control (n=27) n(%)	OR, 95% CI	p value
Normal	24(73)	11(41)	0.14(0.04-0.49)	0.002
Abnormal	5(17)	16(59)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by chi-squared test considering significant level p<0.05 at 95% CI.

Table VII
Neurological outcome at 3 month

Outcome	Case (n=28) n(%)	Control (n=26) n (%)	OR,95% CI	p value
Normal	24(85.7)	10(38)	0.19(0.59-0.60)	0.008
Abnormal	4(14.3)	16(62)		

The results are expressed by n=frequency, %=percentage. Statistical analysis were obtained by Fisher exact test considering significant level p<0.05 at 95% CI.

Discussion

The current treatment for hypoxic-ischemic encephalopathy (HIE) is predominantly supportive, to maintain physiologic parameters. This study showed significant improvement in control of seizure, early initiation of feeding and hospital stay in intervention group with to piramate. Zhu et al[7] found similar result in asphyxiated neonates. This study showed there was significant difference in hospital stay between two groups. In intervention group range of hospital stay was 5-10 days Mean ± SD 6.93±1.91 and in control group range of hospital stay was 3-14 days Mean ± SD 9.13±2.87. That is there was significant reduction of hospital stay in intervention group then control group (p=0.001.

The study shows that topiramate treatment improves outcome at discharge for neonates with HIE. The neuroprotective mechanisms of TPM appear to be related not only to AMPA and kainate receptors inhibition, but also to blockade of Na+ channels, high voltage-activated calcium currents, carbonic anhydrase isoenzymes, and mitochondrial permeability transition pore (MPTP). This causes reduction of neuronal swelling, maintain neuronal cell interigty as result prevent cerebral odema.

This study also showed that topiramate is neuroprotective that was reflected by fewer neonates with neurologic abnormalities in intervention group. The outcome of study population in intervention and control group showed 24(73%) normal at one month in treatment group and 11(41%) in control group, abnormal neurological outcome occurred 5(17%) in treatment group and 16(59%) in control group, the findings are statistically significant (P<0.05).

At 3 months the neurological outcome were normal 24(85.7%) in treatment group and 10(38%) in control group, abnormal neurological outcome occurred 4(14.3%) in treatment group and 16(62%) in control group, the findings are statistically significant (P<0.01). Improvements were assessed clinically by developmental assessment by RNDA method at 3 months. These results consistent with previous findings.

At 1 and 3 month neurological assessment was done by RNDA. For newborns and very young infants, interrate reliability was high and concurrent validity was good between the RNDA and standard psychometric testing for the entire range of functions.[8]

In this study topiramate had no effect in reducing the mortality rate, but the rate of disability was reduced from 62% to 14 % (P=.008) at 3 months. This is analogous to the results noted after head cooling, which reduced significantly the rate of disability.[7]

Clinical seizures also significantly decreased in the topiramate group. These results were consistent with the results of previous studies in which topiramate is used as seizurecontrol in neonate refractory to other anti-epileptic drugs.[9]

Previous studies have shown increased cerebral echogenicity due to cerebral oedema on USG of brain. There is no significant difference in USG of brain findings in treatment and control group during hospital stay. At 1 month 2(7%) in cases are abnormal in case, 13(48%) in control group and normal USG findings at 1 month 28(73%) in case and 14(52%) in control group. The difference is statistically significant (p value =00). And this result is correlates with previous study done by Bhat et al.[10] USG was not done at 3 month follow up in this study due to financial constrain.

Conclusion

Early administration of topiramate to neonates with moderate to severe HIE in perinatal asphyxia wasvery effective in controlling seizures, improving USG findings, and producing favorable neurodevelopmental outcomes at1 and 3 months of age.

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