Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Medical Paediatrics and Oncology

Journal homepage: https://www.ijmpo.com/

Original Research Article

Study comparing the efficacy of Caffeine vs. Theophylline in Asphyxiated newborn for prevention of AKI

P Jagruthi[1], **RH Gobbur**[1,*]

[1]*Dept. of Pediatrics, BLDE (Deemed to be University)Shri B.M.Patil Medical College Hospital & research Centre, Bijapur, Karnataka, India*

ARTICLE INFO

Article history:
Received 22-01-2021
Accepted 26-02-2021
Available online 25-03-2021

Keywords:
Perinatal asphyxia
Caffeine
Theophylline
Cystatin C

ABSTRACT

Background: Perinatal asphyxia is a multisystem disorder involving many organs, but its effect is more significant in the heart, brain, and kidneys. Involvement of kidneys presents as oliguria and sometimes anuria in the newborn. We compared the efficacy of prophylactic caffeine vs. theophylline given in these newborns in preventing AKI.

Materials and Methods : We performed a prospective study on the asphyxiated term and late preterm newborn babies admitted to the NICU. We allotted babies into group C and T, two groups – Group C –was given Caffeine, and Group T – theophylline. Theophylline and Caffeine drugs were given prophylactically as a single dose intravenously within 12 hours of birth. Babies were monitored for the development of renal injury, both clinically and with laboratory values. Serum creatinine and cystatin C levels in both groups were compared.

Results: A total of 100 babies with clinically confirmed perinatal asphyxia were allotted to 2 groups, 50 babies each. In the theophylline group, there were two deaths (4%), and in the caffeine group, only one death (2%) (P = 0.634). Clinically and laboratory wise both groups did not have any acute kidney injury. The cystatin C levels on day 1 were higher in Theophylline group than Group C (Caffeine) in our study. Further, these levels were higher than those in the study by M.Treiber et al. (P = 0.005).

Conclusion: Caffeine group babies had a better outcome, as the caffeine group had lower cystatin C levels on day three than theophylline group. Hence, caffeine is as effective as theophylline in the prevention of AKI in asphyxiated newborns.

1. Introduction

Perinatal asphyxia (PA) is a multisystem disorder and a catastrophic entity observed in a delivery room setting, wreaking havoc in an otherwise uneventful delivery. According to the WHO statistics, around 4 million deaths occur annually due to PA.[1] In low-income countries, approx. 23% of all neonatal deaths are due to perinatal asphyxia. In India, it is estimated that perinatal asphyxia is in the higher range (12 – 16%) compared to the developed nations (1 – 1.5%).[2,3] PA is classified into various entities based on APGAR score[4] done at the first minute of life, as:

1. Mild PA – APGAR of 5-7
2. Moderate PA – APGAR of 4-6
3. Severe PA – APGAR of 0-3

Perinatal asphyxia can involve the kidneys and may lead to oliguria or sometimes anuria in newborns. It is challenging to monitor urine output and serum creatinine in these babies. Term newborn usually does not pass urine till 24 – 48 hours, serum creatinine levels in these babies are generally a reflection of maternal serum creatinine levels, hence cannot be used as a reliable indicator for monitoring AKI.[5] Cystatin C levels are a more sensitive and specific marker to assess kidney injury; thus, cystatin C is used to monitor renal injury.

* *Corresponding author.*
E-mail address: raghavendra.gobbur@bldedu.ac.in (R. H. Gobbur).

https://doi.org/10.18231/j.ijmpo.2021.002

For preventing AKI, a single prophylactic dose of theophylline in the dose of 8mg/kg intravenously can be given, but it can be toxic, can cause seizures. Hence, as an alternative, caffeine can be tried as it is safer and does not cause neonatal seizures. It has minimal to no side effects; thus, caffeine is an appropriate choice for preventing AKI in asphyxiated term and preterm neonate. This is the first study that used caffeine and theophylline to prevent AKI.

2. Aims and Objectives

The objectives were as follows:

1. To study the safety of theophylline and compare with caffeine
2. The renal outcome of infants treated with theophylline vs. caffeine in the management of perinatal asphyxia was compared. Also, the efficacy of theophylline vs. caffeine in preventing AKI in perinatal asphyxia was compared.
3. Comparative evaluation of lab parameters like cystatin C levels and its correlation of severity of renal damage following prophylactic use of theophylline vs. caffeine.

3. Materials and Methods

3.1. Study design

Prospective open-labelled study

3.2. Study approval

Our study was approved by the Institutional Ethics Committee of BLDEDU's Shri BM Patil Medical College, Hospital and Research Centre, Vijayapur.

3.3. Study site

Neonatal Intensive Care Units (Inborn and Outborn)

3.4. Study period

$1^1/_2$ year (January 2019 to June 2020)

3.5. Source of data

The study sample is all term and late preterm and low birth weight neonates admitted in the NICU of Shri B.M. Patil Medical College Hospital with clinically diagnosed perinatal asphyxia and allotted to two groups – group C– Caffeine was given, and group T – Theophylline was given within twelve hours of life, after taking due written and informed consent. Prophylactic antibiotics and other treatments were given to all groups as per the unit protocol.

Blood samples were taken at admission and on day 3 of life (or NICU stay) and collected in a plain bulb (with red cap) or a lithium heparin bulb (with the green cap). After the 1^{st} blood sample was collected for the investigation, the babies were either given caffeine or theophylline slow iv drip over 1 hour. Blood samples were again collected on day 3. All the samples were processed by centrifugation at 3500 rpm over 10 minutes to separate the serum from the plasma. The serum floats over the plasma as a supernatant, pipetted into Eppendorf tubes, and stored at -20°C till further analysis.

Cystatin C, a low molecular weight protein, belongs to the cysteine protease inhibitors superfamily. It is produced by all nucleated cells at a constant rate; its production is not affected by the diet, inflammatory states, lean body weight, or circadian rhythms. The glomeruli, similar to creatinine, freely filter cystatin C. It is reabsorbed by the proximal renal tubular epithelial cells and completely catabolized in them, and not returned to the bloodstream. Cystatin C levels are inversely related to the glomerular filtration rate. Hence cystatin C can be a potential biomarker to determine early insult to the kidney.

3.6. Procedure

We used the standards (recombinant human cystatin C) as control. The samples were incubated in the microtitre plate wells pre-coated with polyclonal anti-human cystatin C antibody for 30 minutes. After incubation, the wells were washed with the wash solution (deionized or distilled water). The horseradish peroxidase enzyme (conjugate solution) was added to all the wells and incubated for another 30 minutes. The plate was rewashed after 30 minutes, then the substrate solution (TMB-tetramethylbenzidine) was added to the wells and allowed to incubate for 10 minutes. The wells acquire a blue color after adding the substrate solution. The plate was again washed after 10 minutes, and the color development was stopped by adding the stop solution (0.2M sulphuric acid), which after addition to the wells changed the blue color to yellow. A microplate reader analyzed the plate for the absorbance range set between 450nm - 630nm. Simultaneously serum creatinine levels were also assessed and compared with the cystatin C ELISA values.

3.7. Sample size

100 (50 per group) babies must have a 90% chance of detecting, a significance at 5% level, a decrease in the primary outcome (Cystatin C) measure from 4.2 in Group A to 1.5 in group B.

Total sample size = 100

Calculation based on the formula:

$n = f(\alpha/2, \beta) \times 2 \times \sigma^2 / (\mu_1 - \mu_2)^2$

where μ_1 and μ_2 are the mean outcomes in the control and experimental group respectively, σ is the standard deviation

3.8. Inclusion criteria

1. Asphyxiated term & late preterm babies (>34 wk gestational age
2. History of decreased activity since birth (Apgar < 7

3.9. Exclusion criteria

1. Severe IUGR
2. Multiple anomalies in babies
3. Systemic disorders in mothers
4. Mother with severe PIH, gestational diabetes, oligohydramnios
5. Mothers addicted to smoking or drinking alcohol
6. Syndromic baby

3.10. Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. We analyzed the data by Chi-square test for Association, comparison of means using t-test, ANOVA, and diagrammatic presentation. If P < 0.005, the results were considered as statistically significant. Data were analyzed using SPSS software v.23 (IBM Statistics, Chicago, USA) and Microsoft Office 2007.

4. Results

We randomized 100 babies to either of the two groups – caffeine or theophylline, with 50 babies in each group. Mortality was more in the theophylline group with the death of 2 babies (4%), and in the caffeine group only in 1 baby (2%) (P-value of 0.634). Both groups were comparable and had equal severity of Asphyxia as all parameters like sex distribution (P-value: 0.677), birth weight (P-value: 0.476), GA (p =0.887), inborn (p=0.309), gravidity (p=0.548), mode of delivery (p=0.663), MBG (p=0.157). Resuscitation measures (p=0.031), treatment given (p<0.001), therapeutic hypothermia (p= 0.307), HIE staging (p=0.017), NICU stay (p=0.036). Cystatin C on day 1 is significant (p=0.005). The results are tabulated as follows for comparison (Table 1). We also compared the results of our study with other studies (Table 2).

Table 2 M Treiber et al. compared cystatin C levels with creatinine levels in the umbilical cord blood of fifty asphyxiated infants and fifty normal infants. They reported that serum cystatin C is a more sensitive marker than creatinine for predicting AKI in newborns.

5. Discussion

The age, in hours since the birth of the babies at admission, between the two groups is not statistically significant (p=0.215). The caffeine group had a lowerage at admission

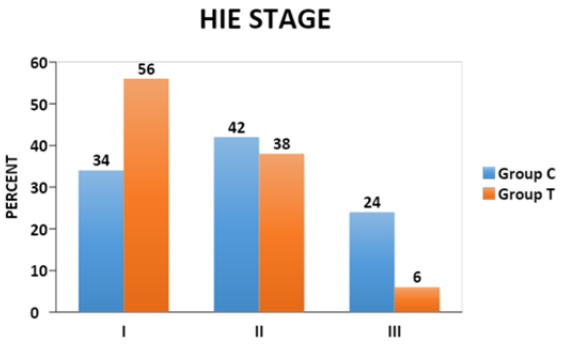

Fig. 1: Distribution of HIE stagein newborn

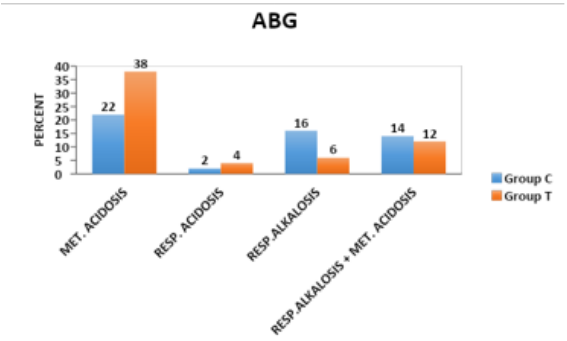

Fig. 2: ABG picturein respiratory distress babies at admission

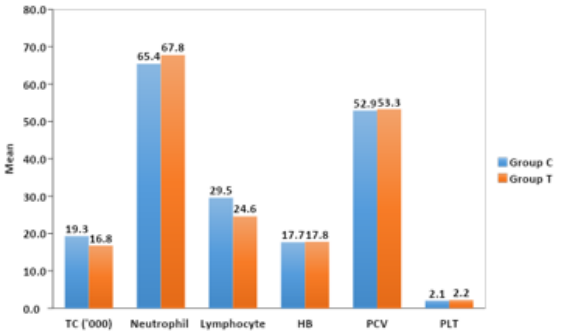

Fig. 3: Lab parameters

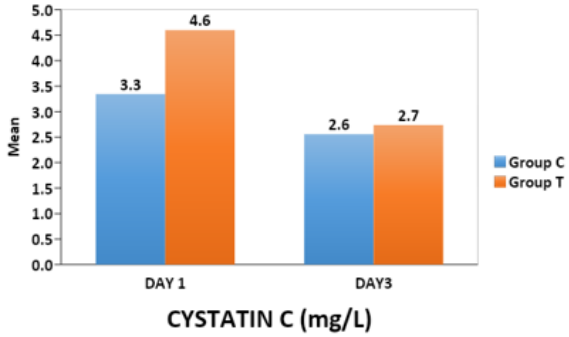

Fig. 4: Cystatin C levels on Day 1 and Day 3

Table 1: Comparison of parameters studied between the groups

	Group C (Caffeine)	Group T (Theophylline)	P - value
Sex distribution	M- 28, F- 11	M- 31, F- 19	0.677
Mean Birth weight (in kilogram)	2.7 (±0.4)	2.8 (±0.4)	0.329
Mode of delivery in no.	LSCS –16(±0.32) NVD-34(±0.68)	LSCS- 14±0.28 NVD- 36±0.72	0.663
Hood O2	18(±0.36)	37(±0.74)	<0.001
O2 nasal prong	39(±0.78)	42(±0.84)	0.444
Ventilation	21(±0.42)	8(±0.16)	0.004
Therapeutic hypothermia	3	1	0.307
Mean hours of life at admission	3.1 (±3) hours	3.9 hours (±3.5)	0.215
NICU stay	10.3 (±7.6)	7.7 (±4.6)	0.036
Number of Patients improved	44 (88%)	42 (84%)	0.564
Number of patients not improved	6 (±12)	8 (±16)	0.564
Number of patients discharged	39	41	0.0634
Number of deaths	1	2	0.0634

Table 2: Comparison of values in our study, with those, in the study by M Treiber et al.[6]

	M. Treiber et al.		Present study	
Laboratory (renal) parameter / No. of babies enrolled	Asphyxia (n=50)	Control (n=50)	Caffeine group (n=50)	Theophylline group (n=50)
Cystatin C day 1 (umb) (mg/l)	2.12 ± 0.53	1.39 ± 0.19	3.3 ± 1.7 (p = 0.005)	4.6 ± 2.6 (p = 0.005)
Cystatin C day 3 (peripheral vein) (mg/l)	1.56 ± 0.32 (p <0.001)	1.34 ± 0.21 (p = 0.137)	2.6 ± 1.3 (p = 0.519)	2.7 ± 1.5 (p = 0.519)
Creatinine day 1 (umb) (mg/dl)	0.72 ± 15.55 (p < 0.001)	0.62 ± 12.84 (p < 0.001)	0.9 ±0.4 (p = 0.384)	0.9 ± 0.4 (p = 0.384)
Creatinine day 3 (peripheral vein) (mg/dl)	0.918 ± 0.22 (p < 0.001)	0.692 ± 0.03 (p < 0.001)	-	-

than the theophylline group. There is not much difference in the statistical significance between the sex of the babies (p=0.677). More male babies are enrolled in the caffeine group, and more female babies are enrolled in the theophylline group. There is not much difference in the statistical significance between the inborn and outborn status of the babies. However, more inborn babies enrolled in caffeine group, and more outborn babies enrolled in the theophylline group (p=0.309). The gestational age of the baby does not have much statistical significance among the groups. However, the caffeine group has more term babies, and theophylline group has more late preterm and post-term babies (p= 0.887). The gravidity does not have much statistical significance, although primigravida and multigravida are equal in the caffeine group, and primigravida is more in the theophylline group (p=0.548). The association between the measures taken and the response seen in both groups is statistically significant. (p=0.031).

There is a statistically significant difference in the number of babies put on hood oxygen between group C and T (p<0.001). More number of babies were put on hood oxygen in the theophylline group compared to the caffeine group.

More number of caffeine group babies were mechanically ventilated as they had a higher degree of asphyxia and also had a good outcome compared to theophylline group. Number of babies who received ventilation had a statistically significant association between the two groups (p=0.004). Even though more caffeine group babies were mechanically ventilated for a longer duration than the theophylline group, they had a much better outcome than the theophylline group. Three babies in caffeine group and one baby in theophylline group were put on therapeutic hypothermia, and all the babies had recovered without any complications (p=0.307). The distribution of HIE stages varied significantly between the two groups. (p=0.017). (Figure 1)

In the 57 babies who developed respiratory distress (Figure 2), allotted to two groups, the incidence of metabolic acidosis and respiratory acidosis is more in the theophylline group. Respiratory alkalosis and mixed acid-base deficit (respiratory alkalosis) is more in the caffeine group. There is not much statistical significance between the two groups.

Babies allocated to the caffeine group had improved condition (44 in 50), and the condition did not improve in 6 babies. In contrast, in the theophylline group, 42 babies had improved, whereas eight babies did not improve.

Only one baby of the caffeine group had died, whereas two babies of the theophylline group died. However, the cause of death is not due to kidney injury. All three of the babies had an intrapulmonary bleed as a complication - DIC and sepsis. The mean duration of NICU stay was longer in the caffeine group, whereas the theophylline group had higher mortality.

The laboratory parameters are statistically significant for the caffeine group compared to the theophylline group. (Figure 3) In contrast, there is not much statistical significance between the other lab parameters like Hb, PCV, Platelet, CRP, serum calcium, and serum creatinine levels. Cystatin C values on day 1 were lower in the caffeine group as compared to the theophylline group. Cystatin C levels were in the normal ranges in both groups; hence there is not much statistical significance on day 3. (Figure 4).

Pharmacologically, a part of theophylline is metabolized to caffeine, a trimethylxanthine in neonates.[7] Theophylline and caffeine also act as diuretics, the former being more potent than the latter.[5,7–10]

6. Conclusion

Babies enrolled in the theophylline group had higher cystatin C levels on Day 1 than the caffeine group babies. The caffeine group babies had low cystatin C levels on the third day compared to the theophylline group. Caffeine appears to be superior to theophylline for managing asphyxia cases in preventing AKI.

A single dose of caffeine citrate 20mg/kg was given to prevent acute kidney injury in asphyxiated newborns in our study. Compared with theophylline 8mg/kg iv, the caffeine group results were comparable to that of the theophylline group.

Acknowledgements

The authors disclose no acknowledgements for the present study.

References

1. World Health Organization. Perinatal mortality: A listing of Available information. FRH / MSM. 96.7. Geneva: WHO; 1996.
2. Deorari A, Paul V, Singh M, Vidyasagar D. News from the regions - newsletter from India. The national movement of neonatal resuscitation in India. *J Trop Pediatr*. 2000;46(5):315–7. doi:10.1093/tropej/46.5.315.
3. Report of the national neonatal perinatal database. (National Neonatology Forum, India) . 2003;.
4. Use and abuse of the Apgar score. Committee on Fetus and Newborn, American Academy of Pediatrics, and Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. *Pediatr*. 1996;98:141–2.
5. Sathe KP, Kulkarni A. Role of methylxanthines in preventing acute renal failure in hypoxic newborns. *Apollo Med*. 2015;12(4):234–8. doi:10.1016/j.apme.2015.02.009.
6. Treiber M, Gorenjak M, Balon BP. Serum Cystatin-C as a Marker of Acute Kidney Injury in the Newborn After Perinatal Hypoxia/Asphyxia. *Ther Apher Dial*. 2014;18(1):57–67. doi:10.1111/1744-9987.12054.
7. Osswald H, Schnermann J. Methylxanthines and the kidney. *Handb Exp Pharmacol*. 0200;(200):391–412.
8. Fulgraff G. Xanthinderivate als Diuretika. vol. 24. Berlin: Springer Verlag; 1969. p. 596–640.
9. Simons FE, Rigatto H, Simons KJ. Pharmacokinetics of theophylline in neonates. *Semin Perinatol*. 1981;5(4):337–45.
10. Pacifici GM. Clinical Pharmacology of Theophylline in Preterm Infants: Effects, Metabolism and Pharmacokinetics. *Curr Pediatr Rev*. 2015;10(4):297–303. doi:10.2174/1573396311666150113213352.

Author biography

P Jagruthi, Junior Resident https://orcid.org/0000-0002-7846-5217

RH Gobbur, Professor

Cite this article: Jagruthi P, Gobbur RH. Study comparing the efficacy of Caffeine vs. Theophylline in Asphyxiated newborn for prevention of AKI. *IP Int J Med Paediatr Oncol* 2021;7(1):6-10.