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

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Original Article

Comparison of Caffeine and Aminophylline in Treating Apnea of Prematurity with Historical Data: A Single Center, Observational Study in Taiwan

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ABSTRACT

Background: For treatment of apnea of prematurity (AOP), aminophylline is the first line medication in Taiwan. There are limited trials in Taiwan regarding the therapeutic benefits and adverse effects of caffeine for the treatment of AOP.
Methods: This observational study conducted between January 2018 and December 2018 investigated the clinical effectiveness and safety of caffeine for AOP in the neonatal intensive care unit (NICU) at a hospital in Taiwan. Very preterm neonates with very low birth weight and apnea were treated with a loading dose of caffeine citrate at 20 mg/kg, followed by a 5–10 mg/kg maintenance dose every 24 h. Preterm infants admitted to the NICU between January 2017 and December 2018 and treated with aminophylline/theophylline were included for comparison.
Results: Seventeen infants receiving caffeine therapy and 43 receiving aminophylline/theophylline therapy were enrolled in this study. Although fewer apneic spells were observed from the second week of commencing caffeine treatment (P=0.028), the mean duration of apnea and episodes of apneic spells during the first four weeks of treatment were similar between the two groups. There were no significant differences in short-term side effects, duration of intubation, noninvasive respiratory support, hospitalization, and medical expenses between the two groups.
Conclusion: Caffeine treatment can reduce the frequency of apnea after one week of administration; however, both caffeine and aminophylline/theophylline showed similar effects in treating AOP.

Keywords: Apnea of prematurity, Caffeine, Methylxanthine, Preterm

Introduction

Apnea of prematurity (AOP), defined as a respiratory pause that lasts for at least 20 s or a shorter cessation of breathing associated with hypoxia and/or bradycardia, occurs in approximately 85% of infants born at less than 34 weeks of gestational age and almost all infants born at less than 29 weeks of gestational age (1, 2). Infants with AOP are more likely to have higher risks for prolonged mechanical ventilation, bronchopulmonary dysplasia (BPD), and long-term neurodevelopmental impairment (3, 4). The medication for AOP is mainly methylxanthines, including aminophylline, theophylline and caffeine. Administration of methylxanthines can reduce the frequency of AOP and the use of mechanical ventilation in premature infants (5). Caffeine can also decrease the incidence of bronchopulmonary dysplasia in infants with very low birth weight (6).

Although caffeine has been used abroad for over 20 years, theophylline and aminophylline are first line medication in neonatal intensive care units in Taiwan for AOP combined with respiratory support (such as nasal continuous

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Please cite this paper as:
Ho FCh, Duh TH, Chung HW, Yang ShT, Chen HL. Comparison of Caffeine and Aminophylline in Treating Apnea of Prematurity with Historical Data: A Single Center, Observational Study in Taiwan. Iranian Journal of Neonatology. 2025 Jan: 16(1). DOI: 10.22038/IJN.2024.75703.2458

positive airway pressure or oxygen therapy). This is due to the limited coverage of health insurance in Taiwan. Unlike caffeine therapy, theophylline or aminophylline therapy requires prescriptions several times a day with regular monitoring of the side effects and serum concentrations (7). Peyona, containing the active substance caffeine citrate and imported from Chiesi Farmaceutici S.p.A., was approved for infant use by the Department of Food and Drug Administration of the Ministry of Health and Welfare in Taiwan in January 2018. To date, there is still no health insurance coverage for this medication, and limited trials of the effect of caffeine on AOP have been conducted in Taiwan. This study aimed to compare the effectiveness and safety of caffeine versus aminophylline/ theophylline on apnea among very preterm infants in the neonatal intensive care unit (NICU) of Kaohsiung Medical University Hospital.

Methods

Participants and treatment protocol

This study comprises two parts. First, we conducted an observational study to evaluate the therapeutic clinical effectiveness and safety of caffeine in treating AOP. Second, using a medical chart review, we compared the therapeutic clinical effectiveness and safety of caffeine and aminophylline/theophylline.

For the first part of this study, very low birth weight (VLBW) preterm newborns (≤ 32 weeks of gestational age) with one or more apneic episodes in 24 hours who were admitted to the neonatal intensive care unit between January 2018 and December 2018 were included. We excluded infants with major congenital malformations and those who underwent aminophylline/ theophylline therapy. Enrolled neonates received a loading dose of caffeine citrate at 20 mg/kg, followed by a 5–10 mg/kg maintenance dose every 24 hours. For the second part of the study, we reviewed all patients admitted to the neonatal intensive care unit of Kaohsiung Medical University Hospital between January 2017 and December 2018. Preterm neonates born at ≤ 32 weeks of gestational age with a birth weight < 1500 g and treated with aminophylline/ theophylline were recruited as the aminophylline/ theophylline group. The loading dose of aminophylline/theophylline was 5 mg/kg, followed by a maintenance dose of 2 mg/kg, administered every 8 h.

Sample size of both groups

Between January and December 2018, our neonatal intensive care unit admitted 57 very low birth weight (VLBW) preterm newborns (≤ 32 weeks of gestational age). Among the 57 infants admitted, 20 who experienced one or more apneic episodes within the first 24 hours of birth were initially considered for our study following IRB approval. After excluding those with major congenital malformations and those previously treated with aminophylline/theophylline, we successfully enrolled 17 participants in the caffeine treatment group. This enrollment was contingent upon obtaining parental consent as required by the IRB and was facilitated by funding support covering caffeine's costs. For historical comparison, we also reviewed data on VLBW infants from the same period and from the year prior to enhance the sample size.

Outcome measures

The baseline parameters were recorded for each enrolled neonate. The data on gestational age, sex, birth weight, APGAR score at 1 and 5 min, antenatal steroid, and

surfactant therapy were recorded. Daily apneic episodes, heart rate within 2 h after methylxanthine administration, and adverse effects were measured. The primary outcome was the frequency of apneic spells per 24 h and the duration of treatment. The secondary outcomes were clinical events of methylxanthines, such as tachycardia, polyuria, incidence of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and death. Bone status in preterm infants, duration of intubation, noninvasive respiratory support and hospitalization, and medical expenses during admission were also analyzed.

Tachycardia was defined as a heart rate > 180 beats per minute (bpm) within 2 h of methylxanthine administration (8). Polyuria was recorded with a urine output > 6 ml/kg/hr (9). BPD was diagnosed and classified according to the definition of the National Institutes of Health 2001 workshop as the need for supplemental oxygen for at least 28 days at 36 weeks' postmenstrual age (PMA) (10). NEC was defined by modified Bell staging criteria (11). Brain ultrasound was used for the diagnosis of IVH and grading according to Papile's classification (12). Grade III and IV IVH were defined as severe IVH groups and recorded. Measurement of tibial bone speed of sound (SOS) by quantitative ultrasound (QUS) has been used to evaluate bone status (13); the assessment was performed at the midshaft of the left tibia in infants with a PMA of 40 weeks. Furthermore,

feeding intolerance is associated with a delay in reaching full feeding in preterm infants (14), and the time to full feeding (milk amount 100 ml/kg/day) in both groups was also assessed.

Ethical approval

For the first part of the observational study, written informed consent was obtained from the parents of each participating infant, and the study was approved by the Institutional Review Board Committee (IRB) of the Kaohsiung Medical University Hospital (approval number: KMUHIRB-F(II)-20170132, date:2018/01/30). The second part of the retrospective study by medical chart review was also approved by the IRB of Kaohsiung Medical University Hospital (approval number: KMUHIRB-SV(I)-20180037, date 2018/07/13). Participant consent was waived for the neonates undergoing aminophylline/theophylline due to the retrospective nature of the study. This research was supported by grants from the Ministry of Health and Welfare (MOHW107-TDU-B-212-123006 and MOHW108-TDU-B-212-133006) and the Kaohsiung Medical University (KMU-M107027).

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 20.0; SPSS Inc. Chicago, IL, USA). Continuous variables, such as gestational age, birth weight, and Apgar score, are presented as mean and standard deviation (SD). Categorical variables, including sex, method of delivery, and administration of antenatal steroids and surfactants, were expressed as numbers and percentages. The independent t-test or chi-square test was used to compare these variables between the caffeine and aminophylline/theophylline groups. Additionally, multiple regression analysis was used to determine the significant factors affecting clinical outcomes in premature infants. A value of $P<0.05$ was considered to be statistically significant.

Results

Seventeen participants treated with caffeine for AOP were enrolled in the first part of the observational study, as detailed in the methods section. Based on the KMUH NICU admission list, 55 infants were diagnosed with apnea of prematurity and treated with aminophylline/theophylline. After exclusion, 43 preterm infants were included in the aminophylline/theophylline group for comparison with the infants treated with caffeine in the second part of the retrospective study (see Figure 1).

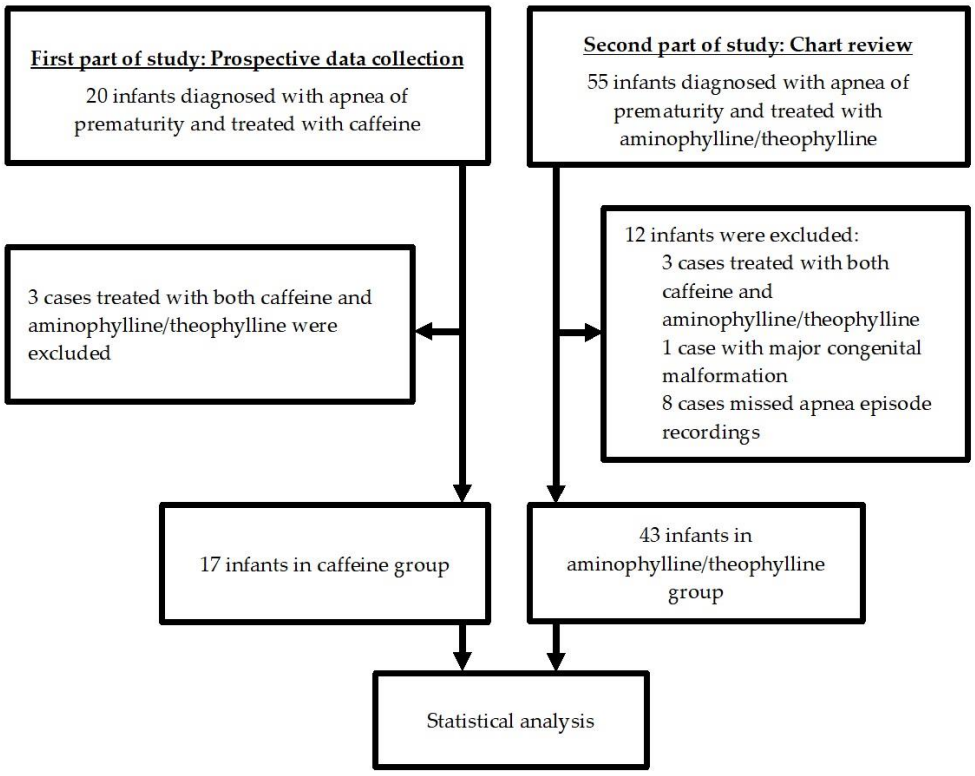

Figure 1. Study flow chart

Table 1. The characteristics of enrolled infants.

Characteristic	Caffeine (n = 17)	Aminophylline (n=43)	P value
Gestational age (weeks)	28.5 (±1.81)	28.7 (±2.22)	0.830
Birth weight (gm)	1025.4 (±239.00)	1184.2 (±259.08)	0.033
Male sex	7 (41.2%)	18 (41.9%)	0.961
Antenatal steroids	12 (70.6%)	28 (65.1%)	0.685
Caesarean delivery	7 (41.2%)	13 (30.2%)	0.418
1-min Apgar score	4.1 (±1.36)	5.7 (1.71%)	0.001
5-min Apgar score	6 (±1.73)	7.2 (±1.56)	0.010
Received surfactant	9 (52.9%)	11 (25.6%)	0.043
PDA	10 (58.8%)	30 (69.8%)	0.418

Data are presented as numbers (%) or means (± standard deviation). PDA: patent ductus arteriosus

Demographics

The characteristics of the infants treated with caffeine or aminophylline/theophylline are listed in Table 1. There was no significant difference in gestational age, sex, antenatal steroids, Caesarean delivery, or PDA in the infants treated with caffeine and aminophylline/theophylline. However, significantly lower birth weight (mean 1025.4 vs. 1184.2 gm, P=0.033), lower Apgar score determined at 1 min (mean 4.1 vs. 5.7, P=0.001) and 5 min (mean 6 vs. 7.2, P=0.010), and more surfactant therapy (52.9% vs 25.6%, P=0.043) were observed in the infants treated with caffeine (see Table 1).

Primary outcomes

The clinical effectiveness of caffeine and aminophylline/theophylline treatments is listed in Table 2. The mean age for commencement of caffeine therapy was 4.82 (±3.84) days, and the total duration of treatment was 49.29 (±26.23) days; no difference was observed in the above results between the two groups (Table 2). Complete resolution of apnea was achieved after a mean duration of 38.41 (±23.82) days in the caffeine group and 48.98 (±33.15) days in the aminophylline/theophylline group (P=0.237). Furthermore, a similar number of apneic episodes during the first four weeks after starting treatment was observed in both groups (Table 2).

Apnea frequency in the first four weeks was analyzed in infants treated with caffeine. Decreasing apnea spells have been experienced since the second week of caffeine treatment (Table 3).

Secondary outcomes

Among the infants treated with caffeine, three preterm neonates died during hospitalization. The deaths were not related to the use of caffeine. They were caused by BPD with pulmonary hypertensive crisis (n=1), septic shock caused by

Table 2. Comparison of effectiveness and outcomes of the study infants.

	Caffeine (n = 17)	Aminophylline (n=43)	P value
Age at commencement of treatment (days)	4.82 (±3.84)	5.49 (±5.62)	0.656
Duration of medication (days)	49.29 (±26.23)	64.47 (±49.42)	0.236
Duration of apnea recorded (days)	38.41 (±23.82)	48.98 (±33.15)	0.237
Apneic episode after starting medication			
1st week	3.18 (±2.60)	2.16 (±1.66)	0.077
2nd week	2.00 (±2.13)	1.60 (±1.99)	0.508
3rd week	1.25 (±1.84)	1.30 (1.51)	0.912
4th week	0.93 (±1.16)	0.91 (±1.56)	0.952
Tachycardia	12 (70.6%)	36 (83.7%)	0.252
Polyuria	6 (35.3%)	22 (51.2%)	0.267
BPD	12 (70.6%)	23 (53.3%)	0.226
Moderate to severe	7 (41.2%)	14 (32.6%)	0.528
IVH (grade III & IV)	1 (5.9%)	1 (2.3%)	0.489
Tibial bone SOS at PMA 40 weeks (m/s)	2758.77 (±130.93)	2827.03 (±131.03)	0.110
NEC	2 (11.8%)	1 (2.3%)	0.131
Time to full feeds (days)	14.07 (±9.85)	14.60 (±12.94)	0.884
Duration of intubation (days)	13.88 (±37.39)	6.07 (±18.49)	0.283
Duration of NIV (days)	39.00 (±22.35)	45. 23 (±29.20)	0.432
LOS (days)	72.18 (±34.01)	74.49 (±39.39)	0.832
Death	3 (17.6%)	0 (0%)	0.005
Medical expenses (TWD)	1,266,559 (±849214) *	1,155,904 (±16038)	0.611

* Costs of caffeine treatment funded by the study program were not included.

Data are presented as numbers (%) or means (± standard deviation). HR, heart rate; U/O, urine output; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; LOS, length of stay; NIV, noninvasive ventilation; SOS, speed of sound; PMA, postmenstrual age; TWD, New Taiwan Dollars.

Table 3. Comparison of the apnea spells per week in the infants treated with caffeine.

Week	Difference of apnea spells	P value
1st vs. 2nd	1.25 (±2.05)	0.028
1st vs. 3rd	2.00 (±2.81)	0.012
1st vs. 4th	2.20 (±2.48)	0.004

Data are presented as mean (± standard deviation).

extended-spectrum beta-lactamase *E. coli* (n=1), and deep vein thrombosis in the right leg (n=1).

The clinical events and outcomes in infants treated with caffeine and aminophylline/ theophylline are listed in Table 2. Clinical events, including sinus tachycardia, BPD, polyuria, time to full feeds, NEC, grade III or IV IVH, were similar in both groups (see Table 2). Sinus tachycardia and polyuria subsided after caffeine therapy was discontinued under an improved state of apnea. Bone status measured by tibial bone SOS for the two groups at PMA 40 weeks was not statistically significant.

The two groups had no difference in the mean duration of intubation, noninvasive ventilation (NIV), and hospitalization. The medical expenses from the Taiwan National Health Insurance in the caffeine and aminophylline/theophylline groups were also analyzed. The extra payment for caffeine offered by this program was not calculated in the caffeine group, and both medical expenses by Taiwan national health insurance were similar, as shown in Table 2.

Multiple regression analysis was used to investigate the significant factors (including the type of methylxanthines) associated with the medical expenses of enrolled premature infants. The variables contributing to medical costs included gestational age (P=0.005), BPD (P=0.016), and duration of intubation (P<0.001). Administration of caffeine or aminophylline/ theophylline was not a significant factor affecting medical payment (P=0.768) (see Table 4).

Our study observed significantly lower birth weights, Apgar scores at one and five minutes, and increased surfactant usage in the caffeine group. To determine the factors significantly associated with clinical outcomes, we utilized multiple regression analysis for the possible risks of the BPD, tibial bone SOS, intubation duration, and hospitalization length. This analysis allowed us to adjust for potential confounders such as birth weight, Apgar scores, and surfactant therapy. Despite these adjustments, the risks of specific clinical outcomes remained statistically insignificant in both the caffeine and aminophylline/theophylline groups. (Data not shown)

Table 4. Multiple regressions of demographics characteristics and clinical outcomes for medical expenses.

Variables	Regression coefficients	SD	P value	95% CI	
				Lower	Upper
Constant	5146322.99	1225891.89	<0.001	2680146.62	7612499.37
Gestational age	-147710.93	50719.02	0.005	-249744.43	-45677.42
Sex	172676.82	124622.16	0.172	-78030.62	423384.25
Birth weight (gm)	-115.26	397.17	0.773	-914.25	683.737
Surfactant used	-20189.17	142267.47	0.888	-306394.40	266016.07
1-min Apgar score	30104.52	84662.50	0.724	-140214.46	200423.50
5-min Apgar score	-22386.53	85308.69	0.794	-194005.48	149232.42
Type of methylxanthines	46979.11	158271.19	0.768	-271421.46	365379.68
NEC	8682.12	287118.31	0.976	-568925.42	586289.66
BPD	324805.77	129864.13	0.016	63552.84	586058.70
IVH (grade III & IV)	-647614.29	354422.46	0.074	-1360620.32	65391.74
Duration of intubation	15146.82	2633.06	<0.001	9849.78	20443.86

NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; IVH: intraventricular hemorrhage.

Discussion

Previous studies reported that caffeine is effective in reducing extubation failure, the use of mechanical ventilation, and the incidence of BPD in preterm infants (15). Caffeine is the mainstay of pharmacologic treatment used in reducing AOP worldwide, but not in Taiwan because of the lack of health insurance coverage (16).

The present study included 17 patients treated with caffeine and 43 treated with aminophylline/ theophylline, with a gestational age of 27 to 31 weeks. Caffeine effectively reduced apneic episodes from the second week after starting treatment (P=0.028), and the frequency of apneic events was less than once a day in the fourth week (=0.93 times/day). Nevertheless, the mean start day and duration of medication administration did not differ between the two treatment groups. Although apneic episodes improved gradually after caffeine administration, there was no significant difference in decreasing apnea frequency or duration between infants treated with caffeine and aminophylline/ theophylline (Table 2). These findings were comparable to

those of previous reports, which showed a similar treatment effect in reducing the frequency of AOP when comparing the efficacy of caffeine and theophylline for managing AOP (5, 8, 17, 18).

In studies comparing the incidence of side effects between caffeine and theophylline for AOP, patients undergoing caffeine therapy had lower rates of feeding intolerance and tachycardia (7). Regarding medical costs, the aminophylline medication itself is cheaper than caffeine. However, because of its wider therapeutic index, longer half-life, and fewer adverse events, caffeine has been the choice of medication worldwide over aminophylline/theophylline in the NICU for apnea (17). If the medical expenses associated with methylxanthine are not considered, caffeine should be prioritized for the treatment of prematurity apnea. However, due to Taiwan National Health Insurance coverage limitations, caffeine is considered a self-pay medication. This issue necessitates a comparison of the efficacy and side effects of aminophylline/theophylline and caffeine for treating prematurity apnea. Our study demonstrated that caffeine was as effective as aminophylline/theophylline in treating AOP with similar rates of adverse drug events. For the short-term adverse effect of methylxanthine therapy for AOP, most previous studies showed that tachycardia was significantly increased in the aminophylline group (17, 19). Although an increased incidence of tachycardia was also noted in infants treated with aminophylline/ theophylline, the difference was insignificant between these two groups (P=0.252). In our study, tachycardia was the major acute adverse event noted in caffeine-treated infants. We defined tachycardia as a heart rate exceeding 180 bpm within 2 hours after administration of therapy. For the property of the clinical study, other variables, such as crying, pain, or fever, might contribute to the episode of tachycardia, which was not evaluated. The measurement of tachycardia may have been overestimated in this study.

Previous studies have compared the short-term adverse effects of caffeine and amino-phylline/theophylline, including BPD, NEC, and IVH. The Caffeine for Apnea of Prematurity (CAP) trial, a large randomized study comparing caffeine and placebo, reported a lower risk of BPD in infants treated with caffeine (adjusted odds ratio, 0.63; 95% CI 0.52-0.76) (20). However, different findings were reported by Jeong et al. in a comparative study of the treatment of caffeine and theophylline conducted in 2015 (8). The authors found that there was no difference in BPD between the two groups, which is consistent with our findings. The disparity in the results can be attributed to the fact that the CAP trial compared caffeine with a placebo rather than comparing it directly with aminophylline. Furthermore, the rates of NEC, IVH, and death were also evaluated in the CAP trial, although no significant difference was observed between the caffeine and placebo groups. These findings are also consistent with our results. Additionally, the duration of assisted respiratory support, including nasal continuous positive airway pressure and mechanical ventilation, was similar to that of the caffeine and theophylline groups in the existing literature (8, 17). We compared the duration of intubation and NIV in infants treated with caffeine and aminophylline/theophylline, and the results were comparable between the two groups. These findings are consistent with those of previous studies (8, 17).

The consumption of caffeine has been recognized as a risk factor for osteopenia of prematurity in preterm infants (21). This is considered to be the result of caffeine-induced increased adverse renal effects, including diuresis, hypercalciuria, and natriuresis (22-24). Our study used quantitative ultrasonography to measure the tibial bone SOS on the left tibia at 40 weeks of PMA, a noninvasive method for evaluating bone status in infants (25,26). The results are shown in Table 2, and no significant difference was observed. However, our study did not analyze laboratory data used for metabolic bone disease screening (27), including serum phosphorous, serum Ca, and serum alkaline phosphatase.

In consideration of the medical expanse between caffeine and aminophylline/theophylline groups, we performed analysis by multiple regression analysis, we found that only gestational age, BPD, and the duration of intubation had effects on health care costs for preterm infants and administration of caffeine or aminophylline/ theophylline did not show significant impact on medical expenses (Table 4). There is an inverse relationship between gestational age and medical expenses. According to a previous study, gestational age is a stronger predictor of neonatal mortality, prematurity-associated medical compli-cations, and the length of hospital stay (28). That means gestational age is the most influencing factor on total medical expenses, which was thought to be from the length of hospital stay. Many studies have also demonstrated that preterm birth and BPD contribute to the large

healthcare burden (29-31). Disappointingly, we found that using caffeine to treat AOP did not reduce medical expenses in our study. This result is because caffeine therapy did not reduce the incidence of BPD in our research. Since caffeine has no health insurance coverage in Taiwan and parents need to pay for treatment themselves, the cost-effectiveness of caffeine was not better than aminophylline/theophylline. This result also makes a point on the reason why our national health insurance does not cover caffeine.

Our study has some limitations. First, this was a single-center, open-label observational study. Attending clinicians and nursing staff were not blinded. Second, serum caffeine levels were not available. Furthermore, the limited number of infants included in our study was due to funding constraints and parental consent requirements. As mandated by the IRB, the need for parental consent introduces the potential for selection bias. It is likely that parents of smaller, more severely affected, and lighter infants were more inclined to consent to participation. This could account for the observed significant differences in birth weight and the increased frequency of surfactant therapy. To bolster our sample size and provide historical context, we also reviewed data on VLBW infants from the same period and the year before. Despite these challenges, the caffeine group—which comprised infants with lower birth weights, lower Apgar scores at 1 and 5 minutes, and higher surfactant usage—showed treatment outcomes comparable to those treated with aminophylline/theophylline. Finally, records of apnea episodes may be incomplete, and death cases have been neglected owing to the retrospective study design of enrolling infants treated with aminophylline/theophylline.

Conclusion

Treatment with caffeine can reduce the frequency of apnea after one week of administration; however, both caffeine and aminophylline/theophylline showed similar effects in treating AOP in our study. A larger, multicenter, randomized controlled study is needed to clarify the short- and long-term adverse effects of caffeine therapy in preterm infants in Taiwan.

Acknowledgments

The authors thank the help from the Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University. We also thank the Ministry of Health and Welfare (MOHW107-TDU-B-212-123006 and MOHW108-TDU-B-212-133006) and the Ministry of Science and Technology of Taiwan (MOST 109-2635-M-037-001) for financially supporting this work.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Williamson JR, Bliss DW, Paydarfar D. Forecasting respiratory collapse: theory and practice for averting life-threatening infant apneas. Respir Physiol Neurobiol 2013;189:223-231.
2. Zhao J, Gonzalez F, Mu D. Apnea of prematurity: from cause to treatment. Eur J Pediatr Eur J Pediatr. 2011;170(9):1097-1105.
3. Janvier A, Khairy M, Kokkotis A, Cormier C, Messmer D, Barrington KJ. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. J Perinatol 2004;24(12):763-768.
4. Taylor HG, Klein N, Schatschneider C, Hack M. Predictors of early school age outcomes in very low birth weight children. J Dev Behav Pediatr 1998;19(4):235-243.
5. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database Syst Rev. 2010;(12):CD000140.
6. Lodha A, Seshia M, McMillan DD, Barrington K, Yang J, Lee SK, et al; Canadian Neonatal Network. Association of early caffeine administration and neonatal outcomes in very preterm neonates. JAMA Pediatr. 2015;169(1):33-38.
7. Morton SU, Smith VC. Treatment options for apnoea of prematurity. Arch Dis Child Fetal Neonatal Ed. 2016;101(4):F352-356.
8. Jeong K, Kim HS, Song ES, Choi YY. Comparison between caffeine and theophylline therapy for apnea of prematurity. Neonatal Med 2015;22(1): 14-20.
9. Mishra G, Chandrashekhar SR. Management of diabetes insipidus in children. Indian J Endocrinol Metab. 2011;15(Suppl3):S180-187.
10. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-1729.
11. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr. 1987;17(4):213-288.
12. Kim KR, Jung SW, Kim DW. Risk factors associated with germinal matrix-intraventricular hemorrhage in preterm neonates. J Korean Neurosurg Soc. 2014;56(4):334-337.
13. Chen HL, Tseng HI, Yang SN, Yang RC. Bone status and associated factors measured by quantitative ultrasound in preterm and full-term newborn infants. Early Hum Dev. 2012;88(8):617-622.
14. Patwardhan G, Soni A, Rachwani N, Kadam S, Patole S, Pandit A. Factors associated with time to full feeds in preterm very low birth weight infants. J Trop

Pediatr. 2018;64(6):495-500.
15. Shrestha B, Jawa G. Caffeine citrate - Is it a silver bullet in neonatology? Pediatr Neonatol. 2017;58(5):391-397.
16. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin Jr DK, Smith PB. Medication use in the neonatal intensive care unit. American journal of perinatology. 2014;31(09):811-822.
17. Henderson-Smart DJ, Steer PA. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev. 2010;2010(1):CD000273.
18. Skouroliakou M, Bacopoulou F, Markantonis SL. Caffeine versus theophylline for apnea of prematurity: a randomised controlled trial. J Paediatr Child Health. 2009;45(10):587-592.
19. 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):279-283.
20. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al; Caffeine for apnea of prematurity trial group. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354(20):2112-2121.
21. Ali E, Rockman-Greenberg C, Moffatt M, Narvey M, Reed M, Jiang D. Caffeine is a risk factor for osteopenia of prematurity in preterm infants: a cohort study. BMC Pediatr. 2018;18(1):9.
22. Gouyon JB, Guignard JP. Renal effects of theophylline and caffeine in newborn rabbits. Pediatr Res. 1987;21(6):615-618.
23. Gillot I, Gouyon JB, Guignard JP. Renal effects of caffeine in preterm infants. Biol Neonate. 1990;58(3):133-136.
24. Zanardo V, Dani C, Trevisanuto D, Meneghetti S, Guglielmi A, Zacchello G, et al. Methylxanthines increase renal calcium excretion in preterm infants. Biol Neonate. 1995;68(3):169-174.
25. Foldes AJ, Rimon A, Keinan DD, Popovtzer MM. Quantitative ultrasound of the tibia: a novel approach for assessment of bone status. Bone. 1995;17(4):363-367.
26. Guglielmi G, Adams J, Link TM. Quantitative ultrasound in the assessment of skeletal status. Eur Radiol. 2009;19(8):1837-1848.
27. Zhang H, Jia Q, Piao M, Chang Y, Zhang J, Tong X, et al. Screening of serum alkaline phosphatase and phosphate helps early detection of metabolic bone disease in extremely low birth weight infants. Front Pediatr. 2021;9:642158.
28. Humayun J, Löfqvist C, Ley D, Hellström A, Gyllensten H. Systematic review of the healthcare cost of bronchopulmonary dysplasia. BMJ Open. 2021;11(8):e045729.
29. Beam AL, Fried I, Palmer N, Agniel D, Brat G, Fox K, et al. Estimates of healthcare spending for preterm and low-birthweight infants in a commercially insured population: 2008-2016. J Perinatol. 2020;40(7):1091-1099.
30. Mowitz ME, Ayyagari R, Gao W, Zhao J, Mangili A, Sarda SP. Health care burden of bronchopulmonary dysplasia among extremely preterm infants. Front Pediatr 2019;7:510.
31. Lai KC, Lorch SA. Healthcare costs of major morbidities associated with prematurity in US children's hospitals. J Pediatr. 2023 May 1;256:53-62.