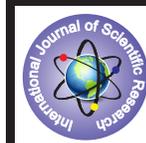


## A Clinical Comparative Study of Efficacy And Side Effects of Caffeine And Aminophylline in Apnea of Prematurity- A Randomized Controlled Trial



### Medical Science

**KEYWORDS :** apnea, prematurity, Caffeine, Aminophylline

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### ABSTRACT

*Recurrent apnea is a common problem in preterms. Two forms of methylxanthines (Caffeine and Aminophylline) have been used to prevent apnea.*

#### Objective:

*To compare the efficacy and immediate side effects of Caffeine with Aminophylline in apnea of prematurity*

#### Intervention:

*Randomized Controlled study done over a period of 1 year .60 Preterm neonates <36 weeks of gestational age who had apnea of prematurity received IV Caffeine (20mg/kg loading – 5mg/kg OD maintenance) or IV Aminophylline (5mg/kg loading-2mg/kg TDS maintenance) for control of apnea, done with randomization of alternate days.*

#### Results :

*Efficacy was defined as reduction in apneic rates by >50% than previous. There was found to be no difference between efficacy of caffeine and aminophylline in control of apneic episodes. But the side were more with Aminophylline than Caffeine.*

#### Conclusion:

*Caffeine is not only equally efficacious to Aminophylline but has lesser side effects with added advantages of once a day dosage, reliable enteral absorption and with wide therapeutic index.*

Apnea of prematurity is a major concern for caregivers in intensive care units. Recurrent apnea is common in preterm neonates, particularly at a very early gestational age. Apnea has been defined as cessation of breathing for more than 20 seconds or cessation of breathing for less than 20 seconds if accompanied by bradycardia or oxygen desaturation<sup>(1)</sup>. These episodes of loss of effective breathing may be severe enough to require resuscitation including positive pressure ventilation.

In addition to general measures – such as maintaining airway, breathing, circulation, avoiding swings in temperature and hypoglycemia and various others. The specific measures include kinesthetic stimulation, drugs, continuous positive airway pressure and mechanical invasive ventilation. Drugs used are Methylxanthines including Aminophylline and Caffeine.

Methylxanthines stimulate skeletal and diaphragmatic muscle contraction, increase the sensitivity of the ventilatory centre to CO<sub>2</sub>, and stimulate the central respiratory drive.

Thus , being a common neonatal problem, the present randomized controlled trial was conducted to study the comparison of efficacy and side effects of Caffeine to Aminophylline in apnea of prematurity (other causes being excluded)

#### METHODS:

This randomized controlled study of a drug based trial was conducted at a level III NICU of a teaching institute carried over a period of 12 months. The study protocol was approved by ethical committee. Informed consent of guardian of neonate was taken.

All preterm neonates < 36 weeks of gestational age and who had apnea of prematurity as defined earlier, with birth weight between 1 to 2 kg were included in the study. Preterm neonates less than 1kg birth weight and the ones with major congenital anomalies and other identifiable causes of apnea (hypoglycemia, anemia, sepsis) were excluded from the studies.

All preterm neonates were managed by NICU protocols. As per protocols details of antenatal, natal and postnatal history, birth weight, gestational age, antenatal steroids given or not, type of delivery, place of delivery, resuscitation required at birth or not,

and other details were recorded.

All preterms in NICU had undergone following investigations – sepsis screen, blood culture, complete blood count, blood glucose monitoring, urine output monitoring and when required serum electrolytes, renal profile and serum bilirubin.

Preterms with above defined criteria were included in the study. All the events and number of episodes of apnea were recorded. Continuous clinical monitoring of heart rate, respiratory rate, retractions, chest expansion, air entry, capillary refilling time, peripheral pulses, status of hydration and oxygen saturation was done.

One or more episode of apnea, as per the mentioned definition was given drugs for the control of apnea. Intravenous aminophylline and intravenous caffeine was used for control of apnea with randomization of alternate days.

Intravenous aminophylline is used as loading dose is 5mg/kg and then 2mg/kg TDS as maintenance dose. <sup>(2)</sup> .Aminophylline was given with dilution in 30ml of normal saline and given over 15-20minutes of duration. Thrice a day dosing given at 6am,2pm,10pm.

Intravenous caffeine is used with loading dose 20 mg/kg and later maintenance as 5 mg/kg OD <sup>(3)</sup> .Caffeine was given with dilution in 30 ml of normal saline and given over 15-20minutes. Once a day dose given at 6am. ( caffeine citrate was used – containing 20mg/ml ).

Both the drugs were given for 7 days after the last episode of apnea or till 34 weeks of maturity

Patients were monitored and apneic rates taken into account. All apneic rates and events taken into account on day to day basis, but the efficacy of drugs compared at the end of 7 days.

Efficacy of the drug was defined as ability to reduce > 50 % apneic rates than the previous at the end of 7 days.

Outcome was described as :

PRIMARY: control of apnea with the use of drugs only

SECONDARY: requirement of other modalities of intervention for control of apnea ( like cpap, ventilation )

Outcome was compared amongst different groups- according to maturity on admission.

And finally results were compared in terms of :

-reduction in apneic rates i.e. > 50% reduction in apneic rates at the end of 7 days of treatment

-any other modality of treatment required for control of apnea.

Adverse reactions to both the drugs were noted :

Tachycardia by pulse oximeter monitoring, jitteriness monitored, hyperglycemia watched for by doing blood glucose monitoring by glucometer, vomiting episodes noted, feeding intolerance in form of increased abdominal distension and increase residual RT feeds.

Data was analyzed in Microsoft excel with the help of MedCalc statistical software (Trial version ). Statistical analysis of the data was performed using chi-square test. Significance was defined as p<0.05

**DISCUSSION:**

During the study conducted over 12 months there were total 60 patients with apnea of prematurity as per the inclusion criteria. All the preterms were managed by NICU protocols.

Results have been analysed in the following manner :

1. demographic characteristics of all preterm neonates and those with apnea of prematurity, like Gestational age, weight on admission.
2. treatment received in form of caffeine or aminophylline.
3. variables seen for treatment or for prophylaxis, while on caffeine or aminophylline , like duration of apnea, oxygen requirement, requirement of ventilation.
4. difference between caffeine and aminophylline in terms of outcome and side effects.

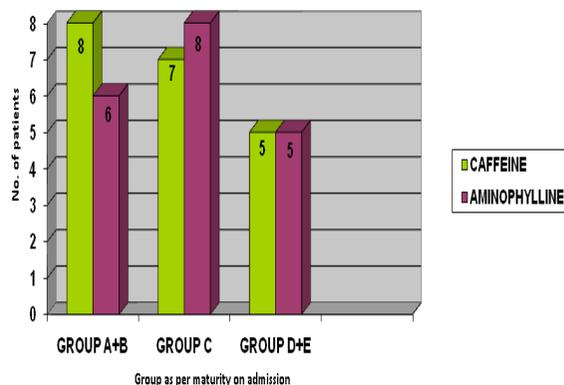
(I)Now, comparing each drug caffeine to aminophylline for control of apnea (>50% reduction in apnea rates at the end of 7 days).The comparison is done within groups divided according to maturity on admission.

Patients were divided in groups as per maturity on admission. Group A+B is 28±2 weeks , group C is 30±2 weeks, group D+E is 32±2 weeks and 34

±2 weeks respectively.

Maturity on admission	Chi square test	P value	Inference
GROUP A+B	2.039	0.153	NS
GROUP C	0.427	0.513	NS
GROUP D+E	0.423	0.515	NS

This shows, that p value being insignificant applying chi square test, means caffeine and aminophylline have equal efficacy in control of apnea of prematurity. (chart 1 below shows---control of apnea with drugs, divided according to maturity on admission)



**Chart 1 –control of apnea with drugs(caffeine / aminophylline) divided according to maturity of preterms on admission**

**The relative risk of control of apnea in our study:**

**Risk Estimate**

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for drugs for apnea (A / C)	.957	.331	2.767
For cohort CONTROL OF APNEA = N	.972	.487	1.939
For cohort CONTROL OF APNEA = Y	1.016	.701	1.472
N of Valid Cases	60		

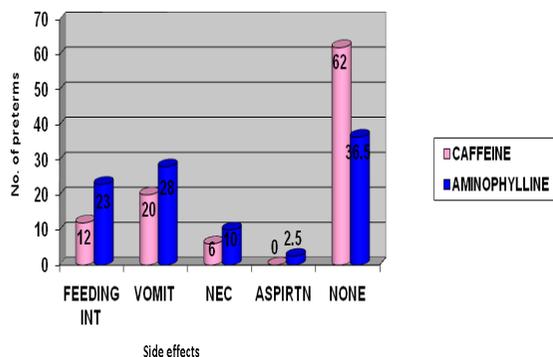
Comparing our study with that of Henderson-Smart Study(2004): In our study, comparing apnea control at the end of 7 days between caffeine and aminophylline- the relative risk is 1.016, 95% CI 0.701, 1.47 whereas Henderson study states that at five to seven days RR is 1.50, 95% CI 0.32, 7.14 (4) Which means at seven days there was no difference in apnea rates in the individual studies.

Comparing the primary outcome within the different groups according to maturity-primary outcome was with use of drugs only, oxygen and tactile stimulation may be done. No difference was found in primary control of apnea as with caffeine or aminophylline. Also, no difference was found statistically between caffeine and aminophylline in secondary outcome in any group (secondary meaning invasive modality of intervention besides drugs like ventilation).

(II) now, comparing the side effects observed with caffeine and aminophylline:

SIDE EFFECTS	NO. OF PRETERMS
FEEDING INTOLERANCE	Caffeine 4(12%) Aminophylline 9 (23%)
VOMITING	Caffeine 7 (20%) Aminophylline 12 (30%)
NECROTIZING ENTERO-COLITIS	Caffeine 2 (6%) Aminophylline 4 (10%)
NONE	Caffeine 21 (62%) Aminophylline 14 (37%)

**The chart-2 below shows no. of preterms observed to have side effects with caffeine/aminophylline**



The most common side effect observed with the drug is vomiting and feeding intolerance, few had necrotizing enterocolitis and majority had non side effects.

Comparing the side effect feeding intolerance between caffeine and aminophylline, Relative risk is 2.405, 95% CI, 0.830, 6.966

Comparing the side effect vomiting between caffeine and aminophylline, Relative risk is 2.420, 95% CI, 0.789, 7.419

Comparing the side effect necrotizing enterocolitis, between caffeine and aminophylline, Relative risk is 2.320, 95% CI, 0.391, 13.753

Comparing no side effects between caffeine and aminophylline, Relative risk is 0.444, 95% CI, 0.156, 1.267

Thus, it shows that side effects were more with aminophylline than caffeine (almost double), as seen above. But, yes a bigger sample size is required to prove it statistically significant, that caffeine has less side effects than aminophylline.

## RESULTS AND CONCLUSION:

The study was conducted over a period of 12 months in level III neonatal intensive care unit of a referral teaching hospital.

Total of 60 preterm neonates less than 36 weeks satisfying the criteria were included in the study.

Out of 60 preterms in the study, 18 (30%) were 28±2 weeks, 25 (41.6%) were 30±2 weeks, 14 (23.3%) were 32±2 weeks, 2 (3.3%) were 34±2 weeks.

Out of 60 preterms in the study, 39 (65%) preterms were required to start methylxanthines on day 1, 20 (33%) started on day 2-7, and the rest 1 preterm after day 7. most of the preterms required to start drugs on day 1, or latest by day 7. apnea of prematurity is rare beyond 7 days.

37 (62%) preterms required methylxanthines for a duration 7 days, 20 (33%) for a duration of 7-14 days, 3 (5%) for a duration more than 14 days.

Out of 60 preterms, 31 received caffeine and 29 received aminophylline. Though not clinically significant but caffeine is being increasingly used nowadays with increased availability and affordability.

In the study, control of apnea in 28 to 28±2 weeks- 8 on caffeine and 6 on aminophylline achieved control of apnea, 30±2 weeks preterms- 7 on caffeine and 8 on aminophylline had control, and 32±2 weeks to 34±2 weeks preterms- 5 on caffeine and 5 on aminophylline.

The primary control of apnea (without any invasive modality)

achieved with methylxanthines- 7 on caffeine and 3 on aminophylline of 28-28±2 weeks preterms, 7 on caffeine and 6 on aminophylline of 30±2 weeks, 2 on caffeine and 3 on aminophylline of 32±2 weeks to 34±2 weeks preterms. Though more number of patients controlled with caffeine but is insignificant.

The secondary control of apnea (with other invasive modality of treatment) - 1 on caffeine and 3 on aminophylline of 28-28±2 weeks preterms, 4 on caffeine and 2 on aminophylline of 30±2 weeks, 5 on caffeine and 3 on aminophylline of 32±2 weeks to 34±2 weeks preterms.

The side effects observed with use of with caffeine and aminophylline :

Feeding intolerance seen in 12% with caffeine and 23% with aminophylline Vomiting seen in 20% with caffeine and 30% with aminophylline Necrotizing enterocolitis in 6% with caffeine and 10% with aminophylline No side effects seen in 62% with caffeine and in 37% with aminophylline Side effects are more with aminophylline than caffeine as observed from the study.

## RECOMMENDATIONS:

Prophylactic use of methylxanthines for the prevention of apnea of prematurity in all preterms < 34 weeks should be considered.

Caffeine is not only equally efficacious to aminophylline but also has advantage of the following parameters :

- Once a daily dose
- Good compliance
- Long half life
- Less toxic, wide therapeutic index
- Less side effects

However, there are multiple variables affecting the outcome of the study.

With easy availability, similar efficacy to aminophylline, less side effects and wide acceptance of caffeine for its use, caffeine has to be the drug of choice for apnea of prematurity.

Though aminophylline is cheaper and freely available in government hospitals, considering the cost-benefit ratio, caffeine is favoured than aminophylline.

Studies with large number of preterms (larger sample size), proper blinding with taking in view the variables affecting should be done. Also, study of the long term side effects with follow up is recommended.

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