Caffeine versus aminophylline in combination with oxygen therapy for apnea of prematurity: A retrospective cohort study

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Abstract. The present study was conducted to investigate the clinical significance of caffeine and aminophylline in the treatment of premature infants with apnea under varying conditions of oxygen (O_2) delivery. The clinical data of 120 premature infants with apnea treated with oxygen therapy and either caffeine citrate (20 mg/kg/day; n=77) or aminophylline (10 mg/kg/day; n=43) were retrospectively examined. The therapeutic performance of the drugs after the completion of the treatment was evaluated primarily according to the risk of recurrent episodes of apnea, the changes in the duration and concentration of inhaled O_2 and the incidence of complications. In contrast to aminophylline, caffeine treatment significantly reduced the duration of O_2 inhalation and the inhaled O_2 concentration in the infants treated with mechanical ventilation or O_2 delivery devices ($P<0.05$). Treatment with caffeine also decreased the incidence of recurrent apnea events and complications in the investigated population ($P<0.05$ or $P<0.01$). Caffeine performs better than aminophylline in the treatment of premature infants with apnea under different conditions of O_2 delivery. The therapeutic performance of caffeine is achieved primarily via improving the efficacy of supplemental O_2 and reducing the incidence of complications.

Introduction

The apnea of premature infants is an interruption of breathing for >15 sec and is accompanied by hypoxia or bradycardia, which is a risk factor for the damage to a developing brain (1,2). Although the apnea usually resolves by the time the infant reaches 36-37 weeks of age (3), the incidence of the disease is higher in the neonates born at 30-31 weeks (4). Within clinical practice, apnea is classified into three types: Central, obstructive and mixed, and the mixed type accounts for 50% of apnea events (5). The pathogenesis of the apnea of prematurity is unclear. However, previous studies have indicated the impairment of neuronal development and the inability to control breathing in preterm infants (6,7).

The management of the apnea of prematurity involves a combination of two major therapies, a pharmacological treatment and the supply of O_2, which is necessary for normal body function (1,3,6). Although caffeine citrate and aminophylline have been the primary treatments of infant apnea within clinical practice (8), a comparison of the efficacy and safety of both drugs in the treatment of apnea still remains to be performed, particularly for those who underwent different strategies of O_2 supply. It has been reported that continuous positive airway pressure and nasal intermittent positive pressure ventilation are safe and effective in improving the respiratory function and decreasing the bradycardia (9,10). Despite the widespread use of mechanical ventilation to treat hypoxia (1), there is considerable uncertainty regarding the performance of these two drugs in the treatment of apnea in the infants receiving different strategies of O_2 delivery.

The current study was performed to investigate the efficacy and safety of caffeine and aminophylline in the treatment of the apnea of premature infants under different conditions of O_2 delivery. The results of the present study indicated that caffeine is more potent than aminophylline in improving the efficacy of the O_2 therapy and reducing the incidence of complications.

Materials and methods

Premature neonates and inclusion criteria. A cohort of 120 premature infants with apnea, who received caffeine or aminophylline therapy from January to December 2017 at the First People's Hospital of Zhengzhou City, were retrospectively included in the present study. The treatment with either caffeine or aminophylline was at the discretion of the

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physician. These hospitalized infants included 63 males and 57 females with a birth weight between 500 and 1,250 g. The demographic characteristics of the infants are presented in Tables I-III. The present study was approved by the Ethics Committee of the First People's Hospital of Zhengzhou City (Zhengzhou, China; approval no. 2017-16).

The infants selected for the current retrospective study fulfilled the following criteria: i) All infants born after <34 weeks of gestation were diagnosed with apnea (the mixed type accounted for ~75% of all the types of apnea); ii) a stay of ≥24 h in hospital occurred; iii) the apnea of prematurity was solely treated with either caffeine or aminophylline under varying conditions of oxygen (O_2) delivery; iv) there were no contraindications to either invasive or noninvasive ventilation; and v) there were no complex congenital malformations occurring in airways, chromosomal abnormalities or inherited metabolic diseases.

Drug treatment and supplemental O_2 delivery. The doses of caffeine (Shanghai Yuduo Biotechnology Co., Ltd.) and aminophylline (Shanghai Yuduo Biotechnology Co., Ltd.) used to treat the apnea were selected according to previous studies (11,12). In the present study, 77 infants with apnea received an intravenous (IV) injection of caffeine at a first dose of 20 mg/kg followed by a maintenance dose of 10 mg/kg per day after birth until the 34th week from the gestation of mother. The other 43 infants were treated by IV administration of aminophylline at a first dose of 5 mg/kg followed by a maintenance dose of 2.5 mg/kg twice per day after birth until the 34th week from the gestation of mother.

The efficacy and safety of the drugs applied for the treatment of apnea were analyzed with regard to the different types of mechanical ventilation and O_2 delivery devices, which were selectively used according to the O_2 requirements of the infants, the reliability of the O_2 supply, the convenience of the therapeutic application and the patients' consent. The overall goal of O_2 administration is to maintain an adequate tissue oxygenation while minimizing the cardiopulmonary load. The infants with apnea started to receive O_2 therapy prior to pharmacotherapy. The various forms of supplemental O_2 delivery included: i) Invasive mechanical ventilation via an endotracheal tube to provide continuous positive airway pressure (CPAP); ii) non-invasive mechanical ventilation via a nasal mask to provide nasal intermittent positive pressure ventilation (NIPPV) or nasal CPAP (NCPAP); and iii) A hood mask or a nasal cannula used to deliver O_2 directly into the nostrils of the infant.

Ventilator settings. The tidal volume (4-6 ml/kg) and respiratory rate (30-40 times/min) were used to calculate the minute ventilation. The sensitivity setting was used to adjust the level of negative pressure required to trigger the SLE5000 infant ventilator (SLE Ltd.). The peak inspiratory (PIP) and end-expiratory pressure settings for all premature infants were adjusted to 16-28 and 5-6 cmH_2O, respectively, according to previous reports (13,14). The pressure settings were adjusted according to the result of the arterial blood gas analysis performed by i-STAT®1 analyzer (LumiraDx, Ltd.), which was routinely checked at 15-30-min intervals until the O_2 saturation (>95%) and the acid-base balance (pH 7.35-7.45) was achieved in a normal range. The levels of the peak inspiratory and expiratory pressures were initially designed to be slightly <16 and 5 cmH_2O in the mode of NIPPV or NCPAP, respectively (15).

Criteria for drug treatment and withdrawal. The indications for caffeine and aminophylline treatment included: i) Appearance of apnea in premature infants or infants remaining at high risk of apnea; and ii) Independent of the types of the mechanical ventilation that would be used, the drug therapy would start within 24 h of disconnecting the ventilator.

The indications for drug withdrawal were the following: i) Infants being free of apnea for at least 7 days, or whom the gestational age reached 34 weeks; and ii) no mechanical ventilation required for 7 days; and iii) serious adverse effects arising from the combined use of the drugs and the mechanical ventilation, such as the slow development of the nerve system, brain and other organs.

Criteria for the efficacy of caffeine and aminophylline in the treatment of apnea. The efficacy of caffeine and aminophylline in the treatment of infants with apnea was assessed according to the frequency of recurrent apneic episodes and of O_2 delivery devices replaced by an invasive ventilation, the alterations in the duration and concentration of inhaled O_2. The efficacy was evaluated according to the following: i) Ease of apnea within 48 h after administering the drugs; ii) apnea episodes of <2 times/day associated with a normal breathing rhythm; iii) no alteration in the frequency of apnea episodes within 48 h after administering the drugs; iv) recurrence of apnea (a time interval of ≥3 days between the first and second apnea episode).

Complications of caffeine- and aminophylline-treated preterm infants. The complications were diagnosed according to the outcomes of clinical and laboratory examinations, including chest or abdominal radiography, echocardiogram, growth of abnormal blood vessels in the area of retina and brain ultrasound (16-20). The complications presented in the current study primarily included patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP) and intraventricular hemorrhage (IVH). The incidence of these complications was calculated as a percentage of the population proportion in the caffeine- and aminophylline-treated infants, respectively.

Statistical analysis. The results are presented as the mean ± standard deviation or a percentage (%) of the population, as appropriate. The statistical analysis was performed using SPSS software version 17.0 (SPSS, Inc). The comparisons between the variables of the infants treated with caffeine and aminophylline were made using the unpaired Student's t-test. The χ^2 test was used to analyze the differences between the population proportions observed in these two treatment approaches. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Effects of drugs on preterm infants receiving invasive mechanical ventilation. Certain premature infants (n=40)

Table I. Characteristics of premature infants with invasive mechanical ventilation.

Group	Sex, M/F	Gestational age at admission, weeks	Birth weight, g	Type of apnea, C/O/M
Caffeine	15/13	29.78±1.42	1,371.07±326.40	6/0/22
Aminophylline	6/6	31.44±1.20	1,723.33±317.70	3/0/9
P-value	0.84	0.76	0.98	0.80

Data are presented as the mean ± standard deviation. M, male; F, female; C, central apnea; O, obstructive apnea; M, mixed apnea.

Table II. Characteristics of premature infants with non-invasive mechanical ventilation.

Group	Sex, M/F	Gestational age, weeks	Birth weight, g	Type of apnea, C/O/M
Caffeine	15/10	31.41±1.26	1,610.80±221.17	4/0/21
Aminophylline	6/9	31.40±1.11	1,640.67±227.11	3/0/12
P-value	0.22	0.51	0.59	0.74

Data are presented as the mean ± standard deviation. M, male; F, female; C, central apnea; O, obstructive apnea; M, mixed apnea.

Table III. Characteristics of premature infants with O_2 delivery devices.

Group	Sex, M/F	Gestational age, weeks	Birth weight, g	Type of apnea, C/O/M
Caffeine	11/13	32.10±0.76	1,794.58±210.51	6/0/18
Aminophylline	11/5	32.27±0.70	1,880.63±238.56	3/0/13
P-value	0.15	0.73	0.38	0.64

Data are presented as the mean ± standard deviation. M, male; F, female; C, central apnea; O, obstructive apnea; M, mixed apnea.

with apnea required a therapeutic intervention of invasive mechanical ventilation according to the severity of their breathing problem. The effects of caffeine and aminophylline on the ventilated infants were examined according to the frequency of recurrent apneic episodes and of the invasive ventilation required additionally after disconnecting the ventilator, the duration of O_2 inhalation and the changes in PIP. The results are presented in Fig. 1. The recurrence of apnea and the frequency of ventilator replacement was similar in the infants treated with both drugs. The population proportion of caffeine- and aminophylline-treated infants (n=28 and 12) reached 28.6% (8/28) and 33.3% (4/12) in terms of the recurrent episodes of apnea, and 10.7% (3/28) and 25% (3/12) in terms of the ventilator reconnection (Fig. 1A and B). There were no statistically significant differences in the aforementioned comparisons between these two therapies. In subsequent analysis, the duration of the O_2 inhalation therapy was similar in caffeine-treated infants compared with aminophylline-treated infants (Fig. 1C). The mean time of O_2 inhalation was 12.71±7.66 and 14.25±10.09 days in caffeine- and aminophylline-treated infants, respectively. Although the duration of O_2 inhalation in caffeine-treated infants was slightly shorter than in aminophylline-treated infants, no statistical difference was observed between these two treatment approaches. The alterations in PIP, which were regulated by the ventilator, were also examined in the treated infants. The treatment with caffeine resulted in a small but significant decline in the PIP level compared with aminophylline treatment, in the ventilated infants ($P<0.05$; Fig. 1D). The mean PIP value was 18.96±1.45 and 20.00±1.04 cmH_2O in caffeine- and aminophylline-treated infants, respectively. In contrast to the duration of O_2 therapy, there was a statistically significant difference in the alteration of the PIP levels between these two treatment options ($P<0.05$).

Effects of drugs on preterm infants receiving noninvasive mechanical ventilation. Certain premature infants (n=40) with apnea required a supplemental O_2 delivery via an NIPPV or NCPAP mode, which provides a steady pressure to the rear of the nose that is transmitted to the lungs, aiding the infant to breathe more conveniently. The efficacy of the drugs in the treatment of infantile apnea was evaluated in the ventilated infants according to the frequency of recurrent apneic episodes and of invasive ventilation used as alternative to non-invasive ventilation, as well as the duration and the concentration of inhaled O_2. The results are presented in Fig. 2. The treatment with either caffeine or aminophylline did not result in apparent alterations in the incidence of recurrent apnea and of the requirement of invasive ventilation. The population proportion of caffeine- and aminophylline-treated infants

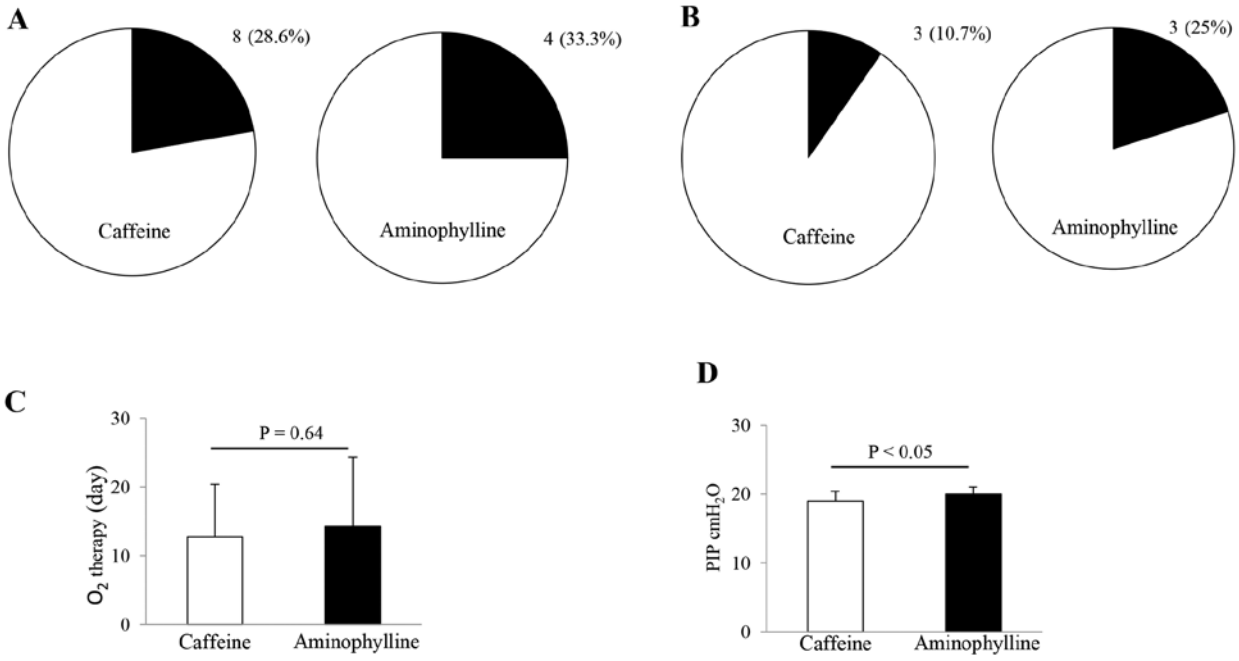

Figure 1. Effects of drugs on the apnea of premature infants receiving invasive ventilation. (A) Risk of recurrent apnea and (B) frequency of additional invasive mechanical ventilation were examined in the presence of caffeine and aminophylline (n=28 and 12, respectively). The proportion (black) of the infants with recurrent apnea and of those requiring additional invasive ventilation was expressed as a percentage of the total population in each group. Data from (C) the duration of inhaled O_2 and (D) alterations in the PIP level are presented as the mean ± standard deviation. PIP, peak inspiratory pressure.

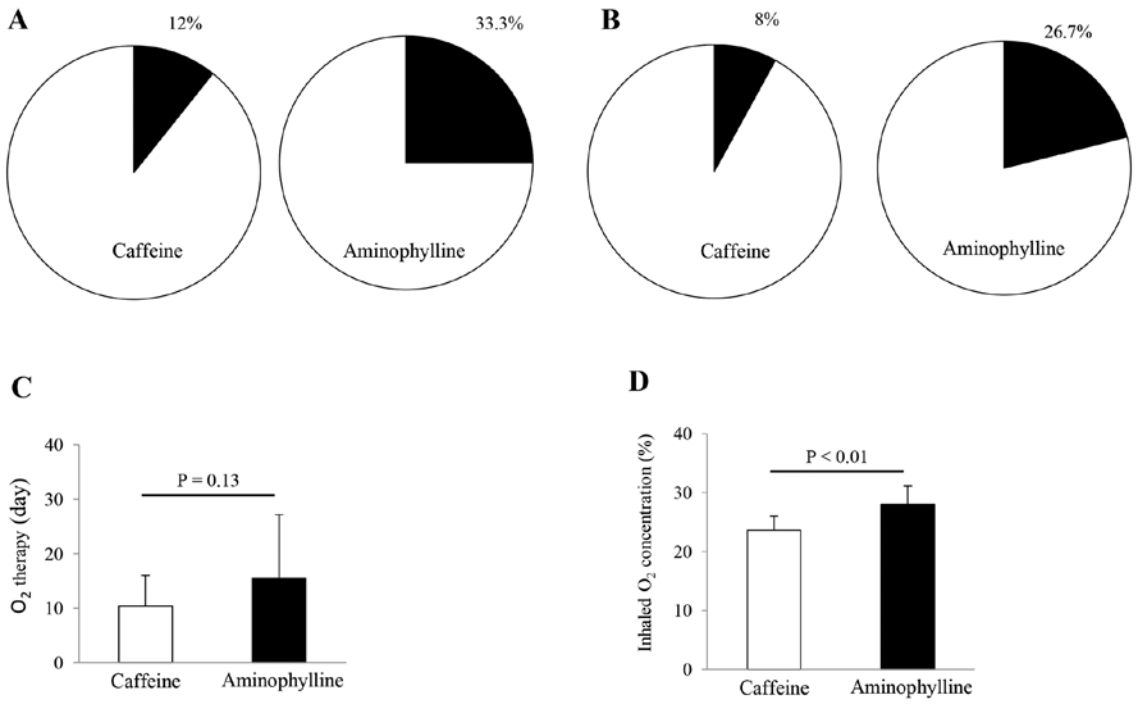

Figure 2. Effects of drugs on the apnea of premature infants receiving a non-invasive ventilation. (A) Recurrence of apnea and (B) frequency of invasive ventilation used as alternative to non-invasive ventilation after disconnection of a ventilator were examined in caffeine- and aminophylline-treated infants (n=25 and 15, respectively). The proportion (black) of infants with recurrent apnea and of those requiring an invasive ventilation was expressed as a percentage of the total population in each group. Data for (C) the duration and (D) the concentration of inhaled O2 are presented as the mean ± standard deviation.

(n=25 and 15, respectively) reached 12% (3/25) and 33.3% (5/15) in the recurrent apnea incidents (Fig. 2A) and 8% (2/25) and 26.7% (4/15) in the incidents of the infants receiving invasive ventilation (Fig. 2B), respectively. There were no significant differences in these clinical outcomes between the two therapies (Fig. 2A and B). In order to clarify the effects of O_2 therapy, the duration and concentration of the inhaled O_2 was examined in the ventilated infants. The average values of the duration and concentration of the O_2 supply were 10.40±5.60 days and 23.60±2.38% in caffeine-treated

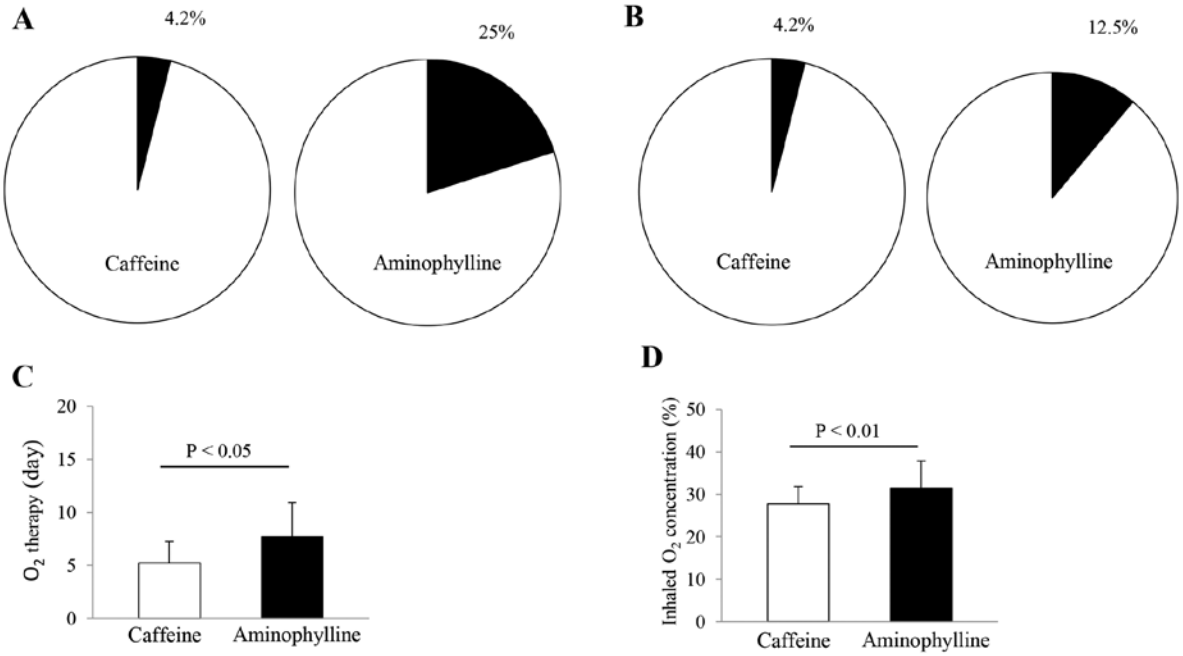

Figure 3. Effects of drugs on the apnea of premature infants receiving a hood mask or a nasal cannula. (A) Recurrence of apnea, (B) frequency of infants requiring an invasive ventilation, and (C) duration and (D) concentration of inhaled O_2 were examined in caffeine- and aminophylline-treated infants (n=24 and 16, respectively). The proportion (black) of infants with recurrent apnea and of those requiring an invasive ventilation was expressed as a percentage of the total population in each group. Data from (C) the duration and (D) the concentration of inhaled O_2 are presented as the mean ± standard deviation.

infants, respectively, and 15.53±11.06 days and 28.00±3.16% in aminophylline-treated infants, respectively. The duration of O_2 intake in caffeine-treated infants was 6 days shorter than that in aminophylline-treated infants (Fig. 2C). However, no statistically significant difference was observed in the duration of the O_2 supply between these two treatment options. The inhaled O_2 concentration in the aminophylline-treated infants was significantly higher than in the caffeine-treated infants (P<0.01; Fig. 2D).

Effects of drugs on preterm infants receiving a hood mask or a nasal cannula. Certain premature infants (n=40) with apnea received O_2 therapy through a hood mask or a nasal cannula. The results are presented in Fig. 3. The population proportion of caffeine- and aminophylline-treated infants (n=24 and 16) reached 4.2% (1/24) and 25% (4/16), respectively, in the recurrence of apnea and 4.2% (1/24) and 12.5% (2/16), respectively, in the frequency of infants requiring an invasive ventilation (Fig. 3A and B). No statistically significant differences were observed in the aforementioned observations between these two therapies. In a subsequent analysis, the duration and concentration of the inhaled O_2 in caffeine-treated infants were reduced compared with aminophylline-treated infants (Fig. 3C and D). The mean values of the duration and concentration of inhaled O_2 were 5.21±2.06 days and 27.75±4.08% in caffeine-treated infants and 7.69±3.20 days and 31.50±6.35% in aminophylline-treated infants, respectively. Statistically significant differences were observed in the duration and concentration of the inhaled O_2 between these two treatment approaches (P<0.05 and P<0.01, respectively).

Efficacy and safety of caffeine and aminophylline in the treatment of apnea. A total of 120 premature infants were selected for the general assessment of the therapeutic efficacy and safety of caffeine and aminophylline in the current retrospective study. The incidence of infants with recurrent apneic episodes and complications following the suspension of drug therapy was assessed under the overall criterium of adequate O_2 supply. The recurrence rate of apnea was lower in caffeine-treated compared with aminophylline-treated infants. The proportion of the infants treated with caffeine and aminophylline (n=77 and 43, respectively) reached 14.3% (11/77) and 32.6% (14/43) in the recurrent incidents, respectively. A statistically significant difference was observed in the incidents between these two treatment approaches (P=0.033).

The risk of complications was also examined in the infants treated with caffeine and aminophylline. The population proportion of the infants with complications in the treatment groups of caffeine and aminophylline was displayed as 5.2% (4/77) and 23.2% (10/43) in PDA, 3.9% (3/77) and 18.6% (8/43) in BPD, 0% (0/77) and 2.3% (1/43) in NEC, 2.6% (2/77) and 2.3% (1/43) in ROP, and 14.3% (11/77) and 16.3% (7/43) in IVH, respectively (Table IV). The risks of NEC, ROP and IVH were similar in the infants treated with caffeine and aminophylline. However, the incidence of PDA and BPD in the caffeine-treated infants was lower than that in the aminophylline-treated infants, with statistically significant differences observed in the occurrence of these complications between these two treatment approaches (P<0.05).

Discussion

The effects of drugs on the recurrence of apnea, the invasive mechanical ventilation replacement, the duration of O_2 inhalation and the alterations in the PIP levels, to the best of our knowledge, were analyzed for the first time in the current

Table IV. Comparison of efficacy and safety between caffeine and aminophylline.

Complication	Caffeine, n=77	Aminophylline, n=43	P-value
Recurrent event of apnea (%)	11 (14.3)	14 (32.6)	0.033
Patent ductus arteriosus (%)	4 (5.2)	10 (23.2)	0.006
Bronchopulmonary dysplasia (%)	3 (3.9)	8 (18.6)	0.016
Necrotizing enterocolitis (%)	0 (0)	1 (2.3)	0.358
Retinopathy of prematurity (%)	2 (2.6)	1 (2.3)	1.000
Intraventricular hemorrhage (%)	11 (14.3)	7 (16.3)	0.794

retrospective study. The results indicated that the efficacy of caffeine in the treatment of apnea in premature infants with an invasive respiratory support was similar to that of aminophylline. However, a lower PIP level was observed in the ventilated infants of the caffeine-treated group, suggesting that treatment with caffeine may result in an increased O_2 delivery into the infant's lungs via decreasing the airway resistance. Caffeine and aminophylline have typically been prescribed as the first-line drugs for treating apnea of premature infants since they function as respiratory stimulants to increase the minute ventilation, and as neural stimulants to drive the diaphragm contraction and the respiratory muscle function (4,21,22). The results of the current study also demonstrated that in contrast to aminophylline, caffeine may be more effective than aminophylline in in infants treated with mechanical ventilation or O_2 delivery. The decrease in the PIP level in the ventilated infants may be attributed to the broader therapeutic range and the longer half-life of caffeine in the plasma compared with aminophylline (23,24). As PIP is the highest pressure level provided to the lungs during inhalation, it was hypothesized that the low pressure occurred as an additional effect of delivering adequate O_2 to the lungs of caffeine-treated infants. In addition, it is worth noting that a low PIP level protects the premature lungs from damage originating from increased O_2 exposure (25). Therefore, the invasive strategy is considered the preferred option to treat the apnea of prematurity.

Although both invasive and non-invasive mechanical ventilation are used for treating premature infants with respiratory insufficiency (26), the latter is increasingly being employed in neonatal units and appears to be safe and efficient when used by specialists (27). The non-invasive respiratory support can be accomplished in a variety of ways; however, to the best of our knowledge, none of them have yet been demonstrated to be superior to invasive ventilation in the management of the apnea of prematurity. NIPPV or NCPAP was introduced as an alternative to invasive mechanical ventilation for treating preterm infants with breathing problems (15). The results of the current study revealed that caffeine treatment did not reduce the duration of O_2 inhalation and the recurrence rate of apnea in the ventilated infants. However, the treatment of the infants with caffeine decreased the level of inhaled O_2 compared with aminophylline treatment, suggesting that caffeine was superior to aminophylline in improving the efficacy of supplemental O_2 under the condition of delivering O_2 via NIPPV or NCPAP. Furthermore, it may be presumed that caffeine was more efficient than aminophylline in maintaining the levels of O_2 saturation, as O_2 desaturation appeared in infants with mixed apnea (28). This effect is apparently associated with the pharmacological action of caffeine in the infants, since the drug has a broader therapeutic index, including increasing the respiratory rate and minute ventilation via stimulating the respiratory center and improving the sensitivity of the central medullary areas to hypercapnia (29,30). Premature infants who experience frequent bouts of apnea may be mechanically ventilated to facilitate their breathing. NCPAP and NIPPV, as primary modes of non-invasive mechanical ventilation, have widely been employed as an alternative to invasive ventilation for the early management of infant apnea (27). Both NCPAP and NIPPV provide steady pressure to the rear of the nose via the ventilator, which is transmitted to the neonatal lungs and counteracts the collapsing lung symptoms, thus facilitating gas exchange (31). Therefore, these two modes of assisted ventilation have been increasingly earning acceptance in the treatment of neonatal apnea (32,33). Given that the efficacy of both drugs in the treatment of infantile apnea was based on the levels of supplemental O_2 required for the infants, it has been suggested that using the non-invasive techniques may be considered as a preferable option for the infants treated with caffeine.

The effects of caffeine and aminophylline on the recurrent episodes of apnea, the invasive ventilation required and the duration and concentration of the inhaled O_2 were examined in premature infants receiving O_2 via a hood mask or a nasal cannula. The results indicated that the duration and concentration of the inhaled O_2, which were required for the caffeine-treated infants, were shorter (2.5 days) and lower (4%) than those for the aminophylline-treated infants. Statistically significant differences were observed in the duration and the concentration of the inhaled O_2 between these two therapies. Based on these findings, it was concluded that caffeine may not only accomplish the supply of the body tissues with adequate O_2 via the devices, but also prevent any inconvenience for the infants undergoing endotracheal intubation and mechanical ventilation. Premature infants are at high risk of developing breathing problems, as their lungs do not produce sufficient amounts of surfactants, which keep the lung alveoli open (34). Therefore, selecting a method of supplemental O_2 delivery should be carefully considered, since in certain cases the artificial breathing machine may result in lung problems, such as BPD (35). Since the majority of the infants in the current retrospective study presented with mixed apnea, which is a combination of central with obstructive apnea (21), a method of efficient O_2 delivery to the infants' lungs is of particular importance for the management of the pediatric

population. Although the application of CPAP is an approach that is used to treat both obstructive and mixed apnea (36), its efficacy in central apnea still remains to be clarified (7). The results of the current study indicated that these simple methods can also provide sufficient O_2 to the patients with mixed apnea. Furthermore, the therapy was not perturbed when feeding was required. Caffeine improved the effects of the pediatric O_2 therapy via stimulating the central nervous system to reduce the apnea episodes and improving the respiratory muscle strength to unblock an obstruction if the airway collapses (37,38). Overall, the results of the current study revealed that the efficiency of these devices used to deliver O_2 was superior to both the invasive and non-invasive neonatal mechanical ventilation in the present retrospective cohort study. Therefore, it is suggested that the application of these O_2 delivery devices should be the primary option for an O_2 supply in the treatment of the infants with apnea, since this method of supplying O_2 would be more practical and economical in developing countries.

A general assessment of the performance of caffeine and aminophylline in the treatment of apnea was accomplished in premature infants requiring ventilatory support or O_2 delivery devices. The results indicated that a population proportion with recurrent episodes of apnea following withdrawal of drug therapy reached to 11 and 14% in the caffeine- and aminophylline-treated infants, respectively, indicating that the efficacy of caffeine was superior to that of aminophylline in treating the apnea of prematurity, under the three conditions of delivering O_2. Compared with infants treated using aminophylline, the proportion of the population with PDA and BPD was reduced in the caffeine-treated infants by 6 and 5%, respectively, in a total population of 120 cases. Based on these findings, it was concluded that the overall performance of caffeine in the treatment of apnea was superior to that of aminophylline in the pediatric population requiring ventilatory support and O_2 delivery devices. Caffeine is one of the most frequently prescribed medications in the neonatal intensive care (39). As a respiratory stimulant, caffeine can reduce the recurrent episodes of apnea in premature infants (4,40). The results of the present study also indicated that the incidence of complications was comparable to previous reports, in which caffeine therapy reduced the risks of PDA and BPD in preterm infants with a low birth weight or who were born at <29 weeks gestation (41,42). Currently, the efficacy and safety of caffeine and aminophylline are not fully elucidated in infants receiving O_2 via mechanical ventilation and O_2 delivery devices. The present study provided novel insights regarding the impact of both drugs on the infants, as they require different strategies of O_2 supply. As the incidence of the recurrent apneic episodes and complications decreases in infants treated with caffeine, it is hypothesized that these benefits of the medication may reduce the financial burden on their families thanks to the reduced requirements for hospitalization and further medical care.

The limitations of the current study primarily include the small sample size and the lack of information regarding the long-term efficacy of caffeine in the treatment of apnea. Severe apnea affects the neurodevelopmental outcome, and caffeine improves the neural respiratory drive to reduce the apnea via multiple physiological and pharmacological mechanisms (43). Therefore, a subsequent study is required to assess the long-term efficacy of caffeine in protecting the cerebral function from neurodevelopmental impairment.

In conclusion, the present study indicated that caffeine had numerous advantages over aminophylline in the treatment of apnea under varying conditions of O_2 supply. Caffeine had high efficacy in the treatment of apnea primarily via improving the efficiency of O_2 therapy and reducing the risk of complications in the pediatric population.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CYZ, DJL and SDH conceived and designed the study. SG, XYL, BZ and LHA collected and analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First People's Hospital of Zhengzhou City (Zhengzhou, China; approval no. 2017-16). Informed consent was obtained from all participants' guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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