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ORIGINAL

The Use of Inhaled Nitric Oxide in the Management of Acute Respiratory Distress Syndrome

El uso de óxido nítrico inhalado en el tratamiento del síndrome de dificultad respiratoria aguda

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ABSTRACT

Acute Respiratory Distress Syndrome (ARDS) Patients' Lung Function (PLF), Morbidity (M), and Death were the primary outcomes the researchers were interested in examining. The standard therapy, or the inhaled nitric oxide inhNO treatment, was administered to 30 ARDS patients divided into two groups. It has been shown that 0,5 to 40 ppm of inhNO is the ideal daily dosage. All treatment methods were standard. In 25 % of ARDS Patients, sepsis was the underlying cause. In the first 24 hours after inhNO, patients had a considerable increase in their hypoxia score, from 114,2 to 170,4 mm Hg. Similar decreases in venous admixture also occurred in the inhNO group to the control group. InhNO did not continue to have any positive effects beyond the first day of therapy. Forty percent of the inhNO group remained alive and weaned off mechanical ventilation thirty days following randomization, whereas only 33,3 % of the control group did so. With Multiple Organ Failure Syndrome (MOFS) as the primary cause of death, the 30-day mortality rate for both groups was comparable. According to the research, inhNO might improve gas exchange but did not lower mortality in this group.

Keywords: COVID-19; Multiple Organ Failure Syndrome (MOFS); Inhaled Nitric Oxide (inhNO); Acute Respiratory Distress Syndrome (ARDS); Patients.

RESUMEN

La función pulmonar (FPL), la morbilidad (M) y la mortalidad de los pacientes con síndrome de dificultad respiratoria aguda (SDRA) fueron los principales resultados que los investigadores analizaron. La terapia estándar, o tratamiento con óxido nítrico inhalado inhNO, se administró a 30 pacientes con SDRA divididos en dos grupos. Se ha demostrado que la dosis diaria ideal es de 0,5 a 40 ppm de inhNO. Todos los métodos de tratamiento fueron estándar. En el 25 % de los pacientes con SDRA, la sepsis fue la causa subyacente. En las primeras 24 horas tras la inhNO, los pacientes experimentaron un aumento considerable en su puntuación de hipoxia, de 114,2 a 170,4 mmHg. También se observaron disminuciones similares en la mezcla venosa en el grupo inhNO en comparación con el grupo control. El inhNO no continuó mostrando efectos positivos después

del primer día de tratamiento. El 40 % del grupo con inhNO sobrevivió y se retiró de la ventilación mecánica treinta días después de la aleatorización, mientras que solo el 33,3 % del grupo control lo hizo. Siendo el síndrome de fallo multiorgánico (MOFS) la principal causa de muerte, la tasa de mortalidad a los 30 días en ambos grupos fue comparable. Según la investigación, el inhNO podría mejorar el intercambio gaseoso, pero no redujo la mortalidad en este grupo.

Palabras clave: COVID-19; Síndrome de Fallo Multiorgánico (MOFS); Óxido Nítrico Inhalado (inhNO); Síndrome de Dificultad Respiratoria Aguda (SDRA); Pacientes.

INTRODUCTION

The high mortality and disability rates are primarily attributable to ARDS, a clinically and epidemiologically heterogeneous illness. Before the 2015 PALICC described PARDS along with recommendations used for treatment as well as additional research, pediatric doctors diagnosed children with ARDS using adult-oriented criteria. [1] iNO is often used in patients with severe ARDS as salvage therapy because it can increase oxygenation in refractory hypoxemia by improving ventilation/perfusion matching. The patient was hospitalized with a history of acute lymphoblastic leukemia after receiving a bone marrow transplant due to severe ARDS associated with COVID-19 pneumonia. However, iNO, while uncommon, can produce methemoglobinemia by oxidizing heme iron.[2] Over 10 % of ICU patients have ARDS, with a 35 % mortality risk. Before this, it was challenging to identify an exact incidence and better understand the epidemiology of RVD acquired during ARDS since there isn't a standard definition of RVD.[3] Low-dose breathed NO (maximum 30 ppm) may reduce the amount of time that SARSCoV-infected patients need ventilator support, according to pilot studies conducted during the 2004 epidemic.[4] It is a challenging condition to identify and treat due to its broad range of symptoms, varying degrees of severity, many causes, rebound in occurrence, and increased public awareness due to the SARS-CoV-2 outbreak. There is a chance that recent advancements in ARDS therapy will enable the management of this prevalent cause of death and morbidity in critically ill patients, particularly when combined with already available medications that have established themselves as mainstays in the treatment of ARDS.[5] inhNO has been proven to have antiviral effects. Figure 1 display the action method.

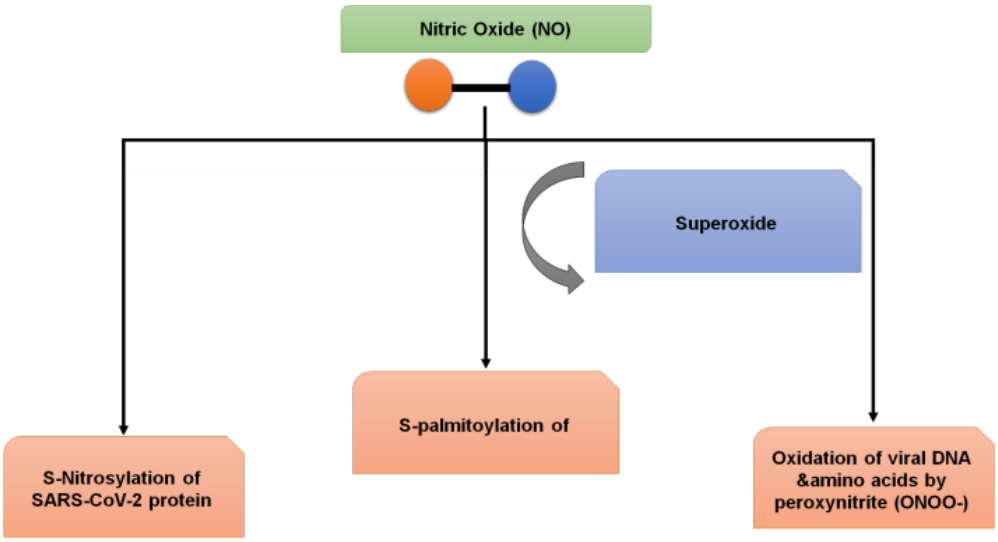

Figure 1. Method of action revealing the antiviral effects of NO inhalation

Ventilator-induced lung injury is a condition that affects ARDS patients and is thought to be exacerbated by the way it was ventilated. Due to this concept, recent years have seen many investigations on the variables influencing and methods for determining if ventilation is appropriate for a particular patient.[6] NO has been utilized in clinical settings to treat PAH since the 1980s. Additionally, the FDA and the EMA both authorized iNO as a routine therapy for neonates with PPHN at 34 weeks of gestation or later in 1999 and 2001, respectively. [7] COVID-19, which causes SARS, have contaminated over 500 million populaces, and over 6 million of them have died. Intractable hypoxemia is frequently the primary reason for humanity in patients with ARDS. On the other hand, some research suggests that R-L shunts might also contribute to hypoxemia. PCD were also seen in autopsies of COVID-19 pneumonia patients, and PVD was shown in dual-energy CT scans.[8]

The research examined neonatal NARDS Patients' aetiological factors, clinical characteristics, and prognosis. [9] NO levels were observed to be lower in most cases and greater in certain COVID-19 Patients compared to

other hypoxemic.[10] While it has been demonstrated that lung-protective breathing strategies improve clinical outcomes for individuals with ARDS, their use in ARDS situations when pregnancy is involved raises the possibility of negative maternal-fetal interactions.[11] To found that infected lungs had significantly lower quantities of m^6A RNA, with METTL3 being the primary cause. Regulator responsible for RNA modification in the absence of m6.[12] To discussed actual iNO usage and results in COVID-19 Patients in who have mild-to-moderate ARDS.[13] The examined the effects of iNO on right ventricular size, purpose, and SPAP in 12 COVID-related patients with ARDS in a serial way.[14] Published a case study of a critically sick patient who received iNO. The patient had bilateral SARS-CoV-2 pneumonia, severe ARDS, hypoxemia, and abrupt, severe PAH, which resulted in RV pressure overload, RVSD, and an imbalance between ventilation and perfusion.[15] The research showed that iNO could be used by a community-based rotor-wing CCT team to move these critically ill Patients to the required tertiary care in a dependable, effective, and safe manner.[16] NO and epoprostenol, two inhaled vasodilators, could be given to MVP using SARF to increase oxygenation.[17] To covered the function of the right heart, ventilatory settings, prone posture, and the pathophysiology of pulmonary hypertension in ARDS, INO, and the choice of individuals who could be candidates for VV ECMO.[18] Examined the arterial or venous blood gas profiles before and during rescue therapy to evaluate the effectiveness of iNO, Almitrine, and iNO + Almitrine combination in improving PaO2/FiO2 (mmHg) ratios.[19] Compared arterial or venous blood gas profiles before and after rescue therapy to assess how well iNO, almitrine, and the iNO + almitrine combination improved PaO2/FiO2 (mmHg) ratios.[20] Highlighted key ideas in ARDS treatment, pointed out important distinctions between ARDS and CARDS, and talked about the common use of inhaled pulmonary vasodilators.[21] Desired to educate pediatric healthcare professionals on the acute therapy options and clinical course of newborn ARDS caused by coronavirus illness. The development of ARDS has a major detrimental effect on the prognosis of patients undergoing heart surgery, who frequently have many concurrent illnesses.[22] Followed by a discussion of treatment options while considering the unusual characteristics of ARDS following cardiac surgery.[23] In this experiment, the main goal was to compare COVID-19 and H1N1-associated ARDS patient outcomes.[24] NO application seems relevant regarding antiviral activity, antioxidants, and anti-inflammatory effects in reducing disease-related symptoms.[25] iNO was administered to critically ill COVID-19 patients with moderate-to-severe ARDS.[26] The documented a case of a 70-year-old female who developed ARDS due to EV-HRV infection despite having cardiac comorbidities, emphysema, 25 years of passive smoking, and being treated for rheumatoid arthritis with methotrexate.[27] Due to a number of mechanisms, iNO has been suggested as a possible therapy for ARDS caused by COVID-19, including its antiviral, antithrombotic, anti-inflammatory capabilities, and vasodilatory effects.[28] Provided a case study of five Patients with COVID-19 ARDS who underwent rotor wing transfer and were put on iNO by the transport crew.[29] All five Patients underwent rotor wing flight and arrived at their destination in stable or better condition. The assessed how well Patients with COVID-19-ARDS responded to iNO.[30]

METHOD

This section describes the methodology for the use of inhaled inhNO in treating ARDS patients. It includes the research protocol, inhaled NO administration optimization of NO levels, statistical analysis, and related protocols.

Inhaled inhNO in the treatment of ARDS

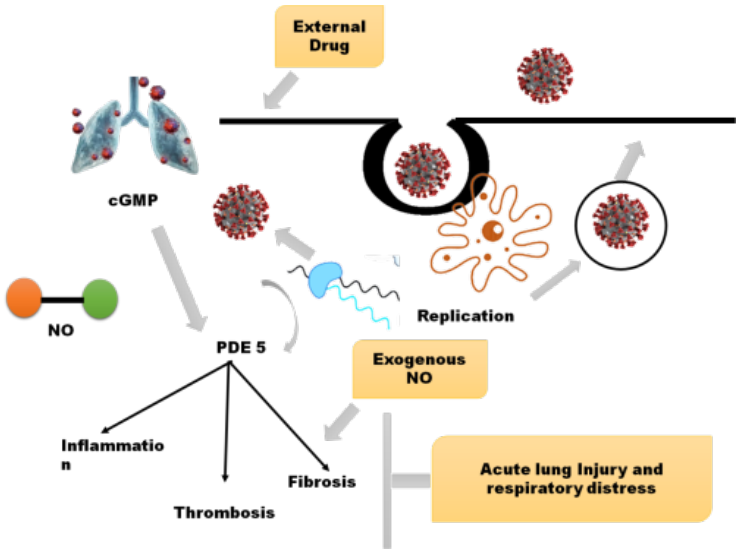

Figure 2. Inflammation, fibrosis, and acute lung damage are reduced by exogenous nitric oxide and drug-induced NO generation through the cGMP-PDE5 pathway

iNO inhaled has been used therapeutically to treat ARDS. NO is a gas that affects pulmonary circulation and functions as a vasodilator. Here is a summary of how inhNO is used to treat ARDS. inhNO have been shown to decrease inflammation, fibrosis, and acute lung damage by blocking the cGMP- PDE5 pathways (figure 2).

Protocol

Study participants

Participants had a LIS greater than 2,5 and were randomly assigned to two groups, one receiving routine care alone.

Exclusion criteria

The exclusion criteria also applied to pregnant individuals who had end-stage neoplasia and CPE. A close relative gave written consent after being fully informed.

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Randomization and data collection

Then, Patients were randomly assigned to receive either standard care without inhNO or routine care alone. On the day of randomization (Day 0), systems for computing severity ratings for each individual were developed. The exact process was used to mechanically ventilate the patients in each group, using the same TV, VM, and PEEP settings. PETCO2 were also continually analyzed. The following measurements were made at least eight hours apart: ABG, PSHP, CPP, pH, VBG, methemoglobinemia, CO.

Inhaled NO Administration

Gas cylinder composition

It was found that N_2 gas cylinders had 900 ppm of NO and five ppm of NO_2 in them. Using an inhNO delivery system created at our institution, the NO/N_2 mixture was cycled into the inspiratory line of the MV. Electrochemical measurements were made of the inspired NO (FINO) and NO_2 ($FINO_2$) fractions given to the Patients. The electrochemical device's calibration carried out at least once a week, was verified by chemiluminescence. Table 1 compares the ideal therapy outcomes for adults with ARDS with those attained by inhNO.

Table 1. Inflammation, fibrosis, and acute lung damage are reduced by exogenous nitric oxide and drug-induced NO generation through the cGMP-PDE5 pathway

Ideal Treatment Objectives	Inthaled nitric oxide's physiological effects (inh NO)
Protection against infection	Direct antibacterial effects, although in one research linked to a rise in ventilator-associated pneumonia.
Reduction or prevention of inflammation	The effectiveness of its anti-inflammatory effects at many molecular and clinical levels is under dispute.
Decreased pulmonary edema	It might be altered by hemodynamic, inflammatory, infectious, and alveolar-capillary membrane effects.
Decreased pulmonary vascular resistance	A selective pulmonary vasodilator (PV) may be helpful for patients with acute right-sided heart failure (AR-SHF), especially those who have increased pulmonary vascular resistance (PVRp) and hypoxemia. However, its efficacy is debatable in acute lung injury or ARDS with moderate pulmonary hypertension (PHT).
Improved oxygenation	According to clinical research, 60 % of patients saw a 20 % improvement for one to two days without any corresponding survival benefit. In dire circumstances, it might significantly improve oxygenation and allow time for introducing other types of aid.

Optimal FI_{NO} Determination

Every day, the lowest FINO in the experimental group that resulted in the highest increase in PaO_2 was identified in equation (1).

$$optimal\ F_{I_{NO}} = 5\ minimal\ dose\ with\ maximal\ efficacy\ on\ Pao_2 \quad (1)$$

No therapy or procedure that might alter the arterial oxygenation or the hemodynamic condition was permitted while determining the optimum FINO.

Initial Optimal FINO Determination

FINO levels at the start were 2,5 ppm. Before and 10 minutes after inhNO delivery, the parameters were measured. Following that, the value of FINO was gradually raised across the concentration ranges of 5, 10, 20, 30, and up to a maximum of 40 ppm. The PaO_2 fluctuations that were observed 10 min following the adjustment in FINO had an impact on the choice to raise FINO. FINO was extended until the PaO_2 rise from the last test was less than 5 %. FINO was potentially preserved at five ppm if there was no positive impact at any deliberate levels. However, this never happened. 24 hours were spent determining and maintaining the first ideal FINO.

FINO Daily Optimal Determination

The FINO levels were steadily lowered each morning using a similar approach; under 2,5 ppm, the 2 phases were along with 0,5 ppm and ideally 0 ppm. When the decrease in PaO_2 reached a level greater than 5 %, the reduction in FINO was stopped. PaO_2 was also taken 10 min after each change. In such a situation, the prior FINO was retained for 24 hours. As previously indicated, the effects of increased FINO were assessed sequentially if the first drop in FINO caused a decline in PaO_2 of more than 5 %.

Inhaled NO Weaning

If inhNO had no positive results during the first two days, planned to stop the treatment. Patients could progressively wean off inhNO thanks to daily optimum FINO determination and consistent reverse dose-response evaluations.

Reinstatement inhaled NO (imh NO)

The medication was restarted if the patient's lung health declined after successful weaning. $FIO_{2,}$ PEEP, and PaO_2 reintroduction standards of 0,4, 10 cm H_2O, and 60 mm Hg. As was noted before, it was discovered that the first FINO.

Statistical Analysis

Response evaluation

The early impact of inhNO and its continuing effect after extended administration was separated into two periods for comparison between groups. The difference between the value obtained under the first optimal FINO and the value at baseline was used to characterize the first response to inhNO. The RC from Day 1 to Day 30 of the follow-up served as the baseline (bl) for evaluating the efficacy of the follow-up. Linear regression analysis (LRA) was used assess individual patient responses to treatment. The appropriateness of using a quadratic component was tested for improving the model fit.

Statistical tests

A t-test was applied to compare the changes in means slopes of the inhNO and control gropus. Then, the LS was determined for each participant. The weights of the various slopes were then determined using the method used to estimate them.

By determining if adding a quadratic component improved each patient's fit to the lung function model in a statistically meaningful way, the applicability of the linear approximation was demonstrated. Since different amounts of patient data were likely utilized to determine each slope, not all slopes were calculated with the same level of accuracy. Each hill was weighted before merging using the square of the standard error. In each group, the success rates of the various therapies were compared using a log-rank test. The first analysis was finished using the intention-to-treat method.

Follow-up- and data interpretation

For a little over 30 days, the deceased patients had ventilation. The outcomes of the patient subgroups remaining under observation were then examined. The information is shown as a mean 6 SE.

RESULTS

Demographic and prognostic characteristics

At random, 30 Patients with ARDS were split into 15 experimental and 15 control groups. 13 medical (M) and 17 surgical Patients (SP) in the ICU had ARDS. Over the course of the trial, ARDS brought on by trauma wasn't seen. The remaining 13 patients in the experimental group and the other 12 in the control group all had toxic inhalation (TI), aspirational pneumonia (IP), or toxic aspiration (A)-related direct lung damage (DLI). Table 2 shows that the bulk of the baseline demographic and prognostic factors were comparable across the two groups. But as compared to the control group, patients receiving inhNO often had somewhat poorer health, as shown by lower HS and higher APACHE II scores.

Table 2. Randomized Patients' clinical characteristics in the CG and EG

	Inhaled Nitrogen Oxide (imhNO) (n = 15)	CG (n = 15)
Smoker, %	53,3	46,6
Alcoholism, %	26,6	20,0
APACHE II score†	27,4 ± 2,6	23,2 ± 1,4
Age, yr	55,7 ± 3,6	54,8 ± 3,7
Sex, % male	66,7	60,0
Hypoxia score, mm Hg‡	119,4 ± 13,6	152,1 ± 18,5
LIS§	2,92 ± 0,1	2,86 ± 0,1

Hemodynamic and respiratory responses

The first optimal FINO reduced pulmonary arterial pressure while maintaining resting heart rate and systemic arterial pressure (table 3). The gas exchange parameters were greatly enhanced by inhaled NO: PaO_2 increased by 66,2 %, as did the concentration of H1, while $PaCO_2$ decreased by 7 % and HCO3 2 increased by 2,8 %.

Table 3. Hemodynamic and respiratory response to inhaled NO

	With Initial Optimal FI_{NO} (n =15)	p Value t	Baseline† (n =15)
Hco_2, mmol/L	24,2 ±1,2	0,0217	24,9 ± 1,2
$PETc_{O2}$, mm Hg	30,6 ± 1,4	0,7683	31,1 ± 1,4
pHa	7,38 ±0,02	0,0025	7,36± 0,02
Pa_{02}, mm Hg	40,1± 1,4	0,0001	43,3 ± 1,4
Sa_{02}, %	97,2 ± 0,5	0,0001	93,9 ± 0,7
HR beats/min	96,4 ± 4,7	0,2851	97,9 ± 4,4

Lung Function evolution

After removing the initial influence, did not see any differences between the groups. The fact that the proportion of patients with SQF never surpassed 20 % indicates that there was never adequate data for any of the lung function tests that were being considered for using a quadratic model. The slope of an acceptable linear regression of lung function on time was used to assess each patient's lung function progression throughout the course of the follow-up period. Table 4 shows that starting on Day 1, the mean weighted linear gradients for PEEP, CL, and VA/T were identical. It was possible to see a difference since the inhNO-treated group tended to see a sharper decrease than the control group. The calculated mean has to be emphasized.

Table 4. Comparison of the Development of Lung Function in the Experimental (Inhaled No) and Control Groups*

	Average Daily Change from Day 1	Day 1 and baseline (BL) differences	Baseline (BL)
p less than Value	0,83	0,05	
CL, ml/cm H_2O			
Inhaled NO group (INO)	-0,2±0,1	+0,2 ± 2,7	31,8 ±2,9
O_{VA}/OT, %			
Control Group (CG)	+0,5±0,2	-4,5 ± 2,2	19,4 ± 2,1
Inhaled Nitrogen Oxide (imhNO) group	±0,07±0,2	10,5 ± 2,1	25,7 ±3,2

Treatment success

The two groups' overall course of treatment success could not be distinguished (figure 3). The EG experienced treatment success at a higher rate and did so earlier than the CG. Five Pa in each group experienced ARDS due to direct lung damage, compared to just one death in the CG. Treatment success for the remaining sepsis-induced ARDS patients was 28 %. Despite the inhNO treatment's 50 % success rate, four out of every five inhNO nonresponders died.

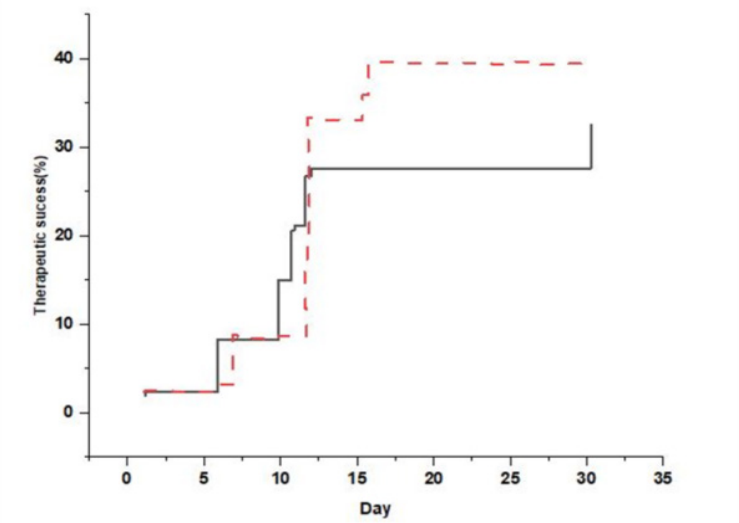

Figure 3. The experimental (NO-inhaled) and control groups' treatment success rates have altered over time

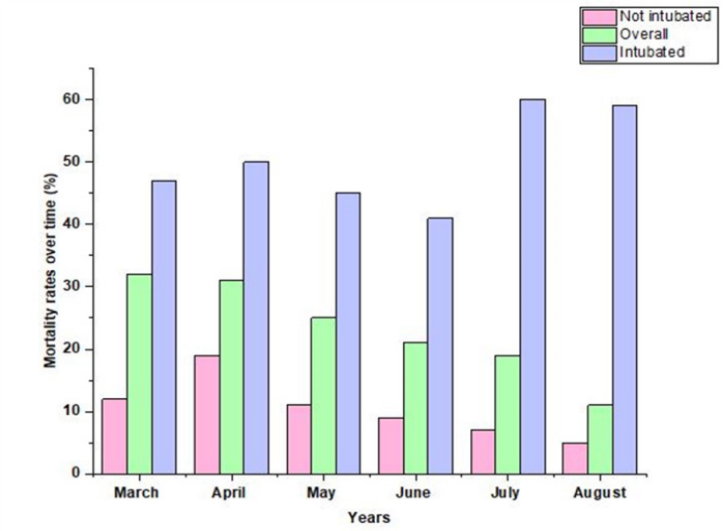

Figure 4. Adults with COVID-19, ARDS, or ARF mortality rates over time

Mortality and mechanical ventilation

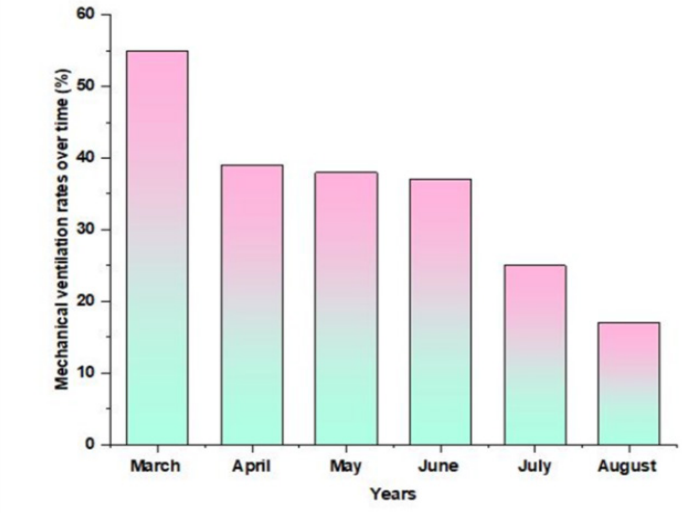

Figure 5. Adults with mechanical ventilation rates with COVID-19, ARDS, or ARF over time

Only patients who required mechanical ventilation at any point in the hospital are counted as part of the overall patient count, as shown in figure 4. The other patients are categorized as not having been intubated during their hospital stays. Figure 5 depicts the gradual improvement in prognosis throughout treatment for child COVID-19 patients initially diagnosed with ARDS or ARF.

DISCUSSION

This is the first description of randomized research that examined these issues in ARDS patients receiving inhNO. Previous research on the impact of inhNO in ARDS patients was constrained by small sample numbers, a variety of treatments, and selection bias. Some of these studies investigated the effects of inhNO on hypoxemia using a crossover design using almitrine or prostacyclin. The findings in tables 2 and 3 demonstrate that inhNO improves alveolocapillary gas exchange, initially has a little pulmonary vasodilatory effect, and has no clinically relevant SHE. This finding is in line with other studies.This steal phenomenon, which is the transfer of blood flow from under-perfused yet vented areas to ventilated sections, most likely has a positive impact and improves oxygenation.Did not see any adverse effects after the administration of inhNO, in contrast to a trial involving patients with chronic obstructive pulmonary disease. Similar findings have been made by other studies that found either no or very little increase in this metric. $PETCO_2$ did not change throughout research. It has never been shown how inhNO functions over time compared to a control group. The underlying disease or trauma often brings on early ARDS fatalities, but MODS usually brings on later deaths.

CONCLUSIONS

The research supports inhNO's early benefits for lung function, but the groups were the same as on the first follow-up day. While lung function, the length of mechanical ventilation, or mortality did not improve in ARDS, blood gas criteria pulmonary abnormalities resolved more quickly. This pilot investigation implies that, even with a large multicenter trial, it would be challenging to show that inhNO reduces the risk of ARDS mortality in this population. This is true even though sample represented a group with preexisting ARDS caused by sepsis that developed into MODS. It has been demonstrated that the overall mortality in ARDS has decreased, even though no one therapeutic approach improved. In these situations, the recommend that future studies concentrate on giving inhNO to particular patient groups, such as those who have ARDS brought on by direct lung damage or those who respond to treatment regardless of the underlying etiology. This is because early intervention (when the sickness is more likely to be treatable) and early intervention are the two circumstances when success is most likely to occur. These people should stand to gain the most from inhNO, which may impact mortality and gas exchange.

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ANNEXE

Acronyms	Description
MOFS	Multiple Organ Failure Syndrome
ARDS	Acute Respiratory Distress Syndrome
PLF	Patients' Lung Function
M	Morbidity
PALICC	Pediatric Acute Lung Injury Consensus Conference
PARDS	Pediatric Acute Respiratory Distress Syndrome
RVD	Right Ventricular Dysfunction
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
NO	Nitric oxide
PAH	pulmonary arterial hypertension
FDA	Food and Drug Administration
EMA	European Medicines Agency
PPHN	Persistent Pulmonary Hypertension of the Newborn
RTL	right-to-left
PCD	Pulmonary capillary deformations
PVD	pulmonary vessel dilatation
NARDS	Neonatal Acute Respiratory Distress Syndrome
ALI	Acute Lung Injury
SPAP	systolic pulmonary arterial pressures
RV	right ventricular
RVSD	right ventricular systolic dysfunction
CCT	critical care transport
MVP	Mechanically Ventilated Patients
SARF	Severe Acute Respiratory Failure
VV ECMO	Veno-Venous Extracorporeal Membrane Oxygenation
cGM	cyclic Guanosine Mono-Phosphate
PDE5	Phospho Di Esterase type 5
CPE	Cardiogenic Pulmonary Edema
TV	Tidal Volume
VM	Ventilation Mode
PEEP	positive end-expiratory pressure
PETCO2	Pulse oximetry and End-Tidal Carbon Dioxide Tension
ABG	Arterial Blood Gases
PSHP	pulmonary and Systemic Hemodynamic Parameters
CPP	Cardio-Pulmonary Profiles
VBG	Venous Blood Gases
CO	Cardiac Output
MV	Mechanical Ventilator
LRS	Linear Regression Slope
LS	Linear Slope
RC	Rate of Change
SQF	Significant Quadratic Factors
SHE	Systemic Hemodynamic Effects

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