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Comparison of the effectiveness of high-flow and conventional nasal cannula oxygen therapy in pulmonary embolism patients with acute hypoxemic respiratory failure

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ABSTRACT

Comparison of the effectiveness of high-flow and conventional nasal cannula oxygen therapy in pulmonary embolism patients with acute hypoxemic respiratory failure

Introduction: The leading cause of mortality in pulmonary embolism (PE) is hypoxemic respiratory failure. The aim of this study was to compare the efficacy of high-flow nasal cannula (HFNC) and conventional nasal cannula (CNC) oxygen therapy in PE patients with hypoxemia.

Materials and Methods: Fifty-eight patients with a PaO_2/FiO_2 ratio below 300 who were admitted to the emergency department with acute respiratory distress and followed up in our intensive care unit due to PE between March and October 2019 were included in the study. One group (n= 29) received HFNC oxygen therapy and the other group (n= 29) received CNC oxygen therapy.

Results: Arterial blood gas analysis showed no significant differences in baseline SpO_2 and PaO_2 between the HFNC and CNC groups, whereas both values were significantly higher in the HFNC group starting at 1 hour (PaO_2 : p= .01, p= .001, p= .001; SpO_2 : p= .009, p= .005, p= .002). Among massive PE patients with contraindications for thrombolytic therapy, there was no significant difference between the HFNC and CNC groups in baseline SpO_2 , PaO_2 , or respiratory rate, but those who received HFNC therapy had significant higher SpO_2 starting at 15 minutes (p= .004 for all), significantly higher PaO_2 starting at 1 hour (p= .01, p= .001, p= .001), and significantly lower respiratory rate starting at 30 minutes (p= .003, p= .001, p= .001, p= .002, p= .002).

Conclusion: In patients presenting with PE and hypoxemic respiratory failure, HFNC oxygen therapy was more effective on both vital signs and arterial blood gas parameters compared to conventional oxygen therapy and can be used safely as primary treatment.

Key words: Acute respiratory distress syndrome (ARDS); oxygen therapy; conventional nasal cannula; high-flow nasal cannula; pulmonary embolism

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ÖZ

Akut hipoksemik solunum yetmezliği gelişen pulmoner emboli hastalarında yüksek akımlı nazal kanül ile oksijen tedavisinin etkinliğinin konvansiyonel oksijen tedavisi ile karşılaştırılması

Giriş: Pulmoner tromboemboli (PTE)'de en önemli mortalite nedeni hipoksik solunum yetmezliğidir. Çalışmamızda PTE'de gelişen hipoksi tedavisinde yüksek akımlı nazal kanül ve konvansiyonel nazal kanül ile takip edilen hastaların karşılaştırılması amaçlanmıştır.

Materyal ve Metod: Mart 2019 - Ekim 2019 tarihleri arasında yoğun bakım ünitemizde PTE nedeniyle yatan PaO_2/FIO_2 oranı 300'ün altında olan hastalar çalışmaya dahil edildi. Hastalar randomize bir şekilde iki gruba ayrıldı. Birinci grup (n= 29) yüksek akımlı nazal kanül (YANK) ile ikinci grup (n= 29) konvansiyonel nazal kanül (KNK) ile takip edildi.

Bulgular: YANK uygulanan hastalarda arter kan gazında bakılan SpO_2 ve PaO_2 değerlerinin ardışık takiplerinde 4. saate kadar anlamlı yükselişte olduğu gözlemlendi ($p= 0,001$, $p= 0,02$, $p= 0,001$, $p= 0,05$). KNK uygulanan hastalarda ise PaO_2 değeri YANK ile uyumlu artış göstermişken SpO_2 değerinde başlangıç ve 1. saat arasında anlamlı farklılık gösteren artışın 4. ve 24. saatler arasında tekrarladığı gözlemlendi ($p= 0,001$, $p= 0,05$, $p= 0,001$, $p= 0,03$). YANK uygulanan hastalarda solunum sayısı düzeyi başlangıç ile kıyaslandığında ilk 30. dakikada anlamlı düzeyde düşüş göstermişken, 30. dakikadan sonra 4. saatte ve 24. saatte düşüş devam etti. ($p= 0,02$, $p= 0,003$, $p= 0,008$) KNK'da ise başlangıça göre ilk değişim 30. dakikada gözlemlendi ve düşüş takip zamanlarında tekrarlanmadı. ($p= 0,02$). Kalp tepe atım düzeyi ise YANK uygulanan hastalarda başlangıça nazaran 30. dakikada anlamlı düşüş göstermişken takip saatlerinde bu değişim tekrarlanmadı ($p= 0,03$). KNK'da ise kalp tepe atım düzeyi takip zamanlarında anlamlı düşüş göstermedi.

Sonuç: PTE ile başvuran hastalarda YANK tedavisi konvansiyonel tedavilere nazaran gerek vital parametrelerde gerekse arter kan gazı parametrelerinde daha etkin özellikle olup başlangıç tedavisinde güvenle tercih edilebilir.

Anahtar kelimeler: Akut solunum sıkıntısı sendromu (ARDS); oksijen tedavisi; konvansiyonel nazal kanül; yüksek akım oksijen; pulmoner emboli

INTRODUCTION

Pulmonary thromboembolism refers to the pathology that develops when a thrombus, usually originating from veins in the lower extremity, moves through the venous system, through the right ventricle, and lodges in the pulmonary arteries. Pulmonary thromboembolism is frequently associated with deep vein thrombosis (DVT) (1,2).

Pulmonary embolism (PE) is one of the main causes of hypoxemic respiratory failure, which refers to a state of hypoxemia without hypercapnia. Obstruction of the pulmonary vascular bed by thrombosis disrupts gas exchange in some areas in the lungs, which triggers the release of mediators (serotonin/histamine) that evoke bronchoconstriction (3). This results in bronchoconstriction in terminal bronchioles, leading to hypoxemia due to subsequent ventilation/perfusion mismatch, reduced diffusion, and shunt development. In many patients, this causes elevated right ventricular pressure. When these patients present with severe hypoxemic respiratory failure, treatment with noninvasive mechanical ventilation further increases right ventricular load due to increased intrathoracic pressure. Therefore, the use of noninvasive mechanical ventilation is often not recommended for these patients in routine practice. Intensive care experience with such patients who present with severe hypoxemia has shown that favorable outcomes can be achieved with high-flow nasal cannula (HFNC) therapy (4).

HFNC is preferred in patients with hypoxemic respiratory failure refractory to oxygen therapy delivered by conventional nasal cannula (CNC). Because a mask is not used in follow-up with HFNC, it increases patient comfort compared to follow-up with noninvasive oxygen support (5,6). Despite high oxygen delivery rate with HFNC, it is better tolerated by patients than noninvasive and CNC oxygen therapy. In addition, its humidifying feature reduces mucus viscosity and facilitates secretion removal. In studies of intensive care patients presenting with severe respiratory failure, HFNC was found to be significantly superior to noninvasive mechanical ventilation in terms of morbidity and mortality (7).

The aim of the present study was to compare the effects of conventional oxygen therapy and follow-up with HFNC on vital signs and arterial blood gas parameters in the treatment of hypoxemic respiratory failure due to PE.

MATERIALS and METHODS

Study Design

Patients with PE admitted to the emergency service of Atatürk University Faculty of Medicine Hospital and hospitalized in the Intensive Care Unit between March-October 2019 were included in this prospective study. Before inclusion in the study, the patients or their relatives were informed in detail about the purpose of the study and the participants' written

informed consent was obtained. The study was approved in advance by the local ethics committee.

Study Population

The study included 58 high risk and intermediate-high risk PE patients with $\text{PaO}_2/\text{FIO}_2$ ratio below 300 who presented to our hospital with the most common complaint of sudden-onset chest pain and shortness of breath and were diagnosed with PE through diagnostic procedures. The patients were evaluated by physical examination, blood pressure measurements, peak heart rate, and finger-tip oxygen saturation monitoring every 15 minutes for the first hour, then at 4 and 24 hours. Arterial blood gas analysis was performed at admission and at 1, 4, and 24 hours.

High risk PE ($n=27$) was defined as sustained hypotension (systolic arterial pressure <90 mmHg or a drop in systolic arterial pressure of at least 40 mmHg for at least 15 min) and cardiogenic shock (including an altered level of consciousness, oliguria, or cool, clammy extremities). Patients with right ventricular dilatation and troponin I elevation without hypotension or signs of shock were classified as intermediate-high risk PE ($n=31$) while those with right ventricular dilatation but no troponin I elevation were considered intermediate-low risk PE.

Patients with high-risk PE who were under 65 years of age were given alteplase as a 10 mg bolus followed by 90 mg infusion over 2h, while patients over 65 years of age received half-dose alteplase. Starting immediately after thrombolytic therapy, enoxaparin sodium was administered at 12-h intervals. Patients with intermediate PE received enoxaparin sodium therapy at 12-h intervals. Intermediate-high risk PE patient group developed hypotension and shock in the first 72 h and were administered thrombolytic therapy as per the high-risk PE protocol.

The patients were randomly assigned to two groups (29 patients per group) by an independent physician by using Microsoft® Excel Data Randomizeon. Patients in Group 1 (HFNC group) received oxygen via HFNC using an Hft 500 (Mek-ics, South Korea) at fraction of inspired oxygen (FIO_2) of 33 and flow rate of 33 L/min. Patients in Group 2 (CNC group) received oxygen via CNC using the hospital's central system with a FIO_2 of 33 and a flow rate of 3 L/min.

Exclusion Criteria

Patients with history of myocardial infarction and associated treatment in the past 3 months, severe hypoxic respiratory failure, PE with concomitant intracranial hemorrhage, diagnosed malignancy, or known history of right heart dilation were not included in the study. Patients who had $\text{PaO}_2/\text{FIO}_2$ ratio below 300 or and required invasive mechanical ventilation according to the Berlin diagnostic criteria during follow-up were also excluded (8).

Measurement of Biochemical Markers

Venous blood samples were obtained from all patients from an antecubital vein after at least 15 min of semi-supine rest. All blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) to prevent coagulation. Troponin I concentrations were measured by chemiluminescent immunoassay using an Immulite 2500 (Siemens Medical Solutions, Erlangen, Germany).

Statistical Analysis

In order for the study to be statistically significant, with the result of Power analysis using the G * Power program, the sample size was determined as 58. Analyses were performed using IBM SPSS Statistics version 20 software (IBM Corp., Armonk, NY). The results were summarized using mean, standard deviation, median, minimum, maximum, number, and percentage values. Continuous variables were tested for normal distribution using Shapiro–Wilk W test if the sample size was <50 and Kolmogorov–Smirnov test was used if the sample size was >50 . Inter-group comparisons were made using independent-samples t test for normally distributed data and Mann–Whitney U test for non-normally distributed data. Paired-samples t test was used to compare data within groups. For multiple comparisons within the groups, repeated measures ANOVA test was used for normally distributed data and Friedman's test for non-normally distributed data. After repeated-measures test, post-hoc tests were performed using Tukey's test if variances were homogenous and with Tamhane's T2 test if not. Friedman's test was followed by post-hoc Friedman 2-way ANOVA by ranks (k samples) test. In 2×2 comparisons between categorical variables, Pearson's chi-square test was used if the expected value was >5 , Yates' chi-square test was used if the expected value was between 3 and 5, and Fisher's exact test was used if the expected value was

<3. A p value <0.05 was considered statistically significant.

RESULTS

A total of 58 PE patients with $\text{PaO}_2/\text{FIO}_2$ below 300 were evaluated in the study. Patients in the HFNC group had a mean age of 67.34 years (20-89 years); 44.8% were females and 55.2% were males. In the CNC group, mean age was 66.00 years (25-93); 51.7% were females and 48.3% were males.

Of the 29 patients treated with HFNC, 48.3% (n= 14) were evaluated as high-risk PE and 51.7% (n= 15) as intermediate PE. Of the 29 patients followed up with CNC, 44.8% (n= 13) had high risk PE and 55.2% (n= 16) had intermediate PE. Thrombolytic therapy was administered to 17.2% (n= 5) of the patients followed up with HFNC and 27.6% (n= 8) of the patients followed up with CNC. There was no significant difference in distribution of PE severity between the HFNC and CNC groups (p= 0.792). There was also no significant difference between the groups in the frequency of thrombolytic therapy (p= .345). Comparison of the rates of thrombolytic treatment by embolism severity showed that thrombolytic treatment was administered significantly more frequently to patients with massive PE (p= .001).

Follow-up arterial blood gas parameters of patients in the HFNC and CNC groups are shown in Table 1. Serial measurements showed that SpO_2 and PaO_2 increased significantly until hour 4 in patients treated with HFNC (p= 0.001, p= .02, p= .001, p= .05, respectively). In the CNC group, PaO_2 value increased significantly as seen in the HFNC group, while SpO_2 values increased significantly between baseline and 1 hour and again between 4 and 24 hours (p= 0.001, p= 0.05, p= 0.001, p= 0.03). Baseline pH, SpO_2 , PaO_2 , PaCO_2 , and HCO_3 values showed no significant difference between the HFNC and CNC groups.

In follow-up measurements, SpO_2 and PaO_2 values were significantly higher in the HFNC group at all time points, while no significant differences were detected in the other parameters (SpO_2 : p= .009, p= .005, p=.002, PaO_2 : p= 0.01, p= .001, P= .001).

Vital signs during the follow-up of patients treated with HFNC and CNC are shown in Table 2. In serial measurements of fingertip SpO_2 , the first significant difference was detected between baseline and 30 minutes, and the next change after 30 minutes was observed at 24 hours (p= .006, p= .008). In the HFNC group, respiratory rate was significantly lower at 30 minutes compared to baseline and the significant decrease continued at 4 and 24 hours (p= .02, p= .003, p= .008). In the CNC group, respiratory rate was reduced at 30 minutes compared to baseline but not at later time points (p= .02). In the HFNC group, cardiac apex beat was significantly decreased at 30 minutes compared to baseline but not at later time points (p= .03). The CNC exhibited no change in cardiac apex beat at any time point. No significant changes in systolic and diastolic blood pressure compared to baseline were observed in the HFNC patients, whereas the CNC group showed a significant decrease only at 15 minutes (p= .04).

Thrombolytic therapy could not be administered to 14 patients despite the presence of high-risk PE due to history of major surgery in the last 3 weeks (n= 5), bleeding diathesis (n= 4), ischemic stroke in the last 6 months (n= 3), and central nervous system tumor (n= 2). HFNC was used in 9 of these patients and CNC in 5 of these patients. Vital signs and ABG parameters that showed statistical differences during follow-up are shown in Table 3. While there was no statistically significant difference between the HFNC and CNC groups in terms of baseline fingertip SpO_2 and PaO_2 values, the HFNC group showed a greater increase after 15 minutes (SpO_2 : p= .004 for all,

Table 1. Comparison of arterial blood gas parameters in patients that received high-flow nasal cannula (HFNC) and conventional nasal cannula (CNC) oxygen therapy

HFNC/CNC	At admission	1 hour	4 hours	24 hours
pH	7.44 ± 0.06/7.41 ± 0.05	7.45 ± 0.05/7.44 ± 0.05	7.34 ± 0.55/7.43 ± 0.05	7.46 ± 0.06/7.45 ± 0.04
SpO_2 (%)	76 ± 12/74 ± 13	91 ± 6/86 ± 8*	94 ± 5/88 ± 8*	95 ± 4/91 ± 5*
PaO_2 (mmHg)	45 ± 10/45 ± 9	70 ± 19/59 ± 13*	79 ± 20/62 ± 13*	80 ± 17/66 ± 13*
PaCO_2 (mmHg)	34 ± 6/37 ± 9	33 ± 7/34 ± 8	34 ± 6/34 ± 8	35 ± 6/35 ± 6
HCO_3 (mmol/L)	23 ± 5/23 ± 5	23 ± 5/22 ± 4	23 ± 4/22 ± 4	24 ± 5/23 ± 4

*p< 0.05 in comparison of HFNC and CNC.

Table 2. Comparison of vital signs in patients that received high-flow nasal cannula (HFNC) and conventional nasal cannula (CNC) oxygen therapy

HFNC/CNC	At admission	15 min	30 min	45 min	1 hour	4 hours	24 hours
SpO ₂ (%)	76 ± 9/75 ± 10	88 ± 8/84 ± 8	91 ± 7/85 ± 7*	92 ± 6/86 ± 6*	92 ± 6/87 ± 7*	92 ± 5/89 ± 6*	94 ± 4/91 ± 4*
Respiratory rate (/min)	28 ± 8/28 ± 5	28 ± 7/27 ± 5	26 ± 7/26 ± 5	25 ± 6/26 ± 6	25 ± 8/26 ± 6	24 ± 7/25 ± 7	21 ± 5/24 ± 7
Cardiac apex beat (/min)	102 ± 19/97 ± 20	100 ± 17/92 ± 20	98 ± 16/94 ± 19	99 ± 15/94 ± 17	99 ± 16/99 ± 16	98 ± 17/93 ± 19	98 ± 16/94 ± 22
Systolic blood pressure (mmHg)	124 ± 21/129 ± 25	124 ± 23/124 ± 26	125 ± 22/125 ± 25	126 ± 20/125 ± 27	124 ± 20/124 ± 22	123 ± 20/120 ± 19	125 ± 18/120 ± 20
Diastolic blood pressure (mmHg)	75 ± 15/80 ± 14	76 ± 19/76 ± 15	77 ± 17/77 ± 17	75 ± 14/75 ± 16	77 ± 15/76 ± 16	74 ± 13/72 ± 14	78 ± 11/73 ± 15
* p< 0.05 in comparison of HFNC and CNC.							

Table 3. Comparison of SpO₂, respiratory rate, and PaO₂ values in blood gas analysis patients who could not receive thrombolytic therapy and were treated with HFNC and CNC oxygen therapy

HFNC/CNC	At admission	15 min	30 min	45 min	1 hour	4 hours	24 hours
SpO ₂ (%)	71 ± 13/72 ± 11	91 ± 7/79 ± 7*	91 ± 7/82 ± 3*	93 ± 4/85 ± 3*	94 ± 3/87 ± 3*	96 ± 2/89 ± 3*	95 ± 2/88 ± 3*
Respiratory rate (/min)	34 ± 8/32 ± 2	29 ± 7/33 ± 3	24 ± 4/32 ± 3*	22 ± 4/35 ± 4*	20 ± 4/32 ± 5*	17 ± 3/33 ± 6*	16 ± 2/32 ± 5*
PaO ₂ (mmHg)	44 ± 11/43 ± 8	-	-	-	71 ± 26/50 ± 3*	85 ± 23/60 ± 5*	90 ± 14/65 ± 7*
HFNC: High-flow nasal cannula, CNC: Conventional nasal cannula. * p< 0.05 in comparison of HFNC and CNC.

PaO₂: p= .01, p= .01, p= .001). In addition, respiratory rate was similar in the two groups at baseline but decreased significantly more in the HFNC group starting from 30 minutes (p= .003, p= .001, p= .001, p= 0.002, p= .002).

No mortality occurred in both groups in the first 24 hours of observation. In the phase after thrombolytic treatment, mortality occurred in only 2 patients (high risk PTE) due to intracranial bleeding and intra-abdominal bleeding.

DISCUSSION

Our comparison of oxygen therapy provided with HFNC and CNC in patients with hypoxemic respiratory failure due to PE showed that SpO₂ and PaO₂ values increased more rapidly and for longer with HFNC compared to CNC. In the analysis of vital signs, it was observed that respiratory rate decreased until 30 minutes and continued after 4 hours in the HFNC group, whereas the decrease in respiratory rate in the CNC group was not observed after the first 15 minutes until the 4 hours. Cardiac apex beat decreased for the first 30 minutes in the HFNC group, but no significant decrease was detected in the CNC group. In massive PE patients who could not receive thrombolytic therapy, the use of HFNC was more effective than CNC on SpO₂ and PaO₂ levels and respiratory rate.

Despite recent advances in diagnostic and therapeutic options, PE is still associated with high mortality and morbidity. Early clinical diagnosis and treatment play an important role in reducing mortality (9,10). Obstruction of the pulmonary vascular bed by thrombosis disrupts gas exchange in some areas in the lungs, which triggers the release of serotonin and histamine, mediators that induce bronchoconstriction (11). The release of these mediators leads to bronchoconstriction in the terminal bronchioles. As a result, hypoxemia develops due to ventilation/perfusion mismatch, reduced diffusion, and shunt development. Hypocapnia occurs due to tachypnea induced by impaired perfusion (12). Vasoconstriction triggered by mechanical obstruction and inflammatory mediators causes an increase in pulmonary arterial pressure. Hypoxia due to dead space ventilation and right ventricular failure is one of the main causes of mortality in PE (13).

Oxygen therapy is as important as early reperfusion therapy in the correction of severe hypoxemia. Progressive hypoxemia can cause renal dysfunction

and the development of ischemic hepatitis secondary to hypoxia. Multiple organ dysfunction increases rates of morbidity and mortality in PE. Oxygen therapy is essential in PE and the target saturation should be above 92% (14). Oxygen therapy with CNC has become the treatment of choice for patients hospitalized for PE. The flow rate in CNC oxygen therapy can be increased up to 15 L/min. However, this may not always be adequate to meet the oxygen demand of a patient with acute respiratory failure. In patients with such refractory hypoxemia, noninvasive and invasive mechanical ventilation can also be used before it progresses to a point that will further increase right ventricular dysfunction. Oxygen therapy with HFNC, which has recently been introduced for use in adults and is being studied for its benefits for many clinical conditions, is a safe and beneficial supportive therapy that can be used at very high flow rates (100 L/min) after the oxygen is heated and humidified (15).

The HFNC apparatus consists of an air/oxygen blender, active heater, humidifier, and nasal cannula. The FIO₂ can be adjusted from 0.21 (room air) to 1.0 (pure oxygen) by the air/oxygen blender. With an active humidifier, the oxygen is saturated with water vapor. The unidirectional inspiratory circuit hose heats the humidified oxygen up to 37°C and delivers it to nasal cannula (16). HFNC oxygen therapy is used in conditions characterized by hypoxemia, such as pneumonia, cardiogenic pulmonary edema, interstitial lung disease, and PE (17). In addition, there are studies on its use in COPD, which is associated primarily with hypercapnic respiratory failure. It is also used in post-extubation respiratory failure, which requires a high FIO₂, as well as in carbon monoxide poisoning (18-20).

Based on the results of our study evaluating patients hospitalized due to PE, HFNC therapy had a greater effect on both arterial blood gas parameters and vital signs than CNC therapy. Vital signs have an important place in the treatment and follow-up of patients hospitalized for PE. Due to various conditions that constitute absolute/relative contraindications, thrombolytic therapy cannot be administered to all patients with high-risk PE. During this follow-up period, patients may be lost due to hypoxemic respiratory failure and subsequent organ dysfunction. In the present study, when HFNC oxygen therapy was compared with CNC oxygen therapy in the follow-up of 14 high-risk PE patients with contraindications to thrombolytic therapy, we observed that vital signs

and arterial blood pressure values improved earlier with HFNC. This may offer guidance in the prevention of secondary organ damage in high-risk PE patients with hypoxemic respiratory failure who cannot receive thrombolytic therapy.

The present study analyzed the vital signs and arterial blood gas parameters of patients followed for PE during the first 24 hours only. More comprehensive studies are needed to report the long-term effects of these two treatment modalities on chronic thromboembolism, pulmonary hypertension, and survival, as well.

In conclusion, our comparative study of HFNC and CNC oxygen therapy is the first to compare these two treatment modalities in PE. In patients presenting with hypoxemic respiratory failure, HFNC oxygen therapy was more effective on both vital signs, and arterial blood gas parameters compared with conventional oxygen therapy and can be used safely as primary treatment.

Ethical Committee Approval: This study approval was obtained from Atatürk University Faculty of Medicine Clinical Researches Ethical Committee (Decision no: 36, Date: 22.04.2019).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: AA

Analysis/Interpretation: BK

Data acquisition: AA

Writing: AA

Clinical Revision: EYU

Final Approval: LS

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