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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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COVID-19 ARDS Patients Successfully Extubated to Extubated to High-Flow Nasal Cannula Oxygen Therapy: A Retrospective Analysis

Yüksek Akışlı Nazal Kanül Oksijen Tedavisine Başarıyla Ekstübe Edilen COVID-19 ARDS Hastalarının Retrospektif Analizi

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ABSTRACT *Objective:* The acute respiratory distress syndrome (ARDS)-associated coronavirus disease-2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 novel coronavirus, is a major cause of death during the pandemic period. Here, we aim to present a retrospective data analysis of the success of extubation to high-flow nasal oxygen (HFNO) among COVID-19 ARDS patients.

Materials and Methods: The data of 22 COVID-19 ARDS patients who were laboratory confirmed and extubated on HFNO while under intubation in the intensive care unit (ICU) were analyzed. Respiratory variables and demographic characteristics were collected at admission. During the intubation period, mechanical ventilation volumes and pressures and blood gas measurements were recorded. HFNO flow rate, FiO_2, and oxygenation variables were collected for 5 days after extubation. After the planned extubation, the 5-day reintubation rate, length of stay in the ICU, and mortality were recorded.

Results: Sixteen of 22 patients were male (72.7%). The mean age was 69.9±13.2 years and the highest comorbidity was hypertension (59.1%). The time between symptom onset and admission to the ICU was 6.5±7.9 days. Almost all patients were intubated on the same day. Twenty patients were successfully extubated to HFNO. Two patients experienced reintubation. The mean duration of HFNO treatment and length of stay in the ICU were 17.4±6 and 4.8±3.6 days, respectively. The ICU mortality rate of these complete data was 13.6% (3/22).

Conclusion: In high-risk COVID-19 ARDS patients undergoing extubation, HFNO therapy should be considered to prevent respiratory failure after reintubation and post-extubation.

Keywords: Acute respiratory distress syndrome, COVID-19, extubation, high-flow nasal cannula oxygen therapy, weaning

ÖZ *Amaç:* Son derece bulaşıcı şiddetli akut solunum sendromu koronavirüs 2 yeni koronavirüsünün neden olduğu akut respiratuvar distres sendromu (ARDS) ile ilişkili koronavirüs hastalığı-2019 (COVID-19), pandemi döneminde önemli bir ölüm nedenidir. Burada COVID-19 ARDS hastalarında yüksek akımlı nazal oksijen (HFNO) tedavisine ekstübasyon başarısının retrospektif veri analizini sunmayı amaçlıyoruz.

Gereç ve Yöntem: Yoğun bakım ünitesinde (YBÜ) HFNO tedavisine ekstübe edilen, laboratuvarca doğrulanmış 22 COVID-19 ARDS hastasının verileri analiz edildi. Solunumla ilgili değişkenler ve demografik özellikler başvuru sırasında toplandı. Entübasyon süresince mekanik ventilasyon hacimleri ve basınçları ile kan gazı ölçümleri kaydedildi. HFNO akış hızı, FiO_2 ve oksijenasyon değişkenleri ekstübasyondan sonra 5 gün boyunca toplandı. Planlanan ekstübasyonu takip eden 5 gün içinde yeniden entübasyon oranı, YBÜ'de kalış süresi ve mortalite kaydedildi.

Bulgular: Yirmi iki hastanın 16'sı erkekti (%72,7) ve yaş ortalaması 69,9±13,2 yıl olup, en yüksek komorbidite hipertansiyon (%59,1) idi. Semptom başlangıcı ile YBÜ'ye kabul arasındaki süre 6,5±7,9 gündü ve hemen hemen tüm hastalar aynı gün entübe edildi. Yirmi hasta HFNO'ya başarıyla ekstübe edildi ve 2 hasta yeniden entübe edildi. Ortalama yüksek akımlı nazal oksijen tedavisi süresi 4,8±3,6 gün ve yoğun bakımda kalış süresi 17,4±6 gündü. YBÜ mortalite oranı %13,6 (3/22) idi.

Sonuç: Ekstübasyon uygulanan yüksek riskli ARDS COVID-19 hastalarında yeniden entübasyon ve ekstübasyon sonrası solunum yetersizliğini önlemek için HFNO tedavisi düşünülmelidir.

Anahtar Kelimeler: Akut solunum sıkıntısı sendromu, COVID-19, ekstübasyon, yüksek akımlı nazal kanül oksijen tedavisi, weaning

Introduction

High-flow nasal oxygen therapy (HFNO) is one of the newer oxygenation methods commonly used in critical care during acute hypoxemic respiratory failure that can deliver heated and humidified gas up to 100% oxygen at a maximum flow of 60 L min^{-1} nasally. It has also been reported that HFNO can generate flow-dependent, low-level positive airway pressure, reduce airway resistance, and washout nasopharyngeal dead space (1).

Performing HFNO to coronavirus disease-2019 (COVID-19) patients with acute respiratory failure as initial support reduced the intubation rate when compared to non-invasive ventilation (NIV) (2). HFNO has been shown to be superior to conventional oxygen therapy (COT) in reducing extubation failure and reintubation rates when used after extubation, as well as reducing treatment failure when used as a primary support strategy (2). Also, in recently published reviews, it was reported that HFNO treatment has similar reintubation and treatment failure rates when compared to NIV (3,4).

However, there is an important concern that the high gas flow used might cause aerosol dispersion leading to the transmission of the virus into the environment. It was demonstrated that HFNO has a similar risk with standard oxygen masks in terms of the generation and dispersion of bio-aerosols (5). The number of studies regarding the comparison of HFNO and NIV in terms of bioaerosol dispersion are limited. The viral dispersion from different respiratory support devices was quantitatively evaluated with a simulated mannequin model in a negative pressure intensive care unit (ICU) room by Avari et al. (6) and they reported that the HFNO has higher bacteriophage concentrations than invasive mechanical ventilation and non-invasive helmet ventilation with a positive end-expiratory pressure (PEEP). However, investigators reported that surgical masks could reduce dispersion distance and viral load in patients under HFNO treatment (7,8).

Thinking about the advantages of HFNO in reducing the risk of intubation and the need for mechanical ventilation, it is not wise to discard this technique for the support of acute respiratory distress syndrome (ARDS) patients with COVID-19. The aim of this study is to evaluate extubation success to HFNO by reporting the outcome data of COVID-19 ARDS patients.

Materials and Methods

After ethics approval was obtained from the İstanbul Faculty of Medicine Clinical Research Ethics Committee (decision no: 12, date: 29.05.2020), this retrospective study was conducted at a university hospital's ICU. Twenty-two ARDS patients whose COVID-19 infection was confirmed with real-time polymerase chain reaction (PCR) test, (18 years of age or older), and who were extubated to HFNO while under mechanical ventilation support between 18 March 2020 and 30 May 2020 in the hospital's four ICUs were included. The exclusion criteria were as follows: 1) The patients who died under invasive mechanical ventilation before the extubation attempt, 2) who did not need any invasive mechanical ventilation support, 3) pregnant patients. The written informed consent from individual patients was not obtained due to collection of the patients data retrospectively. COVID-19 disease was defined as a positive result of reverse transcriptase-PCR testing of a nasopharyngeal swab collected by the local hospital health authority. Under the guidance of the World Health Organization (WHO), a diagnosis of severe acute respiratory syndrome coronavirus 2 pneumonia was made and patients who needed respiratory support with a standard oxygen mask or whose oxygen saturation was below 90% were taken to the ICU. ARDS is defined according to the Berlin definition (9). Data were collected from available electronic medical records and patient files by officers in charge of the university hospital's intensive care department research facilities.

Demographic and clinical data, including age, gender, admission disease severity scores [Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Assessment-II (APACHE-II)], underlying comorbidities (hypertension, chronic heart disease, chronic lung disease, diabetes mellitus, chronic renal failure, chronic liver disease, malignancies, cerebrovascular disease, autoimmune disease and immunosuppressive state), the time between symptom onset and admission to the ICU, and intubation time were recorded.

Arterial oxygen partial pressure/fractional inspired oxygen (PaO_2/FiO_2) ratio before intubation, days in mechanical ventilation were recorded. Blood gas analysis and respiratory parameters including inspiratory support pressure, PEEP, respiratory frequency, tidal volume (Vt), and frequency, as well as PaO_2/FiO_2 ratio right before extubation, were added to the data chart. Mechanical ventilation volumes, pressures,

and blood gas analysis results were recorded during the intubation period.

The weaning of the patients was performed according to daily screening for the respiratory and clinical criteria. Patients were extubated when they fulfill the criteria of extubation. The extubation criteria include 1) low PEEP level (5-8 cm H_2O), 2) without electrolyte disturbance, 3) hemodynamic stability, 4) interrupted sedation and followed up in spontaneous breathing in pressure support mode, 5) good state of consciousness, 6) received sufficient Vt (at least 5 mL kg^{-1}), 7) sufficient cough reflex which was evaluated with sputum amount, character and viscosity, 8) aspiration frequency of more than 2 hours, 9) achieved pain control, 10) breath rate less than 30/min, 11) oxygen saturation (SpO_2) > 90%, 12) PaO_2 > 60 mmHg,13) rapid shallow breathing index <105. The patients were directly switched to HFNO treatment from invasive mechanical ventilation according to the abovementioned criteria without trial of COT. Patients were continuously treated with HFNO alone with a flow and FiO_2 adjusted to achieve adequate oxygenation of at least 92% of SpO_2 as measured by pulse oximetry. The temperature of the heated humidifier was set to 37 °C to ensure adequate humidification. When the following respiratory failure criteria were disappeared during HFNO treatment (respiratory rate >35 $minute^{-1}$ more than five minutes, hypoxemia that SpO_2 <90%, tachycardia that heart rate (HR) >140 $minute^{-1}$ or 20% increase, bradycardia that 20% reduction in HR, hypertension that systolic blood pressure >180 mmHg, hypotension that systolic blood pressure <90 mmHg, acidosis that pH <7.32 and >10 mmHg increase in arterial carbon dioxide partial pressure ($PaCO_2$), consciousness changes that agitation, sweating or anxiety symptoms, cyanosis, findings of increased breathing effort that accessory muscle use, stress symptoms on the face, increased breathlessness), oxygen support was switched to standard oxygen therapy from HFNO.

Oxygenation variables [PaO_2, $PaCO_2$, arterial oxygen saturation (SaO_2)], the flow rate of HFNO, and FiO_2 were recorded daily for 5 days after extubation. Reintubation rate, length of stay in the ICU, and mortality within 48 hours and during 5 days following extubation were also recorded. Data collection was stopped in those patients who were either switch to COT or invasive mechanical ventilation.

Statistical Analysis

The SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) program was used for statistical data analysis. Categorical variables were presented with percentages and numbers. One sample Kolmogorov-Smirnov test was performed to evaluate whether the continuous variables have a normal distribution. The continuous variables' mean, standard deviation, minimum and maximum values were also presented. Spearman correlation analysis was performed to evaluate the relationship between clinical features, pre-extubation mechanic ventilation volumes, pressures, and blood gas parameters. The p-value <0.05 was considered statistically significant.

Results

The patients' clinical and demographic data were presented in Table 1. The mean age was 69.9±13.2 years, and 72.7% (16/22) of patients were male. The patients' mean APACHE-II score was 19.5±6.8 and the median SOFA score at the day of ICU admission was 5.4±2.6.

The leading comorbidities among our patients were chronic cardiac failure, hypertension, and diabetes and their frequencies were 36.4% (8/22), 59.1% (13/22), and 50% (11/22), respectively. The duration between symptom initiation and ICU admission was 6.5±7.9 days, and the duration between symptom initiation and intubation was 6.8±8.1 days. Seventy-two percent of patients (16/22) were intubated on the day of ICU admission. The mean duration between mechanical ventilation and extubation to HFNO was 9±5.3 days. Twenty patients were extubated successfully to HFNO, only a patient was reintubated within two days and the other one patient was reintubated within the following three days. Three out of 22 patients died (13.6%).

Table 2 shows mean records of blood gasses and respiratory parameters right before extubation. The slight increase in HCO_3 (30.3±5.1 mmol L^{-1}) and base excess (6.3±5.3 mmol L^{-1}) levels were observed with a mean respiratory rate of 17.3±3.9 $minute^{-1}$. Mean PEEP was 7.1±1.0 cmH_2O and improvement in the PaO_2/FiO_2 ratio (247.6±73.1) was evident compared with the initial values. The mean HFNO treatment after extubation and the length of ICU stay was 4.8±3.6 days and 17.4±6 days, respectively.

Patients' blood gas parameters, HFNO flow, and FiO_2 following 5 days of extubation were depicted in Table 3. On the fifth day following extubation the mean PaO_2/FiO_2 ratio was 180.3±46.1 with a mean FiO_2 and flow rate of 0.46±0.07 and 42.2±8.7% L $minute^{-1}$, respectively. The correlation analysis between the duration of HFNO treatment, clinical

features, pre-extubation ventilator parameters, and blood gas parameters was presented in Table 4. There was a significant correlation with pH level before extubation and HFNO treatment duration (r=0.438; p=0.041). Although it was not statistically significant, higher pressure support levels before extubation were associated with longer HFNO duration. (r=-0.409; p=0.059).

Table 1. Demographic characteristics and clinical features of study population

	Mean ± SD/n	min-max/%
Age (years)	69.9±13.2	46-89
BMI (kg m^{-2})	27.8±3	23-36
Gender (n/%)		
Male	16	72.7%
Female	6	27.3%
Chronic disease (n/%)		
Cardiac disease	8	36.4%
Hypertension	13	59.1%
Diabetes mellitus	11	50%
Pulmonary disease	5	22.7%
Cerebrovascular disease	2	9.1%
Malignancy	1	4.5%
Renal disease	1	4.5%
Liver disease	1	4.5%
Symptom initiation to ICU admission (days)	6.5±7.9	1-36
Symptom initiation to intubation (days)	6.8±8.1	1-37
APACHE-II score at ICU admission	19.5±6.8	8-34
SOFA score at ICU admission	5.4±2.6	3-13
Maximum SOFA score	7,8±2.3	4-15
PaO_2/FiO_2 before intubation	111.4±31.9	65-185
Duration of mechanical ventilation (days)	9±5.3	2-21
ICU hospitalization (days)	17.4±6	6-28
HFNO treatment (days)	4.8±3.6	1-15
Successful weaning (n/%)	20	90%
Reintubation in 48 h (n/%)	1	4.5%
Reintubation in 5 days (n/%)	1	4.5%
Death (n/%)	3	13.6%

BMI: Body mass index, ICU: intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HFNO: high-flow nasal oxygen, PaO_2/FiO_2: arterial oxygen partial pressure/fractional inspired oxygen, SD: standard deviation

Discussion

The primary finding of this retrospective study is that high-risk ARDS COVID-19 patients can be successfully extubated to HFNO. Among the non-invasive modalities, high flow oxygen therapy offers many physiological benefits which include decreased anatomical dead space, improved oxygenation, decreased production of carbon dioxide, decreased metabolic demand of breathing (10). Most importantly this technique serves up to superior comfort and improved work of breathing (10). In a small group of patients, delivery of humidified and heated oxygen with high-flow nasal cannula has been shown to be superior to high-flow oxygen via a non-rebreathing mask. Inspiratory effort and respiratory frequency were reduced with HFNO compared with the non-rebreathing mask. HFNO therapy reduces work of breathing and neuroventilatory drive after extubation in patients with chronic obstructive pulmonary disease (11). We did not measure electrical diaphragmatic activity, but we think that HFNO treatment reduces the possibility of reintubation due to high ventilatory impulse and respiratory work in patients with extubated COVID-19 ARDS.

Many other studies showed that performing HFNO as an initial oxygen support system was superior to COT in reducing extubation failure rates (12). Several studies reported that, although HFNO reduced the intubation rates when used as

Table 2. Respiratory parameters and blood gas analysis values before extubation

	Mean ± SD
pH	7.45±0.04
PO_2 (mmHg)	93.2±23.7
PCO_2 (mmHg)	43.2±7.1
HCO_3 (mmol L-1)	30.3±5.1
Base excess	6.3±5.3
SaO_2 (%)	96.7±1.7
Respiratory rate (breathe $minute^{-1}$)	17.3±3.9 (median: 15.5)
Tidal volume (mL)	583.1±150.8
RR/Vt	31.1±11.2
PEEP (cm H_2O)	7.1±1.0
Inspiration support (cm H_2O)	11.7±3.3
FiO_2	0.38±0.04
PaO_2/FiO_2	247.6±73.1

PaO_2/FiO_2: Arterial oxygen partial pressure/fractional inspired oxygen, RR: respiratory rate, Vt: tidal volume, SaO_2: arterial oxygen saturation, PEEP: positive end-expiratory pressure, SD: standard deviation

initial oxygen support, showed no superiority when used after extubation in comparison to NIV. Post-extubation respiratory failure and reintubation rates were compared between HFNO and NIV in a group of high-risk patients. In this multicentric randomized clinical trial, HFNO offered many clinical advantages and proved that it is not inferior to NIV in preventing respiratory failure after reintubation and extubation. A higher reintubation rate was reported (19%) with NIV most probably due to switching to COT after 24 hours (13,14). Other data suggest that more prolonged HFNO may improve outcomes in critically ill patients after extubation (15). Maggiore et al. (16) randomized critically ill patients of the general population either receiving HFNO or COT and observed that the HFNO group has more improvement in oxygenation and lower reintubation rate (3.8%) than COT. Thille et al. (17) reported that the reintubation rate was 18.2% within 48 hours of HFNO treatment with high-risk extubation failure patients. The reintubation rate was 10% (2/20) in our retrospective data which was similar to previous trials. We continued HFNO treatment for at least 48 hours after planned extubation. Considering the high risk of COVID-19 ARDS patients for extubation failure, HFNO can be used in COVID-19 ARDS patients after extubation. The benefits provided in this regard; contributing to patient comfort with heating and humidification, maintaining normal physiology, improving the increased ventilatory drive, and being a more sustainable treatment compared to NIV.

Several reports discussed if endotracheal intubation could be prevented by HFNO treatment in COVID-19 patients who presented with moderate ARDS. Twelve randomized controlled trials provided low-certainty evidence that HFNO may reduce invasive ventilation in patients without COVID-19 patients (2). The results did not provide support for differences in mortality or length of stay in ICU. HFNO appears to have been rarely used during the COVID-19 pandemic in the western countries. This is most probably due to the fear of risk of aerosolization and viral dispersion which might lead to infection transmission. However, the WHO and other scientific communities rank HFNO among possible options for ventilator support (18). Three studies evaluating aerosol generations and dispersion and four studies evaluating droplet dispersion provided very low certainty evidence. A crossover study and two simulation studies showed confusing results about the effect of HFNO on droplet dispersion. Two of these simulation studies reported no increase in aerosol dispersion with HFNO, but one reported that higher flow rates were associated with increased regions of aerosol density (19-27). However, *in vitro* and clinical studies have shown that placing a simple surgical mask on patients significantly reduces dispersion

Table 3. The gas flow, FiO_2, and blood gas value results of five days follow-up of patients under HFNO treatment after extubation

	1st day Mean ± SD (min-max) (n=22)	2nd day Mean ± SD (min-max) (n=20)	3rd day Mean ± SD (min-max) (n=16)	4th day Mean ± SD (min-max) (n=11)	5th day Mean ± SD (min-max) (n=9)
pH	7.44±0.7 7.27-7.55	7.44±0.5 (7.29-7.55)	7.44±0.7 (7.21-7.53)	7.46±0.05 (7.32-7.55)	7.42±0.08 (7.30-7.54)
PaO_2 (mmHg)	102.1±27.2 58-146	90.2±27.9 (61-146)	78.8±13.3 (62-109)	83.9±12.2 (65-101)	80.8±15.7 (60-108)
$PaCO_2$ (mmHg)	41.7±7.8 32-64	42.4±9.8 25-66	40.5±7.7 (31-58)	40±5.5 (34-53)	38.4±4.2 (33-45)
SaO_2 (%)	96.6±2.1 91.3-99.6	96.1±2.7 90-99	96±1.9 (92-98)	96.3±2 (93-99)	94.8±2.5 (90-97)
PaO_2/FiO_2	190.5±61.5 96-335	189.2±64 82-315	171.4±48.8 (121-311)	171.3±51.8 (67-254)	180.3±46.1 (125-270)
HFNO flow (L minute-1)	51.3±4.9 40-60	46.7±8.3 20-60	45.9±4.1 (40-50)	43.6±5 (35-50)	42.2±8.7 (30-60)
FiO_2	0.5±0.1 0.4-1	0.4±0.1 (0.3-0.8)	0.4±0.1 (0.3-0.7)	0.49±0.08 (0.3-0.6)	0.46±0.07 (0.3-0.6)

PaO_2: Arterial oxygen partial pressure, $PaCO_2$: arterial carbon dioxide partial pressure, FiO_2: fractional inspired oxygen, SaO_2: arterial oxygen saturation, HFNO: high-flow nasal oxygen, SD: standard deviation, min: minimum, max: maximum

Table 4. Correlation between clinical features and pre-extubation respiratory parameters				
	HFNO duration after extubation (days)		ICU hospitalization (days)	
	r	p	r	p
Age (years)	-0.214	0.339	0.006	0.980
BMI (kg m^{-2})	-0.199	0.381	-0.140	0.536
Duration between semptom initiation and ICU admission (days)	-0.149	0.509	0.384	0.077
Duration between semptom initiation and intubation (days)	-0.158	0.483	0.374	0.086
APACHE-II score at ICU admission	0.117	0.603	0.381	0.080
SOFA score at ICU admission	0.384	0.078	0.186	0.408
Maximum SOFA score	0.352	0.109	0.346	0.114
PaO_2/FiO_2 before intubation	0.312	0.157	0.169	0.452
Duration of mechanic ventilation (days)	-0.334	0.129	0.476	0.025*
pH before extubation	0.438	0.041*	0.119	0.597
PO_2 before extubation (mmHg)	-0.254	0.253	-0.054	0.813
PCO_2 before extubation (mmHg)	-0.055	0.808	0.007	0.975
HCO_3 before extubation (mmol L^{-1})	0.109	0.628	0.138	0.541
Bas excess before extubation	0.137	0.542	0.117	0.605
SaO_2 before extubation (%)	-0.140	0.533	0.037	0.871
Respiratory rate before extubation	-0.069	0.762	0.196	0.382
Tidal volume before extubation (mL)	-0.017	0.941	-0.186	0.408
RR/Vt before extubation	-0.076	0.736	0.198	0.378
PEEP before extubation	0.094	0.678	-0.481	0.023*
Inspiration support before extubation	-0.409	0.059	0.284	0.200
FiO_2 before extubation	0.044	0.846	-0.434	0.043*
PaO_2/FiO_2 before extubation	-0.211	0.345	0.188	0.401

BMI: Body mass index, ICU: intensive care unit, APACHE-II: Acute Physiology And Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, HFNO: high-flow nasal oxygen, PaO_2: arterial oxygen partial pressure, FiO_2: fractional inspired oxygen, RR: respiratory rate, Vt: tidal volume, SaO_2: arterial oxygen saturation, PEEP: positive end-expiratory pressure, *Statistically significant

distance (7). Smoke simulation studies also demonstrated that dispersion with 60 L $minute^{-1}$ flow rate was similar to with a simple oxygen mask at 15 L $minute^{-1}$ flow rate (19,28). We followed the same rule that all patients wore a facial mask during HFNO treatment and the mean flow rates were lower than 50 L $minute^{-1}$ in 5 days' follow-up after extubation which we believed that sustained minimum dispersion.

The first limitation of this study is its retrospective nature. Second, we did not have a control group so that we were not able to compare the data with other oxygen support systems. We haven't used any fixed protocol in terms of time period after extubation. However, patients were switched to a standard oxygen mask when they fulfill the necessary clinical and respiratory criteria. Third, the number of patients might not be enough to come to any strong conclusion however we think that the rate of extubation success in our data of high risk of COVID-19 patients worth considering.

Conclusion

In extubated high-risk COVID-19-associated ARDS patients, HFNO therapy should be considered to prevent respiratory failure after post-extubation and reintubation.

Ethics

Ethics Committee Approval: After ethics approval was obtained from the İstanbul Faculty of Medicine Clinical Research Ethics Committee (decision no: 12, date: 29.05.2020).

Informed Consent: The written informed consent from individual patients was not obtained due to collection of the patients data retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.P., F.E., Design: P.E.Ö., Data Collection and Process: Ö.P., İ.A., G.O., V.T., E.Ç., M.K., M.M., Analysis or Interpretation: P.E.Ö., F.E., Literature Search: G.H.A., Writing: G.H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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