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Evaluation of Prophylactic Caffeine Therapy in Neonatal Bronchopulmonary Dysplasia and Related Acute Comorbidities Running title: Prophylactic caffeine therapy in neonatal bronchopulmonary dysplasia

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ABSTRACT

BACKGROUND: BPD is defined as an increased or persistent use of oxygen at 36 weeks PMA occuring in preterm infants <35weeks GA; exhibits abnormal pulmonary function, airway hyper-responsiveness and emphysematous changes persisting into adulthood. BPD often accompanies with acute comorbidities like pulmonary hypertension, cor-pulmonale. Clinical caffeine is a drug of choice for morbidities of prematurity in current clinical practices. This study checks the use of caffeine as a prophylactic agent for BPD and related comorbidities, its safety and efficacy.

OBJECTIVES: To evaluate the effectiveness of caffeine in the prevention of BPD and related comorbidities in preterm infants along with its side effects, routine uses in neonatal intensive care unit.

METHODOLOGY: A prospective observational studywas carried out; from September 2019 to July 2020 among the NICU patients, of a tertiary care hospital in Kerala. The safety and efficacy of caffeine in preventing neonatal BPD and its comorbidities, the side effects of caffeine therapy, effect of caffeine in assisted respiration were studied.

RESULTS AND DISCUSSIONS: From the 90 patients enrolled, majority of preterm infants had an apneic attack during their stay in NICU (53%). Apnea was prevented in majority of the cases with caffeine administration (n=90). The progression to RDS and further to BPD was successfully prevented. Majority of the infants under caffeine had a shortened duration of assisted respiration (52%). Radio-diagnostic data of the majority of the infants were devoid of any significant findings of BPD and related comorbidities (94%). Tachycardia (n=33) and tachypnea (n=20) were the major side effects seen in most of the infants while weight gain and hyperthermia or drug induced fever were almost nil.

CONCLUSION: Caffeine was found to be effective in preventing BPD and related acute comorbidities. Austere monitoring of the vital signs of the infants should be done to control or cure the major side effects such as tachycardia and tachypnea.

KEYWORDS: Bronchopulmonary dysplasia; apnea; comorbidities; preterm infants; assisted ventilation; tachycardia; tachypnea.

I. INTRODUCTION:

BronchoPulmonary Dysplasia (BPD) is a life-threatening disease among the most vulnerable set of human population, termed as preterm neonates. It contributes significantly to the mortality and morbidity associated with premature birth. According to the most valid physiological definition of BPD, the continued or increasing use of supplemental oxygen at or beyond 36 weeks gestational age is a confirmatory factor for BPD[4].Initially, BPD was defined simply as the requirement of clinical oxygen 28 days after birth(21).Furthermore, the requirement for supplemental oxygen at 36 weeks of corrected postnatal gestational age, irrespective of the gestational age at birth, was deemed a better indication of respiratory problems(21). According to Principi et al; "a definition based on the need for oxygen or tolerance of room air at 36 weeks of life was also not considered fully appropriate because oxygen administration might vary according to clinical practice among different centres, and BPD severity was not categorized." (21)BPD is diagnosed in all infants, whether Extremely PreTerms(EPTs)

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or Very PreTerms (VPTs), who requires oxygen at 28 days. All neonates are examined at 28 days and a second evaluation is performed for EPT at 36 weeks and for VPT at 56 days. If the child can tolerate room air, the BPD is mild or absent, requirement of <30% oxygen is considered moderate and requirement of >30% is considered severe BPD[21].

Caffeine is a major methyl xanthine that promotes lung functionalities. It is considered as a drug of choice in NICU, often called as the "silver bullet of NICU" [10]. Caffeine is used for the treatment of hyaline membrane diseases like apnea of prematurity(AOP), respiratory distress syndrome (RDS) [1]. The use of caffeine in bronchopulmonary dysplasia is yet a matter of uncertainty. The various side-effects of caffeine in the most critically vulnerable set of human population- the premature infants, are not looked into by most of the trials and studies conducted.

II. METHODOLOGY:

STUDY SETTING:

The study was conducted at KIMS Al-Shifa Super Specialty Hospital which is a 500 bedded hospital situated at Perinthalmanna town, in Malappuram district of Kerala, India.

STUDY DESIGN:A prospective observational study was conducted for a period of one year from September 2019 to July 2020 with an aim of evaluating the effectiveness of prophylactic caffeine therapy in bronchopulmonary dysplasia among the preterm neonates of tertiary care hospital within theNICU of KIMS Al-Shifa Super Specialty Hospital, Perinthalmanna, Malappuram. The patients were selected from the department of neonatal intensive care unit as per the inclusion and exclusion criteria.

STUDY PERIOD: The study was carried out for the period of one year, commencing from September 2019 to July 2020 among the inpatients of neonatal intensive care unit (NICU) department of a tertiary care hospital.

ETHICAL CLEARANCE: This study was approved by the ethical committee of the institution and an official consent was also given for the purpose of performing the study. It was certified by the Institutional Ethics Committee and approved the proposal of the study as per letter no: KAS/IEC/MPHARM/2019-01.

STUDY CRITERIA: All the patients from the department were monitored during the study period and an inclusion and exclusion criteria was made. The inclusion and exclusion criteria as specified in the protocol was submitted to IEC and approved by IEC of KIMS Al-Shifa Super Speciality Hospital. Based on inclusion and Exclusion criteria patients were included in the study.

INCLUSION CRITERIA: Neonatal patients of both sex with gestational age ≤34weeks born in the hospital or referred to NICU.Neonates who were administered with caffeine at least once.

EXCLUSION CRITERIA:

Healthy neonates, Neonates of either sex born ≥35 weeks gestational age, Neonates with major congenital anomalies,Neonates referred to other hospitals,Neonatal death cases which were premature and administered with caffeine.

STUDY PLAN

DATA COLLECTION: An optimally designed data collection form was used to collect and record patient data., which include the patient's demographics, maternal demographics and medical history, patient's medication, birth and antenatal history, lab investigation details, brand name, indication, dose, route, frequency, duration, ADRs, respiratory support required during the intensive care, etc. All relevant data for the study were collected from the various sources such as patient case file, treatment chart, laboratory reports, diagnosis and discharge summary were recorded in the data collection form. The demographic data includes gestational age in weeks, gender, weight, MRD number, birth history, maternal comorbidities, date of admission, date of discharge etc.

STUDY PROCEDURE: Various literatures supporting the study were collected from various national and international journals. A specially designed data collection form was developed and used to collect patient data. It included details of patient's demographics, antenatal and birth history, medication history, presenting complaints, medication chart, number of drugs prescribed, results of laboratory data, details of the caffeine therapy and all other essential data required for the study. The data was collected from hospitalized inpatients. Ethical committee approval and formal consent to access patients case file was obtained prior to the initiation of study. The study subjects were selected on the basis of above mentioned inclusion-exclusion criteria and the study was performed.

DESIGN/METHOD: A prospective study was carried out from September 2019 to July 2020 in the NICU of KIMS Al-Shifa Super Specialty Hospital, Perinthalmanna. The prospective method mainly involved evaluating patient's drug therapy

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during admission or before discharge. The patients were randomly selected on the basis of inclusion and exclusion criteria stated above.

A data collection form was used which had the details such as patient demographics, antenatal and birth history, past medication history, the abnormal lab values, the medications prescribed (caffeine and other drugs), the final diagnosis, external respiratory support during intensive care, duration of respiratory support and caffeine therapy. The patient details were obtained from the case files. All the cases were reviewed prospectively and monitored extensively like the pattern of caffeine use, indication, dose, dosage form, administration site, duration, external respiratory support required during the intensive care time, essential vital signs of the neonate and number of drugs in prescription. Various side effects of clinical caffeine citrate following its administration were also monitored in the enrolled patients. The essential vital signs of the neonate were also monitored on a regular basis thus enabling to check on the patient's clinical progress. The vitals were also required to be monitored for assessing the occurrence of the side effects after the caffeine therapy.

Caffeine was administered both as injections and oral drops. In all cases, an initial loading dose of caffeine was given for faster therapeutic action and relief from apnea. The loading dose was followed by frequent administration of maintenance dose. The study also checked into the best dose range as per the weight of the neonate which can be given, to prevent the condition better and faster with minimal side effects. The study also detected whether caffeine was able to reduce the duration or requirement of external respiratory support for the neonate, whether the vitals were improved in an apneic preterm neonate when administered with the drug. It also checked that if the drug was capable of preventing an irreversible lung injury in the neonate.

SAMPLE SIZE: The sample size was calculated to be 87 based on the prevalence of Broncho Pulmonary Dysplasia. The incidence rates were 28.7%, 10.7% & 1.7% in 9nfants less than 28 weeks, 29 to 30 weeks & 31 to 32 weeks respectively.

STATISTICAL ANALYSIS: Statistical analysis was done using collected data, which were analyzed using the SPSS 20 for the windows version. Numerical data were expressed as mean and standard deviation. Results were interpreted with p-value which is probability of accepting null hypothesis. Significant level was set at < 0.05.

III. RESULTS:

Demographics: In this study, preterm neonates of either sex were included. It was seen that the male subjects (n= 56, 62%) were more when compared to female (n=34, 38%) preterm subjects. Most of the preterm neonates were in the age category of 33-34 weeks (n=45, 50%) followed by 30-32 week gestational age preterms (n=29, 32.2%). The extremely preterm babies who are less than 28 weeks were very less(n=6, 6.7%) implying that micropreemies were born too rare.65 preterms (72%) were in the >1350g category which implies that most of the preterms born had satisfactory birth weight as per their gestational age. The 851g-1350g had 19 cases (21%) and 5% (n=4) belonged to the 701g-850g. Only 2 cases presented that were categorized as <700g (2%). 84% (n=76) were born within the tertiary care hospital and the remaining 16% (n=14) were transported to the healthcare facility for advanced intensive care life support.

50% (n=45) were the late preterm category, while 39 (43.3%) subjects were very preterms or VPTs. Only 6 cases were from the EPT category. (n=30) constituted the multiple pregnancy category. 72% were SGAs implying that preterm neonates are having a slow growth rate.

Prophylactic effect of caffeine: The efficacy of caffeine in preventing hyaline membrane diseases like apnea were analyzed and summarized in **figure 1.** The episodes of apnea pre and post to administration of caffeine were analyzed. Requirement of discharge caffeine and /or home oxygen therapy were also analyzed prior to the discharge of the infant from the intensive care unit and findings are depicted in **figure 2.** Prior to the discharge of the infant, radio-diagnostic imaging were done to assess the prognosis of the disease or presence of any Pulmonary findings significant to bronchopulmonary dysplasia (**figure 3)**.The side-effects of caffeine that were analyzed in the study include tachycardia, tachypnea, drug induced weight gain and drug induced fever. Tachycardia and tachypnea were manifested in (n=33) and (n=20) infants respectively at various stages of caffeine therapy. There were literally no cases of drug induced weight gain (n=0) and drug induced fever (n=0). Tachycardiac and tachypneic events at various stages of caffeine therapy have been depicted in(figure 4).

The association of degree of prematurity of the neonate with other clinical factors is depicted in

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table 1. The degree of prematurity divided as EPTs, VPTs and LPTs are directly linked with other neonatal factors such as birth weight, apgar score, feed of the baby, duration of caffeine therapy, concomitant surfactant therapy, etc. The chi square analysis of the associated factors was done and the p-value was determined for each associations.

The value of significance was set at 0.05.

DEGREE OF PREMATURITY WITH BIRTH WEIGHT: Degree of prematurity is inversely associated with birth weight. That is, as the prematurity reduces from (EPT) to (VPT) and then to (LPT), the birth weight tends to increase with a significance value of (p=0.0).

DEGREE OF PREMATURITY WITH APGAR SCORE: Degree of prematurity is inversely associated with apgar scores with a significance of (p=0.0). The more preterm an infant is, the reduced the apgar scorings will be.

DEGREE OF PREMATURITY WITH FEED HABITS OF THE BABY: Degree of prematurity is associated with the feed habits of the infant with a significance of (p=0.0). The less preterm an infant is, the feed habits shift from exclusive formula feed to combination of formula and expressed breast milk. All the extreme pre-term infants were fed on exclusive formula milk while the Very Pre-Terms (VPTs) and the Late Pre-Terms (LPTs) were given a combination of formula milk and expressed breast milk.

DEGREE OF PREMATURITY WITH FREQUENCY OF APNEA: Degree of prematurity is positively associated with frequency of apnea with a significance of (p=0.0). The more pre-term an infant is, greater are the frequencies of occurrence of apneic attacks.

DEGREE OF PREMATURITY WITH DURATION OF CAFFEINE THERAPY: Degree of prematurity is positively associated with duration of caffeine therapy with a significance of (p=0.0). It is obvious from the data collected that all the Extremely Pre-Term (EPTs) were given a caffeine therapy of greater than 2 weeks period. It is reducing to less than 14days in-case of VPTs and less than 7 days in most cases of LPTs.

DEGREE OF PREMATURITY WITH INTUBATION AT BIRTH: Degree of prematurity is positively associated with birth intubation with a significance of (p=0.0). It is obvious from the data collected that all the extremely pre-term cases (EPTs) were intubated at the delivery room without any delay.

DEGREE OF PREMATURITY WITH CONCOMITTANT SURFACTANT THERAPY: degree of prematurity is further positively associated with concomitant surfactant therapy with a significance of (p=0.0). Thus from the data collected, majority of the EPTs (n=5) required concomitant surfactant therapy and most of the LPTs (n=44) did not require any concomitant surfactant therapy.

DEGREE OF PREMATURITY WITH DURATION OF OXYGEN REQUIREMENT: Degree of prematurity is positively associated with duration of O_2 with a significance of (p=0.0). It is obvious from the data collected that all the Extremely Pre-Term (EPTs) were given a supplemental oxygen therapy of greater than 2 weeks period (n=6). It is reducing to less than 14days in-case of VPTs and less than 7 days in LPTs (n=14).

DEGREE OF PREMATURITY WITH TYPE OF RESPIRATORY SUPPORT RECEIVED: Degree of prematurity is positively associated with the type of respiratory support used with a significance of (p=0.001). The extremely pre-term infants required more than one type of respiratory support with one of them as BCPAP. The number of cases using the respiratory support reduced as the prematurity of the infant reduced from EPT to VPT and then LPTs.

DEGREE OF PREMATURITY WITH DURATION OF NON-INVASIVE RESPIRATORY SUPPORT RECEIVED: Degree of prematurity is positively associated with the duration of non-invasive respiratory support received with a significance of (p=0.0). Duration of non-invasive support received by the EPTs are beyond 2weeks while the late pre-terms required no respiratory support or a period of less than 7 days.

IV. DISCUSSION:

Bronchopulmonary dysplasia is a life-threatening disease among the premature neonates and is one of the significant causes that contribute to mortality and morbidity among the premature infants. The frequency of apnea is greater for the <28 weeks infants. All of them had frequent episodes(n=19) of apnea, 24 had occasional apnea and 47 patients with infrequent apnea due to underlying lung immaturity (table1). The findings also depict that as the age in weeks increases towards 32 weeks and greater, the frequency of apnea reduces from frequent to occasional and then to infrequent. It can be inferred to the increased maturation of the lungs with increase in the postnatal gestational age and the additional increased pulmonary functionalities brought about by caffeine administration. In the review of

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Hesham abdel hady et al, similar suggestions are given[1].

All of the cases (n=90) did not have any apneic episodes after the caffeine therapy. Caffeine therapy significantly reduces the future risk for apneic attacks by modulating the respiratory system of the infant. Thus it also prevents the occurrence of respiratory distress syndrome which may degrade to dysplasia stage. Many clinical trials are proven to have demonstrated this effect of caffeine thereby making it an effective and reliable drug for prevention of BPD. Dobson et al have results in concordance to these findings [14-15].

None of the subjects were discharged from the NICU with clinical caffeine citrate as discharge medication or were discharged with home oxygen therapy. It implies that all the infants were stabilized to maintain normal oxygen saturation at room air by the provision of caffeine therapy. The infants are only discharged from the intensive care unit if they are capable of maintaining normal blood oxygen saturation levels at room temperature without any respiratory assistance. Since the provision of caffeine will improvise the pulmonary functionalities including minute ventilation, this goal was achieved for each subject being enrolled into the study and thus none of the preterm infants required caffeine as a discharge medication or home oxygen therapy. Similar reports were suggested by Eleni et al in their study [9].

All the preterm subjects enrolled into the study were performed with any one form radio-diagnostic procedures prior to their discharge from the NICU to rule-out the presence of any forms of lung inflammation, airway remodeling, hypertrophy, alveolar-interstitial damage which are key clinical evidences of BPD. 94% of the infants did not have any major radio-diagnostic findings pertaining to BPD which implies that the caffeine therapy provided helped in preventing major forms of alveolar tissue damage leading to BPD. The respiratory tissue damages, alveolar-interstitial damages, edema, etc are checked into prior to the discharge of the infant. Those who are devoid of any lung tissue or interstitial tissue alterations are considered healthy to be discharged from the NICU, provided they are clinically stable enough to maintain O2 saturations above 92% at room air without any external respiratory support or drug therapy and devoid of any sign and symptoms.Wong et al in their pilot study have supporting results[3]. Similar results were reported by Aukland et al from their study [31].

DEGREE OF PREMATURITY WITH BIRTH WEIGHT: Degree of prematurity is inversely associated with birth weight. That is, as the prematurity reduces from Extreme Pre-Term (EPT) to Very Pre-Term (VPT) and then to Late Pre-Term (LPT), the birth weight tends to increase with a significance value of (p=0.0). Lower birth weight babies have an increased risk of respiratory problem including apnea, respiratory distress and Broncho Pulmonary Dysplasia. Beam et al in their study provide similar findings [32]. Preterm infants who are with sufficient birth weight are less vulnerable to apneic attacks or respiratory distress.

1. DEGREE OF PREMATURITY WITH APGAR SCORE: Degree of prematurity is inversely associated with apgar scores with a significance of (p=0.0). The more preterm an infant is, the reduced the apgar scorings will be. It can be attributed to the immaturity of the lungs and its functionalities along with the cardiovascular under-development of the baby as more preterm it is born.
2. DEGREE OF PREMATURITY WITH FEED HABITS OF THE BABY: Degree of prematurity is associated with the feed habits of the infant with a significance of (p=0.0). The less preterm an infant is, the feed habits shift from exclusive formula feed to combination of formula and expressed breast milk. All the extreme pre-term infants were fed on exclusive formula milk while the Very Pre-Terms (VPTs) and the Late Pre-Terms (LPTs) were given a combination of formula milk and expressed breast milk. Poor nutrition in the first days of life was found to increase the risk associated with developing BPD.
3. DEGREE OF PREMATURITY WITH FREQUENCY OF APNEA: Degree of prematurity is positively associated with frequency of apnea with a significance of (p=0.0). The more pre-term an infant is, greater are the frequencies of occurrence of apneic attacks. It implies that the extremely pre-term (EPTs) infants will have frequent apnea while the late preterms (LPTs) shall have infrequent apneic episodes if they are devoid of any other congenital cardio-pulmonary anomalies.
4. DEGREE OF PREMATURITY WITH DURATION OF CAFFEINE THERAPY: Degree of prematurity is positively associated with duration of caffeine therapy with a significance of (p=0.0). It implies that the more preterm an infant is; greater will be the duration of caffeine therapy it receives. It is obvious from the data collected that all the Extremely Pre-Term (EPTs) were given a

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caffeine therapy of greater than 2 weeks period. It is reducing to less than 14days in-case of VPTs and less than 7 days in most cases of LPTs.

5. DEGREE OF PREMATURITY WITH INTUBATION AT BIRTH: Degree of prematurity is positively associated with birth intubation with a significance of (p=0.0). It can be inferred that greater the prematurity of an infant, greater are the chances for early birth intubation. Intubation at birth depicts the incomplete lung development which persuades the infant to get external support for respiratory resuscitation. The infant can be clinically stable only if the airway systems are properly supported for an effective gaseous exchange to occur. This is further related to the degree of prematurity of the infant. It is obvious from the data collected that all the extremely pre-term cases (EPTs) were intubated at the delivery room without any delay. Dekker et al in their randomized control trial had similar results of very extremely preterm infants being required to intubate soon after birth [24].
6. DEGREE OF PREMATURITY WITH CONCOMITTANT SURFACTANT THERAPY: degree of prematurity is further positively associated with concomitant surfactant therapy with a significance of (p=0.0). This can be attributed to the immaturity of lung development and the stage of development of the pulmonary tissue at which the infant is born. Extremely pre-term infants who are <28weeks are at the cannalicular stage of lung development where the endogenous surfactant production is scarce or very less. Such infants do require external endotracheal administration of a surfactant. Thus from the data collected, majority of the EPTs required concomitant surfactant therapy. As the infant matures from Extreme premature stage to very pre-term and late pre-term stage, the pulmonary tissues mature into saccular stage, capable of producing native endogenous surfactant required for proper gaseous exchange. The data collected implies that most of the LPTs did not require any concomitant surfactant therapy.
7. DEGREE OF PREMATURITY WITH DURATION OF OXYGEN REQUIREMENT: Degree of prematurity is positively associated with duration of O_2 with a significance of (p=0.0). It implies that the more preterm an infant is; greater will be the duration of supplemental oxygen therapy it receives. This depicts the immaturity of the pulmonary system to provide sufficient oxygen required to maintain blood oxygen saturation levels. Only a minority of the subjects (17%) did not require any oxygen therapy. It can be related to the degree of prematurity of the infant. Those who did not have any requirement of oxygen therapy were the late preterms whose lung maturation is almost complete. It is obvious from the data collected that all the Extremely Pre-Term (EPTs) were given a supplemental oxygen therapy of greater than 2 weeks period. It is reducing to less than 14days in-case of VPTs and less than 7 days in most cases of LPTs.
8. DEGREE OF PREMATURITY WITH TYPE OF RESPIRATORY SUPPORT RECEIVED: Degree of prematurity is positively associated with the type of respiratory support used with a significance of (p=0.001). The extremely pre-term infants required more than one type of respiratory support with one of them as BCPAP. The number of cases using the respiratory support reduced as the prematurity of the infant reduced from EPT to VPT and then LPT.
9. DEGREE OF PREMATURITY WITH DURATION OF NON-INVASIVE RESPIRATORY SUPPORT RECEIVED: Degree of prematurity is positively associated with the duration of non-invasive respiratory support received with a significance of (p=0.0). Duration of non-invasive support received by the EPTs are beyond 2weeks while the late pre-terms required no respiratory support or a period of less than 7 days. It implies that as the prematurity increases, lung immaturity too increases owing the infant to longer duration of non-invasive respiratory support. It can be inferred from this that caffeine facilitates transition from invasive to non-invasive respiratory support, reducing the duration of any form of respiratory support by improvising lung compliance, airway resistance, minute ventilation, increasing the diaphragm contractility and also thus preventing the BPD by reducing lung inflammation and improvising airway remodeling.

V. CONCLUSION:

Caffeine citrate was administered to EPTs as prophylactic for AOP as per the NSCG

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guidelines, but in VPTs and LPTs, it was administered as a curative therapy. All preterms <28weeks were compulsorily under caffeine therapy and infants >28weeks were administered caffeine only under presence of apnea or other respiratory problems. The frequency of AOP was found to be reduced after caffeine administration. Progression to RDS was also reduced. The subject infants were also able to maintain adequate O_2 saturation levels. It was noticed that infants under caffeine therapy required less duration of respiratory support with CPAP, HFNC, LFNC, etc. Caffeine citrate increasing the pulmonary function, aids in executing adequate gaseous exchange that was evident from the O_2saturation levels, heart rate and respiratory rate of the infants. Caffeine prevents any tissue damage in the respiratory system. The vitals of the infants along with the radio-diagnostic findings did not depict any significant findings. Most of the patients had a tachycardic or tachypneic event after caffeine administration. Compared to cardiac and pulmonary effects, drug induced weight gain and drug induced fever were very less.

Limitations of the study: It was a single centered study conducted over a short duration of time.The chronic effects of caffeine therapy were not studied.Long term follow up of the patients were not done.

ACKNOWLEDGEMENTS: We wish to thank all the innocent infants who made our study a reality. We express our sincere thanks to all the nursing staffs in the department of neonatology for their valuable suggestions and support during the study period.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTION: Study concept and design, access to data were done by Asha G who is responsible for the integrity of the data and the accuracy of the data analysis. Analysis and interpretation of the data, drafting of the manuscript, acquisition of data was done by Asha G, Neha Jacob, Mohammed Asif & Sreelekha S. All authors were responsible for study supervision and administrative, technical and material support. They also provided assistance in the drafting of the manuscprit.

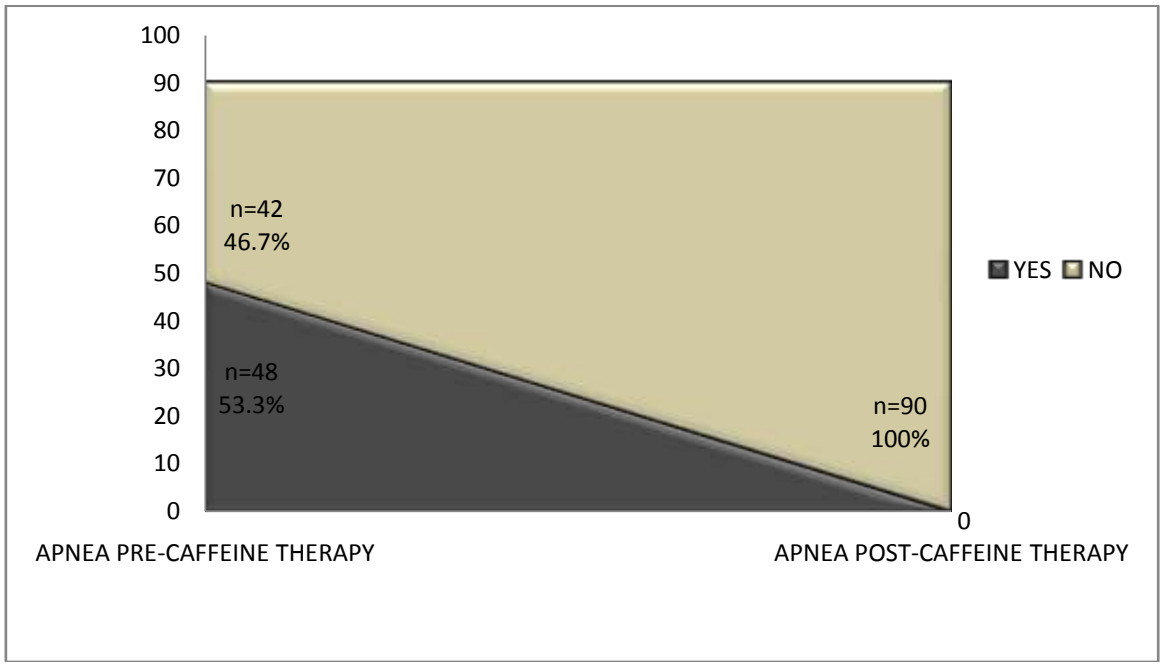

Figure 1: Effect of Caffeine in preventing the hyaline membrane disease, AOP. The analysis of apneic episodes pre and post to caffeine therapy in each preterm infant is depicted in the figure. All the infants were devoid of post-caffeine apnea.

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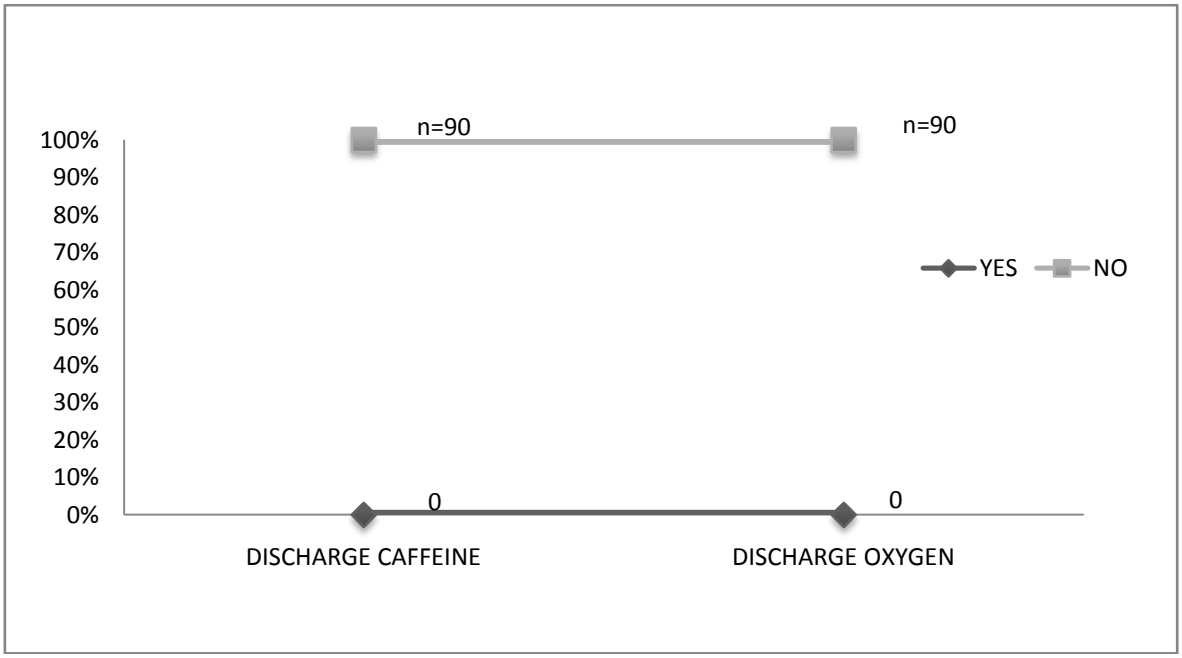

Figure 2: Analysis of infants' discharge therapies, caffeine at discharge and oxygen at discharge. It is seen that none of the subjects were in requirement of home oxygen or discharge caffeine.

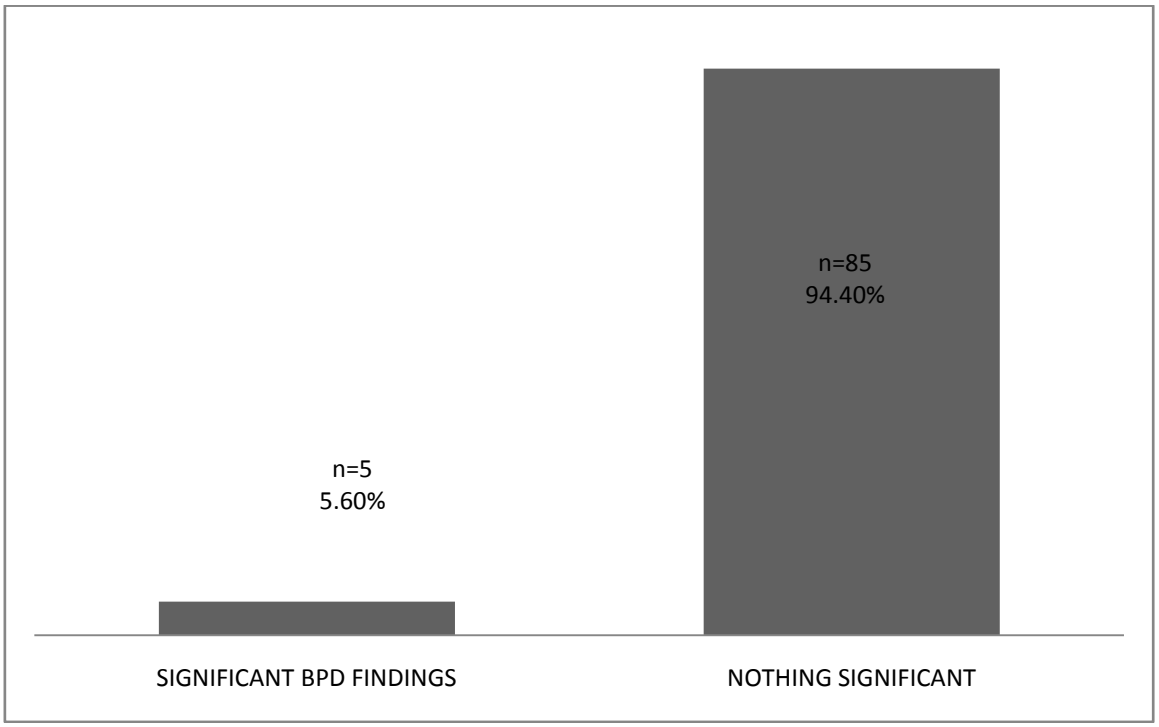

Figure 3: The radio-diagnostic features depict any abnormalities in the respiratory system. (n=5) EPTs had mild BPD characteristics in the reports. Majority (n=85) were devoid of any significant BPD findings.

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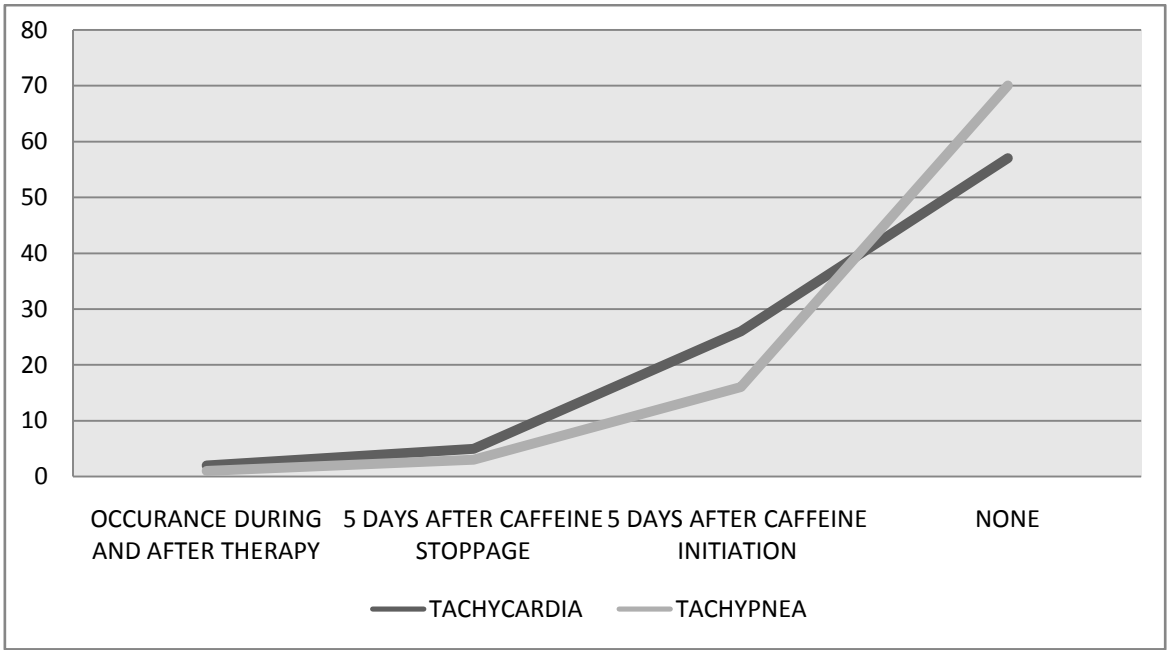

Figure 4: The major side -effects of caffeine, events of tachycardia and tachypnea in preterm infants, at various stages of caffeine therapy illustrated. Tachycardiac events were higher.

		DEGREE OF PREMATURITY			df	p-value
BIRTH WEIGHT		EPT	VPT	LPT	6	0.000
	<700G	2(33.3%)	0(0%)	0(0%)		
	701-850	4(66.7%)	0(0%)	0(0%)		
	851-1350	0(0%)	17(43.6%)	2(4.4%)		
	>1350G	0(0%)	22(56.4%)	43(95.6%)		
	Total	6(100%)	39(100%)	45(100%)		
APGAR SCORE(APGAR)	5-6	6(100%)	22(56.4%)	0(0%)	2	0.000
	7-10	0(0%)	17(43.6%)	45(100%)		
	Total	6(100%)	39(100%)	45(100%)		
FEED HABITS OF BABY	FORMULA MILK	6(100%)	21(53.8%)	9(20%)	4	0.000
	COMBINATION	0(0%)	18(46.2%)	35(77.8%)		
	OTHERS	0(0%)	0(0%)	1(2.2%)		
	Total	6(100%)	39(100%)	45(100%)		
FREQUENCY OF APNEA(FOA)	FREQUENT	6(100%)	13(33.3%)	0(0%)	4	0.000
	OCCASIONAL	0(0%)	18(46.2%)	6(13.3%)		
	INFREQUENT	0(0%)	8(20.5%)	39(86.7%)		
	Total	6(100%)	39(100%)	45(100%)		
DURATION OF CAFFEINE THERAPY	<1 WEEK	0(0%)	11(28.2%)	41(91.1%)	4	0.000
	1-2 WEEKS	0(0%)	23(59%)	4(8.9%)		
	>2 WEEKS	6(100%)	5(12.8%)	0(0%)		

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	Total	6(100%)	39(100%)	45(100%)		
INTUBATION AT BIRTH	YES	6(100%)	28(71.8%)	9(20%)	2	0.000
	NO	0(0%)	11(28.2%)	36(80%)		
	Total	6(100%)	39(100%)	45(100%)		
CONCOMITTANT SURFACTANT THERAPY	YES	5(83.3%)	22(56.4%)	1(2.20%)	2	0.000
	NO	1(16.70%)	17(43.6%)	44(97.80%)		
	Total	6(100%)	39(100%)	45(100%)		
DURATION OF O2 REQUIREMENT	NO REQUIREMENT	0(0%)	2(5.1%)	14(31.1%)	6	0.000
	<1 WEEK	0(0%)	17(43.6%)	30(66.7%)		
	1-2 WEEK	0(0%)	13(33.3%)	1(2.2%)		
	>2 WEEK	6(100%)	7(17.9%)	0(0%)		
	Total	6(100%)	39(100%)	45(100%)		
TYPE OF RESPIRATORY SUPPORT RECEIVED	HOOD O2	0(0%)	1(2.6%)	2(4.4%)	10	0.001
	CPAP	0(0%)	9(23.1%)	6(13.3%)		
	HFNC	0(0%)	4(10.3%)	2(4.4%)		
	LFNC	0(0%)	1(2.6%)	10(22.2%)		
	NONE	0(0%)	2(5.1%)	14(31.1%)		
	MORE THAN ONE TYPE USED	6(100%)	22(56.4%)	11(24.4%)		
	Total	6(100%)	39(100%)	45(100%)		
DURATION OF NON-INVASIVE RESPIRATORY SUPPORT	NONE	0(0%)	2(5.1%)	14(31.1%)	6	0.000
	<1 WEEK	0(0%)	17(43.6%)	30(66.7%)		
	1-2 WEEKS	0(0%)	13(33.3%)	1(2.2%)		
	>2 WEEKS	6(100%)	7(17.9%)	0(0%)		
	Total	6(100%)	39(100%)	45(100%)		

Table 1: Association of degree of prematurity with various clinical factors of the preterm infants enrolled in the study.

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