УДК 616-08:616-24"713"
DOI: 10.25284/2519-2078.4(101).2022.275110

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EFFECT OF NONIVASIVE POSITIVE-PRESSURE VENTILATION ON OUTCOME IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A RANDOMIZED CONTROLLED TRIAL

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Abstract. Non-invasive positive pressure ventilation (NiPPV) is known to be effective in hypercapnic respiratory failure. However, some uncertainty still exists regarding its use in certain subgroups of patients with main consideration that, if ineffective, NiPPV delays time to intubation and may worsen the outcome. 58 subjects with acute exacerbation of COPD, resulting in ICU admission, were included into the randomized, single-blind, controlled study. Study group was treated with NiPPV in PSV or BiLevel mode and increased FiO2, control group – with O2 therapy only. Medical therapy was prescribed to study participants regardless of their group allocation. Rate of tracheal intubation in study group was 7 (25 %) compared to 20 (67 %) in control group (p<0,0001). Relative risk reduction (RRR) was 61,5 % (95 % CI 23-80 %) and absolute risk reduction for study group was 42,0 % (95% CI 17,6-62). Mortality rate in the control group was 36.6 % (11 deaths), while in the study group the mortality rate was 21.4 % (6 deaths). Relative risk of death for the study group in comparison with the control group was found at the level of 0.56 (95 % CI 0.25 – 1.29). Relative risk of death reduction was 43.4 % (95% CI 28.7 – 75.1). Absolute risk of death reduction was 15.2 % (95% CI 5.39 – 38.2). The hospital lengths of stay in the study group was 20.8±11.3 days, in the control group 29.1±12.3 days (p=0.063). Regarding ICU length of stay, no significant difference was found between the groups: 14.7±12.2 days and 10.8±7 days in the control and study groups, respectively (p=0.178).

Conclusion: we found evidence in favor of efficacy of NiPPV in COPD patients with acute exacerbation in terms of mortality and tracheal intubation. No difference in hospital and ICU length of stay was found. No evidence of additional risk, related to NiPPV, were found.

Keywords: COPD, hypercapnic respiratory failure, mechanical ventilation, non-invasive ventilation Introduction.

The course of chronic obstructive pulmonary disease (COPD) is characterized by periods of exacerbation, leading to the worsening of the clinical state of patients and requiring hospitalization, additional visits and, often, ventilatory support [1]. The treatment of patients with COPD and acute respiratory failure with non-invasive ventilation (NIV) improves outcomes [1, 2], but persistent hypercapnia, associated with increased mortality [3, 4] and early re-hospitalization, might persist [5, 6].

Murphy et al., 2017 [7] showed that among patients with persistent hypercapnia, following an acute COPD exacerbation, early initiation of non-invasive positive pressure ventilation prolonged the time to re-hospitalization or death by 12 months.

In our single center randomized clinical trial, we hypothesized that early use of non-invasive positive pressure ventilation (NiPPV) applied to a group of COPD patients with acute exacerbation, treated in ICU settings, could improve the patients' treatment outcomes, especially mortality, and reduce the intubation rate, compared to similar patients treated with standard of care, including oxygen therapy with different devices.

2. MATERIALS AND METHODS

2.1. Study Design and Data Collection.

This was a prospective randomized controlled trial involving a single center, the ICU of Kyiv City Hospital #4, and it included subjects affected by acute

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exacerbation of COPD. The study protocol was defined according to the Consolidated Standard of Reporting Trials (CONSORT) guidelines and was approved by the Ethics Committee of Bogomolets National Medical University. Written informed consent was obtained from all the patients before they entered the study. The study was conducted following the principles of the Declaration of Helsinki.

2.2. Participants.

The recruitment of the participants was carried out from January 2018 to October 2020, with an interruption due to COVID-19 lockdowns and temporary hospital admission regulations change from February to September 2020, at the Kyiv City Clinical Hospital #4 (Kyiv, Ukraine). Research team screened all patients, admitted to ICU or Respiratory care unit within 12 hours after admission.

Participants were included if they fulfilled the following criteria:

- A diagnosis of moderate to severe chronic obstructive pulmonary disease (COPD) according to Vogelmeier et al. [17], both new or known from patient's history.
- Age ranging from 18 to 80 years.
- No COVID-19-related infections associated.
- Exacerbation of COPD with at least two of the following criteria present on admission:
  - Respiratory rate (RR) > 30 per minute.
  - Active involvement of accessory respiratory muscles.
  - Hypercapnia (PaCO2 > 50 mm Hg).
  - Respiratory acidosis (pH< 7.33).

The exclusion criteria were:

- Lack of participation consent from a candidate.
- Advanced heart disease (NYHA class > 2) classes of heart failure (American Heart Association) [21] or hemodynamic instability (vasopressors needed on admission).
- Intubation within 6 hours after admission.
- Severe neurologic conditions (non-hypercapnic coma, disabling stroke, cognitive impairment (Mini-Mental State Examination < 24) [20].
- Facial scull abnormalities, incompatible with proper NIV interface fitting
- History of COPD-related ICU admission, intubation or tracheostomy placement within year before screening.

2.3. Interventions

After screening, the patients were randomized (1:1) using a dedicated web application (https://www.randomizer.org/) and assigned to either the experimental group (NIV+O2) or the control group (only O2). Due to nature of the intervention, this was a single-blind study, and only the statistician involved in the analysis was blind to the group allocation.

Participants were allocated to one of two study groups:

(1) The experimental group (EG): COPD exacerbation patients undergoing medical treatment and NiPPV, using one of three available ventilators: Hamilton C1 (Hamilton Medical AG, Switzerland), Draeger Carina and Draeger Savina (Drägerwerk AG & Co. KGaA, Germany). Ventilation was performed in pressure support (PSV) and biphasic positive airway pressure (BiPAP) modes. The initial level of inspiratory support was set to 12 cm H2O. Later, it was adjusted to reach respiratory volumes of 6-8 ml/kg and respiratory rate < 30 per minute. Initially, the PEEP level was set to 5 cm H2O, and further changed in steps of 1 cm H2O to reach SpO2 > 90% using the lowest possible FiO2 level.

(2) The control group (CG): COPD exacerbation patients undergoing only medical treatment and supplementary oxygen, without NiPPV or CPAP applications by any mean (including PEEP masks). Participants in the control group had oxygen administered through a nasal cannula, Venturi mask or non-rebreathing mask.

2.4. Medical treatment

All medications to study participants were prescribed and monitored by hospital-employed, board-certified pulmonary disease specialists according to current guidelines. Those specialists weren't a part of study staff, acting totally independent, and were blind regarding group allocation.

2.5. Intubation criteria

Patients from both groups were considered for intubation, using the following criteria: respiratory arrest; new-onset severe hemodynamic instability; deterioration of consciousness level or increasing agitation; increase in respiratory rate > 35/min; failure to achieve and maintain SpO2 > 90%; failure to achieve and maintain PaCO2 < 50 mm Hg; the patient's inability to effectively clear sputum, tolerate facial mask or inability to cooperate. Both study staff and on-duty ICU doctors were eligible for final decision making regarding intubation.

2.6. Measurements

Blood gas analyses were performed through an arterial blood withdrawal of 2 mL of arterial blood from the radial or femoral artery using a specific needle and syringe and the use of a blood gas analyzer (EasyBloodGas, Medica Corporation, USA).

Pulse oximetry (SpO2) was performed by using bedside monitors and appropriate sensors, made by Hihon Kohden (Japan)

SAPS-II, Murray and GOLD scales were measured by study staff.

A lung functional test (spirometry) was performed by a respiratory therapist following the latest guidelines [27-9] and using a spirograph (SpiroBank I, MIR, Italy).

Table 1. Initial characteristics of study participants

	Study group (n=28)	Control group (n=30)	P value
Gender (M/F)	17/11	16/14	0,684
Median age (years)	50,8±16,5	49,6±17,8	0,427
Age interval (years)	27-86	17-83	
SAPS-II (points)	26,8±8,2	27,9±8,3	0,2
Murray (points)	2,1±0,5	1,8±0,6	0,312
GOLD stage	3,37±0,6	3,64±0,7	0,16

Table 2. GOLD staging of study participants.

	Study group, n (%)	Control group, n (%)
GOLD I	5 (6,9%)	7 (6%)
GOLD II	7 (32,76%)	6 (24%)
GOLD III	10 (41,38%)	10 (42%)
GOLD IV	6 (20,69%)	7 (28%)
Total:	28 (100%)	30 (100%)

2.7. Outcome Measures

The primary outcome measure was the change in intubation rate between study and control group.

In-hospital mortality, as well as length of hospitalization and ICU stay, were considered as secondary outcomes.

2.8. Statistical Analysis

For all the outcome measures, summary descriptive statistics were calculated at baseline to assess any changes in the scores by study group and between times. Given the relatively small sample size and our expectation of a non-Gaussian distribution, we opted for the use of non-parametric tests. The differences between the two groups were then analyzed using the Mann–Whitney U-Test, while the internal analyses were conducted using the Wilcoxon test. The significance level was set at 0.05. All analyses were performed using the statistical software Statistica (version 6.1).

3. RESULTS

A pool of 110 moderate to very severe COPD individuals in acute exacerbation were identified. Among them, 42 were then excluded because they did not meet the inclusion criteria, and 10 more were excluded later due to early intubation (within 6 hours) or initially unknown history of ICU admission. 58 COPD subjects finally took part in the study. All patients in the study sample were receiving inhalation therapy. Out of the total, 74 % had triple therapy and the remaining percentage received double therapy. In particular, for the intervention group, 75% followed a triple therapy program, while in the control group, the same therapy was received by 73% of the patients. All the subjects participated until the end of the study. At baseline, the experimental and the control group were compatible regarding their sociodemographic features, GOLD stage and acute physiology score (Table 1).

Exact distribution between GOLD stages is shown in Table 2.

3.1. Primary Outcome

Rate of tracheal intubation in study group was 7 (25 %) compared to 20 (67 %) in control group ($p<0,0001$). Relative risk reduction (RRR) was 61,5 % (95 % CI 23-80 %) and absolute risk reduction for study group was 42,0 % (95 % CI 17,6-62). Intubation risk is shown at Fig. 1.

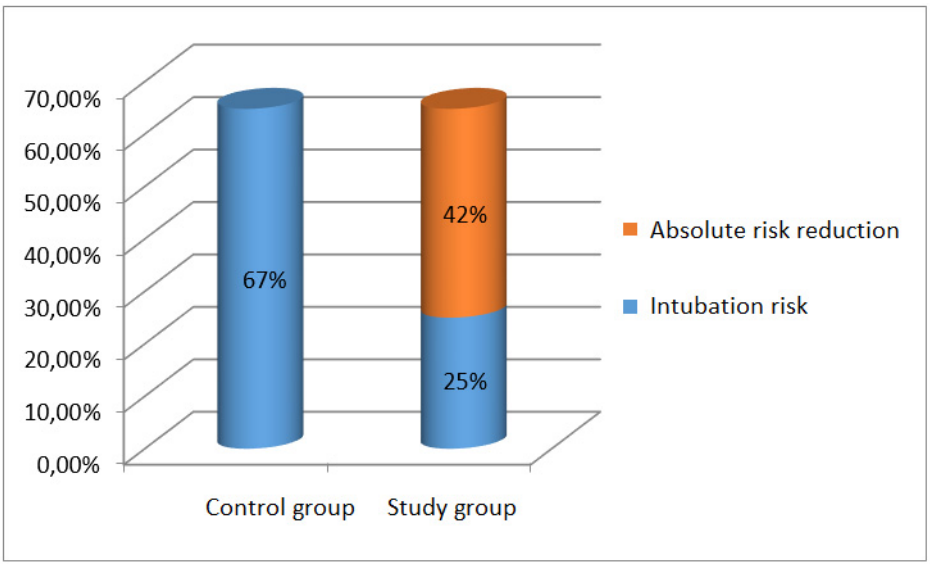

Figure 1. Intubation risks and absolute risk reduction.

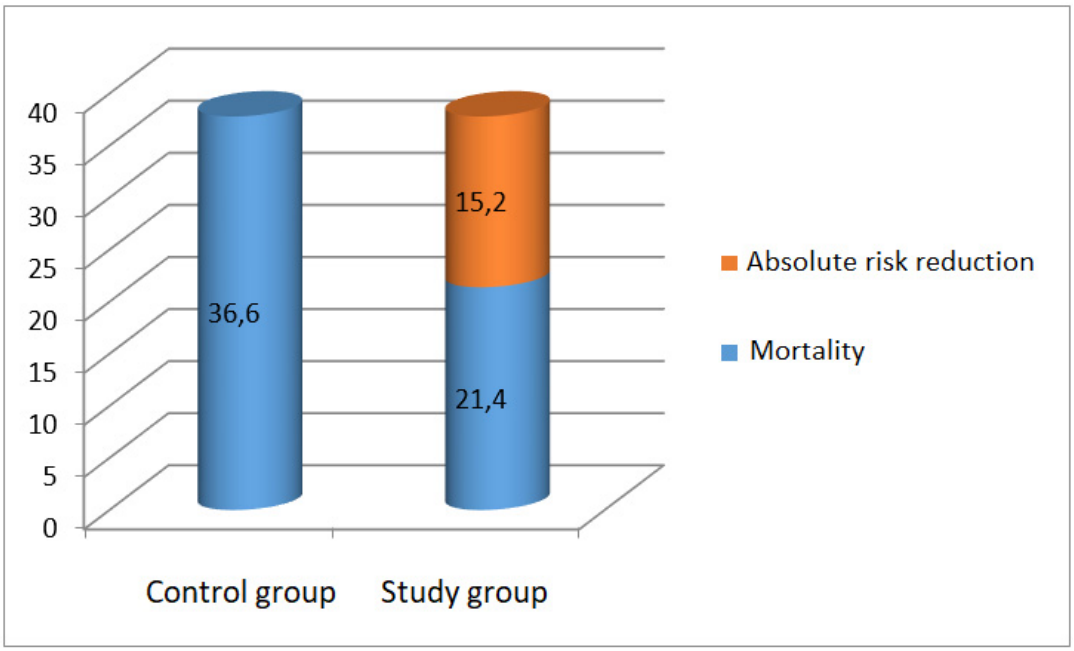

Figure 2. Absolute risks of death.

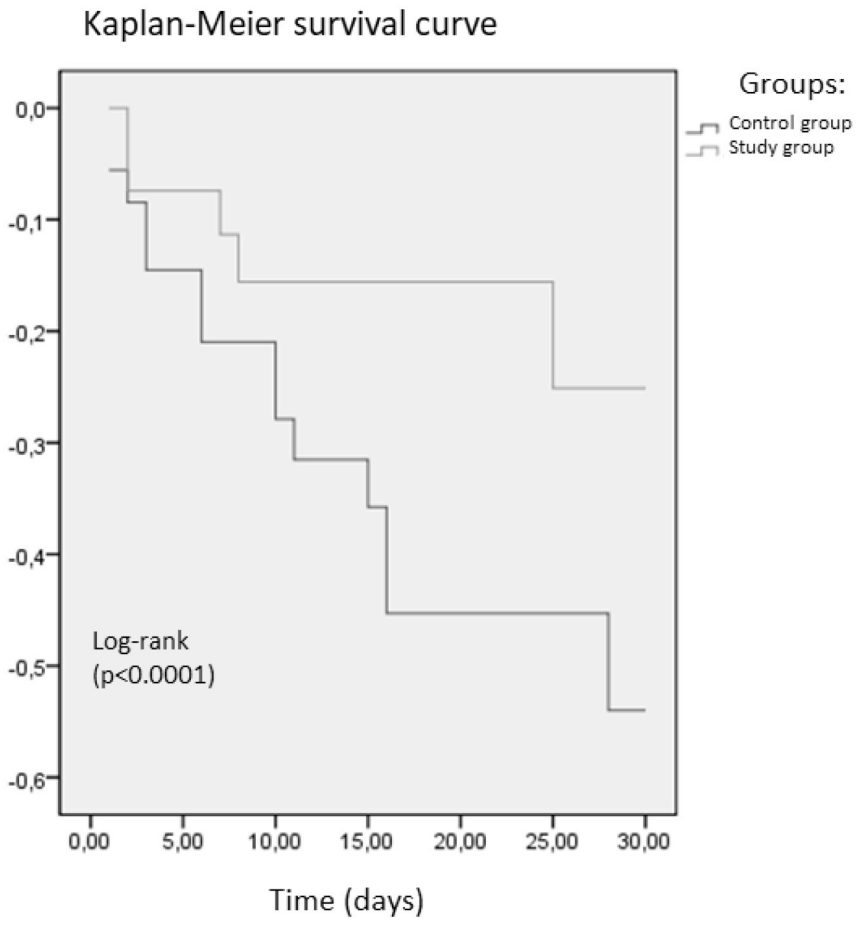

Figure 3. Kaplan-Meier 30-days survival curve for both groups.

3.2. Secondary Outcomes

Our quantitative analysis showed that mortality rate in the control group was 36.6 % (11 deaths), while in the study group the mortality rate was 21.4 % (6 deaths). Relative risk of death for the study group in comparison with the control group was found at the level of 0.56 (95 % CI 0.25 – 1.29). Relative risk of death reduction was 43.4 % (95 % CI 28.7 – 75.1). Absolute risk of death reduction was 15.2 % (95% CI 5.39 – 38.2). Absolute risks of death for both groups are shown at Fig.2.

Additionally, we performed a 30 days mortality analysis with Kaplan-Meier estimator (figure 3).

The hospital lengths of stay (HLoS) in the study group was 20.8±11.3 days, while in the control group this indicator was 29.1±12.3 days, with the P-value approaching significance threshold (p=0.063). When analyzing ICU length of stay (ILoS), no significant difference was found between the groups: 14.7±12.2 days and 10.8±7 days in the control and study groups, respectively (p=0.178).

4. DISCUSSION

Exacerbation of COPD is a common respiratory disease that continues to be a major public health problem and results in significant morbidity and mortality worldwide [37--10]. However, the average mortality rates, according to different sources, differ significantly. In the study by Nair et al. [38-11] reported that the mortality rate for patients with exacerbation of COPD is < 5% for outpatients, rises to 10 % of patients hospitalized in specialized departments and may exceed 30 % in patients admitted to the intensive care unit, which in general coincides with the results obtained by us in the group of conventional tactics of respiratory support. According to other studies [39-12], the mortality rate in patients with severe COPD reaches 58 %.

Despite significant bundle of evidence that NiPPV is effective in COPD exacerbation treatment, still some experts are in doubt about it, mainly because, in case of NiPPV failure, intubation may be delayed, that may worsen the outcome [11].

In our single center, in a randomized clinical trial that enrolled COPD patients with hypercapnic respiratory failure, we found that use of non-invasive ventilation significantly reduces intubation rate and in-hospital mortality. More specifically, no evidence that initial 6 hours NiPPV trial may worsen the outcome of patients with NiPPV failure, were not found. The risk-benefit ratio is clearly in favor of NiPPV in this cohort of patients.

However, this study wasn't designed for assessing mortality as a primary outcome, and a stricter protocol with clear intention-to-treat analysis may be required to confirm the findings.

Unfortunately, long-term follow-up, readmission rate and 1-year mortality were left outside of a scope of our study. However, some significant evidence about long-term outcomes improved by NiPPV exists, prompting further work in that field.

Ranieri et al. reported a mortality rate of 20 % at the 6-year follow-up in a group of older COPD patients discharged after a non-acidotic exacerbation [12].

Some studies have shown that the female gender is more predisposed to developing COPD, with a predominance of small airway disease, probably due to a sex-related differences in the expression and activity of cytochrome P450 enzymes. Moreover, women with severe COPD have a higher risk of hospitalization and death from respiratory failure [40-13, 41-14]. In our study, we did not observe such differences, possibly because of the complexity and clinical severity of the patients included. However, this issue has not been investigated, and it will be the topic of future studies.

No significant difference in ICU and hospital length of stay was found, which might be explained to some in-patient policies in the hospital, and hospital length of stay is not a key performance indicator (KPI) for department staff.

5. CONCLUSION

In our study, we found that the sample of patients recruited with COPD exacerbation showed significantly lower intubation rate and in-hospital mortality for patients, treated with non-invasive positive pressure ventilation than with the standard of care. No significant difference was found in hospital length of stay and in ICU length of stay. No evidence in favor of additional risk for patients with initial NiPPV failure were found.

Фінансування / Funding
Немає джерела фінансування / There is no funding source.
Конфлікт інтересів / Conflicts of interest
Усі автори повідомляють про відсутність конфлікту інтересів / All authors report no conflict of interest
Етичне схвалення / Ethical approval
Це дослідження було проведено відповідно до Гельсінської декларації та затверджено місцевим комітетом з етики досліджень / This study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee.
Надійшла до редакції / Received: 20.11.2022
Після доопрацювання / Revised: 02.12.2022
Прийнято до друку / Accepted: 29.12.2022
Опубліковано онлайн /Published online: 31.12.2022

REFERENCE

1. *Brochard L. Noninvasive Ventilation for Acute Exacerbations of Chronic Obstructive Pulmonary Disease. N. Engl. J. Med. 1995;333:817–822. [Електронний ресурс] / Brochard L., Mancebo J., Wysocki M., Lofaso F., Conti G., Rauss A., Simonneau G., Benito S., Gasparetto A., Lemaire F., et al. Режим доступу до ресурсу: doi: 10.1056/NEJM199509283331301.*
2. *Bott J. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. Lancet. 1993;341:1555–1557. [Електронний ресурс] / Bott J., Carroll M., Conway J., Keilty S., Ward E., Brown A., Paul E., Elliott M., Godfrey R., Wedzicha J., et al. Режим доступу до ресурсу: doi: 10.1016/0140-6736(93)90696-E.*
3. *Connors A.F. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand*

Prognoses and Preferences for Outcomes and Risks of Treatments) Am. J. Respir. Crit. Care Med. 1996;154:959–967. [Електронний ресурс] / Connors A.F., Jr., Dawson N.V., Thomas C., Harrell F.E., Jr., Desbiens N., Fulkerson W.J., Kussin P., Bellamy P., Goldman L., Knaus W.A. Режим доступу до ресурсу: doi:10.1164/ajrccm.154.4.8887592.

4. *Murray I., Paterson E., Thain G., Currie G.P. Outcomes following non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease. Thorax. 2011;66:825–826. [Електронний ресурс] / Режим доступу до ресурсу: doi: 10.1136/thx.2010.152264.*
5. *Chu C.M., Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. Thorax. 2004;59:1020–1025. [Електронний ресурс] / Chu C.M., Chan V.L., Lin A.W.N., Wong I.W.Y., Leung W.S., Lai C.K.W. Режим доступу до ресурсу: doi: 10.1136/thx.2004.024307.*
6. *Suh E.-S., Neural respiratory drive predicts clinical deterioration and safe discharge in exacerbations of COPD. Thorax. 2015;70:1123–1130. [Електронний ресурс] / Suh E.-S., Mandal S., Harding R., Ramsay M., Kamalanathan M., Henderson K., O'Kane K., Douiri A., Hopkinson N.S., Polkey M.I., et al. Режим доступу до ресурсу: doi: 10.1136/thoraxjnl-2015-207188.*
7. *Murphy P.B. Effect of Home Noninvasive Ventilation with Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017;317:2177–2186. [Електронний ресурс] / Murphy P.B., Rehal S., Arbane G., Bourke S., Calverley P.M.A., Crook A.M., Dowson L., Duffy N., Gibson G.J., Hughes P.D., et al. Режим доступу до ресурсу: doi: 10.1001/jama.2017.4451.*
8. *Atwood C.W. Impact of Heated Humidified High Flow Air via Nasal Cannula on Respiratory Effort in Patients with Chronic Obstructive Pulmonary Disease. Chronic Obstr. Pulm. Dis. J. COPD Found. 2017;4:279–286. [Електронний ресурс] / Atwood C.W., Camhi S., Little K.C., Paul C., Schweikert H., Macmillan N.J., Miller T.L. Режим доступу до ресурсу: doi: 10.15326/jcopdf.4.4.2017.0169.*
9. *Graham B.L Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am. J. Respir. Crit. Care Med. 2019;200:e70–e88. [Електронний ресурс] / Graham B.L., Steenbruggen I., Miller M.R., Barjaktarevic I.Z., Cooper B.G., Hall G.L., Hallstrand T.S., Kaminsky D.A., McCarthy K., McCormack M.C., et al. Режим доступу до ресурсу: doi: 10.1164/rccm.201908-1590ST.*
10. *Zhang F. Effect of muscle training on dyspnea in patients with chronic obstructive pulmonary disease: A meta-analysis of randomized controlled trials. Medicine. 2021;100:e24930. [Електронний ресурс] / Zhang F., Zhong Y., Qin Z., Li X., Wang W. Режим доступу до ресурсу: doi: 10.1097/MD.0000000000024930.*
11. *Schroff P. Pulmonary Rehabilitation Improves Outcomes in Chronic Obstructive Pulmonary Disease Independent of Disease Burden. Ann. Am. Thorac. Soc. 2017;14:26–32. [Електронний ресурс] / Schroff P., Hitchcock J., Schumann C., Wells J.M., Dransfield M.T., Bhatt S.P. Режим доступу до ресурсу: doi: 10.1513/AnnalsATS.201607-551OC.*
12. *Ranieri P. Predictors of 6-Month Mortality in Elderly Patients with Mild Chronic Obstructive Pulmonary Disease Discharged from a Medical Ward After Acute Nonacidotic Exacerbation. J. Am. Geriatr. Soc. 2008;56:909–913. [Електронний ресурс] / Ranieri P., Bianchetti A., Margiotta A., Virgillo A., Clini E.M., Trabucchi M. Режим доступу до ресурсу: doi: 10.1111/j.1532-5415.2008.01683.x.*
13. *Barnes P.J. Sex Differences in Chronic Obstructive Pulmonary Disease Mechanisms. Am. J. Respir. Crit. Care Med. 2016;193:813–814. [Електронний ресурс] / P. J. Barnes., Режим доступу до ресурсу: doi: 10.1164/rccm.201512-2379ED.*
14. *Gudmundsson G. Mortality in COPD patients discharged from hospital: The role of treatment and co-morbidity. Respir. Res. 2006;7:109. [Електронний ресурс] / Gudmundsson G., Gislason T., Lindberg E., Hallin R., Ulrik S.C., Brøndum E., Nieminen M.M., Aine T., Bakke P., Janson C. Режим доступу до ресурсу: doi: 10.1186/1465-9921-7-109.*

ДЬОМІН Є., ДУБРОВ С., ГЛУМЧЕР Ф.

ВПЛИВ НЕІВАЗИВНОЇ ВЕНТИЛЯЦІЇ З ПОЗИТИВНИМ ТИСКОМ НА РЕЗУЛЬТАТ У ПАЦІЄНТІВ З ГОСТРИМ ХРОНІЧНИМ ОБСТРУКТИВНИМ ЗАХВОРЮВАННЯМ ЛЕГЕНЬ: РАНДОМІЗОВАНЕ КОНТРОЛЬОВАНЕ ДОСЛІДЖЕННЯ

Відомо, що неінвазивна вентиляція з позитивним тиском (НіШВЛ) ефективна при гіперкапнічній дихальній недостатності. Проте все ще існує певна невизначеність щодо її використання в певних підгрупах пацієнтів, головним чином враховуючи те, що в разі неефективності, НіШВЛ продовжує час до інтубації, що може погіршити результат. У рандомізоване сліпе контрольоване дослідження було включено 58 пацієнтів із загостренням ХОЗЛ, що призвело до госпіталізації у відділення інтенсивної терапії. Групу дослідження лікували НіШВЛ у режимі PSV або BiLevel і збільшували FiO2, контрольну групу — лише оксигенотерапією. Медикаментозна терапія була призначена учасникам дослідження незалежно від їх групового розподілу. Частота інтубації трахеї в основній групі становила 7 (25 %) проти 20 (67 %) у контрольній групі (p <0,0001). Відносне зниження ризику (RRR) становило 61,5 % (95 % ДІ 23 – 80 %), а абсолютне зниження ризику для групи дослідження становило 42,0 % (95 % ДІ 17,6-62). Смертність у контрольній групі становила 36,6 % (11 померлих), а в основній — 21,4 % (6 померлих). Відносний ризик смерті для досліджуваної групи порівняно з контрольною групою виявлено на рівні 0,56 (95 % ДІ 0,25 – 1,29). Зменшення відносного ризику смерті становило 43,4 % (95 % ДІ 28,7–75,1). Абсолютне зниження ризику смерті становило 15,2% (95% ДІ 5,39–38,2). Тривалість перебування в стаціонарі в основній групі становила 20,8±11,3 доби, в групі контролю 29,1±12,3 доби (p=0,063). За тривалістю перебування у ВІТ достовірної різниці між групами не виявлено: 14,7±12,2 дня та 10,8±7 дня в контрольній та основній групах відповідно (p=0,178).

Висновок: ми отримали докази на користь ефективності НіШВЛ у хворих на ХОЗЛ із загостренням з точки зору смертності та інтубації трахеї. Різниці в тривалості перебування в лікарні та у відділенні інтенсивної терапії не виявлено. Жодних доказів додаткового ризику, пов'язаного з НіШВЛ, не виявлено.

Ключові слова: ХОЗЛ, гіперкапнічна дихальна недостатність, ШВЛ, неінвазивна вентиляція

AUTHOR CONTRIBUTION:
F. Glumcher: conceptualization, methodology, statistical analysis, overall supervision
S. Dubrov: protocol development, data aquizition and treatment, manuscript writing
I. Diomin: data treatment and preparation, data visualization, manuscript writing and proofreading