

Phenobarbitone for the Management of Neonatal Seizures - A Single Center Study

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Abstract

Introduction: Phenobarbitone is currently the drug of choice for neonatal seizures. In this study we analyzed the effect of Phenobarbitone in the management of neonatal seizures. **Objectives:** To review the cumulative dosage, efficacy of phenobarbitone and need for second and third anti-seizure medication in the treatment of neonatal seizures. **Methods:** This is a cross sectional retrospective observational study from January-2011 to December-2014. Based on clinical observation, anticonvulsant efficacy was assessed. Need for second Ant seizure drug and Cumulative loading dose were studied. All babies admitted with clinical seizures and those developing seizures during hospitalization who were treated with Phenobarbitone as the first drug were studied. **Interventions:** Management of neonatal seizures as per standard unit protocol. Study was approved by the Institutional Ethical Committee. **Statistical Analysis:** All the data were collected in validated preformatted proforma sheet and analysed using appropriate statistical methods. **Results:** 117 babies received phenobarbitone during the study period. Majority (49.57%) of seizures occurred during day 1 of life. HIE was the commonest cause noted in 42.73%. Seizure control with 20 mg/kg loading dose of phenobarbitone was noted in 40.17% of patients & Seizure control with 30 mg/kg loading dose of phenobarbitone was in 19.65%. Seizure control with phenobarbitone as monotherapy was 59.82% and as combinant therapy with Levetiracetam was 32.47%. **Conclusion:** Phenobarbitone had significant seizure control both as monotherapy and along with levetiracetam as combinant therapy.

Key words: Phenobarbitone, Neonatal Seizure, Cumulative Dose, Seizure Control

Introduction

A seizure is a paroxysmal, time-limited change in motor activity that results from abnormal electrical activity in the brain [1]. Occurrence of seizure is a symptom of an underlying neurological disease which may be a consequence of any systemic or biochemical disturbance [2]. Seizures are more common in the neonatal period than in any other stage and affects approximately 1% of all neonates [3]. In practice phenobarbital remains the drug of first choice for confirmed or suspected seizures [4 -10]. Phenobarbitone's role in the management of epilepsy began a century ago in 1912. The drug had been synthesized a decade earlier and used as a sedative. In 1912, Alfred Hauptmann serendipitously discovered that it controlled seizures in epilepsy patients in whom it was used for sedation. Because of its low cost and ease of use as a broad spectrum antiepileptic drug, it is often

used in low-cost situations [11]. Bialer noted that Phenobarbitone was the only synthetic drug to have registered more than a century of continuous and ongoing clinical use [12]. The efficacy and safety of standard anticonvulsants have not been evaluated extensively in the neonate. In this study we analyzed the therapeutic efficacy of Phenobarbitone in neonatal seizures. There are logistic advantages of use of phenobarbitone over phenytoin (*i*) it enters CSF (presumably brain) rapidly and with high efficacy, (*ii*) the serum level is predictable after the dose [13].

Objectives

We have conducted this study to review the cumulative dosage, efficacy of phenobarbitone and need for second and third anti-seizure medication in the treatment of neonatal seizures.

Methodology

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This is a cross sectional retrospective observational study from January-2011 to December-2014. Seizure patterns were classified as per clinical observation. Based on clinical observation, anticonvulsant efficacy was assessed. Need for second Antiseizure drug and Cumulative loading dose of the antiseizure drugs were studied. All Babies admitted with clinical seizures and those developing seizures during hospitalisation who were treated with Phenobarbitone as first drug were studied. The study was approved by the hospital Research and Ethics Committee. Detailed history especially gestational age, age of onset of seizures was taken. Natal and post-natal history was also taken in detail. The initial relevant investigations included blood complete picture with peripheral film, C-reactive protein levels, blood glucose levels, arterial blood gases, renal function tests, liver function tests, serum calcium, serum magnesium, ultrasound scan brain and cerebrospinal fluid examination for evidence of infection when necessary. Blood culture was done in selected cases to rule out infection. EEG and CT scan were performed according to the presentation to confirm the underlying cause of seizures. MRI brain, plasma ammonia, plasma lactate and urine for metabolic screening were carried out in selected cases to reach the specific diagnosis. Hypoglycaemia was defined as blood glucose less than 40 mg/dl in premature and less than 45mg/dl in term babies while hypocalcaemia as serum calcium less than 7.5 mg/dl. CSF examination was considered abnormal when there were elevated CSF leukocytes, low CSF sugar, elevated CSF protein and/or positive smear for gram staining. Supportive measures such as intravenous fluids, metabolic abnormalities correction and oxygen

Table-1: Baseline Characteristics

Majority of neonatal seizures (almost 49.57%) occurred during 1st day of life. Most of the seizures (88.03%) occurred in term babies. Male: female ratio was 1.72:1. Hypoxic ischemic encephalopathy was the commonest cause noted in 42.73% of babies. EEG was done in 59 babies out of which, 57.62% had abnormal EEG pattern.

therapy were usually given according to the underlying primary diagnosis.

Unit Protocol for Administration of Anticonvulsants

Load with injection Phenobarbitone at 20 mg/kg slow IV-infusion over 30min under cardio respiratory monitoring. If seizures persist, second loading of 10mg/kg slow IV infusion over 20min at <1mg/kg/min was given. If seizure persists, additional dose of Levetiracetam at 20 mg/kg slow IV-infusion over 30min at <1mg/kg/min was given. Cardiac rate and rhythm to be monitored. In case of persistent seizures, second loading of 10mg/kg slow IV-infusion over 20min at <1mg/kg/min was given. In case the baby didn't respond to both anti-seizure medications, they were loaded with phenytoin 20mg/kg. If not responding to above management, Midazolam infusion was started.

Statistical Analysis

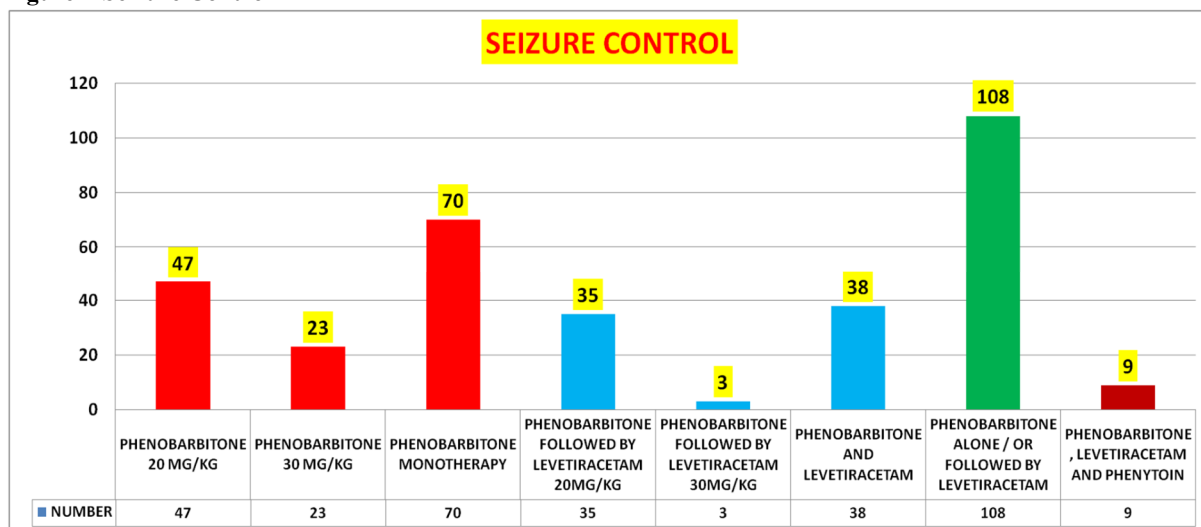
All the data were collected in validated preformatted proforma sheet and analysed using Windostat version 9.2 Software. Categorical variables were analyzed using Chi-square analysis with Yates correction. Student's 't' test was used to compare the means. A p-value of <0.05 was considered significant.

Results

117 babies with neonatal seizures received phenobarbitone as the first drug during the study period.

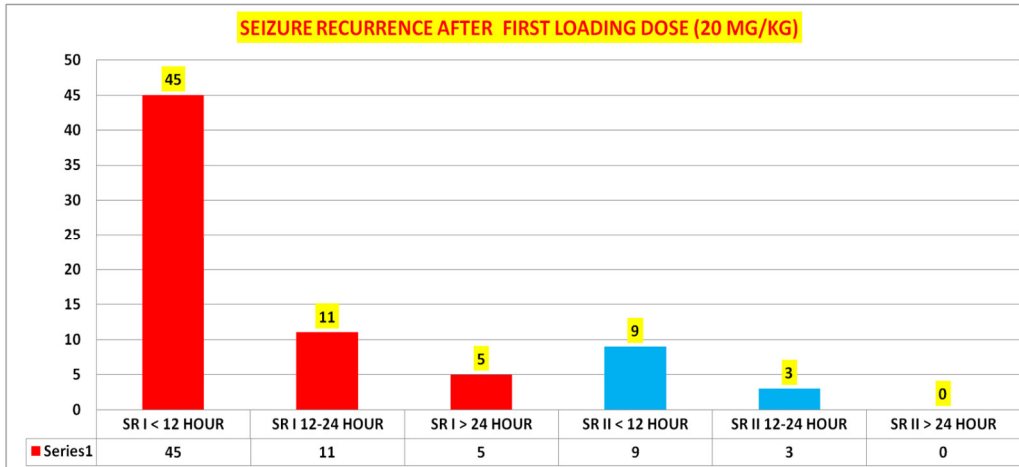
S.N		NO.	%
1	AGE OF ONSET 1st DAY	58	49.57%
2	2-3 DAY	26	22.22%
3	4-7 DAY	17	14.52%
4	8-14 DAY	9	7.60%
5	15-21 DAY	3	2.56%
6	22-28 DAY	4	3.41%
1	TERM	103	88.03%
2	PRETERM	14	11.96%
1	MALE	74	63.24%
2	FEMALE	43	36.75%
1	WEIGHT 1-1.5 Kg	3	2.56%
2	1.5-2 Kg	11	9.40%
3	2-2.5 Kg	24	20.51%
4	>2.5 Kg	78	66.66%
1	RESPIRATORY STATUS : ROOM AIR	29	24.78%
2	O2	55	47%
3	VENTILATED	33	28.20%
1	HIE	50	42.73%
2	IDIOPATHIC	23	19.65%
3	HYPOCALCEMIA	14	11.96%
4	HYPOGLYCEMIA	10	8.54%
5	MENINGITIS	9	7.69%
6	IC BLEED	5	4.27%
7	IEM	2	1.70%
8	INFARCT	2	1.70%
9	CEREBROVENOUS SINUS THROMBOSIS	1	0.85%
10	HYPERNATREMIA	1	0.85%
1	NORMAL EEG	25	42.37%
2	ABNORMAL EEG	34	57.62%

Figure-1 Seizure Control



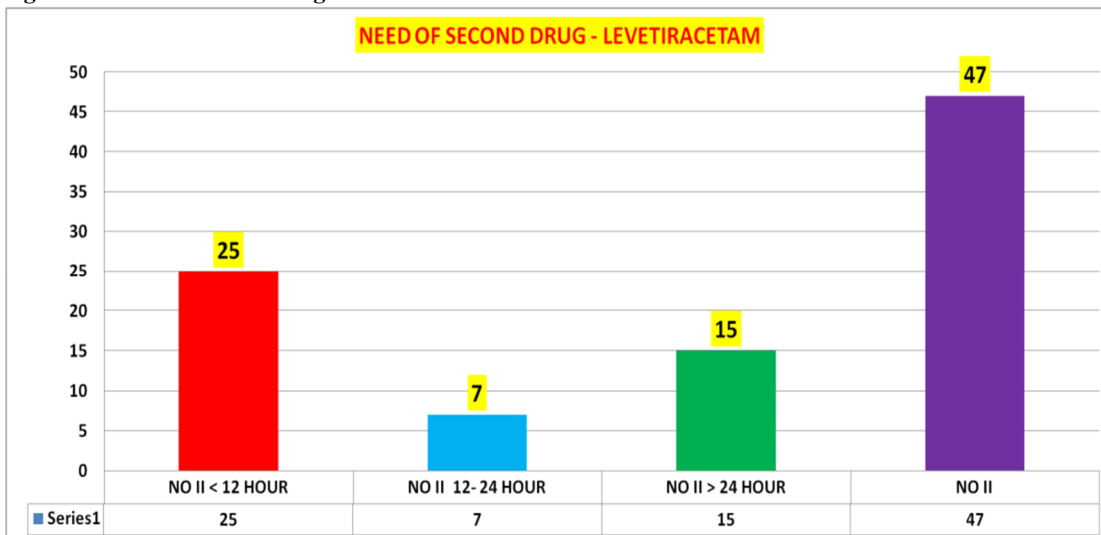
In nearly 47 neonates (40 %) seizures subsided with initial dose of 20 mg per kg of phenobarbitone. Nearly 60 % of seizures subsided when additional dose of 10 mg per kg was given. Levitiracetam was 2nd line drug after phenobarbitone & almost 105 (90 %) neonates have responded with these two drugs.

Figure-2 Seizure Recurrence



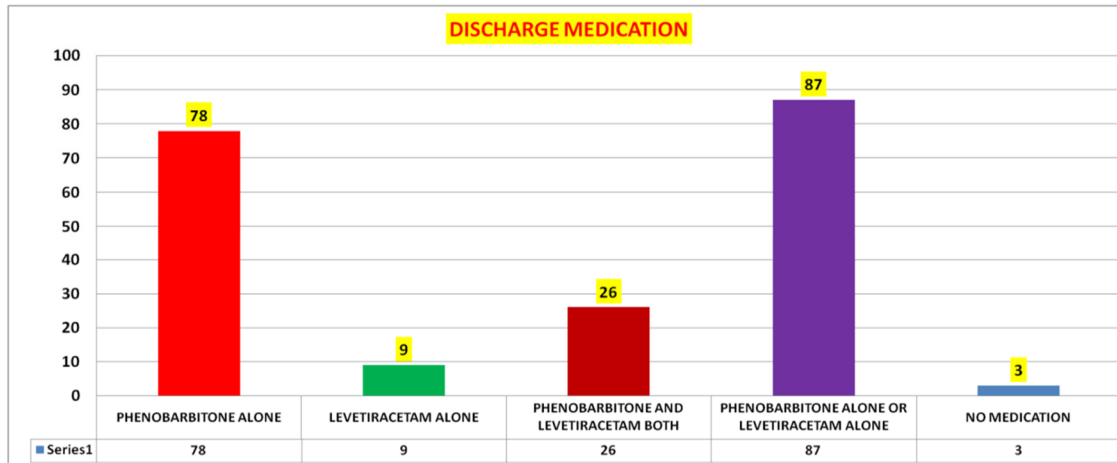
Seizure recurrence within 12 hour after 20 mg/kg loading dose of phenobarbitone was present in 38.46%, recurrence between 12-24 hour was noted in 9.4% of babies. Seizure recurrence within 12 hour was noted in 7.68 % and between 12-24 hours in 2.56 % respectively after levitiracetam.

Figure-3 Need of Second Drug



Need of second antiepileptic drugs within 24 hours were noted in 33 neonates & beyond 24 hours in additional 15 neonates.

Figure-4 Discharge Medication



Majority of babies (66.66%) were discharged with phenobarbitone alone, whereas 22.22% were discharged with phenobarbitone and levetiracetam.

Table-2 Subgroup Analysis

	NO.	CDI 20/30	SR I < 12	SR I 12-24	SR I > 24	DM PHEN	DM LEV	DM BOTH	DM NONE
ONSET FIRST DAY	58	25/33 (43.1%)	26 (44.28%)	5 (8.62%)	2 (3.44%)	36 (62.06%)	3 (5.17%)	16 (27.58%)	2 (3.44%)
2-3 DAY	26	11/15 (42.3%)	9 (34.61%)	3 (11.53%)	3 (11.53%)	16 (61.53%)	4 (15.38%)	6 (23.07%)	0
4-7 DAY	17	13/4 (76.47%)	3 (17.64%)	1 (5.88%)	0	15 (88.23%)	1 (5.88%)	0	1 (5.88%)
8-14 DAY	9	3/6 (33.33%)	4 (44.44%)	2 (22.22%)	0	6 (66.66%)	1 (11.11%)	2 (22.22%)	0
15-21 DAY	3	1/2 (33.33%)	2 (100%)	0	0	2 (66.66%)	0	1 (33.33%)	0
22-28 DAY	4	3/1 (75%)	1 (100%)	0	0	3 (75%)	0	1 (25%)	0
TERM	103	50/53 (48.54%)	40 (38.83%)	9 (8.73%)	4 (3.88%)	70 (67.96%)	7 (6.79%)	22 (21.35%)	3 (2.91%)
PRETERM	14	6/8 (75%)	5 (35.71%)	2 (14.28%)	1 (7.14%)	8 (57.14%)	2 (14.28%)	4 (28.57%)	0
MALE	74	36/38 (48.64%)	27 (36.48%)	7 (9.45%)	4 (5.4%)	48 (64.86%)	6 (8.1%)	17 (22.97%)	3 (4.05%)
FEMALE	43	20/23 (46.51%)	18 (41.86%)	4 (9.3%)	1 (2.32%)	30 (69.76%)	3 (6.97%)	9 (20.93%)	0
WEIGHT 1-1.5 Kg	4	1/3 (25%)	1 (25%)	1 (25%)	1 (25%)	2 (50%)	1 (25%)	1 (25%)	0
1.5-2 Kg	11	7/4 (63.63%)	2 (18.18%)	2 (18.18%)	0	9 (81.81%)	0	2 (18.18%)	0
2-2.5 Kg	24	12/12 (50%)	8 (33.33%)	2 (8.33%)	2 (8.33%)	17 (70.83%)	1 (4.16%)	6 (25%)	0
>2.5 Kg	78	36/42 (46.15%)	34 (43.58%)	6 (7.69%)	2 (2.56%)	50 (64.1%)	7 (8.97%)	17 (21.79%)	3 (3.84%)
NORMAL EEG	25	10/15 (40%)	13 (52%)	2 (8%)	0	-	-	-	-
ABNORMAL EEG	34	17/17 (50%)	11 (32.35%)	3 (8.82%)	3 (8.82%)	-	-	-	-
HIE	50	20/30 (40%)	24 (48%)	4 (8%)	2 (4%)	31 (62%)	4 (8%)	14 (28%)	0
IDIOPATHIC	23	15/8 (65.21%)	6 (26.08%)	2 (8.69%)	0	21 (91.3%)	1 (4.34%)	1 (4.34%)	0
HYPOCALCEMIA	14	6/8 (75%)	6 (42.85%)	0	2 (14.28%)	9 (64.28%)	0	3 (21.42%)	2 (14.28%)
HYPOGLYCEMIA	10	7/3 (70%)	3 (30%)	0	0	8 (80%)	1 (10%)	1 (10%)	0
MENINGITIS	9	4/5 (44.44%)	1 (11.11%)	4 (44.44%)	0	4 (44.44%)	1 (11.11%)	4 (44.44%)	0
INTRACRANIAL BLEED	5	0/5	3 (60%)	1 (20%)	1 (20%)	1 (20%)	2 (40%)	2 (40%)	0
IEM	2	2/0 (100%)	0	0	0	2 (100%)	0	0	0
INFARCT	2	1/1 (100%)	1 (50%)	0	0	1 (50%)	0	0	1 (50%)
THROMBOSIS	1	0/1	1	0	0	0	0	1	0
HYPERNATREMIA	1	1/1	0	0	0	1	0	0	0

The cumulative loading dose of phenobarbitone was 20 mg/kg in about 43% of babies with seizures during first 3 days of life, 33.33% among babies with seizure onset during 2nd & 3rd week of life & 75% with seizure during 4th week of life. Significant difference in seizure control with cumulative loading dose of 20mg/kg was noted among preterm babies compared to term babies(p=0.007); However there was no difference between male & female babies (p=0.9757). The

cumulative loading dose was only 20mg/kg in about 70% of hypocalcemic & hypoglycemic seizures. Seizure recurrence within 12 hour was present in 100% of babies with seizure onset beyond 2 weeks. Babies with HIE had a higher chance of seizure recurrence within 12 hour in nearly 48%. Seizure recurrence between 12-24 hour was present in nearly 44.44% of babies with meningitis. No gestational or sex based significant difference in seizure recurrence within 12 hour or between 12-24 hour after loading dose of phenobarbitone was noted.

Table-3 Subgroup Analysis

	NO.	CDII 20/30	SR II < 12	SR II 12-24	SR II > 24	NO II	NO II < 12	NO II 12-24	NO II >24
ONSET FIRST DAY	58	15/10 (60%)	7 (28%)	2 (85)	0	25 (43.1%)	13 (52%)	4 (16%)	9 (36%)
2-3 DAY	26	11/2 (84.6%)	1 (7.69%)	1 (7.69%)	0	13 (50%)	5 (38.46%)	3 (23.07%)	5 (38.46%)
4-7 DAY	17	2/0 (100%)	0	0	0	2 (11.76%)	2 (100%)	0	0
8-14 DAY	9	3/1 (75%)	1 (25%)	0	0	4 (44.44%)	3 (75%)	0	0
15-21 DAY	3	2/0 (100%)	0	0	0	2 (66.66%)	1 (50%)	0	1 (50%)
22-28 DAY	4	1/0 (100%)	0	0	0	1 (25%)	1 (100%)	0	0
TERM	103	31/9 (77.5%)	7 (17.5%)	2 (5%)	0	40 (38.83%)	21 (52.5%)	6 (15%)	13 (32.5%)
PRETERM	14	4/3 (57.14%)	2 (28.57%)	1 (14.28%)	0	7 (50%)	4 (57.14%)	1 (14.28%)	2 (28.57%)
MALE	74	22/9 (70.96%)	7 (22.58%)	2 (6.45%)	0	31 (41.89%)	18 (58.06%)	3 (9.67%)	10 (32.25%)
FEMALE	43	13/3 (81.25%)	2 (12.5%)	1 (6.25%)	0	16 (37.2%)	7 (43.75%)	4 (25%)	5 (31.25%)
WEIGHT 1-1.5 Kg	4	0/2	1 (50%)	1 (50%)	0	2 (50%)	1 (25%)	0	1 (50%)
1.5-2 Kg	11	2/1 (28.57%)	1 (33.33%)	0	0	3 (27.27%)	2 (66.66%)	0	1 (33.33%)
2-2.5 Kg	24	10/0 (100%)	0	0	0	10 (41.66%)	5 (50%)	2 (20%)	3 (30%)
>2.5 Kg	78	23/9 (71.87%)	7 (21.87%)	2 (6.25%)	0	32 (41.02%)	17 (53.12%)	5 (15.62%)	10 (31.25%)
NORMAL EEG	25	8/3 (88.88%)	2 (22.22%)	1 (11.11%)	0	11 (44%)	6 (66.66%)	1 (11.11%)	3 (33.33%)
ABNORMAL EEG	34	9/5 (64.28%)	5 (35.71%)	0	0	14 (41.17%)	7 (50%)	2 (14.28%)	5 (35.71%)
HIE	50	18/7 (72%)	4 (16%)	3 (12%)	0	25 (50%)	13 (52%)	5 (20%)	7 (28%)
IDIOPATHIC	23	4/0 (100%)	0	0	0	4 (17.39%)	2 (50%)	0	2 (50%)
HYPOCALCEMIA	14	4/0 (100%)	0	0	0	4 (28.57%)	1 (25%)	1(25%)	2(50%)
HYPOGLYCEMIA	10	2/0 (100%)	0	0	0	2(20%)	1(50%)	1 (50%)	0
MENINGITIS	9	3/2 (60%)	2 (40%)	0	0	5 (55.55%)	5 (100%)	0	0
INTRACRANIAL BLEED	5	3/2 (60%)	2 (40%)	0	0	5 (100%)	3 (60%)	0	2 (40%)
IEM	2	0	0	0	0	0	0	0	0
INFARCT	2	0/1	1 (100%)	0	0	1 (50%)	0	0	1 (100%)
THROMBOSIS	1	1/1.	0	0	0	1	0	0	1
HYPERNATREMIA	1	0/0	0	0	0	0	0	0	0

The cumulative loading dose of Levetiracetam as second drug was 20 mg/kg in about 100% of babies with seizures during 3rd & 4th week of life. The cumulative loading dose was only 20 mg/kg in about 100% of hypocalcemic & hypoglycemic seizures. Seizure recurrence within 12 hour was present in 40% of babies with meningitis. No gestational or sex based significant difference in seizure recurrence within 12 hour or between 12-24 hour after loading dose of levetiracetam was noted. No gestational or sex based significant difference in the need of second drug within 12 hour was noted.

Discussion

Gestational Distribution of Neonatal Seizures:

Majority (88.03%) in our study were Term which was comparable to Sanjeev kumar digra et al [14] & Mahjoob N et al[15] who noted that 82.3% & 76% were term in their studies respectively.

Gender Based Distribution of Neonatal Seizures:

Majority (63.24%) in our study were Male which was comparable to Sanjeev kumar digra et al[14] & Taksande et al[16] who noted that 70.5% & 66.4% were male in their studies respectively.

Onset of Neonatal Seizures: Plouin P et al noted that in 80% of cases the onset of neonatal seizures was during the first week [17]. We noted 49.57% seizures in the first 24 hours in comparison to 17.3% noted by Mahjoob N et al, [15] & 45.09% by Sanjeev kumar et al [14]. Seizures on day 2-3 was observed in 22.22% in our study as compared to 40.4% by Taksande et al [16]. We noted 14.52% seizures between day 4 -7 in comparison to 25.49% by Sanjeev kumar et al [14].

Etiological Distribution of Neonatal Seizures: HIE was the predominant cause of neonatal seizures in various studies. In a population-based study by Ronen et al., 2 42% of neonatal seizures were seen following HIE [18]. Sanjeev kumar et al [14], Takshande et al [16], Yildiz et al [19], Cowen et al [20] noted that seizures were due to HIE in 67.65%, 42.7%, 28.6% & 50% of neonates respectively. The most common causes of seizures as per the recently published studies by Kumar A et al [21], Gupta A et al [22], Vasudevan C et al [23] are HIE, metabolic disturbances (hypoglycemia and hypocalcemia), and meningitis. Tegkul et al observed that the common etiologies were HIE and ICH [24]. In our study while analysing the etiology of seizures, HIE was the most common cause noted in 42.73%. Hypocalcemic seizures were observed in 11.96%, hypoglycemia in 8.54% & Meningitis in 7.69%.

EEG Profile: Pathak et al in his study observed after clinical control of seizures, with EEG done in 72 babies that 66 (91.6%) had normal EEG record and 6 (8.4%) had abnormal EEG record [25]. Clinical control of seizure was probably accompanied by electrical control of seizures in majority. However Boylan et al demonstrated that phenobarbitone achieved electrical control of seizures in only 29% as a first line anticonvulsant in whom the background EEG was significantly abnormal [26]. In our study among 117 babies with neonatal seizures, EEG was done in 59 babies. 42.37% had normal EEG recording & 57.62% had abnormal EEG pattern. However, our study did not record background EEG signals, so our results may be difficult to compare to the above study.

The main mechanism of action of phenobarbitone is through prolongation of the opening of the chloride channel in the GABA-A receptor in the post-synaptic cell membrane, producing hyperpolarization and limiting spread of seizure activity. Neonatal seizures are the only situation where Phenobarbitone is practically a drug of choice. Unlike the Na-channel blockers (phenytoin, carbamazepine) Phenobarbitone does not

aggravate primary (genetic) generalized epilepsy and hence may not require EEG confirmation before starting treatment [27]. In a overwhelming majority of neonatal units in both developed and developing world, bedside EEG is not available due to lack of expensive CFM equipments. Thus studies based on abolition of clinical seizures, may have more external validity and generalisability in NICUs, especially in third world countries.

Dose Dependent Seizure Control: In our study the seizure control with 20 mg/kg loading dose of phenobarbitone was achieved in 40.17% of patients & with 30 mg/kg loading dose was 19.65%. Literature review showed that Seizure response rates after a loading dose of 15-20 mg/kg are reported to range from 33% to 40%. With rapid sequential loading doses, up to a total dose of 40 mg/kg, the responsiveness could be improved to 77% [28 -32]. We noted that the Seizure control with phenobarbitone as monotherapy was 59.82% and 32.47% as a combinant therapy with Levetiracetam. Seizure control with either phenobarbitone as monotherapy or as combination therapy with levetiracetam was 92.30%. Seizure control with third anti seizure drug-phenytoin was in additional 7.69% cases. Michael Painter et al, noted that Seizures were controlled in 13 of the 30 neonates assigned to receive phenobarbital (43 %) and 13 of the 29 neonates assigned to receive phenytoin (45 %). When combined treatment is considered, seizure control was achieved in 17 (57 %) of the neonates assigned to receive phenobarbital first and 18 (62 %) of those assigned to receive phenytoin first. With either drug given alone, the seizures were controlled in fewer than half of the neonate [33]. Gilman et al reported 75% control of clinical seizure with phenobarbitone and 85% when combined with phenytoin [11]. Mahjoob N et al noted that 42.1% responded to Phenobarbitone [15].

Painter M J et al observed that Phenobarbitone achieves clinical control in only 30 to 40% of cases [34]. Some claim better clinical control with doses of up to 40 mg/kg and serum levels above 180 $\mu\text{mol/L}$ [11]. A loading dose of 15-20 mg/kg iv usually results in therapeutic plasma levels [21,22,25,28] and is followed by a maintenance dose of 5 mg/kg/d in two divided doses [33-36]. It is preferable to use monotherapy (single drug) for control of seizures. In another study on efficacy, Gal and colleagues studied Phenobarbitone monotherapy and reported ultimate seizure control in 85% [37]. In a similar study by Tegkul et al seizure control was achieved in 78% with cumulative loading

dose of Phenobarbital up to 40-50 mg/kg with the rest (22%) requiring either Phenytoin or lorazepam [24].

Monotherapy Vs Combination Therapy: To assess the efficacy of monotherapy and subsequent combinant anticonvulsant therapy in the treatment of neonatal seizures four studies were examined including three randomised control trials and one retrospective cohort study. Each study used phenobarbitone for monotherapy with doses reaching a maximum of 40 mg/kg. Combinant therapy included midazolam, clonazepam, lorazepam, phenytoin and lignocaine. Monotherapy demonstrated a 29%-50% success rate for complete seizure control whereas combining therapy administered after the failure of monotherapy demonstrated a success rate of 43%-100%. Though the evidence was inconclusive, it would appear that combinant therapy is of greater benefit to infants unresponsive to monotherapy [38]. We noted that the Seizure control with phenobarbitone as monotherapy was 59.82% and Seizure control with either phenobarbitone as monotherapy or as combination therapy was 92.30%.

Conclusion

Phenobarbitone was noted to have benefit in seizure control as noted by significant decrease in seizure recurrence and seizure control both as monotherapy and along with levetiracetam as combinant therapy. Long term outcome studies with appropriately matched controls are needed.

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Permission from IRB: Yes

Conflicts of interest: The authors report no conflicts of interest

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