Journal of Iranian Medical Council, Volume 7, Issue no. 3
http://dx.doi.org/10.18502/jimc.v7i3.15736

Original Article

Check for updates

Investigating the Esophageal Pressure Measurement to Adjust NIPPV to Prevent Pulmonary Barotrauma in Patients with COVID-19 under Respiratory Support Admitted to the ICU

Hossein Naderi Boldaji[1], Ibrahim Hazrati[2], Mehrshad Namazi[2], Behroz Kheradmand[2] and Mohamadreza Rafiei[2]*

1. School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
2. Department of Anesthesiology, Surgical and Trauma Research Center, AJA University of Medical Sciences, Tehran, Iran

Abstract

Background: Respiratory failure following COVID-19 can lead to the death of COVID patients. Monitoring these patients during their ventilation is essential. The present study investigated the effect of measuring esophageal pressure in preventing barotrauma while receiving Noninvasive Positive Pressure Ventilation (NIPPV) in patients with COVID-19.

Methods: The present study is a single-blind clinical trial conducted on patients with COVID-19 hospitalized in the Intensive Care Unit (ICU). The patients were divided into two groups; one group had their esophageal pressure measured while receiving NIPPV, their ventilation was adjusted based on this pressure, and the second group was only ventilated according to anesthesia protocols. Finally, the data was entered into SPSS V.23 software and analyzed according to the study's objectives.

Results: The results of the present study showed that the incidence of subcutaneous emphysema-type barotrauma in the Esophageal Pressure (EP) monitoring group was lower than in the non-Esophageal Pressure (nEP) monitoring group. Also, the IPAP level in the EP group was lower than in NEP. The incidence of complications such as abdominal bloating and gavage intolerance was lower in EP than in NEP. The blood oxygen level in NEP was higher than in EP, but there was no significant difference between them.

Conclusion: Esophageal pressure measurement in patients with COVID-19 receiving NIPPV can reduce barotrauma in the patients.

Keywords: Barotrauma, COVID-19, Intensive care units, Positive-pressure respiration, Respiratory insufficiency

*** Corresponding author**
Mohamadreza Rafiei, MD
Department of Anesthesiology, Surgical and Trauma Research Center, AJA University of Medical Sciences, Tehran, Iran
Tel: +98 21 8609 6350
Fax: +98 21 8609 6352
Email: rafiei_mohamadreza@yahoo.com

Received: 3 Jun 2023
Accepted: 30 Sept 2023

Citation to this article
Naderi Boldaji H, Hazrati I, Namazi M, Kheradmand B, Rafiei Mr. Investigating the Effect of Measuring Esophageal Pressure to Adjust NIPPV to Prevent Pulmonary Barotrauma in Patients with COVID-19 under Respiratory Support Admitted to the ICU. *J Iran Med Counc*. 2024;7(3):579-87.

Introduction

The disease caused by the coronavirus (SARS-CoV-2) started at the end of 2019 in China. This virus spread all over the world and led to the COVID pandemic all over the world (1-4). The first patients with this disease had symptoms such as fever, cough, shortness of breath, and diarrhea. Also, some patients have rhinorrhea, nasal congestion, and sore throat (5-9). The disease also led to multi-organ failure and hospitalization in the ICU, and even death in some cases.

This disease's most common symptom of viral pneumonia is a decrease in blood oxygen level, blood gas changes, and changes in X-ray or other diagnostic modalities, including ground glass changes, patchy consolidation, alveolar exudate, and interlobular involvement in CT scans (10-17).

Acute respiratory failure and hypoxemic pulmonary failure following COVID-19 are one of the fears and complications of this disease, which increases the patient's mortality between 2 and 13% so that in severe cases requiring mechanical ventilation, this mortality rate increases to 14.6%. Noninvasive Positive Pressure Ventilation (NIPPV) [divided into two categories, Bilevel Positive Airway Pressure (BIPAP) and Continuous Positive Airway Pressure (CPAP)] is sometimes life-saving in these patients (9,18,19). However, it can lead to complications such as barotrauma and lung damage caused by ventilation, which causes multi-organ failure in ARDS patients. Barotrauma occurs in more than 2% of patients with severe pneumonia caused by COVID. In a study conducted by Hamori *et al* in 2021, retrospectively, patients who underwent non-mechanical ventilation in 2020 were included in the study and were divided into several groups based on the type of barotrauma on their lungs. The information and their experiments were analyzed, and they concluded that the rate of barotrauma in patients with COVID is higher than in other patients.

Invasive mechanical ventilation has a lower risk of barotrauma than noninvasive mechanical ventilation. Furthermore, the delay in intubating the patient did not affect reducing lung barotrauma (11).

Due to the different lung injuries, careful monitoring during the patient's pulmonary ventilation is necessary to prevent these complications. Measuring transpulmonary pressure, which means the pressure difference between lung alveoli and pleura, is suitable for monitoring during ventilation. Since it is challenging to measure pleural pressure, studies have shown that measuring esophageal pressure in patients can be an index of pulmonary pressure. Therefore, measuring esophageal pressure can be used in monitoring patients undergoing NIPPV (12-17). Jones *et al*, in their study, evaluated subcutaneous emphysema, pneumomediastinum, and pneumothorax in critically ill patients with coronavirus disease; their findings demonstrated that using continuous positive airway pressure or noninvasive ventilation predisposes patients to barotrauma. Accordingly, they suggested that determining whether high-minute ventilation while using continuous positive airway pressure or noninvasive ventilation predisposes patients to barotrauma requires further investigation (18).

According to the above issues, it seems crucial to monitor these patients' pulmonary pressure to prevent lung damage and reduce the mortality of these patients. Since the devices created to measure intraesophageal pressure are expensive, patients with COVID-19, especially hospitalized patients in the intensive care unit, face high costs (14,19,20). Therefore, we decided to conduct this research with a simple and innovative method to help manage patients with COVID under NIPPV.

Materials and Methods

The present study is a single-blinded parallel clinical trial (Ethics code: IR.AJAUMS.REC.1400.305, IRCT: IRCT20200612047740N4) conducted on patients with COVID19 hospitalized in the ICU wards of Imam Reza Hospital in Tehran in 2021 and 2022.

The statistical population was the patients with COVID-19 hospitalized in the intensive care unit of Imam Reza Hospital in Tehran for one year, under noninvasive ventilation with positive pressure. The patients were included in the study by census method; approximately 45 individuals were initially estimated in each group. However, due to the widespread vaccination in Iran and the reduction of COVID patients, the number of patients in each group was reduced to 30.

Inclusion and exclusion criteria

The inclusion criteria for this clinical trial included patients with COVID-19 with a positive PCR or CT scan with a maximum of 30% of lung involvement who were hospitalized in the intensive care unit, receiving NIPPV from the BIPAP type, and were fed through an NG tube. The exclusion criteria were non-cooperation of the patient and companions during the investigation, patients with coagulation disorders (coagulopathy), gastrointestinal bleeding and hematemesis, nasal septal deviation, history of fracture, and trauma to the base of the skull.

Intervention design

After entirely explaining the intervention to the patients and obtaining informed consent, the patients who met the inclusion criteria were included in the study and divided into two groups. Patients' information such as age, gender, and characteristics was recorded. In the first group, daily while receiving BIPAP, their NG tube was raised as far as the distance between the xiphoid and the middle of their sternum so that the end of the tube was placed in the lower third of the esophagus. For NG-tube installation, the distance from the ear tragus to the xiphoid, plus 6 inches, was measured until the end of the tube was placed at the beginning of the stomach. The end of the tube was placed in the lower third of the esophagus by pulling the tube up, and radiography was used to determine the tube's location (Figure 1), then the end of the tube was connected to an air bag through the intravenous infusion set. This study utilized a disposable polyvinyl esophageal suction catheter for noninvasive ventilation in COVID-19 patients. The catheter was connected to a disposable blood pressure transducer and a pressurized system to ensure its patency and signal stability. To facilitate placement, a siliconized guide wire was temporarily inserted into the catheter and bent to match the desired length. The catheter was first positioned in the stomach and then withdrawn to the lower third of the esophagus until the esophageal waveform was confirmed by small cardiac artifacts and spontaneous inspiratory negative deflections. The proper position of the catheter was confirmed through various methods, including chest X-rays, visualization of cardiac artifacts on the esophageal waveform, and equivalent changes in esophageal and airway pressures during the dynamic end-expiratory occlusion test maneuver. A ratio close to unity between esophageal-to-airway pressure changes validated the technique as an adequate estimate of pleural surface pressure and confirmed the proper position of the catheter. This air bag was connected to the manometer and insufflator through the intravenous infusion set, the connection between these three parts was established through a tee, and each of these parts entered the circuit if required. First, the air bag was inflated with an inflator, and then after connecting to the patient's NG tube, it was placed in the path of the manometer. Within a few seconds, the pressure inside the esophagus was shown on the manometer, and the ventilator was

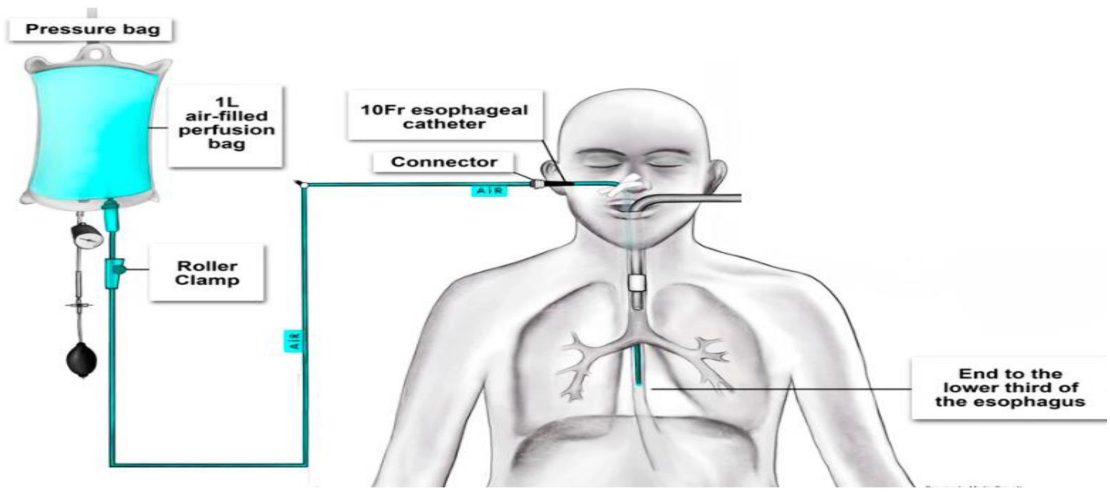

Figure 1. A schematic view of the study intervention (14).

immediately disconnected from the patient's NG tube. So that the pressure inside the esophagus does not lead to the discharge of secretions inside the esophagus, the patient's NG tube was placed in the stomach and washed with normal saline. To prepare for esophageal measurement, the catheter without a closed end is cleansed with 3 *ml* of air using a syringe to eliminate any substances at the far end. The transducer is calibrated to atmospheric pressure.

Since the pressure in the manometer was displayed based on millimeters of mercury, the numbers were multiplied by 1.35 to convert to centimeters of water. The ventilator setting was adjusted based on the guideline and the measurement of the difference in lung pressure (difference between alveolar pressure and intraesophageal pressure) so that there was no more than 35 to 40 *cm* of water. If it was more than this value, the Expiratory Positive Airway Pressure (EPAP) and Inspiratory Positive Airway Pressure (IPAP) setting of the ventilator was reduced due to preventing barotrauma. Daily pressure measurement was done twice while the patient was in ICU and under BIPAP, and the ventilator settings were adjusted accordingly [IPAP 10-16 (max 25) cmH_2O; EPAP 4-6 (max 10) cmH_2O; FiO2 titrated to keep SpO_2 >92%]. The intervention was ended in case of interruption of ventilation, intubation, and discharge from the ICU.

The second group was patients who did not have daily intraesophageal pressure measurements, and BIPAP settings were set for them through guidelines [8-10 (and can go up to 24) cmH_2O for inhalation and 2-4 (up to 20) cmH_2O for exhalation]. Settings of ventilators and barotrauma such as emphysema and pneumothorax, pneumomediastinum, a daily pulmonary pressure difference of patients, time of barotrauma for the patient since the start of BIPAP, patients' O2sat level, EPAP, IPAP, gavage tolerance and the degree of patients' abdominal bloating were recorded [IPAP 10-16 (max 25) cmH_2O; EPAP 4-6 (max 10) cmH_2O; FiO2 titrated to keep SpO_2 >92%].

Statistical analysis

This study used the Chi-square test to investigate qualitative variables such as gender. Descriptive results are presented as number, percent, mean, and SD (Standard Deviation). Moreover, for quantitative variables in two groups, an independent t-test was used. The results were analyzed by SPSS software version 23 (IBM Corp., Armonk, New York, USA), and a p-value ≤0.05 was considered significant.

Ethical approval

Ethical approval was obtained from the Research and Ethics Committee (IR.AJAUMS.REC.1400.305) of the AJA University of Medical Sciences, Tehran, Iran. The trial was registered in the Iranian Registry of Clinical Trials (IRCTID: IRCT20200612047740N4) (Figure 2).

Results

The patients in the present study were divided into two groups, and the following results were obtained from the data analysis. The demographic information of the patients is given in table 1. Men and women were evenly divided between the two groups, and in terms of frequency of age and sex, they had a uniform distribution. There was no significant difference between them (p=0.297).

Comparing the groups in terms of pulmonary barotrauma, none of the patients in the intervention group (EP) suffered barotrauma. In contrast, ten patients in the control group non-Esophageal Pressure (nEP) suffered barotrauma, which was of the subcutaneous emphysema type. The rate of pulmonary barotrauma in the intervention group was lower than in the control group. The variables such as bloating and gavage tolerance show less bloating and better gavage tolerance in the intervention group. The average intraesophageal pressure was 24.176±2.46 cmH_2O (normal range: 17.5±5.7 cmH_2O at end-expiration and 21.2±7.7 cmH_2O at end-inhalation). The mean length of ICU stay was 12.04±4.11 days in the esophageal pressure monitoring group, and in the non-esophageal pressure group, it was 15.65±6.72. When comparing both groups, patients without esophageal pressure monitoring had a high rate of pulmonary barotrauma and significantly more stay in the ICU (p=0.001) (Table 2).

The mean blood oxygen saturation percentage in the intervention group was 87.33±3.36, which was lower than the control group (89.46±2.59). BIPAP ventilator settings in two groups are presented in table 3. Respiratory rate and EPAP were not significantly different between the two groups. However, IPAP was

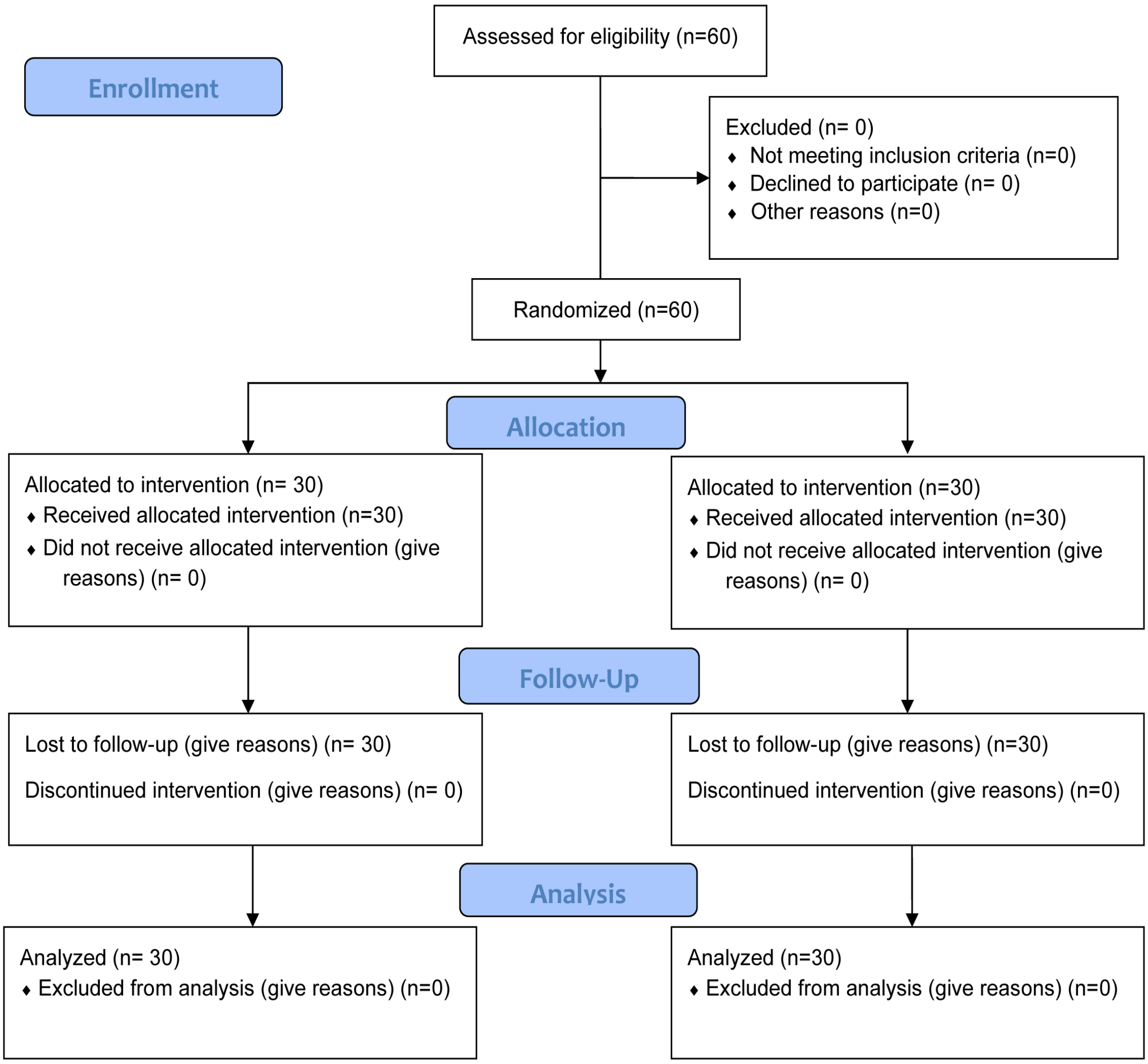

Figure 2. The study flow diagram.

Table 1. The demographic information of the patients

Variables		Groups		Total	p-value
		Esophageal pressure	Non-esophageal pressure		
Sex *	Male	12(40%)	16(53.33%)	28	0.267
	Female	18(60%)	14(46.67%)	32	
Age **		51.3(±8)	50.2(±9.9)	-	0.494
BMI **		28.43(±4.51)	28.24(±3.22)	-	0.311
Smoking **		30	30	60	0.178
PaO_2/FiO_2 ** (*mmHg*)		162±65(61–375)	177±69(61–375)	-	-
$PaCO_2$ (*cm*H_2O) **		50±13(31–88)	53±11(30–82)	-	-
Diabetic/Non-Diabetic **		22/8	24/6	-	-
Total		30	30	60	-

* Chi-square test. ** T-test. ± Standard Deviation. BMI: Body Mass Index.

Table 2. Comparing the groups in terms of pulmonary barotrauma, gavage intolerance, and abdominal blowing

Variables		Groups		p-value
		Esophageal pressure	Non-esophageal pressure	
Baro-trauma *	Yes	0(0%)	10(33.33%)	<0.001
	No	30(100%)	20(66.66%)	
Gavage intolerance *	Yes	24(80%)	17(56.66%)	<0.001
	No	6(20%)	13(43.33%)	
Abdominal blowing *	Yes	4(13.33%)	13(43.33%)	<0.001
	No	26(86.66%)	17(56.66%)	
Length of stay in ICU (days)		12.04±4.11	15.65±6.72	<0.001

* T-test.

Table 3. BIPAP ventilator settings in two groups

Variables	Groups		p-value
	Esophageal pressure	Non-esophageal pressure	
Blood oxygenation *	87.33 (±3.36)	89.46 (±2.59)	0.243
Respiratory rate *	19.36 (±1.99)	19.2 (±.84)	0.314
IPAP *	14.86 (±.73)	16.53 (±1.59)	<0.001
EPAP*	5 (±.00)	5.43 (±.56)	<0.001

*Independent samples t-test. Expiratory Positive Airway Pressure (EPAP), Inspiratory Positive Airway Pressure (IPAP).

higher in the control group than in the intervention group.

Discussion

Intraesophageal pressure is an indicator of pleural pressure that can be measured more conveniently and less invasive way. Respiratory failure can lead to mortality and morbidity in various conditions, including COVID disease. In respiratory failure, invasive and noninvasive methods improve oxygen supply to tissues. One of the noninvasive methods is BIPAP. One of the side effects of this method is pulmonary barotrauma. Studies have shown that measuring pleural pressure more simply and conveniently, such as measuring intraesophageal pressure, can reduce pulmonary barotrauma. Since there is a higher possibility of barotrauma and lung damage during ventilation in patients with COVID-19, the present study was conducted to measure intraesophageal pressure to prevent lung barotrauma in COVID-19 patients (11,15,16).

In a study conducted in 2006 by Daniel Talmor *et al*, the results demonstrated that the measurement of intraesophageal pressure could show the degree of lung tension and was recommended as a method to be used alongside ventilation to reduce lung injuries (15). In 2020, Massion *et al*, by inventing a new open-ended way in patients with COVID-19 under invasive ventilation with a ventilator, showed the proportionality of intraesophageal pressure with pulmonary pressure, which can be effective in mechanical ventilation of patients and prevention of barotrauma (14). The results of these studies were consistent with the present study's findings.

In a study conducted by Hamori *et al* in 2021, retrospectively, individuals who underwent non-mechanical ventilation in 2020 were included in the study and divided into several groups based on the type of barotrauma on their lungs, the data and their experiments were analyzed, and they concluded that the rate of barotrauma in patients with COVID-19 is higher than other patients. In addition, invasive mechanical ventilation had a lower risk of barotrauma than noninvasive mechanical ventilation. Furthermore, the delay in intubating the patient did not affect reducing lung barotrauma (11). In Jones *et al*'s study of 83 admissions with coronavirus disease in 2019, eight suffered barotrauma (occurrence rate 9.6%; 95%CI 4.3–18.1%). Barotrauma cases had longer illness duration prior to critical care admission (10 *vs.* 7 d; interquartile range, 8–14 and 6–10, respectively; p=0.073) and were more often treated with continuous positive airway pressure or noninvasive ventilation as the initial modality of advanced respiratory support (87.5% *vs.* 36.0%; p=0.007). Compared with the non-barotrauma group, a higher proportion of patients with barotrauma had died (62.5% *vs.* 43.2%) (18).

In contrast to the present investigation, Beitler *et al*, in their clinical trial, compared the effect of Titrating Positive End-Expiratory Pressure (PEEP) with an esophageal pressure–guided strategy *vs.* an empirical high PEEP-Fio2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome. Their trial demonstrated that among patients with moderate-to-severe ARDS, PES-guided PEEP, compared with empirical high PEEP-Fio2, resulted in no significant difference in death and days free from mechanical ventilation. Moreover, these findings do not support PES-guided PEEP titration in ARDS. Furthermore, this method is not recommended in acute lung failure patients under mechanical ventilation (17).

The analysis of the results of our study illustrated that significantly, based on the crosstabs test, the incidence of pulmonary barotrauma, including subcutaneous emphysema, was lower in the intervention group than in the control group, thus pulmonary barotrauma did not occur in all the individuals in the intervention group, which shows the effect of intraesophageal pressure measurement on reducing lung tension and thus reducing lung damage. The t-test indicated that the average blood oxygen level in the control group was higher than in the intervention group. However, there was no significant difference between these two groups (89.46 compared to 87.33). However, in Hamouri's study, interestingly, the group who developed PBT was younger and had fewer comorbidities. Excluding the higher prevalence of DM and better PO_2/FIO_2 ratio observed in the NPBT group, no significant difference was observed in the other factors between the two groups to predict the risk of developing PBT in patients receiving PPV (11). A lower PO_2/FIO_2 ratio usually indicates a greater extent of lung injury. Also, many studies have well-described diabetes mellitus as a risk factor for developing severe pneumonia in COVID-19-infected patients (21-23). Our clinical trial excluded diabetic patients and other systemic diseases.

Also, the t-test demonstrated that EPAP and RR were not significantly different in the two groups. However, the average IPAP in the control group was 1.67 units higher than the intervention group. The average intraesophageal pressure in the intervention group was 24.176, less than the risk threshold for lung barotrauma.

Analysis of variables such as abdominal bloating and gavage tolerance with the crosstabs test showed less bloating and better gavage tolerance in the intervention group compared to the control group. Finally, we need an intelligent healthcare system, secure intensive care, and evidence-based medicine to achieve the best outcome for these patients (24,25).

Conclusion

Measuring intraesophageal pressure to adjust BIPAP can reduce the incidence of pulmonary barotrauma and not significantly reduce the amount of oxygen delivery and oxygen saturation level of the patients.

Data availability

All relevant data are included in the study. Additional information is available from the corresponding author on reasonable request.

Protocol

This single-blinded parallel clinical trial (ethics code: IR.AJAUMS.REC.1400.305, IRCT: IRCT 20200612047740N4) was conducted on patients with COVID-19 hospitalized in the ICU wards of Imam

Reza Hospital in Tehran in 2021 and 2022, after obtaining the University's Ethics Committee and patient's approval.

Financial support and sponsorship

There was no funding.

Acknowledgement

We appreciate the research and ethics committee which approved this study at the AJA University of Medical Sciences (IR.AJAUMS.REC.1400.305).

Conflict of Interest

The authors have no conflicts of interest.

References

1. Girdharwal N. COVID-19 lockdown: a study on behavioural pattern-a systematic review in DELHI-NCR, India. J Complement Medicine Res 2020 Aug 14;11(1):199.

2. Valerio A, Nisoli E, Rossi AP, Pellegrini M, Todesco T, El Ghoch M. Obesity and higher risk for severe complications of COVID-19: what to do when the two pandemics meet. J Popul Ther Clin Pharmacol 2020 Jun 29;27(SP1):e31-6.

3. Ghaseminejad S, Chegini MA, Sarikhani-Khorrami E, Fardi M, Ramezani E, Kalvandi A. Association of laboratory abnormalities before the beginning of drug treatment with of hospitalized patients with COVID-19. J Complement Med Res 2021:92-7.

4. Sarda SR, Tekale SU, Kótai L, Domb AJ, Pawar RP. COVID-19: a global pandemic. Eur Chem Bullet 2020;9(8):266-72.

5. Kandeel M, Park BK, Morsy MA, Venugopala KN, Oh-hashi K, Al-Nazawi M. Virtual screening and inhibition of middle east respiratory syndrome coronavirus replication by targeting papain-like protease. Dr. Sulaiman Al Habib Med J 2021;3:179-87.

6. Cooper JA, vanDellen M, Bhutani S. Self-weighing practices and associated health behaviors during COVID-19. Am J Health Behav 2021 Jan 1;45(1):17-30.

7. Halil K, Selcuk O, Mahmoud A. Changes in symptoms and severity of obsessive compulsive disorder in children and adolescent patients following the COVID-19 pandemic. Arch Clin Psychiatry (São Paulo) 2021 May 26;48:83-9.

8. Weaver RH, Jackson A, Lanigan J, Power TG, Anderson A, Cox AE. Health behaviors at the onset of the COVID-19 pandemic. Am J Health Behav 2021 Jan 1;45(1):44-61.

9. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L. Chest CT findings in patients with coronavirus disease 2019 and its relationship with clinical features. Invest Radiol 2020 May;55(5):257.

10. Bauch CT, Lloyd-Smith JO, Coffee MP, Galvani AP. Dynamically modeling SARS and other newly emerging respiratory illnesses: past, present, and future. Epidemiology 2005 Nov 1:791-801.

11. Hamouri S, Samrah SM, Albawaih O, Saleh Z, Smadi MM, Alhazymeh A. Pulmonary barotrauma in COVID-19 patients: invasive versus noninvasive positive pressure ventilation. Int J Gen Med 2021;14:2017.

12. van Gastel LH, Oostdijk EA, Slot S, Weller D. COVID-19 pneumonia and ventilation-induced lung injury: a case report. Rom J Anaesth Intensive Care 2020 Dec 1;27(2):80-2.

13. Madahar P, Beitler JR. Emerging concepts in ventilation-induced lung injury. F1000Res 2020;9.

14. Massion PB, Berg J, Samalea Suarez N, Parzibut G, Lambermont B, Ledoux D. Novel method of transpulmonary pressure measurement with an air-filled esophageal catheter. Intensive Care Med Exp 2021 Dec;9(1):1-4.

15. Talmor D, Sarge T, O'Donnell CR, Ritz R, Malhotra A, Lisbon A, Loring SH. Esophageal and transpulmonary pressures in acute respiratory failure. Crit Care Med 2006 May;34(5):1389.

16. Emeriaud G, Mortamet G, Essouri S, Poirier N, Jouvet P. Esophageal pressure: a reliable monitoring to estimate transpulmonary pressure in children?. InA61. Care of technology-dependent children 2018 May (pp. A2046-A2046). Am Thorac Societ.

17. Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V. Effect of titrating positive end-expiratory pressure (PEEP) with an esophageal pressure–guided strategy vs an empirical high PEEP-FIO2 strategy on death and days free from mechanical ventilation among patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2019 Mar 5;321(9):846-57.

18. Jones E, Gould A, Pillay TD, Khorasanee R, Sykes R, Bazo-Alvarez JC, Cox C. Subcutaneous emphysema, pneumomediastinum, and pneumothorax in critically ill patients with coronavirus disease 2019: a retrospective cohort study. Crit Care Explor 2020 Sep 17;2(9):e0210.

19. Scheidt CE. Editorial: The COVID-19 pandemia. Int J Body Mind Cult. 2021 Jun 15 [cited 2022 Jul 15];8(2):75-7.

20. Monajemi A, Moghadam-Heidari G, Namazi H. Medical humanities reveals the neglected aspects of the covid 19 pandemic. Int J Body Mind Culture 2021 May 29.

21. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020 Oct;36(7):e3319.

22. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States. J Diabetes Sci Technol 2020 Jul;14(4):813-21.

23. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. Lancet Respir Med 2020 Mar 1;8(3):267-76.

24. Hu B, Zhang Z. Evaluation of big data analytics and cognitive computing in smart health systems. J Commercial Biotechnol 2022 Aug 21;27(2).

25. Nasiri AA, Afsargharehbagh R, Sane S, Neisari R. Shargh A. 2019. Treatment of intractable hiccups using phrenic nerve block. J Clin Anesth 2019;57:7-8.