Effect of nebulized furosemide on mortality of adult mechanically ventilated ARDS patients. Protocol of randomized clinical trial. (ENHALE)

Abstract

Acute Respiratory Distress Syndrome (ARDS) is a common clinical entity among ICU patients, particularly those who are mechanically ventilated. ARDS is associated with a high mortality rate worldwide, despite availability of management guidelines, possibly because there is no definitive cure, and the management being mostly supportive. Regardless of the risk factor or underlying cause of ARDS alveolar-capillary membrane inflammation is pathognomonic, characterized by increased capillary permeability and pulmonary edema.

A medication with anti-inflammatory properties that is applied directly to the lung tissue, safe, and readily available may serve as a potential line of treatment. These properties all apply to nebulized furosemide, which has been previously tried in other lung conditions with similar pathophysiology, such as COVID-19 induced ARDS, bronchial asthma, and breathlessness.

We hypothesized that nebulized furosemide may decrease ARDS 28 day mortality among adult mechanically ventilated patients, and this study is aims to test this hypothesis, designed as a superiority parallel arms pragmatic double blinded randomized clinical trial, in which the intervention group will receive nebulized furosemide, while the placebo group receives 0.9% saline, with a primary outcome of 28 day all-cause mortality.

Introduction

Acute Respiratory Distress Syndrome (ARDS) is usually defined as a rapidly evolving hypoxemia due to pulmonary edema originating from causes other than cardiogenic, such as increased alveolar-capillary permeability (1, 2). Although the objective definition by clinical criteria was established by a panel of experts in 2012, and is widely known as the Berlin Definition (1). ARDS encompasses a wide spectrum of risk factors and/or causes that could be generally divided into direct and indirect causes (3), direct causes may include aspiration, pneumonia, lung contusion, inhalational injury, and near drowning (4), whereas examples of indirect causes include sepsis, transfusion, hemorrhagic shock (4) pancreatitis, burns, drugs or toxins (5). Some studies have associated tobacco and alcohol use,

hypoalbuminemia, air pollution, and recent chemotherapy with increased risk of ARDS (2, 6, 7).

ARDS is common among critically ill patients, reaching up to 10% of intensive care unit (ICU) admissions, and 25% of mechanically ventilated patients, affecting 3 million persons annually worldwide (4, 8), and this prevalence is subject to increase if the newly proposed definition including patients on high-flow nasal oxygen is widely adopted (9). Despite substantial improvement in recognition and management of ARDS, reported mortality rates remain as high as 30% - 40% (2), reaching up to 46% in some reports (8), perhaps as a result of the myriad of causes and risk factors of ARDS (2), difficulty to distinguish ARDS itself from its risk factors as the cause of death (10), the challenging setting of ARDS management which usually encompasses multiple organ failure, but possibly more important, due to the lack of definitive therapy, and the management being mainly supportive (11).

A recent multicenter phase – 2 randomized controlled trial (RCT) (12) explored the effect of nebulized furosemide in intubated COVID-19 patients. The study did not reach its target sample size due to lack of recruitment by early 2023, consequently, all of its objectives did not reach the level of statistical significance, yet, there were obvious trends of beneficial effect of nebulized furosemide. The intervention group had a higher change from day 1 to day 6 of partial pressure of oxygen in arterial blood (PaO2) to fraction of inspired oxygen (FiO2) ratio (P/F ratio), lower 60 day mortality, lower hospital length of stay (LOS), and longer ventilator free days, with no reported adverse events.

We hypothesize that the use of nebulized furosemide in adult ARDS mechanically ventilated patients admitted to ICU may decrease 28 day mortality, based on the rationale of the pathophysiology of ARDS and the pharmacodynamics of furosemide.

Rationale of nebulized furosemide in ARDS

Regardless of the precipitating factor, ARDS is characterized by an acute onset of inflammatory lung injury, with impaired gas exchange and non-compliant “stiff” lungs (13). A histologic hallmark of ARDS is capillary endothelial injury and diffuse alveolar damage, manifesting typical inflammation, apoptosis, and necrosis of pulmonary epithelial and endothelial cells, leading to increased alveolar-capillary permeability, ultimately resulting in alveolar edema and proteinosis, other

findings may also include alveolar hemorrhage, pulmonary capillary congestion, interstitial edema, and hyaline membrane formation (14).

An ideal therapeutic agent should poses broad anti-inflammatory activity, and while several agents show such properties, like corticosteroids and immunosuppression agents, their systemic administration imposes draw backs such as myopathy and decreased immunity, in addition to being expensive, difficult to produce, and their lack or shortage in some countries (12). Hence, the ideal therapy would also have to be cost effective, readily available, associated with low toxicity, and could be directly delivered to the lung tissue (12).

Furosemide (4-chloro-5-sulfamoyl-N-furfuryl-anthranilate) is a powerful loop diuretic that acts on the thick portion of the ascending limb of loop of Henle by binding to sodium – potassium cotransporter, it poses a short half-life and low bioavailability, in addition to being inexpensive and readily available (12, 15). Nebulized furosemide has been used for a variety of lung conditions such as dyspnea and bronchial asthma (16, 17) owing to not only the presumed higher concentrations delivered to the pulmonary tissue via nebulization compared to systemic or oral routes, but also due to its anti-inflammatory characteristics (12).

Furosemide is an analogue of 3-hydroxyanthranilic acid (3HA) (a Tryptophan metabolite), 3HA is diffusely found in the human body, and has the ability to suppress T-cell responses (18), thus suppressing the production of several inflammatory cytokines (19). In vitro, furosemide was reported to reduce lipo-polysacchride induced release of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrotizing factor (TNF), in addition to inducing macrophages phenotypic changes from the pro-inflammatory M1 state, to the anti-inflammatory M2 state, and promoting the release of anti-inflammatory cytokines such as arginase (20). Reduction of inflammatory cytokines was also reported by clinical animal studies (21). Similarly, human clinical studies demonstrated a beneficial effect of nebulized furosemide in treatment of pulmonary edema (15), and effectiveness in reducing pulmonary epithelial permeability in smokers, and even restoring it to normal in asthmatic patients (22), hence, the use of nebulized furosemide in the treatment of several lung conditions such as bronchial asthma, dyspnea, breathlessness, and chronic obstructive pulmonary disease (COPD) in many studies, with promising results (23-26).

Materials and Method

Study design

This will be a single center double blind randomized clinical trial. It is a parallel arms superiority trial.

Duration of study intervention: Maximum 28 days.

Duration of outcome ascertainment: Till hospital discharge.

Recruitment will continue until completion of the required sample size, or early stopping according to predefined stopping rules.

Inclusion criteria

We will enroll patients if they fulfill all of the following criteria

1- Adult (age ≥ 18 years) regardless of biological sex.
2- Admitted to ICU
3- Mechanically ventilated by endotracheal intubation for less than seven days (according to Berlin definition).
4- Within 24 hours of the diagnosis of ARDS, according to Berlin definition (1), which includes:
   a- Chest x-ray: Showing bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules.
   b- Respiratory failure not fully explained by cardiac failure or fluid overload, and exclusion of hydrostatic edema (by echocardiography).
   c- Oxygenation and ventilator settings matching one of the three categories of ARDS: Mild: 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2O. Moderate: 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O. Severe: PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O.

Exclusion criteria:

1- Age < 18 years.
2- Pregnant or lactating ladies.
3- Not expected to survive more than 48 hours, according to the treating team.
4- Mechanical ventilation is expected to continue for less than 48 hours (due to rapid recovery) according to the treating team.
5- Advanced directive of Do Not Resuscitate (DNR).
6- Refusal to participate in the trial by the patient, or official surrogate.
7- Known allergy to furosemide.
8- Previously enrolled in the trial (a patient can only be enrolled once).

Study Objectives

- The primary objective will be all cause mortality within 28 days of randomization.
- Secondary objectives include:

1- All cause hospital mortality.
2- ICU and hospital length of stay (LOS).
3- Difference of P/F ratio between day 1 and day 7 (if applicable, this outcome will not be calculated for patients who are censored before 7 days).
4- 28 days ventilator free days (VFD), defined as days without mechanical ventilation till day 28 starting from day of enrollment, as long as the patient is alive, this means that patients still mechanically ventilated at day 28, or died by day 28 will be assigned zero VFD. Patients for whom the artificial airway is shifted from endotracheal tube to tracheostomy, they will still be considered mechanically ventilated until they are liberated from mechanical ventilation and are spontaneously breathing.
5- Successful extubation rate, defined as extubated and did not require re-intubation for 72 hours. Patients for whom tracheostomy is performed are not considered as successful extubation when they are liberated from mechanical ventilation, and they will be excluded from the denominator of this particular outcome.
6- Adverse events comparison between both groups (see details in Adverse Events).

Enrollment, randomization, and allocation concealment

Dedicated study team will round the ICU twice a day (8 AM and 8 PM) to identify patients who could be eligible for enrollment, once an eligible patient who fulfills inclusion criteria and has no exclusion criteria is identified, the patient or legal guardian will be approached for consenting in participation. Only after obtaining an informed consent, randomization will be obtained via phone call to an independent statistician who will provide a study code, without breaking the allocation concealment.

The independent statistician will prepare randomization sequences using variable size blocks (4, 6, 8) stratified by ARDS severity (Mild – Moderate – Severe), with unique study codes. Only the study code will be disclosed to the study team (Appendix 1: Example of randomization sequence).

Blinding

Furosemide and saline are identical in appearance, color, and solution characteristics. The investigational product will be prepared by an independent study pharmacist, put in identical vials, labelled only with study code and patient identifiers (name and MRN), and delivered to the clinical area. The independent study pharmacist will not have any contact with the clinical team, and will not participate in the clinical care, or any other study role.

Once a patient has been randomized to either one of the study groups, the study intervention should begin within 6 hours of randomization. An independent pharmacist will prepare a vial of 4 ml containing either furosemide (intervention) or 0.9% saline (placebo), the medication vial will be delivered to the clinical area labelled with the patient's file number and study code. The bedside nurse will administer the study medication according to the protocol adopted from a previous study (12):

1- Verify that the study medication is correct for the patient.
2- Draw up the study medication using a five mL syringe.
3- Administer the study medication over 30 minutes through the ventilator circuit using the ventilator nebulizer.
4- Document administration of study medication in the patient's CRF.

Study intervention

In this study, we will follow a nebulized furosemide protocol similar to that reported in a study of nebulized furosemide in COVID-19 patients (12), since the protocol of that study was previously approved, and the study reported no adverse events.

The intervention medication is 40 mg furosemide in 4 ml of 0.9% saline, administered every 6 hours via the ventilator circuit over 30 minutes. The intervention continues till extubation, death, or completion of 28 days whichever comes first. The intervention will continue if the artificial airway is shifted from endotracheal tube to tracheostomy, as for patients who require reintubation after being extubated, the intervention will not be resumed.

The control group will receive similar color and volume of 0.9% saline following the same intervals, route, and duration.

Common management

This will be a pragmatic trial, that is to say, the study protocol does not control every aspect of the management, apart from the intervention medication. Pragmatic

trials tend to resemble real life scenarios of management in the ICU, where different treating teams may have slightly different methods of management, and consequently, pragmatic trials are characterized by higher external validity (27).

However, our center follows evidence based guidelines and protocols for the management of ARDS, and treating teams will be encouraged to follow those guidelines, such as:

Ventilator settings recommendations: The current recommendations advise the use of protective lung strategy, including: low tidal volume (< 6–8 ml/kg of predicted body weight), plateau pressure (< 28–30 cmH2O) and driving pressure (< 14 cmH2O). Adjuvant and rescue therapies will be allowed, at the discretion of the treating team, such as (but not limited to) prone positioning and extra-corporial membrane oxygenation (ECMO). There will be no restriction on the use of other medications by the treating, such as glucocorticoids, antibiotics, neuromuscular blocking agents.

Similarly, our center adopts practices of early internal feeding, light sedation and daily sedation vacation when applicable, deep vein thrombosis (DVT) and gastrointestinal (GIT) prophylaxis, and early weaning and extubation.

Our center applies a standardized process for weaning and extubation (Appendix 2).

Sample size calculation

Assuming a mortality rate of 40% in the control group (2, 8), and aiming to detect an effect size of 10% absolute reduction in mortality in the intervention group (intervention group mortality of 30%) with power of 80% and type I error rate of 5%, we estimated the sample size to be 712 patients (356 in each group), with 10% inflation to compensate for possible loss of follow up (patients transferred to other healthcare facilities), we plan to recruit a total of 784 patients, allocated in 1:1 ratio as 392 patients in each group.

Statistical plan

Descriptive statistics:

Continuous variables will be summarized as mean ± standard deviation (SD), or median and interquartile range (IQR) depending on the normality assumption. Data will be tested for the normality assumption by Shapiro-Wilk normality test. Discrete variables will be summarized as frequency (count) and percentage. Time-to-event data will be 28 day mortality as the event (death as the failure), and duration since randomization as the time variable, with right censoring.

Inferential statistics:

For the primary outcome, comparison between both groups for 28 day mortality will take place by chi square test of association. For secondary outcomes, if the variable being compared is a discrete variable, groups will be compared by chi square test of association, or Fisher's exact test, according to data count in each cell of the 2 X 2 contingency table. Continuous variables will be compared between groups by student t-test if the normality assumption is satisfied, otherwise, the non-parametric Wilcoxon Rank-Sum test will be used.

We will perform a survival analysis using the time-to-event data, in the form of Kaplan Meier Survival curve, and present its results as Log-Rank test.

As a sensitivity test for the primary outcome, we will fit two regression models

- Multinomial logistic regression model: Initially, all predictor variables will be included in the model (independent variables), then backward elimination will be used to retain only variables with p value < 0.1, the dependent variable will be 28 day mortality. Severity of ARDS will be used as the multinomial levels in the model.
- Multivariable proportional hazard model (Cox Regression), will be carried out in a similar way as the logistic regression model, utilizing days from randomization to event as the time variable.

Assumptions of logistic and proportional hazard regression will be explored and reported.

We plan a priori to perform sub-group analysis by:

- Sex
- Median age of the cohort.
- ARDS severity.
- Adjunct and rescue therapies used (such as: Corticosteroids, Prone positioning, ECMO).

There will be no correction for multiple testing, accordingly, results of secondary outcomes and sub-group analyses should not be considered conclusive, and must be cautiously interpreted.

All statistical tests were two sided, and considered statistically significant if the p value was < 0.05.

Several statistical packages will be used, including:

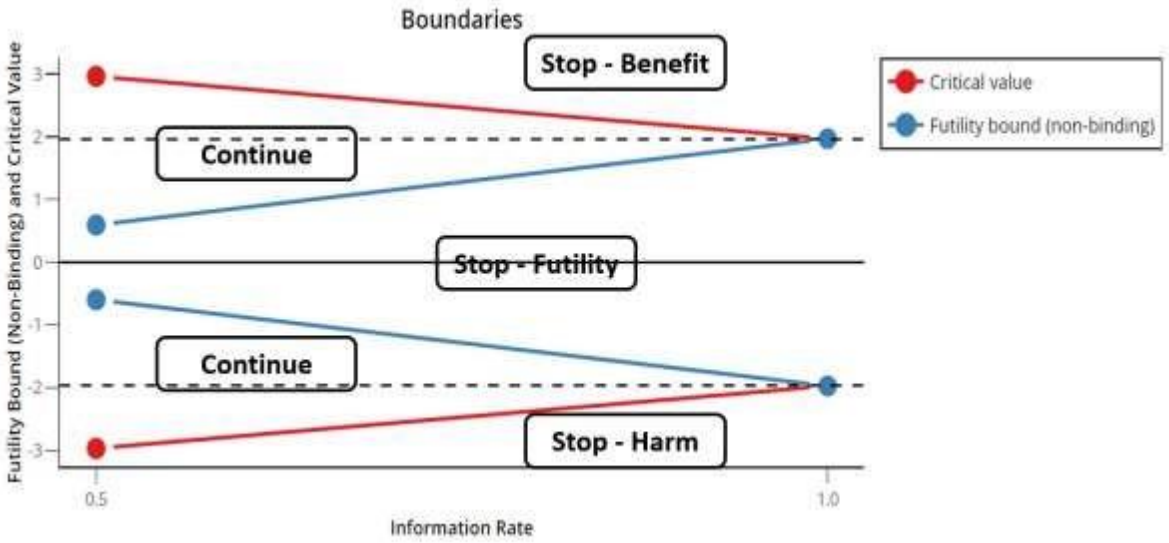
- StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.
- R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Interim analysis and stopping rules:

We will perform one interim analysis when 50% of the sample size is recruited. The aim is to assess efficacy of the intervention, with possible early stopping of the trial. Stopping rules are based on O'Brien-Fleming alpha spending functions (29).

Stopping Rules: Comparison of 28 day mortality between groups by chi square test:

1- Stopping for superiority: If the interim analysis results in a critical z-score of +2.963 or more, yielding a p-value of 0.0031 or less.
2- Stopping for harm: If the interim analysis results in a critical z-score of -2.963 or less, yielding a p-value of 0.0031 or less.
3- Stopping for futility: If the interim analysis results in a critical z-score between +0.595 and -0.595, corresponding to p-value of 0.55



Ethical considerations

IRB Approval

We will seek approval of the local Institutional Review Board (IRB) at King Saud Medical City, Riyadh, Saudi Arabia before initiation of recruitment or data collection.

Informed consent

Patients will be enrolled in the study after signing an informed consent themselves, or their legal surrogates. Similarly, patients/families are totally free to change their opinion about participation in the study, even if an informed consent was previously signed.

(Informed consent, appendix 3)

Adverse events reporting

In general, administration of nebulized furosemide is safe, and is associated with very few adverse events. Several studies using nebulized furosemide reported no adverse events at all (12, 30).

Nevertheless, we will report all adverse events (AEs) defined (according to the definition of Code of Federal Regulation – 21) as: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs will be reported to the institutional review board (IRB) within 24 hours of occurrence.

Specifically, we will include the following AEs in the analysis of the safety population (all randomized patients):

- Hypersensitivity reactions: of any magnitude.
- Abnormal lab investigations, specifically electrolytes and renal function tests.
- Volume of urine output.
- Death.

AEs will be classified as:

- Mild: Require observation only, without intervention.
- Moderate: Require minimal non-invasive interventions.
- Severe: Required prolongation of hospitalization, but not immediately life threatening.
- Life threatening: Required immediate invasive intervention.
- Death

Data collection

The following data will be collected and stored in a de-identified CRF for each patient:

Demographics and baseline clinical data: Age, sex, BMI, SOFA score, Clinical Frailty Scale, Comorbidities, underlying cause of ARDS, diagnostic criteria of ARDS and severity, P/F ratio baseline.

Key dates: Hospital, ICU, and intubation dates.

Key follow up dates and events: Dates of extubation, any subsequent reintubation, tracheostomy, liberation and reconnection from mechanical ventilation (for tracheostomized patients), SOFA score day 7, P/F ratio day 7.

Adverse events: Serum potassium out of normal range, serum creatinine, urine output, acute kidney injury, and positive cultures.

Medication follow up: only names of medications / interventions will be recorded over 28 days.

(CRF, Appendix 4)

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Appendix 1: Example of Permuted blocks, stratified randomization scheme

(THIS IS NOT THE ACTUAL RANDMIZATION SCHEME)

Appendix 2: Weaning and Extubation Protocol:

Appendix 3: Informed Consent:

Appendix 4: CRF

Appendix 1: Example of Permuted blocks, stratified randomization scheme (THIS IS NOT THE ACTUAL RANDMIZATION SCHEME)

A	B	C	D	E	F
block identifier	block size	sequence within block	treatment	Severity	code
1	6	1	Placebo	Mild	VJ8
1	6	2	Furosemide	Mild	QD7
1	6	3	Furosemide	Mild	XY8
1	6	4	Furosemide	Mild	VN2
1	6	5	Placebo	Mild	AA2
1	6	6	Placebo	Mild	HH2
2	6	1	Furosemide	Mild	BR1
2	6	2	Placebo	Mild	JC1
2	6	3	Furosemide	Mild	NB1
2	6	4	Placebo	Mild	QT5
2	6	5	Furosemide	Mild	RG0
2	6	6	Placebo	Mild	MO9
3	4	1	Placebo	Mild	AM0
3	4	2	Furosemide	Mild	KX8
3	4	3	Placebo	Mild	CC0
3	4	4	Furosemide	Mild	CU6
4	4	1	Placebo	Mild	XX9
4	4	2	Placebo	Mild	PW2
4	4	3	Furosemide	Mild	EK9
4	4	4	Furosemide	Mild	KQ3
5	8	1	Placebo	Mild	PH6
5	8	2	Furosemide	Mild	EM1
5	8	3	Furosemide	Mild	DV2
111	8	2	Placebo	Severe	ZZ4
111	8	3	Furosemide	Severe	PY0
111	8	4	Placebo	Severe	VA6
111	8	5	Furosemide	Severe	ST8
111	8	6	Furosemide	Severe	FL7
111	8	7	Placebo	Severe	EA2
111	8	8	Furosemide	Severe	WM9
112	8	1	Placebo	Severe	PI0
112	8	2	Furosemide	Severe	QL5
112	8	3	Furosemide	Severe	IW3
112	8	4	Placebo	Severe	OZ7
112	8	5	Furosemide	Severe	WU7
112	8	6	Furosemide	Severe	RG9
112	8	7	Placebo	Severe	CD7
112	8	8	Placebo	Severe	JH6
113	6	1	Placebo	Severe	OD3
113	6	2	Furosemide	Severe	DN6

Appendix 2: Weaning and Extubation Protocol:

Table S1: Daily Screening:

1- All ventilated patients will be assessing by the Respiratory Therapist (RT) daily between 7:30 am to 9:30am (excluding: Patients on septic shock protocol – Brain Protective strategy – Specific order by the treating consultant).
2- The RT will ensure that the patient meets the following baseline criteria before initiating the spontaneous Breathing Trial (SBT). - Evidence for some reversal of the underlying cause of respiratory failure. - Adequate oxygenation (PaO2/FiO2 = 150/200; PEEP 5/8 cmH2O; FiO2 ≤ 0.4/0.5 and PH ≥7.25). - Hemodynamic stability is defined as the absence of active myocardial ischemia and the absence of clinically important hypotension (i.e., a condition requiring no vasopressor therapy or therapy with only low-dose vasopressors such as dopamine or dobutamine < 5 mcg/kg/min). - Temperature < 38°C. - Hemoglobin 8–10 g/Dl. - GCS < 8. - The capability to initiate an inspiratory effort.

Table S2: Spontaneous Breathing Trial (SBT):

1- SBT can only be initiated if all criteria of daily screening are met.
2- CPAP of 5 cmH_2O and Pressure Support ≤ 8 cm H_2O. Note: For patients with endotracheal tube diameter less than 8.0, consider higher pressure support to compensate for increase airway resistance.
3- The initial 10 minutes of SBT should be monitored closely, before a decision is made to continue (This is often referred to as the screening phase of an SBT). Thereafter, the patient should continue the trial for at least 30 min to 120 min.
4- If the patient experience any of the following during the trial, immediately return patient to the previous ventilator settings and notify the attending physician: - RR > 35 bpm or change in RR > 50% above baseline, for more than five minutes. - RSBI > 105. - SpO2 < 90%, PaO2 < 50 mmHg, increase in PaCO2 > 10 mmHg from the baseline. - Heart rate >140 bpm or sustained increase or decrease in HR of > 20%. - Systolic blood pressure greater than 180 mmHg or less than 90 mmHg. - Change in mental state. - Dyspnea. - Use of accessory muscles, signs of increased WOB. - Onset of anxiety and diaphoresis.

Table S3: Extubation Process:

1- If the patient passes SBT, the following extubation criteria must be checkd: - Adequate cough - Ability to protect the airway - Positive cuff leak test - NIF greater than – 20
2- Cuff leak test can be detected in any of the following: - Qualitative Assessment: is performed by deflating the cuff and then listening for air movement around the ETT using a stethoscope place over the trachea. - Quantitative Assessment: is performed by deflating the ETT cuff and measuring the difference between the inspired and expired tidal volumes of ventilator-delivered breaths during volume-cycled mechanical ventilation. The lowest three expired tidal volumes obtained over six breaths are averaged and then subtracted from the inspired tidal volume to give the cuff leak volume. Cuff leak volumes less than 110 ml or less than 12 to 24 % of the delivered tidal volume have been suggested as thresholds for determining whether airway patency may be diminished.
3- If extubation criteria are met, or the treating consultant opts to over-ride, a clear written physician order will be obtained before extubation.
4- Initiate NIV according to protocol.
5- The RT monitors the patient within 48 hours of extubation for any of the following: - Increase WOB. - GCS. - Vital signs. - Increase FiO2 requirements. - Immobilization of secretion.

Table S4: Post-extubation non-invasive support (NIV):

1- NIV to be delivered continuously immediately after extubation using bi-level positive-airway pressure mode, for a scheduled 24 hours.
2- Inspiratory positive-airway pressure to be adjusted according to patients' tolerance (12–20 cm H2O)
3- Expiratory positive airway pressure at 5–6 cm H2O
4- FiO2 was set to achieve arterial O2 saturation by pulse-oximetry of more than 92%.
5- The position of the head of the bed was kept at 45° if applicable.
6- NIV could be interrupted for eating and drinking, for 15 – 20 minutes.
7- The facial skin is assessed every 4 hours to prevent damage from the tightly fitting face mask used to deliver the ventilation.
8- NIV is applied to achieve a target RR < 25 / minute.
9- Clinical monitoring: heart rate, respiratory rate, blood pressure and appearance of respiratory distress such as the use of accessory muscles of respiration.
10- NIV is discontinued in case of inability to tolerate the mask because of discomfort, deterioration in ventilatory parameters (rise in PCO2, fall in pH or PaO2), deteriorating state of consciousness or hemodynamic instability. Treating Physician informed.

Table S5: Re-intubation Criteria:

1- The decision to re-intubate is a multidisciplinary decision, but ultimately falls under the responsibility of the treating consultant/designee.
2- Immediate reintubation when any of the following major clinical events were present: - Respiratory or cardiac arrest. - Respiratory pauses with loss of consciousness or gasping for air. - Psychomotor agitation inadequately controlled by sedation. - Massive aspiration. - Persistent inability to remove respiratory secretions. - Heart rate below 50/ min, with loss of alertness. - Severe hemodynamic instability without response to fluids and vasoactive drugs.
3- Development of Respiratory Failure: - Respiratory acidosis (arterial pH of 7.35 or less with PaCO2 of 45 mm Hg or more). - Arterial O2 saturation by pulse oximetry less than 90% or PaO2 less than 60 mm Hg at an inspired O2 fraction of 0.5 or more. - Respiratory frequency exceeding 35 / min. - Decreased consciousness, agitation, or diaphoresis. - Clinical signs suggestive of respiratory muscle fatigue and/ or increased work of breathing, such as the use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.
4- Re-intubation is not considered only in the case of a valid Do Not Intubate Order, according to policy.

King Saud Medical City

Research Center

Generic Signed Consent Form

مدينة الملك سعود الطبية

مركز الأبحاث

استمارة موافقة للمشاركة في بحث

Computer Number			**رقم السجل**
Study Number			**رقم الدراسة**
Patient Name			**اسم المريض**
Date of Birth			**تاريخ الميلاد**
Gender (Male/Female)			**الجنس (ذكر | أنثى)**
Nationality			**الجنسية**

تهدف المعلومات الواردة في النموذج على تقديم الشرح الوافي عن جميع الفوائد والأخطار المترتبة على اجراء هذا البحث إذا ماتمت الموافقة على المشاركة.

ان المشاركة في هذا البحث عملٌ طوعي، وأن رفض المشاركة لن يترتب عليه أي عقوبة أو خسارة لمنفعة يستحقها الشخص موضع البحث بسبب آخر، وأن للشخص موضع البحث الحق في الإنسحاب من البحث في أية مرحلة من مراحله دون أن يتعرض لخسارة أو فوات منفعة.

يحق لأعضاء فريق البحث العلمي الخاص بهذه الدراسة إيقاف أو إلغاء مشاركة الشخص موضع البحث إذا مارأوا مصلحة في الإيقاف أو الالغاء أو في حين عدم الالتزام بخطة البحث الموضوعة، أو إذا تبين لهم ضرر أو إصابة جرّاء الدراسة وذلك دون أخذ موافقة الشخص موضع البحث أو من ينوب عنه.

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You are free to ask as many questions as you like before, during or after in this research, you decide to give consent to participate in this research study. The information in this form is only meant to better inform you all possible risks or benefits. Your participation in this study is voluntary. You do not have to take part in this study, and your refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without penalty or loss of rights or other benefits to which you are entitled. The investigator(s) may stop your participation in this study without your consent for reasons such as: it will be in your best interest; you do not follow the study plan; or you experience a study-related injury.

عنوان المشروع	تأثير عقار فيوروسمايد المستنشق على نسبة الوفيات في مرضى متلازمة ضائقة التنفس الحاد البالغين الخاضعين للتنفس الصناعي
Project Title	Effect of nebulized furosemide on mortality of adult mechanically ventilated ARDS patients.
الباحث الرئيسي	د. أحمد فؤاد ماضي
Principle investigator	Dr. Ahmed Fouad Mady

Location and phone numbers: *[provide appropriate daytime contact information and after-hours or on weekends]* King Saud Medical City, Riyadh, Saudi Arabia Adult Critical Care Department (Main building units: 400H, Trauma ICU) (Medical Tower units: T1A1, T1B1, T1A2) Phone number: 011 435 6666 011 435 7777	**موقع إجراء البحث وأرقام الهواتف (أثناء وبعد أوقات العمل، أثناء العطلات)** مدينة الملك سعود الطبية، الرياض، المملكة العربية السعودية. قسم العناية المركزة للبالغين المبنى الرئيسي 400هـ ، عناية الإصابات البرج الطبي الأول: T1A1 , T1B1, T1A2 رقم الهاتف: 011 435 6666 011 435 7777
Each item given below has to be filled. Please write NA, if not applicable	**يجب ملئ كل البنود أدناه وفي حال عدم توافر إإلجابه الرجاء كتابة غير متوفر**
01. Introduction to the research: *[A brief introduction is given about the research, what it hopes to achieve, who is conducting it etc.,]* Acute Respiratory Distress Syndrome (ARDS) is a rapidly evolving hypoxemia due to pulmonary edema originating from causes other than cardiogenic. It is associated with high mortality rates and high prevalence among critically ill patients. Management of ARDS is mainly supportive, and there is no identified definitive management until now. Nebulized furosemide has been tried in many pulmonary conditions including COVID-19 ventilated patients, due to its anti-inflammatory characteristics. Since the pathophysiology of ARDS is mainly an inflammatory response in the alveolar-capillary membrane, we hypothesized that nebulized furosemide may decrease mortality among adult mechanically ventilated ARDS patients.	**1. مقدمة عن البحث الطبي** (وصف موجز للدراسة ومايمكن تحقيقه من إجراء البحث ومن يقوم بإجراء البحث) تمتاز متلازمة ضائقة التنفس الحاد بانخفاض شديد متزايد في نسبة الأكسجين في الدم نتيجة تشبع الرئتين بالسوائل التي لأسباب عديدة غير ناتجة عن ضعف عضلة القلب، تحدث المتلازمة في مرضى الحالات الحرجة وتكون مصحوبة بنسبة وفيات عالية. عدا العلاج الدعمي، لا يوجد حتى الآن علاج محدد لمرضى متلازمة الضائقة التنفسية الحادة. تم تجربة عقار فيوروسمايد المستنشق في حالات مختلفة من أمراض الرئتين بما فيها مرضى كوفيد - ١٩ الخاضعين للتنفس الصناعي بسبب خصائصه المضادة للالتهابات. ما ان التطور المرضي لحالات متلازمة ضائقة التنفس الحاد يكمن في ردة الفعل الالتهابية في الأغشية مابين الشعيرات الدموية والحويصلات الهوائية، كانت فرضية الدراسة ان علاج الفيوروسمايد المستنشق قد يكون له القدرة على تقليل نسبة الوفيات لمرضى متلازمة ضائقة التنفس الحاد البالغين الخاضعين للتنفس الصناعي

02. Purpose of the research: *[Brief, clear description of the purpose, goals, and objectives of the research are provided here]*

Study Objectives

- The primary objective will be all cause mortality within 28 days of randomization.

- Secondary objectives include:

1- All cause hospital mortality.

2- ICU and hospital length of stay (LOS).

3- Difference of P/F ratio between day 1 and day 7 (if applicable, this outcome will not be calculated for patients who are censored before 7 days).

4- 28 days ventilator free days (VFD), defined as days without mechanical ventilation till day 28 starting from day of enrollment, as long as the patient is alive, this means that patients still mechanically ventilated at day 28, or died by day 28 will be assigned zero VFD. Patients for whom the artificial airway is shifted from endotracheal tube to tracheostomy, they will still be considered mechanically ventilated until they are liberated from mechanical ventilation and are spontaneously breathing.

5- Successful extubation rate, defined as extubated and did not require re-intubation for 72 hours. Patients for whom tracheostomy is performed are not considered as successful extubation when they are liberated from mechanical ventilation, and they will be excluded from the denominator of this particular outcome.

6- Adverse events comparison between both groups (see details in Adverse Events).

2. الغرض من إجراء دراسة البحث (وصف مختصر و واضح للغرض و الأهداف من وراء البحث).

تهدف الدراسة إلى مقارنة :

الهدف الرئيسي: نسبة الوفيات خالل 28 يوم.

الأهداف الثانوية:

1- نسبة الوفيات داخل المستشفى

2- مدة الإقامة بالعناية المركزة وبالمستشفى.

3- الفرق بين نسبة الضغط الجزئي للأكسجين/نسبة الأكسجين المستنشق بين اليوم الأول واليوم السابع بين المجموعتين.

4- 28 يومًا بدون استخدام أجهزة التنفس الصناعي وتعرّف بأنها الايام الخالية من جهاز التنفس الصناعي حتى اليوم الثامن والعشرون من دخول الشخص موضع البحث للدراسة، ويعدّ المريض الحي مابعد اليوم الثامن والعشرين خاضعًا للتنفس الصناعي؛ أمّا إذا مات المريض فيعدّ ممّن لم يفصلوا عن جهاز التنفس الصناعي.
اذا ماتم تغيير مجرى الهواء من أنبوب القصبة الهوائية إلى ثقب القصبة الهوائية سيظلون يعتبرون خاضعين للتهوية الميكانيكية حتى يتم فصلهم عن التنفس الصناعي والتحول للتنفس التلقائي.

5- معدل فصل الأنبوب الناجح يعرّف بفصل الانبوب وعدم الحاجة إليه مرّة اخرى خلال اثني وسبعين ساعة من الفصل.
لا يعتبر تحويل مجرى التنفس إلى ثقب القصبة الهوائية فصلًا ناجحًا وسيتم استبعادهم من هذه النتيجة

6- مقارنة الأعراض الجانبية ما بين المجموعتين (انظر لتفاصيل الأعراض الجانبية).

03. Selection of research subjects: *[A brief description on how research participants are selected, the inclusion and exclusion criteria used to select the sample population and an explanation of why this particular participant is being considered for inclusion in the study, and the total number of patients to be recruited in the study]*	3. **اختيار المشاركين بالدراسة** (وصف موجز عن الكيفية التي تم عليها اختيار الأشخاص لمشاركين في البحث, و المعايير التي تم عليها الانضمام أو استثناء العيّنة السكانية مع إيضاح اسباب اختيار هذا الشخص لإلنضمام في هذه الدراسة, بالإضافة الى العدد الإجمالي من المرضى الذين سوف يدخلون الدراسة)
Inclusion criteria We will enroll patients if they fulfill all of the following criteria 1- Adult (age ≥ 18 years) regardless of biological sex. 2- Admitted to ICU 3- Mechanically ventilated by endotracheal intubation for less than seven days (according to Berlin definition). 4- Within 24 hours of the diagnosis of ARDS, according to Berlin definition (1), which includes: a- Chest x-ray: Showing bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules. b- Respiratory failure not fully explained by cardiac failure or fluid overload, and exclusion of hydrostatic edema (by echocardiography). c- Oxygenation and ventilator settings matching one of the three categories of ARDS: Mild: 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2O. Moderate: 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O. Severe: PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O.	معايير المشاركة: ١- أن يكون المريض بالغًا (العمر ≤ 18 سنة) بغض النظر عن الجنس. ٢- منوم في العناية المركزة. ٣- تحت التنفس الصناعي عن طريق الأنبوب لمدة أقل من سبعة أيام (طبقًا لتعريف برلين) ٤- خلال ٢٤ ساعة منذ تشخيص متلازمة ضائقة التنفس الحاد طبقًا لتعريف برلين والذي يشمل: - وجود عتمات جانبية في أشعة الصدر السينية، غير مفسرة بالانصباب الجنبي، انخماص الرئة الكلي او الجزئي او كتل رئوية. - فشل رئوي غير مفسر بفشل في القلب أو تجمع للسوائل مع استبعاد الأسباب الأخرى (بعمل أشعة قلبية صوتية). - تصنف شدة حالات متلازمة ضائقة التنفس إلى ثلاث تصنيفات بناءًا على مؤشر هورويتز (نسبة الضغط الجزئي للأكسجين/نسبة الأكسجين المستنشق): * خفيفة: من 300 - 201 مم زئبق * معتدلة: من 200 - 101مم زئبق * شديدة: ≤ 100 مم زئبق "مع ملاحظة أنّ تعريف برلين يتطلب حدًا أدنى من نهاية ضغط الزفير الإيجابي يبلغ 5 سم ماء." معايير الاستبعاد: 1- العمر أقل من ١٨ سنة. 2- الحامل أو المرضع. 3- من لا يتوقع له النجاة لأكثر من ٤٨ ساعة على حسب رأي الفريق المعالجة. 4- من لا يتوقع له إكمال ٤٨ ساعة على جهاز التنفس الصناعي (بسبب التشافي السريع). 5- من كان له توجيه مسبّق بعدم الانعاش. 6- عدم الموافقة على المشاركة من قبل المريض أو من ينوب عنه. 7- من كان لديه حساسية ضد عقار الفيوروسمايد 8- من سبق له الدخول في نفس الدراسة (يسمح للمريض بالدخول لمرة واحدة).

Exclusion criteria: 1- Age < 18 years. 2- Pregnant or lactating ladies. 3- Not expected to survive more than 48 hours, according to the treating team. 4- Mechanical ventilation is expected to continue for less than 48 hours (due to rapid recovery) according to the treating team. 5- Advanced directive of Do Not Resuscitate (DNR). 6- Refusal to participate in the trial by the patient, or official surrogate. 7- Known allergy to furosemide. 8- Previously enrolled in the trial (a patient can only be enrolled once).	

04. Distinction between routine care and research activities: *[In case the prospective participant is to be recruited from the patient clientele of treating physicians who also are investigators in the research a description is given to the participant about what parts of the treatment constitutes routine treatment and what constitutes research activities]*

Study intervention

The intervention medication is 40 mg furosemide in 4 ml of 0.9% saline, administered every 6 hours via the ventilator circuit over 30 minutes. The intervention continues till extubation, death, or completion of 28 days whichever comes first.

The control group will receive similar color and volume of 0.9% saline following the same intervals, route, and duration.

Common management

This will be a pragmatic trial, the study protocol does not control every aspect of the management, apart from the intervention medication.

Our center follows evidence based guidelines and protocols for the management of ARDS, and treating teams will be encouraged to follow those guidelines, such as:

Protective lung strategy.

Adjuvant and rescue therapies will be allowed, at the discretion of the treating team, such as (but not limited to) prone positioning and extra-corporial membrane oxygenation (ECMO). There will be no restriction on the use of other medications by the treating, such as glucocorticoids, antibiotics, neuromuscular blocking agents.

Similarly, our center adopts practices of early internal feeding, light sedation and daily sedation vacation when applicable, deep vein thrombosis (DVT) and gastrointestinal (GIT) prophylaxis, and early weaning and extubation.

Our center applies a standardized process for weaning and extubation

4- عرف الفرق بين خدمة الرعاية الاعتيادية والأنشطة البحثية (في حالة اختيار مشارك/مشاركة بالدراسة من ضمن الأشخاص الذين تقدم لهم خدمات رعاية صحية او طبية من قبل احد أعضاء فريق البحث، يجب على فريق البحث أن يوضح لمن وقع عليه الاختيار أى جانب من خطة الرعاية الصحية أو الخدمة العلاجية يقع تحت طائلة الخدمة العلاجية التي يحتاجها المشارك وأي جانب من هذه الخطة يقع تحت طائلة دراسة البحث الطبى المقترحة)

تدخل الدراسة: عقار فيوروسيمايد 40 ملليجرام في 4 ملليليتر من محلول الملح الطبيعي عن طريق الاستنشاق كل 6 ساعات لمدة 28 يوم, أو لحين نزع أنبوب القصبة الهوائية أو الوفاة أيهم أقرب. وفي المقابل مجموعة المقارنة تحصل على 4 ملليليتر من محلول الملح الطبيعي عن طريق الاستنشاق بنفس الجرعة.

فيما عدى ذلك, سيتم علاج مرضى المجموعتين وفق أنظمة وبروتوكولات المدينة القائمة على أساس علمي وفق أحدث التوصيات العالمية, مثل: استراتيجية حماية الرئتين. كما يسمح للأستشاري المعالج بإعطاء الأدوية والتدخلات اللازمة كما يتراءى له بما فيه مصلحة المريض, بما في ذلك

المضادات الحيوية, الكورتيزون, وغيرها, والتدخلات مثل: وضع الاستلقاء وعملية الأكسجة خارج الجسم.

كما أن العناية المركزة تتبع التوصيات العالمية في عملية إزالة أنبوب القصبة الهوائية وإيقاف التنفس االصطناعي, وسيتم تطبيقها على مرضى المجموعتين.

05. Explanation of the procedures to be used: *[Brief, clear explanation of procedures involving the subject]*

If the patient is randomized to intervention group, he/she will receive the intervention medication, as well as all the management parameters common to both groups.

Patients randomized to placebo group, will be treated exactly in the same way as the intervention group, except for the intervention medication.

Group allocation is concealed in a double blinded way. Neither the patient nor the treating team is aware of the group in which the patient is included.

5- اشرح الإجراءات التي يتعين استخدامها فى الدراسة (شرح واضح و موجز للإجراءات المتعلقة بالأفراد المشاركين).

في حال اختيار المريض عشوائيًا لمجموعة التدخل, سوف يحصل على دواء فيوروسيمايد بالجرعة والطريقة السابقة. أما مرضى مجموعة المقارنة, فيتم إعطاء محلول الملح الطبيعي.

فيما عدا ذلك, يتم علاج جميع المرضى بنفس الطريقة والأدوية وحسب الخطة العلاجية للطبيب الاستشاري والمتماشية مع أحدث التوصيات العالمية القائمة على أساس علمي.

06. Description of the risks and discomfort involved: *[Describe physiological, psychological and social factors of discomfort or risks involved in the study]* Nebulized furosemide is delivered locally in the lung tissue and has a very safe profile, and no adverse events are expected. However, we will monitor every patient for the common side effects of systemic furosemide, including: increased urine output, mild electrolyte disturbances, and mild rise in renal functions. Pregnant and lactating ladies are excluded.	**6- وصف للمخاطرالناجمة عنه** (وصف الفيزيولوجية,العوامل النفسية والاجتماعية والأخطار المترتبة والناتجة عن البحث). يتمتع دواء فيوروسيمايد بمواصفات آمنة للغاية, وهو من أقل الأدوية سمية, فضلًا عن أن استخدامه عن طريق االرذاذ يجعله يصل بشكل موضعي للرئتين ولا يؤدي إلى الأعراض الجانبية البسيطة المعروفة له عند تناوله بالفم أو عن طريق الحقن. مثل زيادة إدرار البول, اضطراب بسيط في نسبة البوتاسيوم بالدم, وارتفاع طفيف في وظائف الكلى. الحوامل والمرضعات مستثنيات من الدراسة.
07. Description of Safety precautions in this research: *[Describe about the safety precautions that will be taken during study period]* All patients will be monitored daily for any adverse events, whether or not they are related to the study intervention. Any adverse events will be dealt with immediately by the ICU team, and will be reported to the IRB.	**7- وصف إجراءات و احتياطات السلامة** (وصف احتياطات السلامة التي سوف تتخذ أثناء فترة الدراسة). جميع المرضى ستتم متابعتهم وملاحظتهم بشكل يومي طول فترة الدراسة وعند ظهور أي أعراض جانبية سيتم التعامل معها وعلاجها على الفور وإبلاغ مركز الأبحاث بها.
08. Descriptions of the benefits of the study: *[Brief description of any direct or indirect benefits to the subject]* We hypothesize that nebulized furosemide may decrease mortality, decrease LOS and hasten extubation. This may be beneficial to you/your relative in the management of the current condition. If the results of the research proof to be beneficial, this medication may be part of the routine management of ARDS, and millions of patients may benefit from it worldwide.	**8- وصف لفوائد المشاركة بالدراسة إن وجدت** (وصف بإيجاز للفوائد المباشرة أو غير المباشرة والمترتبة للمشارك بهذه الدراسة). طبقا لفرضية الدراسة، قد يؤدي استخدام فيوروسيمايد – بإذن الله – إلى تقليل نسبة الوفاة وسرعة الفصل من جهاز التنفس الاصطناعي, وبالتالي سرعة الخروج من العناية والمستشفى. في حال أثبتت الدراسة جدوى العلاج لحالات متلازمة ضائقة التنفس الحاد قد يتحول إلى علاج روتيني ينتفع منه ملايين المرضى حول العالم فيما بعد.

09. Description of the alternative procedures or treatments for this research: *[A description of all alternative procedures or treatment options available to the potential research participant , so that the participant is free to choose which treatment modality to adopt]* Other than the intervention medication, the patient will be managed exactly according to our hospital's protocols of ARDS, and according to the plan of the treating consultant.	**9- وصف الإجراءات او العلاج البديل لهذه الدراسة(وصف كافة الإجراءات البديلة أو خيارات العلاج المتاحة والمحتملة للمشار له حيث تتوفر حرية اختيار المشارك لأسلوب العلاج).** فيما عدى اعطاء دواء فيوروسيمايد لمجموعة دون الأخرى، سيتم معالجة جميع المرضى بنفس الطريقة ووفق الخطة العالجية للطبيب الاستشاري, والمبنية على التوصيات العالمية ووفق بروتوكولات العلاج ذات الأساس العلمي.
10. Details of the options to remain on the research treatment after termination of the research: *[A description is provided about whether the research treatment would be available to the participant even after the study has concluded]* The intervention medication is given only for a maximum of 28 days. After which, it will be stopped.	**10- تفاصيل عن خيارات البقاء على العلاج المتبع أثناء فترة البحث حتى بعد الانتهاء (تقديم إيضاح للمشارك حول ما اذا كان البحث أو العلاج سيكون متاحا وحق للمشارك حتى بعد انتهاء الدراسة).** مدة التدخل في الدراسة 28 يوم كحد أقصى, ولا يستخدم بعدها.
11. Details of the person to contact in case of Injury or enquiry during the research: *[In case of any types of injury or enquiry, provide name of Supervisor and office phone number to contact at any time of the day or night]* Dr. Ahmed Fouad Madi Critical Care Consultant 0547060770 afmady@hotmail.com	**11. تفاصيل عن الشخص الممكن الاتصال به في حالة وجود استفسار أو حدوث إصابة خلال فترة البحث اسم المشرف, رقم تليفون المكتب للاتصال به في حالة وجود أي ضرر سواء ليل أو نهارا .** د. أحمد فؤاد ماضي استشاري العناية المركزة 0547060770 afmady@hotmail.com
12. Details of the financial or other compensation which might be provided to the research participants if any: *[Provide details of any compensation which might be provided in lieu of their participation in the research]* No financial or other types of compensations for participation in this study.	**12- تفاصيل عن التعويضات المالية أو غيرها المحتمل إعطائها للمشاركين في البحث (وضح بالتفصيل إن كان هنالك مكافأة مالية أو عينية للمشارك بالدراسة)** لا يوجد تعويضات من أي نوع مادية أو غير ذلك نظير المشاركة في الدراسة

13. Duration of the research: *[Describe how long the prospective participant is expected to be in the research and what expectations the investigator might have about the participant's time spent in the research]* Intervention medication: 28 days, or extubation, or discharge from the ICU, or death which ever happens first. Follow up (regardless of the study intervention): Till hospital discharge.	**13- مدة إجراء البحث** (وصف المدة المتوقعة للمشاركة في البحث و ما هي توقعات الباحث للوقت المستغرق في إجراء البحث). مدة البحث 28 يوم كحد أقصى, أو الفصل من جهاز التنفس الصناعي أو الوفاة لا قدر الله، أيهم أسبق. وستتم متابعة حالة المريض فقط بعد مدة 28 يوم حتى خروجه من المستشفى

14. Names of the sponsors of the research: *[if applicable, and details about where the research is going to be conducted. Give information to the participant about all the sponsors of the research, any issues of conflict of interest and also where the research will be conducted]* NONE	**14 - اسماء مصادر تمويل البحث** (إذا تواجد.أعطى تفاصيل للمشاركين عن اسم الجهات التي قامت بتمويل البحث، وما إذا كان لهذه الجهات مصلحة أو عائد مادي منتظر). **هذه الدراسة غير ممولة من أي جهة**
15. Assurance of anonymity and confidentiality: *[Confidentiality about the results/specimen/laboratory or any other data) Describe steps to protect confidentiality of data and anonymity of the participant information]* No personal identifications will be recorded or stored in this study. Each enrolled patient will be given a code number. All recorded data will be kept under lock and key with the primary investigator. Published data will not contain any identifying information, and will be in an abstracted form, making it impossible to identify any single value for an individual patient.	**15- السرية حول النتائج، العينةالمختبرية أو أي بيانات أخرى (صف** خطوات حماية سرية البيانات، العينة المختبرية أو أي بيانات أخرى من شأنها الكشف عن هوية او اسم أي مشارك بالدراسة) **لن يتم تسجيل أي بيانات شخصية للمرضى, ولا أي معلومات يمكن أن تؤدي للتعرف عليهم.** **كما أن جميع النتائج ستنشر على شكل متوسط مما لا يسمح بمعرفة النتائج الفردية لكل مريض على حدة.** **جميع البيانات المسجلة ستكون مسؤولية الباحث الرئيسي ولا يسمح بالاطلاع عليها**
16. Non-coercive disclaimer: *[A statement that there is no pressure on the prospective subject to participate in the study , that he/she is free to choose any of the treatment modalities offered and that there is no pressure on the participant to continue in the study even after enrollment]*	**16- تنويه بعدم القسرية** (اقرار بعدم ممارسة ضغوط على المشارك للموافقة و أنّه حر في اختيار الوسيلة المناسبة للعلاج و أنه غير ملزم بالاستمرار في الدراسة حتى بعد التسجيل).

Participation in this study is totally voluntary, you are not under any kind of pressure or obligation to take part in the study. Refusal to participate will not affect in any way the management of the patient, nor the family support.	المشاركة في هذه الدراسة اختيارية تماما, وليس هناك أي نوع من الضغط عليك / على قريبك للمشاركة. رفضك للمشاركة هو حق مكفول, ولن يؤثر بأي شكل من الأشكال على علاجك / علاج قريبك.
17. Option to withdraw from the study without penalty: *[An option is given to the potential participant to continue or withdraw from the study even after enrollment in the research]* If after consenting you decide to withdraw the consent at any time, you are freely allowed to do so, without the need to provide reasons, without any penalty or negative consequences, and any previously recorded data for you/your relative will be deleted and not included in the study.	**17- إمكانية إنسحاب المشارك من الدراسة أو البحث دون عواقب** (أعطي الخيار للمشارك في البحث لالستمرار أو الانسحاب من الدراسة حتى بعد التسجيل في الدراسة) لك حق الانسحاب في أي وقت من الدراسة، بدون ابداء أسباب, ولن ينتج عن ذلك أي عواقب أو نتائج سلبية, وسيستمر علاجك / علاج قريبك كما هو مقرر من الطبيب الاستشاري. وعند الانسحاب من الدراسة سيتم شطب أي بيانات أو معلومات كان قد تم تسجيلها من قبل ولن تكون مشمولة في التحليل الاحصائي
18. Details about termination of the study: *[A description is given on when and how the study is expected to be completed, what happens when the study is completed, whether the participant is further entitled to contact the investigators after such time, whether the findings of the research will be revealed to them and if the results of the research would be applied to them or not]* Recruitment will continue till completion of the required sample size or early stopping, the study ends when the hospital outcome of the last enrolled patient is known. Results of the study will be published.	**18- تفاصيل عن إنهاء الدراسة أو البحث** (أعطى شرحا وافيا عن التوقعات بشأن المدة الزمنية والطريقة التى يتم بموجبها إعلان اكتمال الدراسة أو البحث. أشرح ماذا يحدث بعد إنتهاء الدراسة أو البحث، حد المشارك الحق فى للاتصال بفريق البحث بعد فترة من الزمن، الاطلاع على نتائج البحث، وما إذا كانت النتائج ستطبق على المشاركين. سوف يستمر ادخال أفراد جدد في الدراسة حتى إكمال حجم العينة المقرر مسبقا أو إيقاف الدراسة طبقًا للشروط المحددة بالبروتوكول. وتنتهي الدراسة عند معرفة حالة آخر مريض تم اشراكه بالدراسة من حيث الخروج من المستشفى.
19. Details of the instances in which there might be incomplete disclosure of information: *[Description of the instances in the study in which the investigator might not provide all information needed to take an informed consent at the outset of the study, why this is so and when there will be debriefing if any of the undisclosed information to the participant]* NONE.	**19- تفاصيل عن الحالات التي قد يكون فيها افشاء المعلومات غير مكتمل** (وصف الحالات في الدراسة والتى قد يقدم فيها الباحث عن عدم توفير أو إفشاء جميع المعلومات المطلوبة لاتخاذ إجراء الحصول على الموافقة المستنيرة الخطية في بداية الدراسة, ولماذا إتخذ الباحث هذا الموقف ومتى يتم استخلاص المعلومات إن وجدت وتوفرها كي يطلع عليها المشارك بالدراسة).

	لن يكون هناك أي افشاء لمعلومات المرضى.
Signed Consent for Study Participation Consent: You (the participant) have read or have had read to you all of the above. *[principle investigator name]*or his/her authorized representative has provided you with a description of the study including an explanation of what this study is about, why it is being done, and the procedures involved. The risks, discomforts, and possible benefits of this research study, as well as alternative treatment choices, have been explained to you. You have the right to ask questions related to this study or your participation in this study at any time. Your rights as a research subject have been explained to you, and you voluntarily consent to participate in this research study. By signing this form, you willingly agree to participate in the research study described to you. You will receive a copy of this signed consent form. As long as the study is renewed as required by the IRB, your signature on this document is valid for the duration of the entire research study. Should any changes occur during the course of the study that may affect your willingness to participate, you will be notified.	**الموافقة المستبينة للمشاركة فى البحث** *الموافقه المستبينة الخطية: عزيزي المشارك في هذا البحث قد قمت بقراءة أو قد قرىء عليك المرفق أعلاه. **د. أحمد ماضي أو من** ينوب عنه قد قام بإعطائك شرح للدراسة متضمنًا اسباب القيام بهذه الدراسة و الإجراءات المتضمنة في هذه الدراسة. كما تم اعطائك شرح عن الأضرار و المخاطر و الفوائد المحتملة من وراء هذه الدراسة و إذا ما كان لك خيارات بديلة للعلاج. لك حق الاستفسار و طرح أي سؤال متعلق بهذه الدراسة أو مشاركتك فيها. تم القيام بتقديم شرح عن حقوقك كمشارك في هذه الدراسة و ان موافقتك على المشاركة في هذا البحث هو عمل تطوعي. بالتوقيع على هذه الورقة, إقرار منك بالموافقة على المشاركة في هذا البحث. سوف تعطى لك نسخة من هذا الإقرار بالموافقة. توقيعك على هذه الوثيقة يعتبر صالح في حال تم تجديد هذا البحث طوال فترة الدراسة البحثية. سوف يتم إبلاغك في حال حصول أي تغيير في الدراسة مما قد يؤثر على موافقتك على المشاركة.

***By signing this consent, I hereby agree that all the 19 elements from pages 1-9 has been fully explained to me and that I agree to participate in this study.**			
Participant or Guardian's Name	Signature & Date	**التوقيع وتاريخه**	**اسم: المشارك أو الوصي**
Witness Name	Signature & Date	**التوقيع وتاريخه**	**اسم الشاهد**
Principal Investigator's Name	Signature & Date	**التوقيع وتاريخه**	**اسم الباحث الرئيسي**
For use of Research Center only			**إستخدام مركز الأبحاث فقط**

For use of IRB only		**استخدام لجنة اخلاقيات البحث فقط**

Effect of nebulized furosemide on mortality of adult mechanically ventilated ARDS patients. (ENHALE)

Study Code	

Demographics and baseline clinical data:

Age	
Sex	
SOFA (on day of randomizaton)	
Clinical Frailty Scale	
BMI	

Key Dates:

Date of Hospital Admission	mm/dd/yyyy
Date of ICU Admission	mm/dd/yyyy
Date of Endotracheal Intubation	mm/dd/yyyy

ARDS Diagnosis:

PaO2 (mm/Hg)	
FiO2 (Decimal)	
P/F Ratio	
PEEP/CPAP (CmH2O)	
Severity of ARDS	

Underlying Cause of ARDS:

Bacterial Pneumonia	Viral Pneumonia	Pneumonia, other.	Sepsis, abdominal	Sepsis, other.	Trauma, Lung.
Trauma, abdomen	Trauma, CNS	Trauma, other	Transfusion	Inhalational	Pancreatitis
Other, Specify:					

Co-morbidities:

Diabetes	Hypertension	Chronic Kidney Disease	Chronic Liver / Cirrhosis	Heart Failure
Ischemic Heart	Malignancy	Immunocompromised	Transplant	Cerebrovascular Accident
Smoker	Other			

Follow Up:

P/F Ratio day 7	
SOFA day 7	

Key Follow up Dates (within 28 days of randomization, if applicable):

First Extubation	mm/dd/yyyy	**First Liberation**	mm/dd/yyyy
First Reintubation	mm/dd/yyyy	**First Reconnect**	mm/dd/yyyy
Second Extubation	mm/dd/yyyy	**Second Liberation**	mm/dd/yyyy
Second Reintubation	mm/dd/yyyy	**Second Reconnect**	mm/dd/yyyy
Third Extubation	mm/dd/yyyy	**Third Liberation**	mm/dd/yyyy
Third Reintubation	mm/dd/yyyy	**Third Reconnect**	mm/dd/yyyy
Tracheostomy	mm/dd/yyyy	**Fourth Liberation**	mm/dd/yyyy

(Liberation is after tracheostomy)

Extra dates if needed (indicate the event):

	mm/dd/yyyy		mm/dd/yyyy
	mm/dd/yyyy		mm/dd/yyyy
	mm/dd/yyyy		mm/dd/yyyy
	mm/dd/yyyy		mm/dd/yyyy
	mm/dd/yyyy		mm/dd/yyyy

Outcome:

Date of ICU Discharge	mm/dd/yyyy
Date of Hospital Discharge	mm/dd/yyyy
Status at day 28	**Died - Alive MV – Alive and Spontaneous**
ICU Discharge Status	**Died – Ward – Other Hospital – Home/DAMA**
Hospital Discharge Status	**Died – Other Hospital – Home/DAMA**
Readmitted to ICU	**YES - NO**

Adverse Events:

Increase serum creatinine > 26.5 micromol/L in 48 hours or more	
Increase serum creatinine 1.5X baseline	
UP < 0.5 ml / kg / hour, for 6 hours	
Positive culture	
3.5 >Serum Potassium > 5.5 mEq/L	
UOP > 2000 ml / 24 hours	
Other:	
Other:	

Other:	
Other:	
Other:	

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Urea																												
Creatinine																												
Potassium																												
UOP																												
Med:																												
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Sequential [Sepsis-Related] Organ Failure Assessment Score					
	Score				
System	0	1	2	3	4
Respiratory[1]					
PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) and mechanically ventilated	<100 (13.3) and mechanically ventilated
Coagulation					
Platelets, x $10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular[2-3]	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
Glasgow coma scale score	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (µmol/L) or urine output,	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) or <500 mL/day	>5.0 (440) <200 mL/day

PL Ho, TC Wu, David VK Chao, Ivan FN Hung, Leo Lui, David C Lung, Tommy HC Tang, Alan KL Wu (ed). 2017. Reducing bacterial resistance with IMPACT, 5th edition, Hong Kong

Clinical Frailty Scale

1. Very fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.

3. Managing well – People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5. Mildly frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6. Moderately frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

7. Severely frail – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. Very severely frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia,** recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia,** they cannot do personal care without help.

Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005 Aug 30;173(5):489-95.