ORIGINAL ARTICLE

The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the neonatal intensive care unit of Shahid Motahhari Hospital, Urmia, during a year

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ABSTRACT

Due to the importance of prevention of apnea of prematurity in the very preterm infants and the side effects of using methylxanthines in preterm infants, the present study was conducted and aimed at investigating the effects of prophylactic caffeine on the incident of apnea (short-term consequence). This is a clinical–experimental trial, in which the infants were included after receiving written consent from their parents. The infants were randomly divided into two groups, namely, Group A (receive caffeine) and Group B (did not receive caffeine). After sampling of the collected data, the two groups were analyzed using statistical tests using SPSS software 23. Among the 50 infants in the caffeine group and 50 infants in the control group, 1 (2%) and 2 (4%) infants required long-term oxygen, respectively. Three (6%) infants from the caffeine group and 2 (4%) infants from the control group had an intraventricular hemorrhage. Two (4%) infants from the caffeine group and 1 (2%) infant from the control group had a positive patent ductus arteriosus and needed treatment. Among the 50 infants in the caffeine group and 50 infants in the control group, 7 (14%) and 9 (18%) infants had apnea, respectively. According to the Fisher's exact test, there was no significant difference between the incident of apnea in the two groups ($P = 0.58$). Ten (20%) infants from the caffeine group and 7 (14%) infants from the control group died. The prescription of prophylactic caffeine had no effect on the incident of apnea in the infants. Hence, the use of that should be limited to the preterm infants lower than 1250 g in the prophylactic form.

Key words: Apnea, methylxanthines, very-low-birthweight infants

INTRODUCTION

In general, mortality of the preterm infants, especially the low-weight infants, is more than the normal infants, and these infants are prone to different kinds of short- and long-term diseases after birth.[1] Apnea of prematurity is one of the problems with which the very preterm infants face.[2] Experts have not still achieved a joint conclusion about the prevention and treatment of apnea; there are many uncertainties up to the present time.[3] Methylxanthines such as caffeine, theophylline, and aminophylline are considered as the major treatments of apnea through nasal continuous positive

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airway pressure (CPAP); however, dose, usage period, and the long-term complications of using these strategies have not been still exactly specified.[4] Treatment with methylxanthines is used for the prevention of the following attacks of apnea in the preterm infants with apnea.[5] Methylxanthines improve the lung mechanics by increasing minute ventilation, reducing the respiratory depression caused by hypoxia, increasing the brainstorm sensitivity to the density of the blood carbon dioxide, improving the contraction and activity of diaphragm and bronchodilation, and reducing the periodic breathing.[2,6] Hydrophobic properties of caffeine let it easily pass through all biological membranes such as the blood–brain barrier and enter central nervous system (CNS).[4] The ability of methylxanthines regarding the competitiveness of the adenosine receptors in CNS is a mechanism that stimulates respiratory rhythm by these factors. A secondary mechanism may also occur by the effects of methylxanthines on gamma-aminobutyric acid receptors, phosphodiesterase inhibition, and calcium release (Ca^{2+}).[7] The objective of the present study was to determine the effect of the venous caffeine on the prevention of apnea of prematurity.

MATERIALS AND METHODS

This study is a clinical–experimental trial that was conducted on the very preterm infants with a gestational age ≤32 weeks and a birthweight ≤1500 g in the Neonatal Intensive Care Unit (NICU) Department of Shahid Motahhari Hospital, Urmia. The infants were included in the study after receiving written consent from their parents. They were randomly divided into two groups, namely, Group A and Group B. 20 mg/kg of venous caffeine was injected to Group A in the 2nd day of birth (24–48 h). Then, a maintenance dose was injected 24 h after the first injection with the daily dose of 5 mg/kg. Group B did not receive caffeine. The infants were taken under cardiovascular-pulmonary monitoring, control of the number of heartbeats and number of breaths, and the control of arterial oxygen saturation. Due to the effectiveness of the birthweight on the study consequences, the patients were divided into three groups (<1000 g, 1000–1249 g, and 1250–1500 g) regarding the birthweight. After sampling of the collected data, the two groups were analyzed by the statistical tests using SPSS 23, IBM SPSS Statistics for Windows (IBM SPSS, Armonk, NY, USA).

RESULTS

In this study, 100 very preterm infants hospitalized in the NICU Department of Shahid Motahhari Hospital, Urmia, were included in the study with a weight of 1228.80 ± 22.26 g (with a minimum of 600 and maximum of 1500 and the weight median of 600 g). They were divided into two groups: caffeine and control groups (50 infants in each group). The average gestational age was 29.21 ± 0.11 weeks, and the average Apgar score was 6.23 ± 0.11 weeks. Among 100 infants of the study, 52 (52%) were female and 48 (48%) were male. Twenty-seven (27%) and 73 (73%) infants were born through natural delivery and cesarean, respectively. Among the infants of the caffeine group, 11 (22%) infants weighed <1000 g, 15 (30%) weighed between 1000 and 1249 g, and 24 (48%) weighed between 1250 and 1500 g. Among the infants of the control group, 4 (8%) infants weighed <1000 g, 17 (34%) weighed between 1000 and 1249 g, and 29 (58%) weighed between 1250 and 1500 g. According to the Chi-square test, there was no significant difference between the weight of the infants in the two groups ($P = 0.14$). The average weights in the caffeine and control groups were 1192.0 ± 249.61 g and 1265.50 ± 187.32 g, respectively. According to the *t*-test, there was no significant difference between the average weight in the two groups ($P = 0.09$). The average gestational ages in the caffeine and control groups were 29.04 ± 1.30 and 29.38 ± 1.0 weeks, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the gestational age ($P = 0.14$). The average Apgar score in the caffeine and control groups were 6.14 ± 1041 and 6.32 ± 0.81, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the Apgar score ($P = 0.45$). Among 50 infants of the caffeine group, 27 (54%) were female and 23 (46%) were male. Among 50 infants of the control group, 25 (50%) were female and 25 (50%) were male. According to the Chi-square test, there was no significant relationship between the two groups in terms of the patients' gender ($P = 0.68$). Among 50 infants in the caffeine group, 14 (28%) and 36 (72%) were born through natural delivery and cesarean, respectively. Among 50 infants in the control group, 13 (26%) and 37 (74%) were born through natural delivery and cesarean, respectively. According to the Chi-square test, there was no significant difference between the two groups in terms of the infants' type of birth ($P = 0.77$). The average respiratory distress syndrome (RDS) score in the caffeine and control groups were 5.58 ± 0.97 and 5.34 ± 1.13, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of RDS score ($P = 0.25$). Among 100 infants of the study, 55 (55%) received surfactant and 45 (45%) did not receive it. Among 50 infants in the caffeine group, 31 (62%) received surfactant and 19 (38%) did not receive surfactant. Among 50 infants in the control group, 24 (48%) received surfactant and 26 (52%) did not receive surfactant. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the use of surfactant ($P = 0.14$). In the caffeine and control groups, 7 (14%) and 9 (18%) infants had apnea, respectively. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the incident of apnea ($P = 0.58$). In the caffeine (50 infants) and control (50 infants) groups, 9 (18%) and 9 (18%) infants had bradycardia (the heart rate <100 beats per minute), respectively. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the incident of bradycardia ($P = 1$).

In the caffeine (50 infants) and control (50 infants) groups, 10 (20%) (<85%) and 10 (20%) infants had saturation decline. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the incident of saturation decline (P = 0.1). Among 50 infants of the caffeine group, 19 (38%) needed environmental oxygen and 31 (62%) did not need environmental oxygen. Among 50 infants of the control group, 11 (22%) needed environmental oxygen and 39 (78%) did not need environmental oxygen. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the need for environmental oxygen (P = 0.08). Among 50 infants of the caffeine group, 38 (76%) needed a headbox and 12 (24%) did not need an oxygen headbox. Among 50 infants of the control group, 42 (84%) infants needed a headbox and 8 (16%) infants did not need an oxygen headbox. According to the Chi-square test, there was no significant difference between the two groups in terms of the need for the oxygen head (P = 0.31). In the caffeine (50 infants) and control (50 infants) groups, 43 (86%) and 37 (74%) infants needed NCPAP, respectively. According to the Chi-square test, there was no significant difference between the two groups in terms of the need for NCPAP (P = 0.13). In the caffeine (50 infants) and control (50 infants) groups, 7 (14%) and 4 (8%) infants needed a medical ventilator, respectively. According to the Chi-square test, there was no significant difference between the two groups in terms of the need for a medical ventilator (P = 0.33). The average days of the need for environmental oxygen in the caffeine and control groups were 7.13 ± 3.12 and 6.77 ± 3.32, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the need for environmental oxygen (P = 0.64). The average days of the need for a headbox in the caffeine and control groups were 3.79 ± 2.62 and 3.28 ± 2.78, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the need for a headbox (P = 0.4). The average days of the need for NCPAP in the caffeine and control groups were 3.81 ± 2.34 and 3.43 ± 2.56, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the need for NCPAP (P = 0.48). The average need for mechanical ventilation in the caffeine and control groups was 4 ± 3 and 4.50 ± 5.06 days, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the duration of mechanical ventilation (P = 0.83). The average hospitalization period in the caffeine and control groups was 13.88 ± 6.74 and 15.72 ± 10.23, respectively. According to the *t*-test, there was a significant difference between the two groups in terms of the hospitalization period (P = 0.02) [Table 1].

Table 1: Comparison of the mean and standard deviation of the need for environmental oxygen, headbox, nasal continuous positive airway pressure, mechanical ventilation, and the hospitalization period in the two groups

Variable	Caffeine group	Control group	*P*
Need for environmental oxygen	7.13±3.12	6.77±3.32	0.64
Need for headbox	3.79±2.62	3.28±2.78	0.4
Need for NCPAP	3.81±2.34	3.43±2.56	0.48
Need for mechanical ventilation	4±3	4.50±5.06	0.83
Hospitalization period	13.88±6.74	15.72±10.23	0.02

NCPAP: Nasal continuous positive airway pressure

In the caffeine (50 infants) and control (50 infants) groups, 3 (6%) and 2 (4%) infants had positive intraventricular hemorrhage (IVH), respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of IVH (P = 0.81). In the caffeine (50 infants) and control (50 infants) groups, 2 (4%) and 1 (2%) infant had positive patent ductus arteriosus (PDA) and needed treatment, respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of PDA (P = 0.55). In the caffeine (50 infants) and control (50 infants) groups, 1 (2%) and 2 (4%) infants needed to receive long-term oxygen, respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of the need to receive long-term oxygen (P = 0.55). Ten (20%) and 7 (14%) infants in the caffeine and control groups died, respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of the infants' consequence (P = 0.42).

DISCUSSION

Caffeine is extensively used for the treatment of apnea; it stimulates the respiratory system and improves the function of the respiratory muscles.[8] The present study was a randomized control trial research in a health center that was conducted on the very preterm infants with a weight <1500 g and the gestational age of <32 weeks. The results of the study did not indicate a significant difference in the two groups of control and intervention (caffeine citrate injection) during hospitalization in terms of the incident rate of apnea, hypoxia, and bradycardia. The results of the studies of Schmidt *et al*.[9] showed that prophylactic caffeine significantly reduced apnea and the chronic lung disease (CLD). They mentioned the reason for the reduction as the reduced time of the need for oxygen, CPAP, and mechanical ventilation in the infants receiving prophylactic caffeine. In the present study, there was no difference between the two groups in terms of the time needed for complementary oxygen, NCPAP, and mechanical ventilation; as such, there was not also any difference between the two groups in terms of CLD. In the caffeine group, an infant was affected by a severe CLD, hospitalized for approximately 2 months, and discharged after recovery. Maybe, the difference between the present study and that of Schmidt *et al*. known as CAP Trial is the small sample

size of the first and the very large sample size as well as the multicentric study of the latter. Moreover, the infants of the present study were <1500 g and they were heavier than the infants in the study of Schmidt *et al*.[9] Furthermore, this study recommends not using methylxanthines in the prophylactic way for the infants in the weight range of 1250–1500 g; the use of prophylactic should be limited to the infants who are <1250 g. In the present study, there was no difference in terms of the need for environmental oxygen, NCPAP, mechanical ventilation, and the usage period. Besides, there was no difference in terms of the incident of complications such as CLD, PDA, and IVH. Zhao *et al*.[10] conducted a study and showed that there is no difference between the two groups who received high- and low-dose caffeine in terms of the incident of the complications due to caffeine such as tachycardia, irritability, problem in feeding, hyperglycemia, high blood pressure, digestive disorders, and electrolyte disorders. Lodha *et al*.[11] conducted a study and the results indicated that, in the infants who received caffeine in the first 3 days of their life, their CLD and PDA significantly decreased compared to the group that received caffeine after 72 h. There was a difference between the two groups in terms of the hospitalization period. The infants who received caffeine had a lower hospitalization period; this may be because caffeine is a stimulating drug and makes the infants more conscious and results in better feeding. However, the study of Schmidt *et al*. showed that the caffeine group had a lower weight in the first 3 weeks compared to the placebo group.[10]

CONCLUSION

The prescription of prophylactic caffeine had no effect on the incident of apnea in the infants. Regarding the fact that the drug may cause some side effects and influence the infant weight, the use of that should be limited to the preterm infants with lower weights in the prophylactic form; it can be therapeutically used for the infants with higher weights in the case of apnea.

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Conflicts of interest

There are no conflicts of interest.

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