IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Prophylactic Methylxanthines for Preventing Extubation Failure in the Preterm Neonates with the Gestational Age of ≤30 Weeks: A Randomized Controlled Trial

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ABSTRACT

***Background*:** Preterm neonates are at a high risk of respiratory depression at birth. Incidence of respiratory distress is reported in 60-80% of the neonates born with the gestational age of less than 28 weeks and 15-30% of the neonates with the gestational age of less than 32-34 weeks. The present study aimed to compare the incidence and risk of failed extubation in using caffeine and aminophylline in the preterm neonates with the gestational age of ≤30 weeks in the periextubation period.

***Methods*:** This single-centered, parallel, open-label, randomized controlled trial was conducted in a tertiary care referral hospital in India during June 2014-2016. Neonates with the gestational age of ≤30 weeks who were intubated for a minimum of 24 hours were enrolled in the study. Neonates with major anomalies, heart disease, and sepsis were excluded from the study. After the random allocation of the infants to treatment with the standard dose of caffeine citrate and aminophylline methylxanthine, intubation continued for seven consecutive days with or without non-invasive ventilatory support. As the primary objective, the incidence and risk of failed extubation were assessed. Secondary objective of the research was to compare the relative incidence of acute adverse effects, persistent apnea, and the associated morbidities.

***Results*:** Neonates treated by caffeine were at a higher risk of extubation failure (1.09 times) adjusted with birth weight (31.5% versus 21.4%; RR=1.09; 95% CI: 0.81-1.46; P=0.55), which was not statistically significant. In addition, risk of apnea within seven days and after seven days of methylxanthine therapy was 1.57 (95% CI: 0.95-2.61) and 1.10 (95% CI: 0.95-2.61) times higher in the neonates with caffeine treatment. Also, rate of tachycardia was high in the neonates treated by aminophylline, which was statistically significant (RR=0.27; 95% CI: 0.13-0.56; P<0.001). Duration of non-invasive ventilator support, length of admission in the neonatal intensive care unit, O_2 requirement at discharge, death before hospital discharge, and the associated morbidities were similar between the groups.

Conclusion: According to the results, the incidence and risk of extubation failure were clinically high in the caffeine-treated neonates. However, aminophylline administration could continue as a prophylactic agent in developing countries under medical supervision.

Keywords: Aminophylline, Caffeine, Extubation failure, Mechanical ventilation

Introduction

Preterm neonates are at a high risk of respiratory depression at birth. Incidence of respiratory distress is reported in 60-80% of the neonates born with the gestational age of less than 28 weeks and 15-30% of the neonates with the gestational age of less than 32-34 weeks.

Respiratory depression at birth may require intubation with invasive positive pressure ventilatory support (MV) (1). Prolonged ventilation exposes these neonates to the complications associated with endotracheal tubes and positive pressure ventilation, including mortality, neurodevelopmental impairment, and bronchopulmonary dysplasia (BPD) (2, 3). As such, weaning of the

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Please cite this paper as:
Shivakumar M, Najih M, Bhat Y R, Jayashree P, Lewis LES, Kamath A, Shashikala. Prophylactic Methylxanthines for Preventing Extubation Failure in the Preterm Neonates with the Gestational Age of ≤30 Weeks: A Randomized Controlled Trial. Iranian Journal of Neonatology. 2017 Sep: 8(3). DOI: 10.22038/ijn.2017.23031.1281

ventilatory support and expeditious extubation are of paramount importance. Weaning is often difficult in such neonates and might lead to extubation failure and reinstitution of positive pressure ventilation, as the success rate of extubation is only 60-73% in the neonates weighing less than 1000 grams (4).

Post-extubation non-invasive ventilation (NIV) only partially prevents extubation failure (5). Furthermore, re-intubation has been associated with complications such as increased duration of MV and length of hospital stay and higher mortality rates (2). Therefore, it is extremely important to increase the possibility of effective extubation.

Methylxanthines have been shown to reduce the incidence of extubation failure (6). Conventionally, theophylline derivatives are used before extubation, while studies conducted in developed countries have emphasized on the effectiveness of caffeine in this regard. Nevertheless, aminophylline remains a viable option in resource-poor settings. Since limited trials have compared the dose response in the standard doses of caffeine and aminophylline, the present study aimed to evaluate this parameter on an individual patient level using prospective data.

Methods

Study Design

This single-centered, parallel, open-label, randomized controlled trial was conducted during June 2014-2016 on the preterm neonates with the gestational age of ≤30 weeks, requiring invasive ventilation at birth. Study setting was a tertiary neonatal intensive care unit (NICU) at the Department of Pediatrics, Kasturba Medical College of Manipal University in Manipal, India.

Participants

All the preterm neonates with the gestational age of ≤30 weeks, who were intubated in their immediate postnatal period for respiratory distress syndrome and continued on mechanical ventilation for a minimum of 24 hours, were enrolled in the study. Neonates with major anatomical congenital anomalies interfering with normal respiration, positive blood culture for sepsis, complex congenital heart diseases, and history of methylxanthine treatment were excluded from the study.

Randomization and Concealment

Computer-generated block randomization was used with the blocks of 10 neonates, and five subjects were allocated to each intervention group. Allocation concealment was adopted using sequentially numbered, sealed, opaque envelops matched for equal sizes and shapes. Both random allocation sequence and concealment procedure were carried out by the research officer, who was not concerned with the current trial or in the management of the recruited infants.

Treatments were assigned by the attending clinical practitioner at the NICU. Neonates were ventilated using Dräger Babylog 8000 plus (software version 3, Dräger Inc, Lubeck, Germany) for a minimum of 24 hours. Clinical blood gas improvement and minimum ventilator requirements were considered for extubation as per unit protocol. Neonates were randomly allocated to each inter-vention group within 24 hours before planned extubation or within six hours before unplanned extubation.

Newborns allocated to the caffeine treatment group received a loading dose of 20 mg/kg of caffeine citrate (10 mg caffeine base/kg) and continued on a maintenance dose of 5 mg/kg (2.5 mg caffeine base/kg) Q24h via intravenous administration or oral preparation of a 20 mg/ml solution. Neonates in the aminophylline group received a loading dose of 5 mg/kg, followed by a maintenance dose of 1.5 mg/kg Q8h via injection (aminophylline 250 mg/10 ml) and oral preparation of 10 mg/ml of theophylline. Methylxanthine administration continued until day seven of the therapy, and the neonates who developed apnea of prematurity during this period remained on respective methylxanthines until week 34 of the corrected gestational age.

Neonates were extubated to nasal continuous positive airway pressure at the same positive end-expiratory pressure (PEEP) in order to prevent post-extubation atelectasis and extubation failure (7). Only Synchronized intermittent mandatory ventilation was used as the weaning method; a ventilated neonate was considered for extubation on a minimum parameters of FiO_2 ≤0.3, PIP: 12-14 cm H_2O, PEEP≤6 cm H_2O with a rate of 24-28 bpm (8), and respiration of above the set ventilatory rate. If used, sedation was discontinued at least 12 hours before extubation.

Neonates were provided with standard nursing care in accordance with the thermo-neutral environment and positioning. Continuous monitoring was performed using Philips MP20 Intellivue neonatal monitors, with the alarms set at <85% saturation and <100 bpm heart rate (HR). If the neonates were on supplemental oxygen, SpO_2 of 90-95% was targeted.

Baseline demographic characteristics were recorded, including the number of the neonates

born in the study setting, use of antenatal steroids, gestational age, growth classification, mode of delivery, Apgar scores, gender, received surfactant, birth weight, and duration of MV. In addition, we documented the apneic episodes, their frequency, associated events, and the applied resuscitation method. Any adverse events were also noted by continuous monitoring and based on the nursing reports.

Sepsis workup, echocardiography, and blood and radiological investigations were ordered upon inclusion and repeated based on the clinical indications of the neonates. Feeding practices were standard and similar in the two study groups. Reinstitution of invasive mechanical ventilation was considered if Downe's score deteriorated >7 in the infants with NIV, requirement of FiO_2>60% to maintain the target saturation of 90-95%, pCO_2 of >55 mmHg or PaO_2 of <50 mmHg, pH of <7.20 by arterial blood gas test, and severe apnea (>3 in one hour) requiring positive pressure ventilation.

Drug Monitoring

After reaching plasma concentration (4-5 $t_{1/2}$ after the initiation of therapy), a blood sample was obtained to measure the plasma levels of theophylline and caffeine in order to achieve their recommended therapeutic concentrations. Sampling was carried out at the trough levels before the next dose was due. Plasma caffeine and theophylline concentrations were quantified by the LC-MS/MS assays.

Outcome Measures

Primary objective of the study was to assess the incidence of failed extubation within one week after initiating therapy. Failed extubation was defined as the inability to wean from mechanical ventilation within 48 hours of methylxanthine initiation and need for re-intubation within the first week of therapy. Secondary objectives were to assess the mean HR in the first 24 hours and on day seven of methylxanthine therapy, incidence of apnea, incidence of BPD (need for oxygen therapy at 36 completed weeks of gestation), duration of NIV support, adverse events leading to the cessation of therapy (e.g., feeding intolerance, tachycardia, abnormal blood glucose levels, and the associated morbidities), and association of failed extubation with the recommended therapeutic range of methylxanthines.

Sample Size Estimation

Based on the previous studies, the hypothetical failure rate was considered to be 32% in the neonates treated by caffeine (9). Assuming the difference in the 50% reduction in the incidence of extubation failure (16% in the infants treated by aminophylline), sample size of the study was calculated with 80% test power, set alpha error of 5%, and 95% confidence interval. In addition, an expected total sample size of 140 (70 subjects in each group) was calculated using the following two-proportion formula:

$$n = \frac{2\left\{Z1-\frac{\alpha}{2}\sqrt{2\bar{p}\bar{q}}+Z1-\beta\sqrt{p1(1-p1)+p2(1-p2)}\right\}^2}{d^2}$$

Assuming an attrition rate of 10%, expected sample size would be 78 in each arm, and a total 156 neonates were planned to be recruited in the research.

Statistical Analysis

Data analysis was performed in Microsoft Excel and SPSS for Windows (version 15, Bangalore, South-East Asia). Continuous variables were summarized using mean and standard deviation (SD). For non-normal distribution, median and interquartile range (Q1, Q3) or minimum-to-maximum range were used for summarization. For primary outcome analysis, we used the Poisson log-linear regression model adjusted for covariates. Covariates with a P-value of less than 0.2 (or those improving the predictability of the model) were included in the final model to determine extubation failure. Moreover, Mann-Whitney U test was used to evaluate the statistically significant differences between the groups in terms of the duration of MV support and NIV support, length of NICU stay, and weight gain in the first week of therapy. Also, repeated measures ANOVA was applied to compare the changes in HR at different times, and Chi-square and Fisher's exact test were used for binary outcomes as appropriate. Association of the occurrence of extubation failure within the recommended methylxanthine therapeutic range was assessed by Pearson's chi-squared test. In this study, two-sided P-value of less than 0.05 was considered statistically significant.

Ethical Considerations

Study protocol was approved by the Institutional Ethics Committee of Kasturba Hospital in Manipal, India. Before the enrolment of neonates, informed consent was obtained from at least one parent to cooperate in the study. The current trial has been registered in the public trial registry (No

CTRI/2012/08/002904). As part of the study, Data Safety Management Board was formed for the periodical review of the collected data.

Results

During the study period, 156 neonates requiring methylxanthines for extubation met the inclusion criteria and were randomized. Of note, there was no parental refusal for the participation of these infants in the research. Progress of the neonates has been depicted in the flow diagram in Figure 1. Findings of the study indicated no significant differences in the baseline characteristics of the neonates, with the exception of gender and small for gestational age. The study was neither gender-dependent nor growth-category-dependent (Table 1).

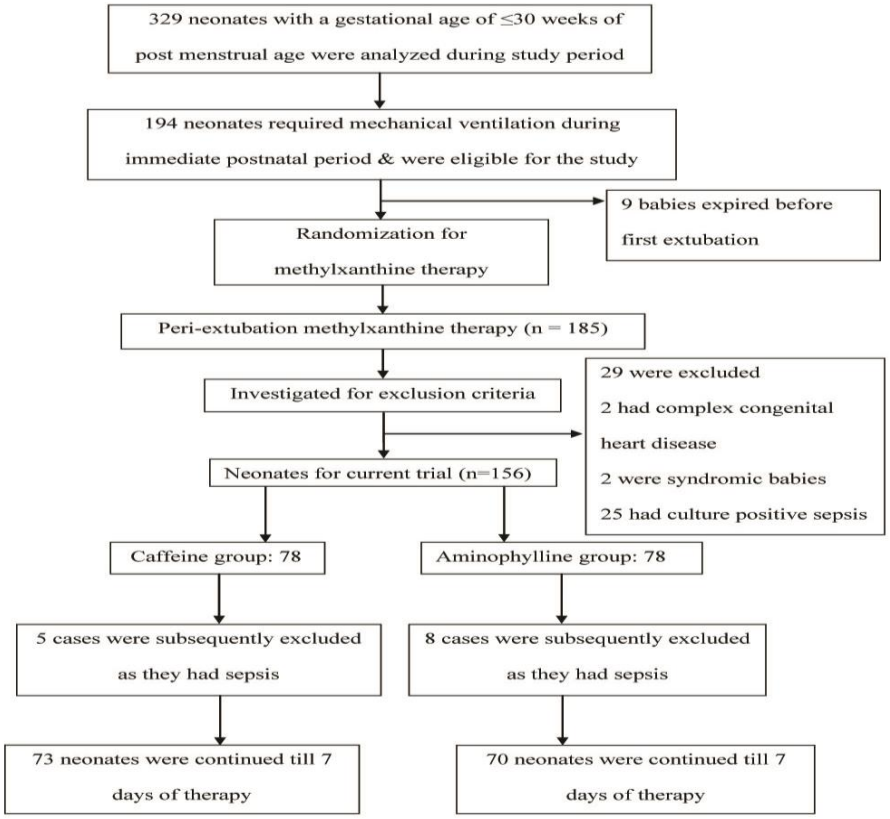

Figure 1. Flow Diagram of Participants

Table 1. Baseline Characteristics

Characteristic	Caffeine (n=78)	Aminophylline (n=78)	P-value
Born at Study Setting[a]	69 (88.5)	72 (92.3)	0.58
Antenatal Steroids[a]			0.15
Complete	24 (30.8)	22 (28.2)	
Partial	18 (23.1)	9 (11.5)	
Dexamethasone[a]	11 (14.1)	8 (10.3)	0.18
Betamethasone[a]	11 (14.1)	4 (5.1)	
Gestational Age (week)[a]			0.70
<28	19 (24.4)	17 (21.8)	
28-30	59 (75.6)	61 (78.2)	
Small for Gestational Age (%)[a]	13 (16.7)	24 (30.8)	0.02
Caesarean Section[a]	60 (76.9)	56 (71.8)	0.39
Low One-Minute Apgar score (<7)[a]	49 (62.8)	42 (53.8)	0.51
Low Five-Minute Apgar Score (<7)[a]	20 (25.6)	17 (21.8)	0.67
Female[a]	35 (44.9)	47 (60.3)	0.05
Received Surfactant[a]	63 (80.8)	62 (79.5)	0.83
Birth Weight (g)[a] Mean±SD	1044.73±252.27	1034.10±316.41	0.81
Duration of MV[b] (day)	2 (1, 4.5)	2 (1, 4)	0.74

a: Data presented as n (%), analysis by Chi-square or Fisher's exact test as appropriate; b: data presented as median (25th percetile, 75th percentile), analyzed by Mann-Whitney U test

Table 2. Comparison of Effectiveness

Variable	Caffeine (n=73)	Aminophylline (n=70)	Relative Risk (95% CI)	P-value
Extubation Failure[a]	23 (31.5)	15 (21.4)		
No Extubation	8 (11)	8 (11.4)	1.09 (0.81-1.46)	0.55
Re-Intubation	16 (21.9)	8 (11.4)		
Days of NIV Support[b]	10 (4.5, 20)	9 (4, 15)		0.42
Days of NICU Stay[b]	38 (21, 55)	34 (14.75, 48.25)		0.43
Mean HR on Day 1 (bpm)[c]	142.74 (11.63)	143.70 (10.17)		<0.001
Mean HR on Day 7 (bpm)[c]	148.60 (11.30)	152.38 (10.05)		
Documented Apnea within 7 Days[d]	28 (38.4)	17 (24.3)	1.57 (0.95-2.61)	0.07
Documented Apnea after 7 Days[d]	45 (61.6)	41 (58.6)	1.01 (0.79-1.31)	0.88
Weight at 1st Week[b]	980 (875, 1200)	947.5 (812.5, 1105)		0.43

a: data presented as n (%), outcome adjusted for birth weight, analyzed by Poisson regression model; b: median (25th percetile, 75th percentile), analyzed by Mann-Whitney U test; c: mean (SD), analyzed by repeated measures ANOVA; d: n (%), analyzed by Chi-square

Table 3. Incidence of Acute Adverse Events and Comorbidities

Variable	Caffeine (n=73)	Aminophylline (n=70)	Risk Ratio (95% CI)	P-value
Feeding Intolerance	19 (26)	19 (27.1)	0.95 (0.55-1.65)	0.88
Tachycardia	8 (11)	28 (40)	0.27 (0.13-0.56)	<0.001
Abnormal Blood Glucose	2 (2.7)	4 (5.7)	0.47 (0.09-2.53)	0.37
PDA Requiring Therapy	15 (20.5)	20 (28.6)	0.64 (0.30-1.39)	0.26
NEC	3 (4.1)	10 (14.3)	0.28 (0.08-1.00)	0.03
Abnormal Neurosonogram	27 (55.1)	22 (44.9)		
PVL	2 (2.7)	3 (4.3)		0.32
ICH Grade 3-4	5 (6.8)	5 (7.1)		
Incidence of ROP				
I	4 (5.5)	7 (10)		
II	4 (5.5)	1 (1.4)		0.31
III	1 (1.4)	2 (2.9)		
IV	6 (8.2)	2 (2.9)		
Incidence of O2 Requirement at 36 Weeks	3 (4.1)	0	-	0.08
Death before Hospital Discharge	16 (21.9)	15 (21.4)	1.02 (0.54-1.90)	0.94

Data presented as n (%), analyzed by Chi-square or Fisher's exact test as appropriate

As per protocol analysis, data adjusted with the birth weight showed the risk of extubation failure to be 1.09 times higher in the caffeine-treated infants (31.5% versus 21.4%) (RR=1.09, 95% CI: 0.81-1.46; P=0.55) compared to the aminophylline-treated neonates; however, this was found to be statistically similar. Incidence of inability to wean from mechanical ventilation within 48 hours was similar in both groups. Risk of developing apnea was 1.57 and 1.01 times higher in the neonates treated by caffeine within and after seven days of therapy, respectively; however, this was statistically similar in both groups.

Among the serial measurements of HR on days one and seven of therapy, mean HR in the aminophylline group was observed to be higher, which was statistically significant (P<0.001) (Table 2). Although no significant differences were observed in the adverse events, tachycardia (mean 24-hour HR of >180bpm) was reported prominently in the neonates treated by aminophylline (P<0.001). Furthermore, higher incidence of necrotizing enterocolitis (NEC) was documented in the aminophylline group (4.1% versus 14.3%) (RR=0.28, 95% CI: 0.08-1.00), compared to the caffeine treatment group (Table 3).

In 13 neonates, who received the standard maintenance doses of caffeine, mean plasma level was estimated to be 15.42±4.7 mg/l. Approximately 92.9% (n=12) of these neonates were classified in a recommended, wider therapeutic range, whereas only 7.7% (n=1) exceeded the therapeutic range. Odds of the occurrence of extubation failure in the recommended therapeutic range of caffeine was 0.75 (95% CI: 0.54-1.04; P=0.56), as that of the supra-therapeutic levels.

In 15 neonates treated by aminophylline, median levels of the principal agent was 9.08 (Q1-2.35 to Q3-15.39) mg/l; the majority of these infants (46.7%; n=7) reached above the therapeutic range, 40% (n=6) were within the sub-therapeutic range, and only 13.3% (n=2) reached the recommended therapeutic range. Odds of the occurrence of extubation failure in the recommended therapeutic range of aminophylline was 0.50 (95% CI: 0.12-1.99; P=0.08), as that of the inadequate therapeutic levels.

Discussion

Methylxanthines are used as the approved adjunctive treatment to facilitate weaning and extubation (6). Theophylline has long been used for the prevention of extubation failure and apnea (10, 11). In the current era, caffeine is recommended as

a rapid and convenient option to facilitate extubation (12, 13). Compared to aminophylline, similar effects have been reported by older trials regarding the short-term outcomes in the weaning of preterm neonates from respirators (9).

Aminophylline is the most frequently used methylxanthine in resource-poor neonatal care setups. However, no comparative trials have evaluated the effectiveness of methylxanthines in preventing extubation failure in low- and middle-income countries. As such, the current trial aimed for the comparative evaluation of caffeine and aminophylline for the facilitation of extubation. This was the first randomized controlled trial that confirmed the positive association of caffeine with the higher incidence of extubation failure. Although no statistically significant difference was observed in terms of extubation failure, clinical use of caffeine was associated with a higher incidence of re-intubation in the present study.

In the current research, extubation failure was confirmed in the case of inability to extubate the neonate within the first 48 hours of therapy or need for re-intubation within seven days of therapy. In their study, Sims ME. et al. (9) defined successful extubation in the case of extubation within 72 hours of therapy and considered extubation failure in the case of re-intubation within five days of therapy. Methylxanthines are the main responsible agents in contributing ventilator dependence through multiple physiological and pharmacological mechanisms. These agents have been shown to function by increasing minute ventilation, improving CO_2 sensitivity, stimulating the surfactant pathway, decreasing hypoxic depression of breathing, and enhancing diaphragmatic activity (14, 15).

In the present study, mean HR and incidence of apnea within and after seven days of therapy were recorded using respiratory and cardiac monitors and clinical records. Mean HR was observed to be higher in the infants treated by aminophylline, which was also associated with significantly higher tachycardia ($P<0.001$). This is in congruence with the results of a recent study conducted to assess the clinical safety and efficacy of aminophylline (16).

According to our findings, adverse clinical impressions leading to changes in the dosing or discontinuation of therapy were similar in the two study groups. Some published reports have proposed conflicting results regarding the most appropriate dose of caffeine to wean preterm neonates from mechanical ventilation. For instance, PA Steer et al. (13) claimed that two high-dose regimens (maintenance doses: 15 and 30 mg/kg) could significantly reduce the incidence of extubation failure and post-extubation apnea compared to a low-dose regimen (maintenance dose: 3 mg/kg). Furthermore, the same authors have stated that a high dose of caffeine citrate (20 mg/kg) before extubation could effectively reduce the rate of extubation failure compared to the dose of 5 mg/kg (17). However, administrating higher doses of pure caffeine (25 mg/kg) via intravenous infusion (30 minutes) and oral route were reported to diminish blood flow velocity in the cerebral and intestinal arteries (18, 19).

Methylxanthines are potent adenosine receptors of A1A and A2A antagonist, which is a vasodilator (20). Inhibition of this vasodilatation by higher doses of methylxanthines leads to the vasoconstriction of the cerebral and intestinal blood vessels. Reduced cerebral and intestinal blood flow in preterm infants may increase the risk of periventricular leukomalacia (PVL), intracranial hemorrhage, and NEC (19). Previous observations have reported that the toxicity of aminophylline might trigger gastric irritation, thereby leading to NEC (21). Findings of the current study showed no significant differences in the short-term PVL and high-grade intracranial hemorrhage. However, the incidence of NEC was found to be clinically higher in the infants allocated to the aminophylline group, which was not statistically significant (RR=0.28, 95% CI: 0.08-1.00).

BPD is defined as the need for O_2 at 36 weeks postmenstrual or at discharge (22). The most important risk factors for this adverse pulmonary outcome are prematurity, exposure of immature lungs to O_2, and positive pressure ventilation (23). Apnea of prematurity (AOP) is defined as the sudden cessation of breathing (lasting for about 20 seconds) or paused breathing, which is associated with desaturation and bradycardia in the infants born earlier than 37 weeks of gestation. Methylxanthines are considered to be effective in the pharmacological interventions for AOP (16). In a large randomized clinical trial by the CAP trial group, a significant reduction in the incidence of BPD was reported in the infants treated by caffeine for AOP (12). It is also notable that the mentioned trial compared the AOP outcomes between caffeine-treated neonates and a placebo group.

In the current trial, only three neonates in the caffeine treatment group required O_2 at 36 weeks of gestation, BPD occurred in no infants in the aminophylline group, and risk of mortality was similar in the two groups. Moreover, evaluating the association of the occurrence of extubation failure with the recommended therapeutic ranges

indicated that the aminophylline-treated neonates had both sub- and supra-therapeutic ranges, which were assessed in reference to the inadequate therapeutic levels based on the recommended therapeutic range. On the other hand, no neonates in the caffeine treatment group showed sub-therapeutic plasma levels, and therefore, only the supra-therapeutic range was assessed in reference to the therapeutic range. According to the results of the present study, odds of the occurrence of extubation failure were lower in the neonates who were exposed to the recommended therapeutic range in both treatment groups.

One of the limitations of the present study was the single-centered design, and the open-label design was due to the administration of a single drug once a day, while another drug was administered three times a day. Another limitation was that we only assessed the short-term outcomes, and therapeutic drug monitoring was not performed on all the recruited neonates due to the lack of facilities.

Conclusion

According to the results, methylxanthine therapy is beneficial in increasing the possibility of successful extubation in preterm neonates within one week of therapy. Caffeine and aminophylline were observed to be equally effective in facilitating the weaning of preterm neonates from MV. In order to discover more effective therapeutic drugs and help clinicians in decision-making, long-term neurodevelopmental outcomes must be assessed. In the current research, caffeine was found to be the safer option, while aminophylline could also be initiated for the facilitation of extubation under medical supervision.

Acknowledgments

Authors are highly indebted to ICMR for providing the essential funding to carry out this research project. Hereby, we extend our gratitude to the parents who voluntarily consented for the participation of their infants in the study. We hereby declare that the aforementioned funding agency does not have any role in the study design, data collection, data analysis, interpretation of the research data, writing of the report, and decision to submit the article for publication.

Conflicts of interests

None declared.

References

1. Holme N, Chetcuti P. The pathophysiology of respiratory distress syndrome in neonates. Paediatrics and child health. 2012; 22(12):507-12.
2. Miller JD, Carlo WA. Pulmonary complications of mechanical ventilation in neonates. Clin Perinatol. 2008; 35(1):273–81.
3. Venkatesh V, Ponnusamy V, Anandaraj J, Chaudhary R, Malviya M, Clarke P, et al. Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events. Eur J Pediatr. 2011; 170(2):223–7.
4. Stefanescu BM, Murphy WP, Hansell BJ, Fuloria M, Morgan TM, Aschner JL. A randomized, controlled trial comparing two different continuous positive airway pressure systems for the successful extubation of extremely low birth weight infants. Pediatrics. 2003; 112(5):1031–8.
5. Danan C, Durrmeyer X, Brochard L, Decobert F, Benani M, Dassieu G. A randomized trial of delayed extubation for the reduction of reintubation in extremely preterm infants. Pediatr Pulmonol. 2008; 43(2):117–24.
6. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. Cochrane Database Syst Rev. 2010; (12):CD000139.
7. Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. Cochrane Database Syst Rev. 2003; (2):CD000143.
8. Sant'Anna GM, Keszler M. Weaning infants from mechanical ventilation. Clin Perinatol. 2012; 39(3):543–62.
9. Sims ME, Rangasamy R, Lee S, Chung H, Cohen J, Walther FJ. Comparative evaluation of caffeine and theophylline for weaning premature infants from the ventilator. Am J Perinatol. 1989; 6(1):72–5.
10. Armanian AM, Badiee Z, Afghari R, Salehimehr N, Hassanzade A, Sheikhzadeh S, et al. Prophylactic Aminophylline for prevention of apnea at higher-risk preterm neonates. Iran Red Crescent Med J. 2014; 16(8):e12559.
11. Harris MC, Baumgart S, Rooklin AR, Fox WW. Successful extubation of infants with respiratory distress syndrome using Aminophylline. J Pediatr. 1983; 103(2):303–5.
12. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, et al. Caffeine for Apnea of Prematurity trial: benefits may vary in subgroups. J Pediatr. 2010; 156(3):382–7.
13. Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG. Periextubation caffeine in preterm neonates: a randomized dose response trial. J Paediatr Child Health. 2003; 39(7):511–5.
14. Supinski GS, Deal EC Jr, Kelsen SG. The effects of caffeine and theophylline on diaphragm contractility. Am Rev Respir Dis. 1984; 130(3):429–33.
15. Aranda JV, Turmen T. Methylxanthines in apnea of prematurity. Clin Perinatol. 1979; 6(1):87–108.
16. Shivakumar M, Jayashree P, Najih M, Lewis LES, Bhat Y R, Kamath A, et al. Comparative efficacy and

safety of caffeine and aminophylline for apnea of prematurity in preterm (≤34 weeks) neonates: a randomized controlled trial. Indian Pediatr. 2017; 54(4):279-83.
17. Steer P, Flenady V, Shearman A, Charles B, Gray PH, Henderson-Smart D, et al. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2004; 89(6):F499-503.
18. Lane AJ, Coombs RC, Evans DH, Levin RJ. Effect of caffeine on neonatal splanchnic blood flow. Arch Dis Child Fetal Neonatal Ed. 1999; 80(2):F128-9.
19. Hoecker C, Nelle M, Poeschl J, Beedgen B, Linderkamp O. Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. Pediatrics. 2002; 109(5):784–7.
20. Schoen K, Yu T, Stockmann C, Spigarelli MG, Sherwin CM. Use of methylxanthine therapies for the treatment and prevention of apnea of prematurity. Paediatr Drugs. 2014; 16(2):169–77.
21. Gannon BA. Theophylline or caffeine: which is best for apnea of prematurity? Neonatal Netw. 2000; 19(8):33–6.
22. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, et al. Validation of the national institutes of health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005; 116(6):1353–60.
23. Kinsella JP, Greenough A, Abman SH. Broncho-pulmonary dysplasia. Lancet. 2006; 367(9520): 1421–31.