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Effect of prone positioning in patients with severe SARS-CoV-2 pneumonia treated with noninvasive ventilation

Submission date
01/05/2021

Recruitment status
No longer recruiting

Registration date
02/06/2021

Overall study status
Completed

Last Edited
19/07/2024

Condition category
Respiratory

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.

In 2020, the virus has spread to many countries around the world and neither a vaccine against the virus or specific treatment for COVID-19 has yet been developed. As of March 2020, it is advised that people minimize travel and social contact, and regularly wash their hands to reduce the spread of the virus.

Groups who are at a higher risk from infection with the virus, and therefore of developing COVID-19, include people aged over 70 years, people who have long-term health conditions (such as asthma or diabetes), people who have a weakened immune system, and people who are pregnant. People in these groups, and people who might come into contact with them, can reduce this risk by following up-to-date advice to reduce the spread of the virus.

Despite ongoing trials of antivirals and immunomodulatory therapies against COVID-19, the treatment of moderate/severe disease remains mainly supportive and mortality among invasively ventilated COVID-19 patients with severe respiratory failure remains overwhelmingly high.

Prone positioning (PP) therapy (lying on the front) is a non-pharmacological treatment that has been shown to improve oxygenation through several mechanisms: improved ventilation /perfusion matching, relief of the compression of dependent lung regions, and change in chest wall elastance. PP applied for at least 16 hours per day has been shown to halve mortality in intubated patients with severe acute respiratory distress syndrome (ARDS) and is now recommended for this population.

Although PP is a low-cost, low risk and widely available behavioral therapy, it is not a standard of care for awake patients with respiratory failure, and data in awake patients with severe SARSCoV 2 pneumonia are scarce, limited to few cases.

We aim to assess if, in patients with moderate-to-severe acute respiratory failure due to SARS CoV2 pneumonia who require NIV, the early use of prolonged (i.e., at least 8 consecutive hours /day) PP combined with NIV can reduce NIV failure, the need for intubation, and overall mortality.

Who can participate?
Patients with moderate-to-severe acute hypoxemic respiratory failure due to SARSCoV2 pneumonia treated with NIV at the HUMANITAS Gradenigo COVID Subintensive Care Unit.

What does the study involve?
Patients with moderate-to-severe acute hypoxemic respiratory failure due to SARSCoV2 pneumonia who require treatment with NIV are required to lie prone for at least 8 hours/day for at least 2 consecutive days while receiving NIV. The outcomes of these patients will be compared to the outcomes of a group of patients with the same characteristics who have been treated with NIV delivered in the conventional way (i.e. with the patient lying supine or in lateral decubitus) from March 1st, 2020 to Dec 31st, 2020 in the same subintensive care unit by the same healthcare staff.

What are the possible benefits and risks of participating?
The expected benefits are a reduction in the rate of NIV failure, in the need for endotracheal intubation and in overall mortality.
These are no major risks of prolonged PP therapy as compared with NIV delivered in the conventional way(i.e., delivered in the supine or lateral decubitus position)

Where is the study run from?
HUMANITAS Gradenigo COVID Subintensive Care Unit (Italy)

When is the study starting and how long is it expected to run for?
December 2020 to September 2021

Who is funding the study?
Hospital HUMANITAS Gradenigo (Italy)

Who is the main contact?
Dr Giovanni Musso, giovanni_musso@yahoo.it

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
Protocol version 1.0 March 31st, 2021 Ethics committee protocol number: 0046392

Study information

Scientific Title
Effect of prolonged prone positioning on intubation rate and mortality in noninvasively ventilated patients with SARS-CoV-2 pneumonia and moderate-to-severe hypoxemic respiratory failure: a controlled trial

Acronym
PRO-NIV

Study objectives
A prolonged prone position in patients with moderate-to-severe acute hypoxemic respiratory failure due to COVID-19 pneumonia treated with noninvavive ventilation is safe and associated with a reduced rate of NIV failure, endotracheal intubation and overall mortality than noninvasive ventilation delivered in a conventional posture (i.e. with patient lying supine or in lateral decubitus)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/01/2021, Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino, (Interhospital Ethics Committee-AOU City of Health and Science of Turin, Corso Bramante 88/90, 10126, Turin, Italy; +39 11-6331633; no email provided), ref: 0046392

Study design
International non randomized controlled trial

Primary study design

Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format. Please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Moderate-to-severe acute hypoxemic respiratory failure due to COVID-19 pneumonia

Interventions
In both arms, patients receive noninvasive ventilation (NIV) for at least 16 hours/day during at least the first 2 calendar days. Continuous NIV without interruptions in the first 24 hours of treatment is recommended. and only brief interruptions are allowed for eventual adjustments, if needed, lasting no more than few minutes, immediately restarting NIV.
Subsequently, NIV is reduced progressively in accordance with the degree of clinical improvement. Each patient is then evaluated daily without ventilatory support while breathing supplemental oxygen: if the patients' clinical status deteriorates, NIV is reapplied; otherwisw, weaning from NIV is started.

Experimental arm
Patients of the experimental (prone position, PP) qrm will be asked to remain in prone position (i. e. lying straight on the stomach) throughout the day as long as possible, with at least 1 PP session lasting at least 8 hours each day. Patients completing at least one 8-hour proning session per day during the first 2 calendar days will be considered to have successfully completed PP therapy
Daily breaks, not lasting more than 2 hours, in PP will be allowed for meals and nursing care, according to patient tolerance.
A call bell and pillows will be offered for maximizing comfort at chest, pelvis and knees.
In both arms, oxygen saturation, other vital signs and ECG will be continuously monitored and FiO2 is titrated to maintain a capillary saturation of 95% or higher
Staff intensivists and nurses will continuously monitor adherence to protocol and patient's status on a 24-hr basis.

Control arm (NIV delivered in a conventional, supine position)
The control patients are selected among consecutive patients with acute respiratory failure due to severe SARSCoV2 pneumonia treated in the HUMANITAS Gradenigo Subintensive Care Unit with NIV (CPAP or PSV) delivered in the conventional way (supine position or lateral decubitus) from March 1st, 2020 to Dec 31st, 2020.

The ratio will be 2 controls-to-1 experimental treatment patient.
All controls had the same enrollment criteria described for the experimental arm.
Each patient will be followed for up to 28 days after discharge from Subintenvise Care Unit by reviewing patient notes, in-presence or phone patient interview

Intervention Type
Behavioural

Primary outcome measure
Occurrence of NIV failure at 28 days, defined as the occurrence of endotracheal intubation (for those patients with a full treatment indication) OR death for those patients with a Do-Not-Intubate (DNI) order. This will be assessed by reviewing patient notes or in-presence or phone patient interview.

Secondary outcome measures
Current secondary outcome measures as of 22/10/2021:

Secondary clinical outcomes censored at 28 days after enrolment from patient records were:
1. Death
2. Intubation (after excluding patients with a do-not-intubate, DNI, order)
3. Time to NIV failure/intubation/death
4. Daily hours of PP therapy
5. Duration of the longest PP session each day
6. Total number of PP sessions each day
7. Daily hours of NIV
8. Days of PP therapy
9. Days of NIV
10. Length of Subintensive Care Unit/hospital stay
11. Days of invasive mechanical ventilation
12. Death in invasively mechanically ventilated patients
13. Device-related discomfort and dyspnoea: via the Numeric Pain Rating Scale(NRS) and the Critical-Care Pain Observation Tool(CPOT), respectively
14. Predefined safety outcomes as prospectively recorded by investigators

The following outcomes were recorded during the initial 7 days after enrollment to explore physiological response to PP (physiological substudy):
1. Lung ultrasound (LUS) indices of lung aeration and recruitment assessed at baseline (within 24 hrs of enrollment) and at day 5 (details of the assessment and justification of the timing are
2. paO2/FiO2 ratio, pCO2, respiratory rate (RR) obtained from ABG drawn 1 hour after initiating NIV in supine position, 1 hour after starting the 8-hr PP session and 1 hour after resupination following the 8-hr PP session. RR and VTe were recorded at the time of each ABG.
3. Physiological dead space indices(DSIs): Ventilatory Ratio(VR) and corrected Minute Ventilation (MVcorr).
4. Change in 18 blood laboratory parameters from admission to day 7, including inflammatory and procoagulative biomarkers.

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Previous secondary outcome measures:

1. The need for endotracheal intubation at 28 days among patients with a full treatment indication. This will be assessed by reviewing patient notes or in-presence or phone patient interview.
2. Mortality at 28 days. This will be assessed by reviewing patient notes or in-presence or phone patient interview.
3. Change in oxygenation parameters. The main oxygenation parameter will be the paO2/FiO2 ratio, which will be obtained from daily arterial blood gas (ABG) during NIV 1-hour after starting ventilation in supine position, 1-hour after each prone session and 1-hour after resuming supine position. The following exploratory parameters, which combine oxygenation with RR, will be also obtained:
3.1. ROX index (SpO2/FiO2/RR)
3.2. HACOR score (which includes heart rate, respiratory rate, paO2/FiO2, arterial pH and Glasgow Coma Scale). These two parameters predicted NIV failure in acute hypoxemic respiratory failure of varying aetiology.
4. Change in laboratory inflammatory and coagulative parameters recorded from admission to COVID Subintensive Care Unit to discharge, obtained by daily blood sample analysis.

All the following outcomes will be obtained by reviewing sanitary patient notes.
5. Safety endpoints: the reason for NIV failure and/or ETI, adverse effects of prone positioning therapy (skin ulceration/decubiti, back pain, intravenous/arterial lines dislodgement), infections (with time of onset) at 28 days.
6. Daily hours of prone positioning at 28 days.
7. Hours of the longest prone session each day, at 28 days.
8. Total number of prone sessions each day, at 28 days.
9. Daily hours of NIV at 28 days
10. Total days of prone positioning therapy, at 28 days.
11. Total days of NIV, at day 28
12. Intermediate Care Unit length of stay, at 28 days
13. Hospital length of stay, at 28 days.

Overall study start date
15/12/2020

Completion date
12/09/2021

Eligibility

Key inclusion criteria
1. Presence of acute (i.e. symptom onset <14 days of hospital access) hypoxemic respiratory failure
2. Confirmed severe SARSCoV2 pneumonia based on the Center for Disease Control guidelines: SARSCoV2 infection confirmed by PCR AND bilateral opacities on chest X-ray or CT scan not fully explained by effusions, lobar or lung collapse, or nodules, with sO2<90% in room air on pulse oxymetry
4. Cardiac failure not the primary cause of acute respiratory failure
5. Moderate to severe hypoxemia, defined by a PaO2/FiO2 ratio <200 mm Hg while receiving oxygen therapy through either a Venturi mask with FiO2 50% or a non-rebreather reservoir bag-mask, with FiO2 estimated as 0.21+ oxygen flow rate in L/min×3

Participant type(s)

Patient

Age group
Adult

Sex
Both

Target number of participants
165

Total final enrolment
138

Key exclusion criteria
1. Age less than 18 years-old
2. Pregnancy
3. Immediate need of invasive mechanical ventilation (altered mental status, fatigue, hemodynamic instability).
4. Contraindications for prone positioning therapy (recent abdominal or thoracic surgery or wound; facial, pelvic, or spine fracture)
5. Vomiting or bowel obstruction
6. Palliative care
7. Multiorgan failure
8. Pneumothorax
9. Inability of the patient to provide informed consent
10. Uncooperativeness or refusal to lie on abdomen for at least 8 hours

Date of first enrolment
05/01/2021

Date of final enrolment
14/08/2021

Locations

Countries of recruitment
Italy

Study participating centre
HUMANITAS Gradenigo Hospital
Corso Regina Margherita 8
Turin
Italy
10153

Sponsor information

Organisation
Ospedale Humanitas Gradenigo

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
http://www.gradenigo.it/

ROR
https://ror.org/017j6af40

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Ospedale HUMANITAS Gradenigo

Results and Publications

Publication and dissemination plan
We planned to publish the results of this controlled trial to an international journal following peer review.

Intention to publish date
31/08/2021

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study referring to de-identified individual patients will be available upon request from the PI Dr Giovanni Musso (phone: +39-11-19101244; e-mail: giovanni_musso@yahoo.it) since study publication for up to 5

years. Patients are required to consent to make their deidentified data publicly available for up to 5 years upon giving consent to study participation, as clearly stated in the protocol approved by local Ethics committee.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		29/04/2022	03/05/2022	Yes	No
Protocol file	version 1.2	15/12/2020	04/10/2022	No	No
Results article		26/05/2023	30/05/2023	Yes	No
Results article		10/06/2023	19/07/2024	Yes	No