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# The effect of caffeine with a low maintenance dose compared to a high dose on the respiratory function of preterm infants of ≤ 34 weeks

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**ABSTRACT**

**Background:** Although caffeine is an effective drug in premature babies, there is still no consensus regarding its effective dose. This interventional study aimed at the effect of caffeine with a low maintenance dose compared to a high dose on the respiratory function of premature infants of ≤ 34 weeks.

**Methods:** In this clinical trial, 60 premature babies with a gestational age ≤34 weeks diagnosed with respiratory distress syndrome were included in the study. Patients randomly and equally received an initial dose of 20mg/kg and then a maintenance dose of 10mg/kg and 5mg/kg of caffeine. Extubation failure rate, CPAP duration, hospitalization duration, adverse effects and outcome of patients were compared in two groups.

**Results:** Both groups had no statistically significant differences in terms of basic variables. The frequency of failure in extubation (36.7 vs. 13.3%), the duration of mechanical ventilation (6.4 ± 2.8 vs. 3.5 ± 0.5 days), the duration of NCPAP requirement (8.2 ± 6.3 vs. 4.3 ± 2.7 days) and the number of apneas (2.7 ± 2.4 vs. 1.9±1.6) in the group with higher dose was found to be lower as compared to other group, where a statistically significant difference was found. There was no statistically significant difference between the two groups in terms of side effects.

**Conclusion:** Our data has shown the effectiveness of a maintenance dose of 10 mg caffeine compared to 5 mg caffeine, which can be associated with a better short-term outcome in premature babies.

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## INTRODUCTION

Prematurity accounts for about 10% of all births, and prematurity accounts for about 80-60% of the cause of morbidity and mortality worldwide in infants without congenital anomalies [1,2].

Premature birth can lead to respiratory failure and the need for mechanical ventilation. Mechanical ventilation in premature babies is associated with severe pulmonary complications and extrapulmonary consequences [3,4]. Among the complications of lung prematurity are Bronchopulmonary dysplasia (BPD), neurodevelopmental disorders and even death [5,6]. BPD is linked to poor neurodevelopmental outcome, long-term respiratory complications, and higher mortality in survivors [7,8]. One of the most important causes of morbidity and death due to prematurity is respiratory problems, among of which respiratory distress syndrome (RDS) is seen as a result of surfactant deficiency and underdeveloped lung anatomy. So that approximately 55% of babies with 501-1500 grams will have RDS. Respiratory distress is described as any signs of breathing difficulties in neonates [9]. Clinical signs of respiratory distress in infants include tachypnea, audible grunting cyanosis, nasal flaring, intercostal or subcostal retractions requiring respiratory support.

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In case of improper treatment, it may lead to the death of the baby due to insufficient gas exchange, pneumothorax, and emphysema, as well as lung bleeding, and bleeding inside the ventricles of the brain [9], thus oxygenation, ventilation, and surfactant replacement are among intervention used for such patients.

Premature birth represents a significant burden on the health care of any country and is one of the main causes of infant mortality and long-term complications in these infants; therefore, prevention of diseases related to prematurity should be considered as a health priority. The number of premature babies who survive is likely to increase in the coming years; therefore, it is expected that the frequency of babies with respiratory complications such as chronic lung disease (i.e., BPD) will also have an upward trend.

To reduce lung damage and disease associated with prematurity, pediatric specialists have focused on non-invasive ventilation methods in the first minutes of life. International guidelines have advocated non-invasive ventilation methods for these infants. Nowadays, strategies have been used to improve the success rate of non-invasive ventilation in infants with apnea of prematurity (AOP).

However, non-invasive methods are usually not effective and fail in 50% of cases in premature babies with very low weight, the most common cause of which is the insufficiency of the respiratory system. Therefore, apnea is a recognized challenge in preterm infants and a major cause of the need for invasive ventilation. Since the 1970s, methylxanthines have been routinely prescribed in preterm infants to prevent apnea of prematurity and to reduce the need for invasive ventilatory support. Among the methylxanthines, caffeine Citrate is the drug of choice due to its longer half-life, better tolerability, wider therapeutic index, cost-effectiveness, lack of serious side effects and reduced need for drug level monitoring compared to other methylxanthines, especially theophylline. However, the optimal dose of caffeine administration and therapeutic drug monitoring (TDM) in premature babies are controversial [9-14].

It has been hypothesized that caffeine is capable of stimulating the central nervous system to increase breathing due to the increase of carbon dioxide in the blood and has a direct effect on the contractile activity of the diaphragm [6]. A number of studies have also shown that caffeine consumption in preterm infants may have a neuroprotective effect, although research in animal models has shown conflicting results, possibly influenced by animal species, caffeine dose used, neurodevelopmental stage at the time of administration and duration of drug exposure [11,15]

Available evidence suggests that high-dose caffeine may have other benefits, including reduced risk of BPD and reduced extubation failure [12,16]. The effects of caffeine for the treatment of apnea in premature infants have been well established over the past few years. However, to date there is no agreed standard protocol regarding the optimal dose and timing of caffeine therapy in infants. Therefore, this clinical trial was aimed at investigating the effect of caffeine with a low maintenance dose compared to a high dose on respiratory function in premature infants.

## MATERIAL AND METHODS

### Ethical considerations

This study was carried out in coordination with the University of Medical Sciences. Informed consent was obtained from the parents of the patients before participating in the study. Additional costs were not imposed on patients. The data of the study was collected without individual characteristics and the results were announced in general. The study was registered in the Iranian Clinical Trial Center (IRCT20160523028008N17).

### Study design

This clinical trial was conducted on 60 premature infants of ≤34 weeks suffering from RDS who were admitted to Fatemieh Hospital in the period of 2021-2022. The sample size was based on the formula of comparing two ratios (frequency of extubation failure in two groups) and the study of Charles et al. (2008) [17]. Considering the test power of 80% and the first type error equal to 0.05, 30 premature infants in each group (total of 60 babies) were calculated.

Inclusion criteria included premature babies with a gestational age of ≤34 weeks who were admitted to the hospital's NICU. Exclusion criteria were major congenital anomaly, congenital heart disease, infants with asphyxia and tachycardia, sepsis.

Based on ultrasound findings and a detailed history of the mother, the infants who were admitted to the NICU department were included in the study by Consecutive Sampling, and were randomly divided into two groups. On the first day after birth, the first group of infants received an initial caffeine loading dose of 20 mg/kg and then a maintenance dose of 10 mg/kg intravenously. The second group received an initial caffeine loading dose of 20 mg/kg and then a maintenance dose of 5 mg/kg intravenously.

Babies of both groups were subjected to cardiopulmonary monitoring, control of heart rate and O2 saturation. Furthermore, required information such as age of delivery, sex, type of delivery, average Apgar score of 1 and 5 minutes, number of days requiring oxygen, extubation failure, BPD, Severe Intraventricular Haemorrhage, tachycardia, length of hospitalization, apnea, retinopathy, PDA, number of days requiring mechanical ventilation or Continuous positive airway

pressure (CPAP) or the need for supplemental oxygen were recorded and compared in both groups.

### Randomization method

In this study, the participants in the research were randomized using a computer and the website (http://www.randomization.com). The outcome assessor and the researcher were unaware of who received which medicine until the end of the study. Therefore, the study was conducted in a double-blind manner.

### Statistical analysis

After collecting the data, the data was entered into the statistical software SPSS version 16 and analyzed. Mean and standard deviation were used to describe quantitative data, and median, interquartile range, ratios and percentages were used to describe qualitative data. Chi-square tests or Fisher's exact test were used to compare nominal or rank quality results in two groups with high dose and low dose. Comparison of quantitative data was done using Student's t-test for normally distributed variables, and non-parametric Mann-Whitney test was used if the data was not normal. Frequency distribution was used to determine the distribution of variables. P<0.05 was considered to be statistically significant.

## RESULTS

In this clinical trial, 60 infants were randomly and equally assigned to two intervention groups (high and low dose caffeine). On average, the two groups had a gestational age of 30 weeks. Most of the babies were male and were born by cesarean section. Most of the babies had received steroids before birth. Babies had low birth weight, and both groups had no statistically significant differences in terms of the studied variables. Other information is shown in Table 1.

**Table 1: Comparison of baseline variables and clinical status in two intervention groups**

| Variable | , n= 30 Low | High, n= 30 | P-value |
|---|---|---|---|
| Gestational age (weeks) ، Mean ± SD | 30/1 ± 2/1 | 29/8 ±2/8 | 0*/858 |
| Birth weight (grams) ،Mean ± SD | 1343/3 ±392/29 | 1286/7 ±369/8 | *0/441 |
| Mother's age (years) ،Mean ± SD | 29/6 ± 4/4 | 27/8 ± 4/5 | *0/063 |
| Apgar first minute ، Mean ± SD | 6/0 ± 1/2 | 5/9 ± 1/9 | *0/716 |
| Apgar minute 5 ،Mean ± SD | 7/4 ± 1/1 | 7/9 ± 1/2 | *0/168 |
| gender (male); frequency (percentage) | (56/7) 17 | (53/3) 16 | †0/795 |
| perform cesarean section; frequency (percentage) | (73/3) 22 | (66/7) 20 | †0/573 |
| Prenatal steroid intake, frequency (percentage) | (73/3) 22 | (70/0) 21 | † 1/00 |
| Surfactant injection, frequency (percentage) | (66/7) 20 | (73/3) 22 | †0/573 |
| Maternal underlying disease, frequency (percentage) | | | |
| No | (60/0) 18 | (50/0) 15 | † 0 /501 |
| Gestational Diabetes | (13/3) 4 | (20/0) 6 | |
| Preeclampsia | (20/0) 6 | (13/3) 4 | |
| Hypothyroidism | (6/7) 2 | (16/6) 5 | |

Not: *: Mann-Whitney, †: chi2 or fisher exact

The average duration of hospitalization, the number of days requiring mechanical ventilation, NCPAP, and the days requiring supplemental oxygen were lower in the group of infants receiving a high dose of caffeine, and the difference between the two groups in terms of the number of days requiring mechanical ventilation, NCPAP was statistically significant. The frequency of apnea was lower in the high dose caffeine group, when a statistically significant difference was found (Table 2). Hospitalization duration in neonatal intensive care unit in two groups is shown in figure 1.

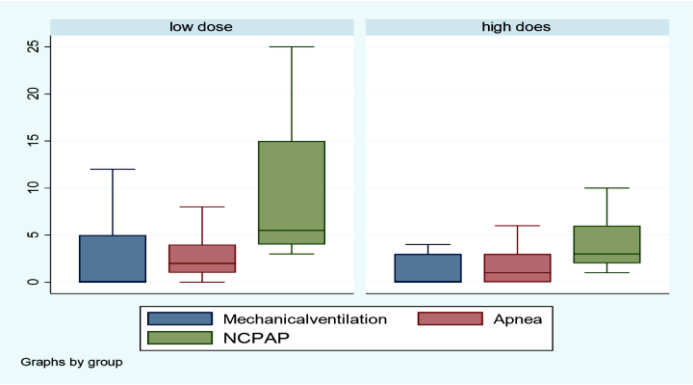


**Figure 1: Box plot diagram of hospitalization duration in neonatal intensive care unit in two groups**

**Table 2: Comparison of quantitative outcomes in two study groups**

| Variable | ,n= 30 Low | High,n= 30 | P(Mann-Whitney) |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Length of hospitalization (days) | 35/5 ± 24/5 | 24/4 ±13/0 | 0/167 |
| Need for mechanical ventilation (day) | 6/4± 2/8 | 3/5± 0/5 | 0/001 |
| Duration of NCPAP (days) | 8/2 ± 6/3 | 4/3± 2/7 | 0/001 |
| Number of days requiring supplemental oxygen | 10/7 ± 9/5 | 7/7 ± 7/4 | 0/06 |
| Number of apneas | 2/7± 2/4 | 6± 1/91/ | 0/022 |

The incidence of extubation failure in the high dose group was significantly lower than the low dose group. Other complications were less frequent, except for tachycardia, which was more common in the high dose group (Table 3).

**Table 3: Comparison of qualitative outcomes in two study groups**

| Variable | ,n= 30 Low | High, n= 30 | P(Fisher's exact ) |
|---|---|---|---|
| | Frequency (%) | Frequency (%) | |
| Bronchopulmonary dysplasia | (20/0) 6 | (16/7) 5 | 1/00 |
| Retinopathy | (13/3) 4 | (10/0) 3 | 1/00 |
| Failure to extubate | (36/7) 11 | (13/3) 4 | 0/037 |
| tachycardia | (13/3) 4 | (23/3) 7 | 0/317 |
| Intraventricular hemorrhage | (13/3) 4 | (10/0) 3 | 1/00 |
| PDA | (26/7)8 | (20/0)6 | 0/542 |

## DISCUSSION

Several interventions such as continuous positive airway pressure and pharmacologic therapies (i.e., methylxanthines have been applied to decrease apneic event and its duration [18]. For more than 4 decades, methylxanthines have been used in premature infants as a pharmacological method to reduce the risk of apnea. The results of the studies demonstrated that caffeine citrate is more effective in reducing respiratory complications and improving the outcome of these children compared to placebo in premature babies. This drug is one of the most effective and widely used drugs in these patients due to its efficacy, proper intestinal absorption, tolerability, wider therapeutic index, longer half-life, low cost, and lack of significant side effects [11,19].

However, there is still a difference of opinion regarding the optimal dose of caffeine administration [11] and TDM [14]. Based on the findings presented herein, a higher dose of caffeine compared to a lower dose had better short-term outcomes in premature infants with a gestational age of ≤ 34 weeks who required hospitalization in the intensive care unit due to respiratory problems. Many studies have reported effectiveness of higher doses of caffeine with negligible adverse effects in decreasing episodes of apnea and decreasing extubation failure rates [20,21].

Some meta-analyses reported that higher caffeine dosage regimens could reduce the risk of BPD and extubation failure [22-25]. A meta-analysis conducted by Vliegenthart et al. (2018) reviewed 6 clinical trial studies consisting of a population of 620 infants< 32 weeks of gestational age who received a high dose of caffeine compared to a standard dose [26]. Their findings demonstrated that infants who received high doses of caffeine had lower rates of BPD and BPD-related mortality and extubation failure. However, the authors stated that it is not possible to comment with certainty regarding the appropriate dose due to the low quality of the studies conducted. In addition, a high dose is associated with a reduction in the risk of extubation failure, a decrease in apnea frequency, and a reduction in the risk of lung dysplasia. A decrease in apnea frequency and a shortened duration of mechanical ventilation have been reported by Brattstrom et al. (2019) [25].

Based on the findings of the meta-analysis study by Pakvasa et al. (2018), early initiation of caffeine treatment and higher doses can reduce the risk of BPD in premature infants [23]. Brattstrom et al. (2019) examined high and low doses of caffeine in premature infants in 6 studies with a population of 816 individuals [25]. The initial dose varied from 20 to 80 mg and the maintenance dose from 3 to 20 mg. Higher doses did not affect the mortality rate of patients, however, it caused a decrease in extubation failure, apnea and pulmonary dysplasia, and caused a shorter time of mechanical ventilation. However, it cannot be said that high doses are more effective and safer than low doses due to the low quality of the studies.

Saroha et al., reported that a higher dose of caffeine may reduce the risk of BPD and less failure of extubation compared to a standard dose adapted to the age of infants; however, side effects such as cerebral palsy and convulsions should not be ignored in these babies [13]. In the clinical trial studies conducted with different designs, the effect of caffeine in premature babies has been associated with different results. The results of aforementioned study showed that the high dose was associated with a lower risk of tracheal extubation failure in mechanically ventilated patients and a significant increase in tachycardia episodes. The frequency of apnea and the number of days of apnea were lower in high-dose patients, when a statistically significant difference was found. In line with our findings, meta-analyses reported higher risk of tachycardia with higher dose of caffeine, [22,23], which was not an obstacle to the use of caffeine.

The findings of Zaho et al., revealed that patients receiving a higher dose had a lower rate of apnea (10 [8, 15] vs. 18 [13, 22], Z = -2.610, P = 0.009), more rate of isolation from mechanical ventilation (80 vs. 70% P=0.015) and more healing

rate (85 vs. 70% P=0.003) [20]. In terms of side effects, the two groups were comparable as in the present study. Several findings demonstrated the benefits of higher doses of caffeine for VLBW preterm infants (better neurodevelopmental). A maintenance dose as high as 10 mg/kg better has been reported to be capable of reducing the duration of apnea and caffeine treatment in this population [27].

A pilot RCT reported that a higher-dose caffeine citrate (loading 80 mg/kg) was associated with an increased incidence of cerebellar hemorrhage (CBH) in infants < 31 weeks' gestation [28]. Early high-dose caffeine has been linked to an increase in seizure incidence (40 vs 58%, p = 0.1) and burden (48.9 vs 170.9, p = 0.1) [29]. However, there are still not enough studies related to its long-term complications. Certainty in the use of higher dose caffeine regimens and how to optimize the dose of caffeine is still questionable.

In the current study, the short-term effect of caffeine was investigated until the time the infants were in the hospital, and the long-term effect on the nervous system and other outcomes in the infants was not measured. Additionally, the small number of examined patients was another limitation of the study. Comprehensive multicenter studies and longer follow-up of patients are needed to obtain definitive results

## CONCLUSION

Based on the results presented herein, caffeine with a higher maintenance dose can have a better short-term outcome in premature babies_ < 34 weeks. A higher dose was not associated with clinically significant complications.

## CONFLICT OF INTEREST

None

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