Early View

Original article

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Self-Proning in COVID-19 Patients on Low-Flow Oxygen Therapy. A Cluster Randomised Controlled Trial

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Author Contributions: AK and DA designed the study. AK, CC, CM, OG, SL, FL, JP, JPJ and PMS contributed to enrollment and data acquisition. EDL performed statistical analyses. AK and DA draft the first version of the manuscript. All authors assisted with data interpretation, manuscript preparation, and final manuscript review.
Sources of Support: None.

Running Head: Self-Proning in COVID-19 Patients

Word Count: 2423; 2 Table; 2 Figures and 2 online supplementary files.

Summary “Take Home Message”

This randomised controlled trial analyses the effect of self-prone positioning in COVID-19 associated pneumonia. Prone positioning was easy to implement and oxygen needs were lower in the self-prone group although not reaching statistical significance.

Characters (including spaces): 251
Abstract

Rationale and objectives: Prone positioning as a complement to oxygen therapy to treat hypoxemia in coronavirus disease (COVID-19) pneumonia in spontaneously breathing patients has been widely adopted, despite a lack of evidence for its benefit. To test the hypothesis that a simple incentive to self-prone for a maximum of 12 h per day would decrease oxygen needs in patients admitted to the ward for COVID-19 pneumonia on low-flow oxygen therapy.

Methods: Twenty-seven patients with confirmed COVID-19 pneumonia admitted to Geneva University Hospitals were included in the study. Ten patients were randomised to self-prone positioning and 17 to usual care.

Measurements and Main Results: Oxygen needs assessed by oxygen flow on nasal cannula at inclusion were similar between groups. Twenty-four hours after starting the intervention, the median oxygen flow was 1.0 L/min (interquartile range, 0.1-2.9) in the prone position group and 2.0 L/min (interquartile range, 0.5-3.0) in the control group (P = 0.507). Median oxygen saturation/fraction of inspired oxygen ratio was 390 (interquartile range, 300-432) in the prone position group and 336 (interquartile range, 294-422) in the control group (P = 0.633). One patient from the intervention group who did not self-prone was transferred to the high-dependency unit. Self-prone positioning was easy to implement. The intervention was well tolerated and only mild side-effects were reported.

Conclusions: Self-prone positioning in patients with COVID-19 pneumonia requiring low-flow oxygen therapy resulted in a clinically meaningful reduction of oxygen flow, but without reaching statistical significance.
Keywords: prone position, coronavirus disease; pneumonia; oxygen therapy

Word count: 240
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-associated pneumonia is associated with severe hypoxemic respiratory failure requiring treatment in high-dependency or intensive care units (ICUs) in approximately 5-10% of hospitalized patients (1, 2). Given the rapid increase of cases during the recent pandemic, many high dependency units and ICUs have been overwhelmed in their capacity to provide care (1, 3). In addition, several pharmacological agents for the treatment of SARS-CoV-2-associated pneumonia remain of uncertain benefit or have been associated with potentially life-threatening side-effects (4). In patients hospitalized in a medical ward with a diagnosis of coronavirus disease (COVID-19) pneumonia, any simple intervention to limit the progression of hypoxemia and avoid transfers of patients to critical care units for mechanical ventilation may be of benefit for the management of hospital resources.

Lung protective mechanical ventilation and intermittent prone positioning with neuromuscular blockade are standard care and evidence-based strategies in the management of severe acute respiratory distress syndrome (5-7). Use of low tidal volume ventilation (4-8 ml/kg of predicted weight) targeting a plateau pressure <30 cm H2O, with high positive end-expiratory pressure and prone mechanical ventilation for 12 to 16 h/day has been integrated in the Surviving Sepsis Campaign guidelines for the management of critically-ill adults with COVID-19 (8). The rationale behind the prone position is to reduce ventilation/perfusion mismatch and thus hypoxemia. The prone position decreases the pleural pressure gradient between dependent and non-dependent lung regions, which is believed to generate a more homogeneous lung ventilation in acute respiratory distress syndrome patients (9). As the prone position does not appear to alter blood flow distribution, a subsequent reduction in shunting might be observed (10).
At present, no published trials have documented the effect of the prone position in awake patients with COVID-19 pneumonia. Case series suggest that the prone position in awake patients treated with high-flow nasal oxygen therapy or non-invasive ventilation is feasible, easier to perform than in heavily-sedated more severely-ill patients, and is not associated with major side-effects (11-16). However, it remains unknown whether prolonged periods of prone position in patients admitted for COVID-19 pneumonia on low-flow oxygen therapy are associated with a persistent improvement in oxygen saturation (SpO2) and lower needs of oxygen. We designed this single-center, cluster randomised controlled trial to test the hypothesis that the prone position is associated with lower needs of oxygen in patients admitted to the medical ward for COVID-19 pneumonia.

**Methods**

**Study Design and Participants**

We conducted a single-center cluster randomised controlled trial in 6 medical wards in Geneva University Hospitals (Geneva, Switzerland). As the intervention (incentive to self-prone) was not blinded and delivered by physicians and nurses involved in patient monitoring during the COVID-19 pandemic, a cluster randomised controlled trial design was chosen to minimize contamination between groups (i.e., to prevent patients in the control group from receiving the intervention if admitted to the same ward as those in the intervention group). Inclusion criteria were patients of 18 years of age or older admitted to a medical ward for treatment of COVID-19 pneumonia with low-flow oxygen therapy (defined by 1 L/min to 6 L/min) through nasal cannulas to obtain a SpO2 level of 90-92%. Exclusion criteria were: patients initially treated in the ICU or high-dependency unit and recovering from acute respiratory distress syndrome; those with oxygen needs higher than 6L/min using a nasal cannula or with >40% fraction of inspired
oxygen (FiO₂) using a Venturi mask to obtain a SpO₂ level of 90-92%; pregnant women; terminally-ill patients; and those unable to self-prone. Patients were screened by a daily review of admissions to each ward.

**Randomisation**

The randomisation unit was a medical ward in the division of internal medicine of our hospital with a 15-bed capacity. Six clusters were selected and a computer-generated randomisation scheme was used to assign each medical ward randomly in a 1:1 ratio to either the intervention or usual care. As of April 14, 2020, most wards dedicated to the care of COVID-19 pneumonia gradually closed because of effective COVID-19 containment measures and a favorable evolution of the epidemic in our region. Four more patients were individually randomised by the computer generated program in the wards which remained open. From April 25 to May 29, 2020, no further eligible patients were admitted to the ward for COVID-19 pneumonia and we decided to close enrollment, despite not having reached the number required by our sample size calculation.

**Intervention**

We compared an add-on to usual care versus usual care alone. Usual care consisted of: (1) Oxygen titration with nasal cannula according to our institutional recommendations to target SpO₂ values between 90% and 94%. Nurses carried out at least six routine rounds per 24 hours to monitor oxygen needs and adapt oxygen flow to the prescribed SpO₂ target; (2) empirical antibiotics for community-acquired pneumonia; (3) an association of hydroxychloroquine and lopinavir/ritonavir as proposed by our institutional guidelines; and (4) a restrictive fluid strategy. Regarding the intervention, an intern (CC) and a resident (AK) from the Division of Lung Diseases promoted self-proning for 12 h a day as an addition to usual care for 24 h. After an
initial demonstration with the study investigators, all patients were given an explanatory brochure with photographs of the prone position and it was suggested that they use their mobile phone “timer function” to alternate their body position every 4h. Nurses regularly visited patients to encourage them to change their bed position during their rounds. All patients were given an explanatory brochure with photographs of the prone position and it was suggested to use their mobile phone’ “timer function” to alternate their body position every 4 h. Vital signs were recorded after 24 h and patients answered a brief survey on tolerance and estimated time of prone positioning.

**Data Collection and Study Outcomes**

Oxygen flow (L/min), estimated FiO2 (%), SpO2, respiratory rate, and heart rate were retrieved directly from the institutional electronic patient health record. Transfers to critical care units or home discharge were also recorded. Time spent in the prone position was self-reported in a diary. SpO2 and other vital signs were recorded at 24hours when the patient was lying on his back at rest for one hour. SpO2 was recorded after its value had stabilized for at least one minute. The pre-specified primary outcome was oxygen needs assessed by nasal cannula oxygen flow at 24 h. Secondary outcomes were the SpO2/FiO2 ratio (defined as SpO2 in percent divided by the fraction of inspired oxygen (FiO2)) at 24 h (17), respiratory and heart rate at 24 h, patient trajectory (transfer to critical care unit), and potential intervention-related adverse effects as defined by neck pain, position-related discomfort and gastroesophageal reflux.

**Statistical Analyses**
Continuous variables were summarized as medians and interquartile ranges (IQR) and categorical variables as numbers and percentages. Differences between groups were assessed using the Mann-Whitney-Wilcoxon test for continuous outcomes.

**Sample-Size Estimate**

We based our sample size estimation on a preliminary unpublished observation in 20 patients admitted to the respiratory wards for COVID-19 pneumonia on low-flow oxygen therapy. In these patients, prone position for 15 minutes was associated with an immediate improvement in SpO2 allowing to decrease oxygen flow by 1L/min with a standard deviation of 1L/min. Flow meters used in our institution for oxygen therapy allow reading of oxygen flow with a precision of 0.5L/min. We also considered that a treatment effect of 1L/min would be clinically relevant for triage strategies in an overwhelmed health care system. To show a difference of 1L/min of oxygen flow with a standard deviation of 1L/min in an individually randomised trial with a two-sided significance level of 0.05 and a power of 0.8, enrollment of 32 patients would be needed.

To take into account the correlation between patients of the same medical ward, the sample size was multiplied by a design effect of 2.4 corresponding to an intraclass correlation coefficient of 0.1 and a number of patients per ward equal to 15. Therefore, enrollment of 76 patients would have been required.

Analyses were performed with R statistical language (18).

**Ethics**

The institutional ethics review committee approved the trial (CCER 2020-00705). The study was registered on the Swiss National Clinical Trial portal (SNCTP000003718). All participants provided written informed consent before screening.
Results

7 medical wards were approached to participate in the trial and 6 wards were randomized in a 1:1 ratio to the intervention or the usual care. From April 6 to April 25, 2020, 54 patients were screened and 27 were enrolled in the trial. Causes for non-inclusion were: (1) refusal to participate (n=19) and (2) impossibility to self-prone due to morbid obesity, hemiplegia or cervical minerva (n=5); and (3) end-of-life support care (n=3). Ten patients were randomised to self-prone and 17 to usual care (Figure 1). Baseline characteristics are described in Table 1. Mean (± standard deviation) age of participants was 58±12 years; 10/27 (37%) were women. Among these, 12/27 (44%) had hypertension, 5/27 (19%) had diabetes, and one patient had chronic kidney disease. Time from first symptoms to inclusion was 10.5±5.1 days.

Estimated self-prone time was 295±216 min in the self-prone group and 7±29 min in the control group due to a single patient who spent an estimated time of 120 min in the position. At baseline, median oxygen flow on a nasal cannula was 2.5 L/min (IQR, 2.0-3.0) in the self-prone group and 2.0 L/min (IQR, 1.0-3.0) in the control group. At 24 h, median oxygen flow was 1 L/min (IQR, 0.1-2.9) in the self-prone position group and 2.0 L/min (IQR, 0.5-3) in the control group (P = 0.507). This corresponded to a SpO₂/FiO₂ ratio of 390 (IQR, 303-432) in the self-prone group at 24 h compared to 336 (IQR, 294-423) in the control group (P = 0.633) (Figure 2, superior and inferior panel). Changes of oxygen flow and SpO₂/FiO₂ ratio for individual patients are shown in a Supplementary Figure (Supplementary Figure 1A and 1B). Main and secondary physiological endpoints are presented in Table 2. Median respiratory rate decreased with the intervention, whereas no effect was observed for heart rate. One patient randomised to the self-prone position was admitted to the high-dependency unit because of increased oxygen needs versus none in the
usual care group. This patient was a 45-year-old male with a body mass index of 27.8 kg/m² without known comorbidities. He had an estimated prone position time of 6 min over 24 h and a reported side-effect of mild discomfort. Five (50%) other patients in the intervention group reported intervention-related adverse events, mainly mild position-related discomfort. No other intervention-related side effects were reported.

Discussion

In this cluster randomised trial, self-prone positioning in patients admitted for COVID-19 pneumonia requiring low-flow oxygen therapy appeared to be effective in decreasing oxygen needs at 24 h. A clinically meaningful reduction of oxygen flow and an improved SpO2/FiO2 ratio were observed, although they did not reach statistical significance. With an unprecedented number of ill patients in a small geographic area and the risk of overwhelming local health resources, a reduction of oxygen flow by 1L/min could be of importance to select stable patients for home discharge with an oxygen supply or to prevent unnecessary or premature transfers to intermediate care units.

The intervention consisted of a simple incentive to self-prone for 12 h over a period of 24 h. Invitation to self-prone was easy to implement after an initial demonstration and distribution of an explanatory brochure and resulted in a substantial time spent in this position. The intervention was also well tolerated and only mild adverse events were reported. Our results are in line with already published case series and expand current knowledge on the prone position in awake patients with hypoxemic respiratory failure associated with COVID-19 pneumonia (12-16). Prone position is believed to improve hypoxemia by generating a more homogeneous lung ventilation without altering blood flow distribution (9, 10) as also illustrated by data from our trial.
In this unique pandemic situation, health professionals have often been forced to provide immediate medical assistance rather than generating reliable data from randomised trials to inform clinical practice. Awake prone positioning has been widely adopted by physicians around the globe (19) and proposed in conscious COVID-19 patients by the UK Intensive Care Society, but without strong evidence (20). Such a recommendation may discourage the scientific community to run trials, although most professional bodies emphasize the need for higher quality evidence (21,22). Therefore, we specifically focused this randomised trial on a selected population of non-severe COVID-19 patients with no therapeutic limitations who could all be admitted at any time to the ICU for mechanical ventilation in the event of clinical deterioration. The main explanation for not reaching statistical significance is a small sample size most probably related to the early interruption of study enrollment. Indeed, a very sharp decrease in COVID-19-related admissions was observed since mid-April 2020 as a result of effective containment measures in Switzerland. The results of this trial are promising but adequately powered trials are still needed. Our data is also in agreement with previous physiological studies and observational reports on prone positioning (11-16, 23).

Our study has some additional limitations. The intervention and assessments of endpoints were limited to a 24-h time-frame. It is therefore not possible to assess medium-term effects on outcomes and follow-up of self-prone positioning. Moreover, according to recent published reports on prone positioning, the effect on oxygenation is transient (14, 15). As assessment at 24 h was performed in the supine position, the effect of the intervention on oxygen needs could have been minimized although our data also suggest that alternating supine and prone position over 24 hours may be associated with lower oxygen needs at 24 hours even in the supine position. Finally, follow-up time in the medical ward was very short and the oxygen needs of patients with
acute respiratory failure related to COVID-19 pneumonia should be closely monitored for longer than 24 hours as rapid clinical deterioration is well described in a time window of 7-10 days after the onset of first symptoms (2, 24).

In summary, self-prone positioning in patients with COVID-19 pneumonia requiring low-flow oxygen therapy showed a reduction of oxygen needs in our study, which did not reach statistical significance most probably due to a small sample size and insufficient statistical power. However, the observed reduction of oxygen needs at 24 h is clinically promising without any reported major side-effects. Our findings need to be corroborated by larger randomised trials to confirm the potential beneficial effects of self-prone positioning on oxygen needs. This information would be of particular interest for healthcare systems in low-income countries with a limited access to ICUs.

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**Figure legend**

**Figure 1.** Flowchart

**Figure 2.** Oxygen flow on nasal cannula in the self-prone group and in the control group (superior panel). SpO₂:FiO₂ ratio in the self-prone group and in the control group (inferior panel). The horizontal lines in boxes indicate median; lower and upper edges of boxes, interquartile ranges; and whiskers above and below the box, 90\(^{th}\) and 10\(^{th}\) percentile.

**Supplementary Figure 1.** Changes of oxygen flow for individual patients (fig 1A) in the self-prone group and the control group. Changes of SpO₂:FiO₂ ratio for individual patients in the self-prone group and the control group (fig 1B).

**Supplementary Material.** Completed CONSORT Checklist
**Table 1. Clinical Characteristics of the Study Population**

|                              | Whole population (n=27) | Self-proning (n=10) | Usual care (n=17) |
|------------------------------|-------------------------|---------------------|------------------|
| **Gender**                   |                         |                     |                  |
| - Male, n (%)                | 17 (63)                 | 6 (60)              | 11 (65)          |
| **Age (yr), mean ± SD**      | 58±12                   | 54±14               | 60±11            |
| **Body mass index (kg/m²), mean ± SD** | 28.2±4.7              | 29.7±5.3            | 27.3±4.2         |
| **Comorbidities**            |                         |                     |                  |
| - Hypertension, n (%)        | 12 (44)                 | 3 (30)              | 9 (53)           |
| - Diabetes, n (%)            | 5 (19)                  | 2 (20)              | 3 (18)           |
| - Chronic kidney disease, n (%) | 1 (4)                  | 0                   | 1 (6)            |
| - Self-reported heart disease, n (%) | 0                     | 0                   | 0                |
| - COPD, n (%)                | 0                       | 0                   | 0                |
| **Time onset symptoms until inclusion (d), mean +/-SD** | 10.5±5.1               | 10.6±5.1            | 10.5±5.3         |
| **Treatment received**       |                         |                     |                  |
| - Azithromycin, n (%)        | 2 (7)                   | 1 (10)              | 1 (6)            |
| - Hydroxychloroquine, n (%)  | 19 (70)                 | 6 (60)              | 13 (77)          |
| - Lopinavir/ritonavir, n (%) | 15 (56)                 | 5 (50)              | 10 (59)          |

SD, standard deviation; COPD, chronic obstructive pulmonary disorder; IQR, interquartile range.
Table 2. Primary and secondary outcomes.

The difference between medians of the two randomised groups have been computed with their 95% confidence interval obtained by bootstrap using 1000 replications.
|                          | Respiratory rate, breaths/min (IQR) | Heart rate, beats/min (IQR) |
|--------------------------|------------------------------------|-----------------------------|
|                          | at baseline                        | at baseline                 |
|                          | 22.0 (20.0-25.8)                   | 83 (71-96)                  |
|                          | 20.0 (17.3-22.8)                   | 83 (72-89)                  |
|                          | 20.0 (16.0-26.0)                   | 82 (75-89)                  |
|                          | 20.0 (18-24.0)                     | 80 (70-86)                  |
|                          | 0 [-6.5 ; 3.5]                     | 3 [-13 ; 15]                |
Figure 1. Flowchart

7 wards assessed for eligibility

- 1 ward excluded
  - Not meeting inclusion criteria as receiving ICU transfers of patients recovering from COVID-19 severe pneumonia

6 wards randomised

3 wards randomised to invitation to self-prone (intervention group)

- 37 patients met inclusion criteria

- 8 patients excluded:
  - 4 refused to participate
  - 2 non-french speaker
  - 1 delirious when approached
  - 1 communication difficulties (secondary to cardio-vascular accident)

10 patients were included in the prone position group

3 wards randomised to standard care (control group)

- 25 patients met inclusion criteria

- 27 patients excluded:
  - 19 refused to participate
  - 5 were unable to self-prone
  - 3 were in end-of-life support care

17 patients were included in the control group
| Section/Topic       | Item No | Checklist item                                                                 | Reported on page No |
|--------------------|---------|--------------------------------------------------------------------------------|---------------------|
| **Title and abstract** |         |                                                                                |                     |
| Title              | 1a      | Identification as a randomised trial in the title                            | 0                   |
|                    | 1b      | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2                   |
| **Introduction**   |         |                                                                                |                     |
| Background and     | 2a      | Scientific background and explanation of rationale                           | 4                   |
| objectives         | 2b      | Specific objectives or hypotheses                                             | 5                   |
| **Methods**        |         |                                                                                |                     |
| Trial design       | 3a      | Description of trial design (such as parallel, factorial) including allocation ratio | 5                   |
|                    | 3b      | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | 6                   |
| Participants       | 4a      | Eligibility criteria for participants                                         | 5-6                 |
|                    | 4b      | Settings and locations where the data were collected                          | 5-6                 |
| Interventions      | 5       | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 6-7                 |
| Outcomes           | 6a      | Completely defined pre-specified primary and secondary outcome measures, including how and when they were actually assessed | 7                   |
|                    | 6b      | Any changes to trial outcomes after the trial commenced, with reasons         | N/A                 |
| Sample size        | 7a      | How sample size was determined                                                | 8                   |
|                    | 7b      | When applicable, explanation of any interim analyses and stopping guidelines   | N/A                 |
| **Randomisation:** |         |                                                                                |                     |
| Sequence generation| 8a      | Method used to generate the random allocation sequence                        | 6                   |
|                    | 8b      | Type of randomisation; details of any restriction (such as blocking and block size) | 6                   |
| Allocation         | 9       | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | 6                   |
| Allocation         |         |                                                                                |                     |
| concealment        |         |                                                                                |                     |
| mechanism          |         |                                                                                |                     |
| Implementation     | 10      | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | 6                   |
| Blinding           | 11a     | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | N/A                 |
| Item | Description |
|------|-------------|
| 11a  | Assessing outcomes and how |
| 11b  | If relevant, description of the similarity of interventions |
| 12a  | Statistical methods used to compare groups for primary and secondary outcomes |
| 12b  | Methods for additional analyses, such as subgroup analyses and adjusted analyses |
| 13a  | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome |
| 13b  | For each group, losses and exclusions after randomisation, together with reasons |
| 14a  | Dates defining the periods of recruitment and follow-up |
| 14b  | Why the trial ended or was stopped |
| 15   | A table showing baseline demographic and clinical characteristics for each group |
| 16   | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups |
| 17a  | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) |
| 17b  | For binary outcomes, presentation of both absolute and relative effect sizes is recommended |
| 18   | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory |
| 19   | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) |
| 20   | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses |
| 21   | Generalisability (external validity, applicability) of the trial findings |
| 22   | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence |
| 23   | Registration number and name of trial registry |
| 24   | Where the full trial protocol can be accessed, if available |
| 25   | Sources of funding and other support (such as supply of drugs), role of funders |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmaceutical treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).
Supplementary figure 1A: Changes of Oxygen flow for individual patients
Supplementary figure 1B: Changes of SpO2/FiO2 ratio for individual patients