Original Article

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TANAFFOS

Effect of Oral Caffeine on Weaning from Mechanical Ventilation in Intubated ICU Patients

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Background: The role of caffeine as a brain stimulant in improving the respiratory characteristics of patients under mechanical ventilation is unclear. This study aimed at determining the effect of oral caffeine in helping to release (Liberation) from the ventilator in intubated patients under mechanical ventilation admitted to the intensive care unit.

Materials and Methods: General ICU patients with more than 48 hours of dependency on a ventilator were randomly divided into two groups. The intervention group received 200mg caffeine tablets twice a day through a gastric tube, while the control group received a placebo of the same amount. Every day, patients were assessed for the likelihood of being disconnected from the device. If their clinical condition was deemed suitable, the device mode was switched to spontaneous, and their Rapid Shallow Breathing Index (RSBI) was calculated. Based on this information, a decision was made regarding whether to proceed with weaning.

Results: Caffeine use in ICU patients significantly reduced the airway resistance index of patients ($P < 0.05$). However, although this drug reduced the length of hospital stay in the ICU and the duration of intubation of patients, these changes were not statistically significant ($P > 0.05$).

Conclusion: Caffeine may improve respiratory status and reduce the duration of intubation and hospitalization in the ICU.

Keywords: Caffeine; intubation; ICU; Respiratory system; Mechanical ventilator

INTRODUCTION

Mechanical ventilation in intensive care units is one of the primary measures in patient cares in situations such as emergencies and dysfunction of vital organs, especially respiratory disorders (1). While mechanical ventilation can be life-saving for patients, it also has the potential to cause various physical and psychological complications and stress (2). It is recommended to start preparing for the patient's removal from the ventilator as soon as they start receiving mechanical ventilation (3). On the other hand, the lack of equipped beds in intensive care units and mechanical ventilation facilities in hospitals, especially in developing countries, has been an essential daily issue in the intensive care system (4). It is important to note that 3-10% of ICU patients require long-term mechanical ventilation, accounting for 37-40% of ICU resources (5).

Successful isolation of patients from mechanical ventilation depends on several factors such as age, lack of underlying disease, nutritional status, muscle strength, and lung function (6,7). One reason for the delay in the process

of separating from mechanical ventilation is due to a lack of awareness and attention to the predictable characteristics of the separator (8). When attempting to separate from mechanical ventilation, certain parameters are important to consider. These include arterial blood gases, maximum inspiratory force, current volume, minute ventilation, and respiratory rate. These factors can all impact the success of separating from mechanical ventilation (9-11).

Proper nutrition is one way to improve isolation parameters for patients. Nutritious food can strengthen the immune system and respiratory muscles (12). Tea and caffeinated foods are commonly consumed in many countries, particularly in Iranian culture. It is notable that the average daily consumption of these products is approximately 3 mg/kg among adults in the United States, 4 mg/kg in the United Kingdom, and 7 mg/kg in Denmark (13-15).

The primary source of caffeine among various foods is coffee beans (16). After caffeine is taken orally, it is rapidly and almost entirely (99%) absorbed into the bloodstream through the digestive system, penetrates quickly into the brain, and reaches its peak plasma concentration in approximately 30 to 60 minutes after ingestion (17). This alkaloid belongs to the methyl family of xanthine which is similar to theophylline and theobromine. Methylxanthines, including theophylline and caffeine, have many benefits including increasing respiratory center stimulation and increasing the ability of respiratory muscles to contract (18). In the human infant, methylxanthines including caffeine are used to prevent and treat apnea and safe removal of the endotracheal tube, increase minute ventilation, and improve system capacity. It also improves respiratory effort and reduces diaphragmatic fatigue. Early initiation of caffeine use is associated with a reduction in the duration of mechanical ventilation and an improvement in short-term pulmonary outcomes (19-21). Studies have shown the anti-inflammatory and stimulant properties of caffeine urine (22). Caffeine has also been shown to reduce neonatal endotracheal failure (23), reduce neonatal cardiomyopathy (24), and prevent intermittent neonatal hypoxia.

This study investigates the effect of oral caffeine in helping to separate the intubated patient from the ventilator.

MATERIALS AND METHODS

The present double-blind clinical trial study has been registered (Registration number: IRCT20210110049990N2) and approved by the ethics committee in biomedical research of Shahid Beheshti University of Medical Sciences with code number: IR.SBMU.RETECH.REC.1400.515. Patients admitted to the general ICU of Imam Hossein Hospital in Tehran were included in the survey if they met the inclusion criteria (18<Age< 80, written consent to participate in the study, intubated patients in the general ICU who are expected to be dependent on a ventilator for more than 48 hours). Also, excluded criteria were: myopathy, ischemic heart problems, cardiac arrhythmia, neurosurgery patients, caffeine sensitivity, defect inpatient record, and dissatisfaction. Patients were enrolled after providing full explanations and obtaining written consent. The research physicians were blinded to the patient group, and the patients were blinded to the drug (double-blind). In the end, 70 patients were included in the study and randomly divided into two groups: intervention and control (Figure 1).

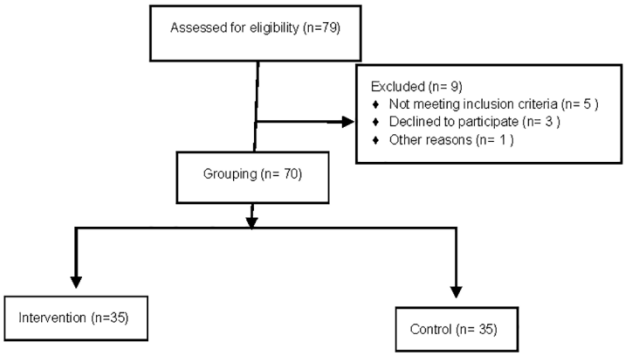

Figure 1. Consort diagram

In the intervention group, a dose of 200 mg caffeine (From Karen Pharmaceutical co) was given to patients

every 12 hours for 5 days, through the gastric tube. In the control group, placebo capsules were administered precisely same as the above intervals. Then, variables were measured during the study period. All statistical analysis performed with a level of significant 0.05 using Stata software (Version 17.0, StataCorp, College Station, Texas, USA).

RESULTS

A total of 79 patients participated in the study between 20 August 2019 and 20 August 2020. Of whom, 70 (78.65%) with an average age of 70.85 years, provided complete data on variables included in the present analyses. According to Table 1, 52 (74.28%) of all individuals were men and 18 (25.71%) were women. No significant difference was observed between the two groups regarding their demographic data (p>0.05) (Table 1).

Table 1. Evaluation of the demographic conditions of the patients

INDEXES	Control	Intervention	P-Value
Age (year) (m± SD)	69.2±15.0	72.51±16.0	0.4702
Gender (Male) (n)	27(77.14%)	25(71.42%)	0.137
Height (m± SD)	172.43±57.19	174.01±58.09	0.137
Weight (m± SD)	73.63±31.05	71.84±29.23	0.093
Tobacco (n)	24 (68.57%)	6 (42.85%)	0.069
Opium (n)	2 (5.71%)	1 (2.85%)	0.064
APACHE 2 score (m± SD)	9.89±4.23	9.21±4.18	0.107

Accordingly, 29.33% of patients had a history of COPD. However, asthma, bronchiectasis, pneumonia, and atelectasis were the most common underlying diseases. No significant difference was observed between the two groups in this regard (p>0.05) (Figure 2).

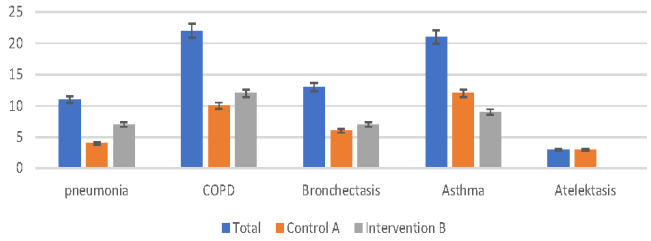

Figure 2. Evaluation and comparison of factors causing ICU hospitalization in patients

Based on the results in Table 2, RR (respiratory rate), EX-V (expiratory volume), VT (tidal volume), peak pressure, and plateau pressure were evaluated in two groups. No noticeable changes were seen (P> 0.05) (Table 2).

Table 2. Evaluation and comparison of assessment indicators of respiratory status and hemodynamic indicators in the patients

Indexes	Control (m± SD)	Intervention (m± SD)	P-Value
RR	19.75±3.9	20.51±3.5	0.595
EX V	0.51±0.09	0.48±0.1	0.093
VT	476.21±98.24	474.44±103.71	0.168
Peak pressure	22.94±9.21	23.33±8.96	0.127
Plateau pressure	19.59±6.71	20.03±11.03	0.100

Based on the results in Table 3, respiratory indicators are shown during day 1, day 2, day 3, and day 4 of intubation in two groups. The airway resistance index in the intervention group decreased significantly over time (day 2, day3, and day4) (P <0.05). Other indicator did not show a significant change over time (Table 3).

Table 3. Comparison of indicators of respiratory and hemodynamic status in patients using ANOVA test

	Control	Intervention	P-value
RSBI			
1	40.6(19.00)	42.77(21.30)	0.184
2	39.33(18.97)	41.50(21.10)	0.161
3	37.71(18.26)	40.84(19.97)	0.083
4	37.05(19.07)	38.19(19.23)	0.235
PEEF			
1	5.62(1.26)	5.51(1.93)	0.315
2	5.13(1.61)	5.03(1.29)	0.130
3	4.18(1.07)	4.03(1.01)	0.090
4	3.45(0.98)	3.37(0.86)	0.187
PSUPP			
1	13.37(4.23)	12.96(6.70)	0.185
2	12.40(5.01)	12.22(4.8)	0.301
3	11.43(4.25)	11.33(4.61)	0.470
4	10.54(4.02)	10.44(3.98)	0.410
Compliance			
1	34.62(17.23)	33.31(17.01)	0.260
2	36.30(18.73)	35.67(17.90)	0.198
3	36.71(17.84)	35.88(18)	0.183
4	41.180(19.34)	38.08(17.25)	0.062
Airway resistance			
1	0.05(0.01)	0.05(0.01)	0.823
2	0.15(0.08)	0.04(0.01)	0.037
3	0.09(0.02)	0.03(0.00)	0.049*
4	0.10(0.07)	0.04(0.00)	0.049*

According to the results in Figure 3, the patients in the intervention group underwent intubation for an average of 9.92 days and were hospitalized in the ICU for 15.33 days, while the duration of intubation for patients in the control group was 10.64 days and the time of ICU stay was 15.62 days.

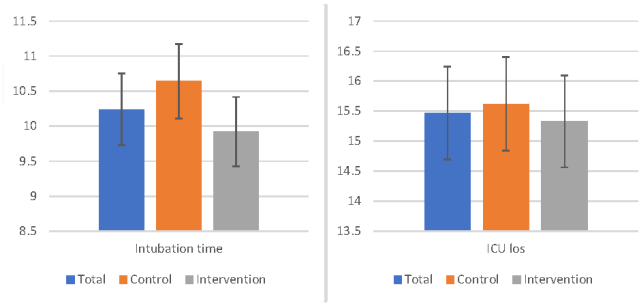

Figure 3. Comparison of hospitalization and intubation duration in the ICU patients

DISCUSSION

This randomized trial evaluated the effect of oral caffeine administration on the duration of mechanical ventilation. According to the results of the present study, the airway resistance index in patients receiving caffeine has significantly decreased. On the other hand, although the duration of ICU hospitalization and intubation duration in patients undergoing intervention did not change significantly, however, a decrease in the numerical average of these two indicators was observed in this group.

Many studies have shown that increasing the length of hospital stay and intubation of patients can be related to their mortality rate. A large retrospective cohort study also reported higher mortality in the group with late caffeine consumption (24). However, as noted by the authors of that study, this difference may be partly explained by the survival bias in the late caffeine group, i.e., although all patients in the primary group received caffeine, only those in the early days received caffeine after hospitalization survived. Late caffeine consumption is a standard procedure by prescribing caffeine bolus before intubation in most centers (25).

Chapman and Mickleborough have shown that the use of caffeine has increased athletes' precise ventilation at rest and in all types of exercise volumes (26). Also, as a result of this increase in ventilation, the amount of oxygen saturation in the blood has increased. Even in non-athlete studies, caffeine has been found to stimulate respiration by enhancing the sensitivity of environmental chemical receptors (27).

The effects of caffeine on improving asthma symptoms in adults have also been shown (28). According to the report of Hassanein et al., the oxygen saturation levels in the blood of neonates improved after receiving injectable caffeine. Additionally, this treatment was found to reduce the duration of their stay in the intensive care unit (29). In their study, Hoecker et al. found that when preterm infants began consuming caffeine, 6 out of 8 infants who were on mechanical ventilation were able to remove their endotracheal tube within 23 hours after consumption (30).

Studies have shown that caffeine is as effective as injecting theophylline or aminophylline in improving patients' breathing. But, it can be used safer and easier; it has even better healing properties. Therefore, it is preferred in the treatment of neonatal apnea (31,32).

In the present study, several respiratory characteristics were measured and the effect of caffeine on them was investigated. So, it is useful to study the effects of caffeine on more respiratory indicators and its subsequent consequences. It seems that more research is needed to investigate the effect of caffeine on respiratory characteristics and physical and mental conditions in patients with various disorders and to evaluate its consequences. Further research is also needed to ensure that caffeine consumption is safe in adult patients, especially those with mechanical ventilation hospitalized in the ICU.

CONCLUSION

The use of caffeine to decrease the duration of intubation in intensive care unit patients has shown some positive effects like reducing hospital stay and intubation time. However, these benefits were not significant enough. To improve outcomes, larger sample sizes and higher

doses of caffeine may be necessary, which could lead to better treatment protocols.

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Conflict of Interest

The authors declare there is no conflict of interest.

REFERENCES

1. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? ***Intensive Care Med*** 2004;30(6):1117-21.
2. Bunburaphong P, Riyagoon W, Ramdit W, Werawatganon T, Techapichetvanich K. Length of surgical intensive care unit stay and risk factors. ***J Med Assoc Thai*** 2001;84(8):1103-8.
3. Yang PH, Hung JY, Yang CJ, Tsai JR, Wang TH, Lee JC, et al. Successful weaning predictors in a respiratory care center in Taiwan. ***Kaohsiung J Med Sci*** 2008;24(2):85-91.
4. Esteban A, Alía I, Ibañez J, Benito S, Tobin MJ. Modes of mechanical ventilation and weaning. A national survey of Spanish hospitals. The Spanish Lung Failure Collaborative Group. ***Chest*** 1994;106(4):1188-93.
5. deBoisblanc MW, Goldman RK, Mayberry JC, Brand DM, Pangburn PD, Soifer BE, et al. Weaning injured patients with prolonged pulmonary failure from mechanical ventilation in a non-intensive care unit setting. ***J Trauma*** 2000;49(2):224-30; discussion 230-1.
6. Mahanes D, Lewis R. Weaning of the neurologically impaired patient. ***Crit Care Nurs Clin North Am*** 2004;16(3):387-93, ix.
7. Zhu L, Niu SF, Zhang SP, Xu XW, Li SQ, Li YQ, et al. A retrospective study on the treatment of patients with chronic obstructive pulmonary disease by face mask mechanical ventilation. ***Zhonghua Jie He He Hu Xi Za Zhi*** 2003;26(7): 407-10.
8. Pilcher DV, Bailey MJ, Treacher DF, Hamid S, Williams AJ, Davidson AC. Outcomes, cost and long term survival of patients referred to a regional weaning centre. ***Thorax*** 2005;60(3):187-92.
9. Carson SS, Bach PB, Brzozowski L, Leff A. Outcomes after long-term acute care. An analysis of 133 mechanically ventilated patients. ***Am J Respir Crit Care Med*** 1999;159(5 Pt 1):1568-73.
10. Datta D, Scalise P. Factors affecting weaning and survival outcomes in patients on prolonged mechanical ventilation. ***Chest*** 2005;128(4):369S.
11. Gracey DR, Hardy DC, Koenig GE. The chronic ventilator-dependent unit: a lower-cost alternative to intensive care. ***Mayo Clin Proc*** 2000;75(5):445-9.
12. Schönhofer B, Guo JJ, Suchi S, Köhler D, Lefering R. The use of APACHE II prognostic system in difficult-to-wean patients after long-term mechanical ventilation. ***Eur J Anaesthesiol*** 2004;21(7):558-65.
13. Jolliet P. Place de la ventilation non-invasive lors du sevrage de la ventilation mécanique [Role of noninvasiveness ventilation in the weaning phase of mechanical ventilation]. ***Schweiz Med Wochenschr*** 2000;130(50):1948-53.
14. Gursel G. Determinants of the length of mechanical ventilation in patients with COPD in the intensive care unit. ***Respiration*** 2005;72(1):61-7.
15. Arroliga A, Frutos-Vivar F, Hall J, Esteban A, Apezteguía C, Soto L, et al. Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. ***Chest*** 2005;128(2):496-506.
16. Barrientos-Vega R, Mar Sánchez-Soria M, Morales-García C, Robas-Gómez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. ***Crit Care Med*** 1997;25(1):33-40.
17. Todorova L, Temelkov A. Weaning from long-term mechanical ventilation: a nonpulmonary weaning index. ***J Clin Monit Comput*** 2004;18(4):275-81.
18. Weichelt U, Cay R, Schmitz T, Strauss E, Sifringer M, Bührer C, et al. Prevention of hyperoxia-mediated pulmonary inflammation in neonatal rats by caffeine. ***Eur Respir J*** 2013;41(4):966-73.
19. Nagatomo T, Jiménez J, Richter J, De Baere S, Vanoirbeek J, Naulaers G, et al. Caffeine Prevents Hyperoxia-Induced Functional and Structural Lung Damage in Preterm Rabbits. ***Neonatology*** 2016;109(4):274-81.

20. Köroğlu OA, MacFarlane PM, Balan KV, Zenebe WJ, Jafri A, Martin RJ, et al. Anti-inflammatory effect of caffeine is associated with improved lung function after lipopolysaccharide-induced amnionitis. ***Neonatology*** 2014;106(3):235-40.
21. Fehrholz M, Speer CP, Kunzmann S. Caffeine and rolipram affect Smad signalling and TGF-β1 stimulated CTGF and transgelin expression in lung epithelial cells. ***PLoS One*** 2014;9(5):e97357.
22. Aly H, Massaro AN, Patel K, El-Mohandes AA. Is it safer to intubate premature infants in the delivery room? ***Pediatrics*** 2005;115(6):1660-5.
23. Dargaville PA, Aiyappan A, De Paoli AG, Dalton RG, Kuschel CA, Kamlin CO, et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. ***Neonatology*** 2013;104(1):8-14.
24. Kumar VHS, Lipshultz SE. Caffeine and Clinical Outcomes in Premature Neonates. ***Children (Basel)*** 2019;6(11):118.
25. Support Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network; Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus surfactant in extremely preterm infants. ***N Engl J Med*** 2010;362(21):1970-9.
26. Chapman RF, Mickleborough TD. The effects of caffeine on ventilation and pulmonary function during exercise: an often-overlooked response. ***Phys Sportsmed*** 2009;37(4):97-103.
27. Ruíz-Moreno C, Lara B, Brito de Souza D, Gutiérrez-Hellín J, Romero-Moraleda B, Cuéllar-Rayo Á, Del Coso J. Acute caffeine intake increases muscle oxygen saturation during a maximal incremental exercise test. ***Br J Clin Pharmacol*** 2020;86(5):861-7.
28. Welsh EJ, Bara A, Barley E, Cates CJ. Caffeine for asthma. ***Cochrane Database Syst Rev*** 2010;2010(1):CD001112.
29. Hassanein SM, Gad GI, Ismail RI, Diab M. Effect of caffeine on preterm infants' cerebral cortical activity: an observational study. ***J Matern Fetal Neonatal Med*** 2015;28(17):2090-5.
30. Hoecker C, Nelle M, Poeschl J, Beedgen B, Linderkamp O. Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. ***Pediatrics*** 2002;109(5):784-7.
31. Mueni E, Opiyo N, English M. Caffeine for the management of apnea in preterm infants. ***Int Health*** 2009;1(2):190-5.
32. Miao Y, Zhou Y, Zhao S, Liu W, Wang A, Zhang Y, et al. Comparative efficacy and safety of caffeine citrate and aminophylline in treating apnea of prematurity: A systematic review and meta-analysis. ***PLoS One*** 2022;17(9):e0274882.