RESEARCH PAPER

Comparative Efficacy and Safety of Caffeine and Aminophylline for Apnea of Prematurity in Preterm (≤34 weeks) Neonates: *A Randomized Controlled Trial*

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Objective: To compare the efficacy and safety of standard doses of Caffeine and Aminophylline for Apnea of prematurity.

Study design: Randomized controlled trial.

Setting: Tertiary-care referral centre and a teaching institution in Southern India. Trial was conducted from February 2012 to January 2015.

Participants: 240 preterm (≤34 wk) neonates with apnea of prematurity.

Interventions: Neonates randomized into two groups: Caffeine group received loading dose of caffeine citrate (20 mg/kg) followed by 5 mg/kg/day maintenance dose every 24 hour. Aminophylline group received loading dose of Aminophylline – 5 mg/kg and maintenance dose of 1.5 mg/kg 8-hourly.

Outcome measures: Difference in apneic spells, associated respiratory morbidity, and acute adverse events were assessed. Association of efficacy with therapeutic drug levels was also evaluated.

Results: Infants on aminophylline experienced less apnea spells in 4-7 days of therapy (P=0.03). Mean apnea rate and isolated desaturations were similar in 1-3, 4-7 and 8-14 days of therapy. No difference was noted in duration of Neonatal Intensive Care Unit stay and hospital stay. Mean heart rate was significantly high in Aminophylline group (P<0.001). Risk of developing tachycardia was less (RR 0.30; 95% CI range 0.15 to 0.60; P<0.001) in Caffeine- over Aminophylline-treated infants.

Conclusion: Aminophylline is as effective as caffeine for prevention of apneic spells in preterm neonates; however, dosage optimization needs to be done to reduce toxicity.

Keywords: *Apneic spells, Methylxanthines, Preterm neonates*.

Trial Registration: CTRI/2012/08/002904

Apnea of prematurity (AOP) itself is not a major threat to infant health but frequent recurrent episodes accompanied by hypoxemia and bradycardia significantly causes brain damage in preterm population [1]. A cochrane meta-analysis has reported significant reduction in apneic episodes and subsequent usage of mechanical ventilation in neonates treated with methylxanthines [2].

There are limited trials emphasizing effectiveness and safety on caffeine *versus* aminophylline in developing country. Besides, Small for Gestation Age (SGA) growth category or Intrauterine Growth Retarded (IUGR) babies are a significant problem in many developing and underdeveloped countries, and the effect of methylxanthines in them is incompletely understood [3]. Therefore the present study was designed to compare the effectiveness of methylxanthines in preterms, particularly the SGA babies.

Methods

This single centered, parallel, open label, randomized controlled trial was conducted from February 2012 to January 2015 in a tertiary level Neonatal Intensive Care Unit (NICU) at Kasturba Hospital, Manipal University. The study was approved by the Institutional Ethics committee, and written informed parental consent was obtained for each participating infant.

Preterm newborns with ≤34 completed weeks of GA who experienced six or more apneic spells in 24 hours, or preterm neonates with apneic episode requiring bag and mask ventilation for termination of apnea were included. Sepsis work-up, echocardiography, relevant blood, and radiological investigations were done at inclusion in order to evaluate and exclude neonates with secondary causes of apnea. Investigations were further repeated based on clinical signs. Some other exclusion factors included major congenital anomalies, respiratory depression from medications and Patent Ductus

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Arteriosus (PDA) as a cause of apnea (defined as - ductus diameter of 1.5 mm and absent/ retrograde diastolic flow in the post-ductal aorta).

Computer generated block randomization was used with block size of 10. Allocation concealment was executed by using sequentially numbered, sealed, opaque envelops. Both random allocation sequencing and concealment was done by research officer who was not concerned with current trial or in management of recruited infants. The treatment assignment was carried out by attending clinician in Neonatology unit.

Infants allocated to Caffeine group received a loading dose of 20 mg/kg of caffeine citrate (10 mg/kg caffeine base) diluted in 5% dextrose given for 30 minutes and were continued on a maintenance dose of 5 mg/kg (2.5 mg caffeine base) 24 hourly (iv or oral preparation of caffeine citrate solution 20 mg/mL). If adequate response was not seen then the dose was optimized up to 7.5 mg/kg. Neonates allocated to aminophylline group received a loading dose of 5 mg/kg of aminophylline, diluted in 5 % dextrose followed with a maintenance dose of 1.5 mg/kg 8 hourly (Inj. aminophylline 250 mg/10 mL). If adequate response was not seen, the dose was titrated up to 2 mg/kg.

Baseline parameters were measured for each participant at inclusion. Gestational age was calculated from maternal menstrual history or from first trimester ultrasound scan. If neither of these were available or in case of discrepancies, a new Ballard's assessment was performed and considered as final. Intrauterine Growth categorization was done at birth based on Lubchenco growth chart. The data on antenatal steroids, APGAR score at 1 and 5 minutes, need for surfactant, gender and birth weight was noted. Continuous monitoring of vitals and SpO_2 was done by Phillips IntelliVue MP20 neonatal monitors with alarms set to alert at SpO_2 <85% saturation and heart rate (HR) <100 bpm; SpO_2 of 90-95% was targeted. Clinical assessment was done every 24 hours after commencement of methylxanthines. Daily apneic episodes, isolated desaturations, intervention used, mean of 24 hours HR and adverse effects were recorded. Neonates were discharged when 1800 g in weight, self-feeding, euthermic, and apnea-free for 7 days off-methylxanthines. Follow-up of these high risk neonates was done as per unit protocol.

After reaching plasma concentration (4-5 $t_{1/2}$ after initiation of therapy) a blood sample (0.25 mL) was taken to measure plasma theophylline and caffeine levels aiming to achieve a therapeutic concentration (5 to 12 mg/L theophylline and 5 to 20 mg/L caffeine). Sampling was done at the trough levels before the next dose was due. Sampling was planned during change in IV lines or with other blood samples to avoid unnecessary sampling pricks. Plasma caffeine and theophylline concentrations were quantified with LCMS assay.

Primary outcome was frequency of apneic episodes (number of apnea spells per 24 hour) at an interval of 1 to 3 day, 4 to 7 day and 8 to 14 day of therapy. Secondary outcomes were Mean apnea rate (MAR) (defined as the average number of desaturations with bradycardia per neonate over 24 hours period), frequency of desaturations (Number of isolated desaturation per 24 hour) recorded in set interval of 1 to 3 day, 4 to 7 day and 8 to 14 day of therapy, time for apnea resolution, duration of hospital stay, HR variability on 1st, 2nd, 3rd, 7th and 14th day of methylxanthine therapy, and safety profile with respect to some known reported adverse events of methylxanthines (tachycardia, jitteriness, feed intolerance and abnormal blood sugar).

Sample size: Based on anticipated SD of 5 apneic episodes in 24 hours and minimal relevant difference at 3 continuing apneic episodes in 24 hours, a power of 90%, 5% as a level of significance, it was estimated that 84 neonates would be needed in each arm. Assuming 30% attrition rate, a sample of 120 in each arm was taken.

Statistical analysis: Mann- Whitney U test was used to compare episodes of apnea, MAR, isolated desaturations, time taken for apnea resolution, NICU stay and hospital stay. Repeated measures ANOVA was used to compare changes in HR at various time periods. Difference in Mean HR on individual day was analyzed by applying Independent sample *t* test. Adverse effects and co-morbidities were analyzed by Pearson's chi-square test. Association of occurrence of apnea and isolated desaturation was analyzed by Pearson's chi-square test. A subgroup analysis for the outcomes was carried out stratified by intrauterine growth status. In each growth strata the difference in apnea spells, MAR, desaturation frequencies and adverse events between the groups were compared using generalized linear model with poisson loglinear scale response. Factorial ANOVA was adopted to compare significant difference in Median days of apnea resolution, hospital stay, NICU stay, and Mean HR between groups in different growth category. $P<0.05$ was considered to be statistically significant.

A Data Safety Management Board (DSMB) periodically reviewed the study progress.

RESULTS

During the period of 36 months, out of admitted preterm neonates, 240 (23%) newborns were identified experiencing AOP and underwent randomization. The

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study flow is depicted in ***Fig.* 1.** Baseline characteristics were similar in both the groups (***Table* I**).

Apneic episodes during 4-7 days of therapy was found to be significantly higher in Caffeine group (P=0.03). Complete resolution of apnea was achieved after similar duration of median 6 days in either group. There was no difference in median (IQR) duration of methylxanthine administration [24 (14, 35.5) d *vs* 22 (14, 38) d; P=0.97]. No difference was noted in median length of hospital stay and NICU stay between both the groups. Mean HR was significantly higher in aminophylline group at various time intervals (P=0.001) (***Table* II**). Among caffeine-treated neonates, the risk of developing tachycardia was lesser than Aminophylline group (RR 0.30; 95% CI range 0.15 to 0.60, P<0.001). No significant difference found in the risk of developing feed intolerance (17% *vs* 22.8%, RR 0.74; 95% CI range 0.39 to 1.40, P=0.35). jitteriness (8% *vs* 9%, RR 0.87; 95% CI range 0.31 to 2.49, P=0.81) and glucose abnormality (3% *vs* 3%, RR 1.02; 95% CI range 0.21 to 4.92, P=0.97) were also similar in both the groups.

In 42 neonates who were on standard maintenance doses of caffeine, mean (SD) plasma caffeine level was 14.4 (5) mg/L. Approximately 93% (n=39) fell within a recommended wider therapeutic range whereas only 7.1% (n=3) had exceeded therapeutic window. Odds ratio (95% CI) of occurrence of apnea and isolated desaturation in the recommended therapeutic range of caffeine was 0.34 (0.02, 6.04) and 0.09 (0.007, 1.17), respectively as that of supra-therapeutic levels. In 50 neonates on aminophylline, median (IQR) level of the

TABLE I BASELINE DEMOGRAPHICS CHARACTERISTICS

Characteristic	*Caffeine (n=120)(%)*	*Aminophylline (n=120)(%)*
Born at study hospital	100 (83.3)	104 (86.7)
Antenatal steroids		
Complete	27 (22.5)	32 (26.7)
Partial	27 (22.5)	20 (16.7)
SGA	27 (22.5)	28 (23.3)
Delivery by Caesarean section	87 (72.5)	77 (64.2)
Low APGAR at 1min (<7)	59 (49.2)	51 (42.5)
Low APGAR at 5min (<7)	22 (18.3)	19 (15.8)
Female sex	56 (46.7)	66 (55)
Surfactant received	68 (56.7)	57 (47.5)
Birth weight (g) (mean, SD)	1149.7 (307)	1155.9 (313)
Gestational age, wks (mean, SD)	29.4 (2)	29.3 (1.9)

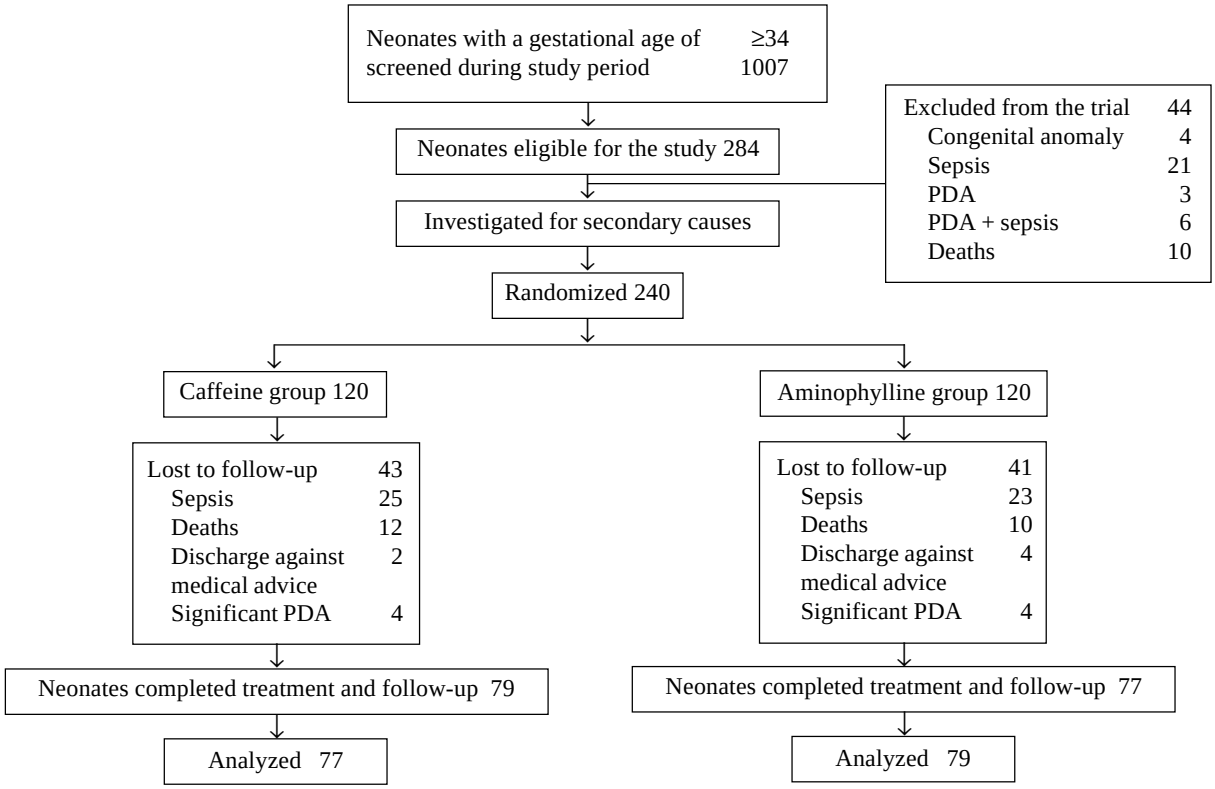

FIG.1 *Study flow.*

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TABLE II COMPARISON OF APNEA FREQUENCY AND SECONDARY OUTCOMES

Variable	*Caffeine (n=77)*	*Aminophylline (n=79)*	*P value*
*Continuing apnea at days of therapy**			
1-3 d	0 (0,14)	0 (0,5)	0.03
4-7 d	0 (0,20)	0 (0,8)	0.05
8-14 d	0 (0,15)	0 (0,13)	0.82
*Apnea rate (per 24hrs) at days of therapy**			
1-3 d	0 (0,7)	0 (0, 1)	0.53
4-7 d	0 (0,9)	0 (0,4)	0.27
8-14 d	0 (0,5)	0 (0,2)	0.12
*Isolated desaturations (per 24hrs) at days of therapy**			
1-3 d	0 (0,13)	0 (0,8)	0.12
4-7 d	0 (0,15)	0 (0,25)	0.24
8-14 d	0 (0,20)	0 (0,90)	0.50
Time taken for apnea resolution (d)[$]	6 (1, 19)	6 (1, 16)	0.89
NICU stay (d)[$]	38 (23, 55.5)	35 (24, 48)	0.45
Hospital stay (d)[$]	43 (27.5, 61.5)	39 (28, 55)	0.43
Heart rate trend (beats per min)[‡]			
Day 1	143.4 (10)	143.4 (9.2)	<0.001
Day 2	144.9 (10.4)	147.9 (10.2)	
Day 3	143.8 (10.5)	148.8 (11.4)	
Day 7	149.3 (11.2)	150.7 (11.3)	
Day 14	147.4 (8.7)	147.4 (9.9)	

**values representing in Median (minimum, maximum); [$]Median (IQR); [‡]Mean(SD).*

drug was 12.9 (6.3, 19.5) from minimum 0.68 to maximum 50.37 mg/L. Majority of them 52% (*n*=26) had achieved above the therapeutic range. 24% of neonates had attained therapeutic (*n*=12) and sub-therapeutic range (*n*=12). Odds (95% CI) of occurrence of apnea and isolated desaturation in the recommended therapeutic range of aminophylline was 0.30 (0.05, 1.58), and 0.93 (0.08, 10.0) as that of inadequate therapeutic levels, respectively.

One neonate was LGA from each group were excluded for subgroup analysis as the number of LGA babies were too less to analyze. In AGA category continuing apnea episodes during first week of therapy was consistently high in Caffeine group [1-3 days (*P*=0.01) and 4-7 days (*P*<0.001)]. During 4-7 days of therapy caffeine group proved to have higher MAR (*P*=0.001). Persistent desaturation in caffeine group was more than aminophylline during first 3 days of therapy (*P*=0.006) than in second week of therapy, aminophylline group reported high desaturation episodes (*P*=<0.001). Among SGA infants, during first 3 days of therapy apnea episodes were higher in caffeine group (*P*=0.01). Neonates in caffeine group had significant higher isolated desaturations during first week of treatment [1-3 days (*P*<0.001) and 4-7 days (*P*<0.001)]. In AGA babies, aminophylline group had higher mean HR on day 2 (*P*=0.007) and day 3 (*P*=0.002) (***Table* III**).

DISCUSSION

In present study, apneic episodes were found to be similar in both the caffeine- and aminophylline-treated groups during first 3 days and second week of therapy. No differences were also noted in MAR, isolated desaturations and time to resolution of apnea. Risk of developing tachycardia in caffeine treated neonates was less compared to aminophylline group. However, there were significant differences noted in efficacy or adverse events between caffeine and aminophylline in subgroup of AGA and SGA neonates.

Limitations of present study was that it was a single center, open label study. Attending clinicians were not blinded. There are only few trials reported that have compared the effectiveness and safety of caffeine and aminophylline [4-7]. Most of the trials were conducted in developed countries. A recent study [8] compared the incidence of apnea between caffeine and aminophylline treated babies and followed up recruited neonates for 10 days of life. The study reported infants with aminophylline dihydrate had approximately 10% less risk of developing apnea compared to anhydrous caffeine. The results of the present study were comparable to that of Scanlon, *et al*. [6] that standard doses of aminophylline resulted in less apnea frequency in first week of therapy when compared with standard doses of caffeine. Tachycardia was the major acute adverse event noted in aminophylline-treated neonates and was comparable to observation with other studies [4-8].

In conclusion both caffeine and aminophylline are equally effective in reducing apneas. Perhaps further research should be undertaken to compare the safety and effectiveness of methylxanthines in AGA and SGA separately. Since tachycardia is prominently seen in aminophylline-treated infants, dosage optimization of aminophylline can be tried for preterm population in developing countries. Aminophylline usage can be continued under close supervision at resource poor settings in India.

Contributors: SM, MN, Shashikala: acquisition of data, drafting the article or analysis and interpretation of data; LEL, JP, RBY: substantial contribution to concept and design, revising the work critically for important intellectual content and final approval of the version published; AK: revising the

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WHAT IS ALREADY KNOWN?

- Both caffeine and aminophylline are used for reducing apneic spells in preterm babies with apnea of prematurity.

WHAT THIS STUDY ADDS?

- Aminophylline administration is as effective as caffeine for apnea of prematurity both in AGA and SGA category, and can continued to be used in resource-poor setting.

TABLE III COMPARISON OF APNEA IN AGA AND SGA NEONATES TREATED BY CAFFEINE AND AMINOPHYLLINE

	Appropriate for Gestational Age infants			*Small for Gestational Age infants*		
	C(n=57)	*A(n=58)*	*RR (95% CI)*	*C(n=19)*	*A(n=20)*	*RR (95% CI)*
Apnea (Number of episodes per 24hrs)*						
1-3 days	2.1 (2.1)	1.5 (1.7)	1.9 (1.2 to 3.0)	2.1 (1.7)	1.8 (1.9)	2.5 (1.2 to 5.0)
4-7 days	2.1 (2.6)	1.9 (1.9)	2.3 (1.5 to 3.5)	1.8 (1.5)	4.9 (2)	1.4 (0.7 to 3.1)
8-14 days	3.3 (2.7)	2.3 (2.2)	1.3 (0.9 to 1.8)	3.3 (1.7)	5.9 (2.3)	0.8 (0.5 to 1.3)
Apnea Rate[*]						
1-3 days	3.7 (2.4)	0	9.2 (1.2 to 72.2)	0	0	-
4- 7 days	3.6 (2.1)	1.9 (1.9)	3.9 (1.7 to 9.0)	0	0	-
8-14 days	2.8 (1.8)	0	16.2 (2.1 to 122.7)	0	0	-
Desaturation[*] *(Number of episodes per 24hrs)*						
1-3 days	3.6 (2.4)	2.1 (2)	1.8 (1.2 to 2.8)	4 (2)	1 (1)	20.5 (4.9 to 85.0)
4-7 days	4.8 (2.6)	4 (3)	1.1 (0.8 to 1.5)	4.6 (1.8)	4 (0)	6.8 (2.4 to 19.6)
8-14 days	4.2 (2.5)	5.9 (3.4)	0.5 (0.4 to 0.7)	2.3 (1.9)	1.9 (2.5)	1.2 (0.6 to 2.5)
Heart rate trend (beats per min)[#$]						
Day 1	142.8 (9.5)	143.3 (8.2)	0.75	145.4 (11.5)	142.5 (10.6)	0.34
Day 2	143.6 (10.1)	148.8 (9.7)	0.007	147.6 (9.7)	144.9 (11.1)	0.40
Day 3	145.3 (10.1)	149.6 (11.4)	0.002	145.7 (11.7)	146.4 (11.5)	0.86
Day 7	149.7 (12.0)	151.2 (11.5)	0.47	148.6 (8.6)	148.3 (10.6)	0.93
Day 14	146.9 (8.2)	147.6 (10.4)	0.69	149.4 (9.8)	146.3 (8.2)	0.30

[*]*Exponential values for Mean (SD) of logarithmic form;* [#]*Data is presented in Mean(SD);* [$]*Comparison done by two-way ANOVA and P value is presented.*

work critically on research methodology and Statistical guidance: SM: co-author who should be approached for the access to raw data.

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