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Effect of Magnesium Sulfate Therapy in Term Neonate with Hypoxic Ischemic Encephalopathy: a Randomized Controlled Trial

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Key words:
Hypoxic ischemic encephalopathy, magnesium sulphate.

Abstract:

Background: Perinatal asphyxia *is one of the most common causes of neonatal mortality and morbidity. The most severe complication of PNA is HIE. Perinatal hypoxic-ischemic encephalopathy (HIE) occurs in 1 to 3% of term or near-term births as a result of hypoxic and/or ischemic insults during labor and delivery. Magnesium sulphate is cost-effective and readily available, and is easily administered in comparison to cooling therapy. The aim of the study. The aim of the study to assess effect of magnesium sulphate in Hypoxic ischemic encephalopathy.* ***Methods:*** *This was a Randomized controlled trial conducted in the Department of Neonatology, Sir Salimullah Medical College Mitford Hospital for a period of 18 (eighteen) months from January 2022 to June 2023. Term neonates who were admitted as Perinatal asphyxia with Hypoxic Ischemic Encephalopathy are the study population. All term inborn/outborn babies, reaching within 6 hours of delivery to Department of Neonatology, Sir Salimullah Medical College Mitford Hospital and fulfilling the operational definition of HIE stage II & III, were included. Experiment Group were given magnesium sulphate 250mg/kg/dose 3 times 24 hour apart within 6 hour of post-natal age with monitoring of vitals. Control group received similar supportive and symptomatic treatment (conventional therapy) with regular monitoring as experiment group. Baseline serum magnesium level was done before first dose then at day 2, day 3 before giving magnesium sulphate in experiment group & control group. Serum Mg level were measured by Vitros 5600 Micro-slide Biochemistry Analyzer (Made in USA). The system software determines the test results of patients automatically.* ***Results:*** *A total of 160 patients were randomized (80 in experiment group and 80 in control group). Both groups had similar baseline characteristics (P> 0.05) including severity of HIE. Median age of starting MgSO4 infusion is 5 hour. In experiment group frequency of seizure (single episode (33.3%), multiple episode (66.7%), time of control of seizure (<48 hrs (70%), >48 hrs (30%), abnormal neurologic status at discharge (36.7%), absent direct breast feeding at discharge (21.7%), the corresponding values in control group (38.3%), (61.7%), (61.7%), (38.3%), (35%), (23.3%). In experiment group duration of hospital stay (<7 day (25%), ≥7 days (75%)), mortality (22.5%), the corresponding values in control group (20%), (80%), (20%). The differences were not statistically significant (P>0.05). Serum Mg level in experiment group, day 1 (0.72±0.14), day 2 (1.18±0.24), day 3 (1.64±0.28), in control group corresponding values are (0.74±0.18), (0.8±0.9), (0.84±0.17). The difference was not statistically significant in day 1 but significant in day 2 and day 3.* ***Conclusion:*** *Infusion of MgSO4 after birth did not improve features of HIE in newborn with PNA. There was higher trend of mortality observed in MgSO4 group although statistically not significant.*

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Introduction:

Perinatal asphyxia is defined as the inability of the newborn to initiate and sustain respiration after delivery and is characterized by a marked impairment of gas exchange. It is one of the most common causes of neonatal mortality and morbidity[1]. The incidence of perinatal asphyxia in developed countries is 2 per 1000 live births, but the rate is 10 times greater in developing countries[2] where there is no adequate access to maternal and neonatal care. Of those asphyxiated neonates, 15-20% die in the neonatal period and 25% of survivors have permanent neurologic deficits[2].

The most severe complication of PNA is HIE . Perinatal hypoxic - ischemic encephalopathy (HIE) occurs in 1 to 3% of term or near-term births as a result of hypoxic and/or ischemic insults during labor and delivery[3,4]. In the developing countries 3% of all infants (3.6 millions) suffer from moderate to severe birth asphyxia, of which 23% (840,000) die and appropriately the same number develop serious sequelae[5,6].Year book of Sir Salimullah Medical College Mitford Hospital 2022 showed incidence of birth asphyxia 49% and among death cases PNA is 42% [7]. Those who survive after asphyxia at birth may have chance to develop neurological complications including epilepsy, cerebral palsy and developmental delay[8]. Hypoxic ischemic encephalopathy (HIE) is a central nervous system dysfunction during the neonatal period , and it is due to ischemic and hypoxic insult[9].

Brain injury in infants is a process that evolves over hours to days proving an opportunity for neuro-protective interventions[10]. The first six hours is the therapeutic window for intervention in perinatal asphyxia following the primary energy failure which occurs within minutes of the hypoxic -ischemic insult. These would cause immediate neuronal death if uninterrupted by therapy and induces the secondary phase of energy failure. Perinatal asphyxia leads to excessive release and reduced uptake of glutamate in the newborn brain. Increased glutamate concentration opens N-methyl -D-aspartate (NMDA) channels allowing excessive calcium influx into the neurons and causes irreversible neuronal injury[11,12].

More recently, attention has been drawn to many pharmacologic agents with anti – inflammatory and neuroprotective properties. These include erythropoietin , melatonin, magnesium sulphate (MgSO4), topiramate, xenon, and allopurinol[13] MgSo4 is essential for the key cellular process, like glycolysis, oxidative phosphorylation, protein synthesis, DNA and RNA aggregation. MgSO4 has been found to block N-Methyl D – Aspartate receptors (NMDA receptors) occupying the binding site within these ion channels preventing the neuronal cell damage caused by activation of these receptors and this may explain its neuroprotective effect in cases of HIE[14]. Magnesium is an ionized mineral essential to hundreds of enzymatic processes, including hormone receptor binding, energy metabolism, muscle contractility as well as neuronal and neurotransmitter function. It is primarily an intracellular cation, and stores are distributed between bone (53%), muscle (27%), soft tissue (19%). Serum magnesium levels are tightly controlled and homeostasis is maintained through intestinal absorption, storage in bones and renal excretion[15,16].

In human serum, the physiological magnesium concentration is 0.6-1 mmol/L Serum concentration over 6 mmol/L can result in coma, respiratory insufficiency and cardiac arrest[17]. In patients with renal failure, magnesium may quickly accumulate and result in hazardous side effects[18].

MgSO4 acts as an endogenous calcium channel antagonist at neuronal synapses, thought to prevent excessive activation of N- methyl-D-aspartate receptors by excitatory amino acids, such as glutamate, and by down regulation of proinflammatory pathways[19]. Magnesium sulphate was shown to improve neurologic outcome of severely asphyxiated newborns in a randomized, placebo controlled trial[20]. This low cost , low technology, readily available intervention could be a possible coping strategy for stemming the tide of perinatal asphyxia and hypoxic ischemic encephalopathy in low resource settings[21].

Though therapeutic hypothermia therapy or hypothermia with other adjunct therapies, like magnesium, has been recommended in moderate to severe hypoxia ; but there is no optimal treatment modality available for birth asphyxia in low income resource-deprived settings, apart from giving supportive and symptomatic treatment[22]. Therapeutic hypothermia for moderate to severe neonatal encephalopathy in term and near-term

infants improves survival without disability[23], but nearly half of all infants still died or survived with disability[24].

In a nested cohort study within a randomized clinical trial recruiting 408 neonates with moderate or severe HIE from 7 tertiary neonatal intensive care units in South Asia, whole-body hypothermia was not associated with reductions in brain injury measured by magnetic resonance biomarkers at age 2 weeks among neonates born at either a tertiary care center or other facilities[25].

So the objective of this study is to assess short term effect of magnesium sulphate in term newborn with Hypoxic- ischemic encephalopathy compared to controls, from randomized controlled trial.

Methods:

This open level Randomized controlled trial (RCT) was carried out at department of Neonatology , Sir Salimullah Medical College Mitford Hospital , Dhaka from January 2022 to June 2023.

Neonates born at Term(37-42 weeks gestation) with post natal age less than 6 hour who were admitted in the Department of Neonatology, Sir Salimullah Medical College Mitford Hospital, with diagnosis of PNA were assessed for eligibility by Sarnat staging. Informed written consent was taken from each patients' legal guardian. After proper counseling about the objectives and procedure of the study only positive respondents were recruited for the study. Enrolled neonates were randomly allocated into two groups, one is control group and the other is experiment group by randomized block permutation which was done through a tool that uses computer generated randomization scheme to create a blocked randomization list for trial.

At first, demographic charateristics of the neonates, incuding weight, gestational age gender, mode of delivery, place of delivery, HIE grade and maternal characteristics (Parity, antenatal check up, maternal condition) were taken. Then serum magnesium were performed for all participants. Sepsis screening done to exclude sepsis.

Both groups got symptomatic and supportive treatment(respiratory support in the form of supplemental O_2, CPAP care, Mechanical ventilation, ionotropes, antiseizure medication, antibiotics) according to institutional policy. Experiment Group were given magnesium sulphate with dose of 250mg/kg (0.5 ml/kg) diluted in 10ml 10% D/A over 2 hour in slow infusion with dopamine(10ug/kg/min) by seperate channel using syringe pump at admission and once daily for 3 doses. Vitals (pulse rate, respiratory rate, blood pressure, oxygen saturation, capillary refill time) monitored during and after administration, every 10 minutes for 1hr, then hourly for 12 hr. Non-invasive blood pressure (NIBP) is monitored by Patient monitor CETUS x12 (made in Germany) and Hwatime: XM750 (made in China). Inj. G-Magsulph(2.47gm/5 ml) of Gonoshasthaya pharmaceuticals LTD was supplied by the government. Serum magnesium level were repeated on day 2, day 3. All data were collected in individual structured data collection form. Ultrasonogram of brain were done to exclude central nervous system malformation and echocardiogram to exclude congenital cyanotic heart disease in NICU(bed side) during hospital stay as per institutional policy. Effect of magnesium sulphate was assessed by frequency of seizure, time of control of seizure, establishment of direct breast feeding at discharge and neurological status at discharge and duration of hospital stay & mortality in both group. Presence of hypotonia/hypertonia, abnormal(absent/weak) primitive reflexes like sucking reflex, moro reflex, palmar grasp, planter grasp (any one) was considered abnormal.

2ml venous blood was collected aseptically from median cubital vein and allowed to clot for 20 minutes. Then serum samples were prepared by centrifugation at 4000 rpm for 10 minutes for estimation of serum Mg level.

Serum Mg level were measured by Vitros 5600 Micro-slide Biochemistry Analyzer (Made in USA). The system software determines the test results of patients automatically. in Serum magnesium level done in Popular diagnostic center Dhaka-1010. The unit of results is mg/dl. Then converted to mmol/L by multiplying with conversion factor 0.4113.

Results:

This is a randomized control study. Study conducted in Sir Salimullah Medical College& Mitford Hospital, Dhaka. Study Period was January 2022 to June 2023. At first 167 eligible sample 7 were excluded due to not given consent.

Then total 160 patient were enrolled, 80 in experiment group and 80 in control group.Again 4 patient excluded due to left against medical advice and 2 due to congenital heart disease and 18 patient died in experiment group, 16 patient died in control group. Analysis of neurologic status and hospital stay at discharge done on 120 participant.

There is no difference in both experiment and control groups in respect to age, sex, birth weight, length, OFC, type of delivery, place of delivery, grade of hypoxic ischemic encephalopathy as evidence by P value > 0.05 in all variable. NVD was higher in experiment group than control group but the difference is not statistically significant (p=0.175). Inborn is higher in experiment group than control group but the difference is not statistically significant (0.33). APGAR score assessed in experiment group 30 patient and in control group 26 patient (Table I).

There is no difference in two groups in terms of antenatal checkup and maternal medical condition. Mother of both groups have suffered from preeclampsia, obstructed labor, MSAF, breech presentation, prolonged labor, eclampsia but there is no statistically difference in both groups. Antenatal check-up is higher in control group than experiment group but statistically not significant (p=0.635). Obstructed labor, MSAF, Breech presentation, prolonged labor are higher in experiment group than control group but statistically not significant (Table II).

Mortality more in experiment group (22.5%) than control group (20%) but statistically not significant (P=0.841) (Table III).

Single episode of convulsion is higher in control group than experiment group. Multiple episodes of convulsion is higher in experiment group than control group but statistically is not significant (P=0.708).Time of control of seizure (<48 hr) is higher in experiment group than control group and time of control of seizure (≥48hr) is higher in control group than experiment group but statistically not significant(P=0.442).Duration of hospital stay (<7 day), (≥7 day) is almost similar in both group and is statistically not significant (P=0.662).Abnormal neurologic status is lower than normal in both experiment and control group but statistically nonsignificant(p=1.000). Direct Breast feeding is almost similar in both group and statistically not significant(P=1.0000) (Table IV).

Serum magnesium levels were comparable in experiment and control group in day-1 but are significantly higher in experiment group at day 2 and day 3(P<0.001) (TableV).

Table I: Neonatal demographic profile in experiment and control group (N=160)

	Experiment group(n=80)	Control group(n=80)		p-value
1.	Age (hours)	2.69 ± 1.87	2.41 ± 1.95	[a]0.364
2.	Sex			
	Male	44 (55.0)	50 (62.5)	[b]0.335
	Female	36 (45.0)	30 (37.5)	
3.	Birth weight (kg)	2.85 ± 0.39	2.88 ± 0.39	[a]0.375
4.	Length (cm)	48.93 ± 2.02	49.04 ± 1.99	[a]0.723
5.	OFC (cm)	35.00 ± 1.42	35.40 ± 1.48	[a]0.083
6.	Type of delivery			
	NVD	75 (93.8)	70 (87.5)	[b]0.175
	Cesarean section	5 (6.2)	10 (12.5)	
7.	Place of delivery			
	Inborn	51 (63.8)	45 (56.2)	[b]0.333
	Out born	29 (36.2)	35 (43.8)	
8.	Gestational age	39.87 ± 1.59	39.50 ± 1.12	[a]0.088
9.	HIE grade			
	HIE-II	50 (62.5)	50 (62.5)	
	HIE-III	30 (37.5)	30 (37.5)	
10.	APGAR Score			
	At 1 min	1.50 ± 1.13	1.64 ± 1.05	[a]0.425
	At 10 min	5.50 ± 1.13	5.56 ± 1.10	[a]0.723
11.	Time of first $MgSO_4$ infusion (hour after birth)	5 (1-6)		

[a]Unpaired t test and [b]Chi-Square test was done.

Table II: Maternal characteristics (N=160)

	Experiment group (n=80)	Control group (n=80)	p-value
Parity			
Primi	49 (61.2)	47 (58.8)	[a]0.865
Multipara	31 (38.8)	33 (41.2)	
Antenatal checkup			
Yes	36 (45.0)	39 (48.8)	[a]0.635
No	44 (55.0)	41 (51.2)	
Maternal risk factor for PNA			
Preeclampsia	7 (8.8)	4 (5.0)	[b]0.532
Obstructed labor	20 (25.0)	18 (22.5)	[a]0.862
MSAF	10 (12.5)	7 (8.8)	[a]0.610
Breech presentation	7 (8.8)	6 (7.5)	[a]1.000
Prolonged labor	13 (16.3)	10 (12.5)	[a]0.654
Eclampsia	0 (0.0)	2 (2.5)	[b]0.475

[a]Chi-square test and [b]Fisher's Exact test was done.

Table III: Mortality of the study subjects in experiment and control group (N=160)

Mortality	Experiment group(n=80)	Control group(n=80)	p-value
Yes	18 (22.5%)	16 (20.0%)	0.841
No	62 (77.5%)	64 (80.0%)	

Chi-Square test was done

Table IV: Outcome variable of study subjects (N=120)

	Experiment group(n=60)	Control group(n=60)	p-value
Frequency of seizure			
Single	20 (33.3)	23 (38.3)	0.708
Multiple	40 (66.7)	37 (61.7)	
Time of control of seizure			
<48 hours	42 (70.0)	37 (61.7)	0.442
≥48 hours	18 (30.0)	23 (38.3)	
Duration of hospital (days)			
<7	15 (25.0)	12 (20.0)	0.662
≥7	45 (75.0)	48 (80.0)	
Neurological status at discharge			
Normal	38 (63.3)	39 (65.0)	1.000
Abnormal	22 (36.7)	21 (35.0)	
Direct breast feeding at discharge			
Yes	47 (78.3)	46 (76.7)	1.000
No	13 (21.7)	14 (23.3)	

Chi-Square test was done

Table V: Serum magnesium level at different follow up in experiment and control group (N=160)

Serum magnesium (mmol/L)	Experiment group(n=80)	Control group(n=80)	p-value
Day 1	0.72 ± 0.14(0.51 – 0.91)	0.74 ± 0.18(0.27 – 1.17)	0.270
Day 2	1.18 ± 0.24(1.02 – 1.72	0.80± 0.10(0.50 – 1.10)	<0.001
Day 3	1.64 ± 0.28(1.53 – 2.53)	0.84 ± 0.17(0.41 – 1.71)	<0.001

Unpaired t test was done.

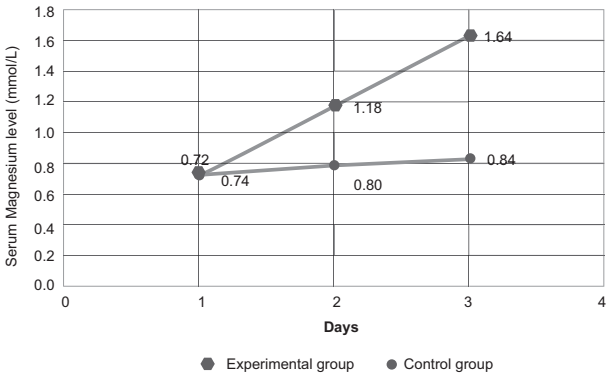

Figure 1: *Line diagram showing magnesium level at different days in experiment and control group*

Discussion:

In this open-label Randomized controlled trial 160 term Neonates with HIE stage II & III were enrolled, 80 in experiment group & 80 in control group. The results of the present study indicated that MgSO4 did not improve features of HIE when given postnatally. There is higher trend of mortality observed in MgSO4 group.

In the present study the mean age at admission is 2.69 ± 1.87 hours in experiment group and 2.41 ± 1.95 hours in control group. No significant difference of age between two groups (p = 0.36). In both group males are more than female. Male to female ratio in experiment group 1.2:1 and in control group 1.7:1 which is statistically not significant (0.33). It is probably due to the social custom of our country where still male offspring is more preferred and taken care of by the parents and family members and they are less interested to spend time and money for female offspring by taking them to distant higher level hospitals. Most of the patients are delivered by NVD in both groups. It is 75 (93.8%) and 70 (87.5%) in experiment group and control group respectively. Most of the patients are inborn in both group. There were no significant difference in Gestational age, Birth weight, length and head circumference of the study and control groups.

Similarly, H Ichiba et al. in a study of 30 cases, 17 (56.66%) were male and 13 (44.44%) were female. Similarly, 18 (60%) were delivered via normal vaginal delivery, 12 (40%) by cesarean section[25].

A study done by Levene et al. has shown that MgSO4 given to term babies with HIE , as slow IV infusion in a dose of 250mg/kg/dose once a day for 3 days (low dose) is less likely to produce hypotension as compared to a dose of 400 mg/kg/dose once a day for 3 days (high dose)[26]. The Bhat et al. and Khashaba et al. have also shown no difference in the incidence of hypotension between the MgSO4 and control groups. Both studies used low dose MgSO4 (250mg/kg/dose once a day). None of these studies used a concomitant hypothermia therapy[27,21]. We also used low dose MgSO4 (250mg/kg/dose once a day) as IV infusion with dopamine(10μg/kg/min) over 2 hour without the concomitant use of standard therapeutic hypothermia therapy.

In a multicenter randomized controlled trial by Ichiba H et al. reported the use of dopamine as a proactive pragmatic step to guard against systemic hypotension in their cohort. Respiratory depression as an outcome is difficult to evaluate as it might be due to birth asphyxia rather than from the use of magnesium. They showed no significant differences in blood pressure, heart rate or respiratory rate between the two group[25]. In our study, no significant differences in blood pressure, heart rate and respiratory rate in between experiment group and control group were found.

Reference levels of serum magnesium signifying hypermagnesemia vary from > 1.15 mmol/L (2.3mg/dl) to >1.5mmol/L (3.0 mg/dl). Bradycardia, hypotension, cardiac arrest with toxic magnesium levels (ie, >7.5mmol/L or 18mg/dl) [18]. In a experimental study , serum concentrations of 2.0-2.5 mmol/L showed the highest neuroprotective effect[28].

With the dosage schedule used in the present study , mean(±SD) serum Mg levels in experiment group on day 1, day 2, day 3 were ((0.72±0.14), (1.18±0.24), (1.64±0.28)) mmol/L over a period of 48 hours, the corresponding values in control group were ((0.74±0.18), (0.8±0.10), (0.84±0.17)) mmol/L. This is possibly the reason why we did not find any side effect or neuroprotective effect.

In the current study, mortality is higher in experiment group(22.5%) as compared with control group (20%) .

Similarly, a systematic analysis and meta-analysis done by Tagin et al., at Winnipeg, Canada, have reported a statistically insignificant higher trend in mortality in the MgSO4 group. However, it is statistically not significant (P>0.05)[29].

In the current study, frequency of seizure (single) is 33.3% in experiment group compared with 38.3% in control group and frequency of seizure (multiple) is 66.7% in experiment group compared with 61.7% in control group but statistically is not significant (P> 0.05). Time of control of seizure (<48hour) is

70.0% in experiment group compared with 61.7% in control group and time of control of seizure (e"48 hours) is 30% in experiment group compared with 38.3% in control group. This differences was not statistically significant (P> 0.05). In our study, Duration of hospital stay (<7 day), (e"7 day) is almost similar in both group and is statistically not significant (P> 0.05).

Similarly in a study from Haryana , India Gathwala G et al. reported seizures occurred in 50% of the neonates in the control group compared with 35% in the study group. However, this differences was not statistically significant (P> 0.05)[30].

In another study, Groenendaal et al.reported in a double-blinded single-center RCT no significant effect on aEEG or long-term neurodevelopment[31].

In the present study abnormal neurologic status in experiment group is 36.7% as compared with 35% in control group which is statistically nonsignificant (P>0.05) and direct breast feeding absent at discharge in experiment group is 21.7% as compared with 23.3% in control group (P> 0.05).

In a prospective, double-blind controlled multi-center randomized controlled trial, Rahman S et al., have reported there were no differences in the short-term adverse outcomes (death, seizures) between the two groups (p>0.05), the trend of mortality was higher in the placebo group which was also statistically nonsignificant[32].

Gathwala et al. also found CT scan abnormalities(focal, multifocal or diffuse hypodensities) occurred in 62. 5% of the control group compared with 37.5% of the experiment group (P > 0.05). Gathwala et al. also found normal motor development in 13 (68.7%) patient in control group as compared with 11(81.2%) in experiment group at 6 month of age but statistically not significant (P > 0.05)[30].

In contrast, another prospective, longitudinal, placebo- controlled trial Bhat et al. have reported at discharge, 22% (4 of 18) of infants in the treatment group had neurologic abnormalities, compared with 56% (10 of 18) of infants in the placebo group. Also, neuroimaging (head computed tomography) performed on day 14 yielded abnormal findings for fewer infants in the treatment group than in the placebo group (16% vs 44%). Infants in the treatment group were more likely to be receiving oral feedings (sucking) at discharge than were those in the placebo group (77% vs 37%)[21].

Levene MI from UK reported that Magnesium sulphate appears to be neuroprotective in animal and human studies, although its effects are most beneficial when used shortly after the asphyxia event[33].

Another study done by Kashaba et al. at Mansoura, Egypt demonstrated that the excitatory neurotransmitters, glutamate and aspartate , are released in the cerebrospinal fluid of asphyxiated newborns immediately after birth and decline by 72 hour. As the role of magnesium is to block the NMDA receptors in the face of increased excitatory neurotransmitters, it seems prudent to initiate magnesium therapy as soon as possible after the hypoxic insult for newborns with moderate to severe HIE[27].

Conclusion:

Infusion of MgSO4 after birth did not improve features of HIE in newborn with PNA. There was higher trend of mortality observed in MgSO4 group although statistically not significant.

Limitations:

Single-center and the relatively short study duration might limit validity. Future multi-center studies with longer follow-up periods will provide more comprehensive insights.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there was no conflict of interest in this study.

Funding:

This research received no external funding.

Ethical consideration:

The study was approved by the Ethical Review Committee Kurmitola General Hospital, Dhaka, Bangladesh. Bangladesh. Informed consent was obtained from each participant or caregivers of the patients.

Author Contributions:

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; had agreed on the journal to which the article had been submitted; and

agreed to be account able for all aspects of the work.

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