Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Effectiveness of dexmedetomidine combined with high flow nasal oxygen and long periods of awake prone positioning in moderate or severe COVID-19 pneumonia

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"To the Editor": Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in December 2019. Although most patients have a favorable evolution, some patients progress to acute respiratory distress syndrome (ARDS) [1]. In the treatment for moderate or severe ARDS, high flow nasal oxygen (HFNO) has demonstrated to improve survival rate among patients with acute hypoxemic respiratory failure [2–3]. Prone positioning (PP) has been also demonstrated that improves oxygenation and had a mortality reduction when applied for prolonged time periods in intubated patients [4]. During the COVID-19 pandemic several authors have proposed the use of HFNO and awake PP sessions to improve oxygenation, trying to avoid intubation [5–7], however, tolerance of long awake PP sessions is sometimes a limitation of the technique. Recently, there has been a debate about the possible benefits of dexmedetomidine (DEX) in COVID-19 patients [8–10]. Dexmedetomidine is a centrally acting sedative and anxiolytic, which may reduce anxiety and discomfort, and decrease the respiratory rate helping to improve oxygenation in patients with respiratory failure [8–10]. It has a minimal effect on respiratory drive, a rapid onset and elimination and is easily titratable. In addition, DEX has both cytoprotective and anti-inflammatory properties [8–10] and could help reduce the inflammation produced by COVID-19. The objective of present study was to evaluate the effectiveness of dexmedetomidine combined with high flow nasal oxygen and long periods of awake prone positioning in ICU patients with moderate or severe COVID-19 pneumonia. The study protocol was approved by the ethics committee of Galicia (code No. 2020–184), and all participating subjects provided informed consent.

From September 1, 2020, to February 25, 2021, patients admitted to the Intensive Care Unit (ICU) at Clinical University Hospital Santiago of Compostela with laboratory-confirmed COVID-19 disease were enrolled. Inclusion criteria were moderate (100 mmHg $<$ PaO2/FiO2 $\leq$ 200) or severe ARDS (PaO2/FiO2 $\leq$ 100), 18 years of age or older, and those who was able to be in a PP. Exclusion criteria were inability to collaborate with PP or refusal, unstable hemodynamic status, patients with severe ARDS needing urgent intubation and mechanical ventilation. Patients were monitored with continuous electrocardiogram, oxygen saturation, and invasive arterial blood pressure. The flow rate was initially set a 50–60 L/min, and the fraction of inspired concentration (FiO2) was titrated (0.5–1.0) to maintain the oxygen saturation (SpO2) $\geq$ 90%. Patients were instructed to remain in PP during periods of 2–5 h during the day and for long periods of PP at night, as tolerated. During PP sessions, patients received intravenous infusion of DEX (0.2 μg-1.2 μg/kg/h) that was initiated 30–60 min prior to PP. DEX was titrated to maintain a Richmond Agitation Sedation Scale (RASS) score between 0 and − 3. Sedation with DEX was also used during ICU admission when patients was anxious or agitated. The primary outcome was the proportion of patients who were successfully weaned from HFNO, whereas failure was defined as a need for intubation or death on HFNO. Per protocol, patients needed intubation when they had signs of respiratory fatigue (respiratory rate $>$ 30, and obvious accessory respiratory muscle use), unstable hemodynamic status, lethargy, or unconsciousness.

The following information was collected in all patients: patient characteristics, comorbidities, inflammatory biomarkers, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, PaO2/FiO2, ICU treatments, number and duration of PP sessions, need of mechanical ventilation, duration of ICU admission and ICU outcomes. Data were presented as mean ± standard deviations or median and interquartile range as appropriate taking into account variable distribution. Chi-square and Wilcoxon rank-sum test were used to test for differences between categorical or numeric variables. Multiple testing was addressed by the Benjamini-Hochberg procedure. All analyses were conducted in Rv.3.6.

Among the 89 patients with moderate or severe ARDS by COVID 19 admitted to the ICU during the study period, sixty-three (70.8%) were treated with DEX, HFNC and long periods of PP sessions, and they were finally included in this study (Supplementary Fig. 1). The characteristics of the study population and clinical ICU course are shown in Table 1. ICU outcomes, total hours of DEX infusion, HFNC, and PP sessions of each patient are described in Table 2. Among 63 patients, 43 (68.3%) were weaned from HFNO (successful treatment), 7 (11.1%) died, and 6 (9.5%) remain in ICU. Prone positioning was applied with a median of 4 (IQR: 2.5–8) sessions per subject. Nineteen (30.2%) patients required intubation. Bradycardia (<40 lpm) during DEX infusion was observed in 5 patients (7.9%). Forty-nine (77.8%) patients were discharged from the

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Table 1
Clinical Characteristics of patients with moderate or severe ARDS by COVID-19 where DEX, HFNO and long awake PP sessions were used (No = 63).

Characteristics				
Demographics	Long PP and HFNO treatment No = 63	Long PP and HFNO Success No = 43 (68.3%)	Long PP and HFNO Failure No = 20 (31.7%)	*P* value
Age, y, mean (SD)	67 ± 12	67 ± 11	66 ± 13	1
Weight, Kg, mean (SD)	84 ± 15	83 ± 14	86 ± 15	0.92
Male sex, No. (%)	47	34 (72.3%)	13 (27.7%)	0.83
BMI, Kg/m^2, mean (SD)	30 ± 5.1	30 ± 4.9	32 ± 5.3	0.55
Coexisting conditions, No. (%)				
Hypertension	30 (48%)	22 (51%)	8 (40%)	0.99
Hyperlipidemia	29 (46%)	23 (53%)	6 (30%)	0.59
Obesity (BMI ≥ 30 Kg m-2)	27 (43%)	16 (37%)	11 (55%)	0.76
Diabetes	12 (19%)	10 (23%)	2 (10%)	0.83
Chronic pulmonary disease	6 (9.5%)	3 (7.0%)	3 (15%)	0.99
Chronic Heart disease	5 (7.9%)	3 (7.0%)	2 (10%)	1
Immunosuppression	3 (4.8%)	1 (2.3%)	2 (10%)	0.94
Home treatments, No. (%)				
ACE inhibitors	2 (3.2%)	2 (4.7%)	0 (0%)	1
Anticoagulants	2 (3.2%)	1 (2.3%)	1 (5.0%)	1
Corticosteroids	9 (14%)	5 (12%)	4 (20%)	0.99
Statins	34 (54%)	24 (56%)	10 (50%)	1
Laboratory parameters, median (IR)				
Lymphocyte count, /μL	550 [385–680]	580 [410–755]	475 [310–612]	0.55
Lactate dehydrogenase, U/L,	560 [358–768]	548 [364–724]	590 [340–938]	0.83
D-dimer, ng/mL,	948 [631–1740]	868 [679–1739]	974 [614–1668]	1
C-reactive protein, mg/L.	11 [4.7–18]	11 [4.6–18]	11 [6.6–22]	1
Procalcitonin, ng/mL	0.1 [0.075–0.24]	0.1 [0.065–0.22]	0.14 [0.098–0.44]	0.76
Serum Ferritin, μg/L	1130 [650–1585]	1222 [650–1585]	1028 [673–1594]	1
Initial severity of disease, median (IR)				
APACHE II	14 [11–17]	13 [11–16]	16 [13–17]	0.52
PaO2, mmHg	62 [56–68]	64 [57–69]	59 [56–65]	0.69
FiO2, %	65 [55–90]	60 [55–90]	70 [58–90]	1
PaO2:FiO2 ratio,	93 [72–108]	92 [72–107]	98 [71–114]	1
Oxygen saturation, %	90 [88–92]	90 [88–92]	90 [88–91]	0.76
StO2:FiO2 ratio	135 [99–162]	136 [97–162]	131 [100–158]	1
Respiratory rate, breaths per min	27 [25–32]	26 [25–31]	29 [26–32]	0.7
Hospital medical treatments, No. (%)				
Remdesivir	12 (19%)	9 (21%)	3 (15%)	1
Intermediate anticoagulant dose	23 (37%)	19 (44%)	4 (20%)	0.55
High anticoagulant dose	36 (57%)	22 (51%)	14 (70%)	0.76
Tocilizumab	30 (48%)	20 (47%)	10 (50%)	1
Anakinra	6 (9.5%)	4 (9.3%)	2 (10%)	1
Corticosteroids	59 (94%)	41 (95%)	18 (90%)	0.8
Characteristics during Hospitalization				
Time between ICU admission and MV, days, median (IR)	3 [1.5–9]	–	3 [1.5–9]	–
Mechanical Ventilation, No. (%)	19 (30.2)	–	19 (95)	–
Duration of MV, days, median (IR)	9 [7–13]	–	9 [7–13]	–
Length of ICU stay, days, median (IR)	9 [6–15]	7 [5.5–10]	18 [12−20]	0.0051
Duration of DEX infusion, median (IR)	60 [32–96]	65 [38–96]	49 [28–76]	0.84
Duration of HFNO treatment, median (IR)	96 [66–140]	96 [71–128]	71 [32–168]	0.74
Number of PP sessions, median (IR)	4 [2.5–8]	5 [3–8.5]	4 [2–7.2]	0.74
Duration total of PP sessions, median (IR)	36 [24–72]	41 [24–74]	30 [22–52]	0.83
Nosocomial infection, No. (%)	9 (14.3)	1 (2.3)	8 (40)	0.005
Hemodiafiltration, No. (%)	3 (4.8)	0	3 (15)	0.32
Death during ICU stay, No. (%)	7 (11.1)	–	7 (35)	–

Date are number (percentage), median (interquartile range), or mean (standard deviation). ACE: Angiotensin-converting-enzyme inhibitors; BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health disease Classification System II; IR: interquartile range; HFNO: high-flow nasal oxygen; FiO2: inspired oxygen fraction; ROX: ratio of oxygen saturation to FiO2, divided by respiratory rate; ICU: intensive care unit.

ICU during the study period.

In this prospective observational study, we found that DEX was used satisfactory for COVID-19 patients with moderate or severe ARDS treated with HFNC facilitating the acceptance of long periods of awake PP. The benefits of DEX in these patients could be multifactorial. First. DEX is an anxiolytic and sedative agent that may reduce the anxiety of a patient with respiratory failure, decreasing the respiratory rate and improving oxygenation. Second, this sedative properties of DEX can help awake patients with ARDS stay in PP for long periods of time. In intubated patients, Guerin et al. [4] had shown how long periods of PP may improve oxygenation and survival in patients with ARDS. We might expect a similar benefit with long periods of PP in awake COVID-19 patients with ARDS. Third, recent studies suggest DEX may enhance hypoxic pulmonary vasoconstriction, improve ventilation/perfusion ratio, and consequently improve oxygenation [8–10]. Four, DEX has an anti-inflammatory effect that can help the inflammation produced by COVID-19, and it has been proposed as a novel therapeutic strategy to attenuate multi-organ dysfunction of COVID-19 patients [8–10].

Limitations of our study include that it was performed in a single center, there was no control intervention, and the study sample was small. Regardless, these preliminary results are shared in an effort to inform other clinicians the possibility of the use a combination of DEX, HFNO and long periods of PP to treat patients with moderate or severe ARDS by COVID-19, trying to improve oxygenation and avoiding intubation and mechanical ventilation.

Table 2
Characteristics of 63 patiens with moderate or severe ARDS by COVID-19 where DEX, HFNO and long awake PP sessions were used.

Patient No. Sex/Age/y	Apache II score	PaO2/ FiO2 ICU	No. PP sessions	Duration of PP sessions, h	Total hours PP	Duration of HFNC, h	Duration of DEX, h	Need of MV, d	ICU length stay, d	ICU outcomes
1/F/53	16	130	1	13	13	18	14	Yes (12)	17	Discharge
2/F/53	9	73	3	13/15/11	39	60	45	Yes (8)	13	Discharge
3/M/70	19	108	4	8/9/3/4	24	96	30	No	10	Discharge
4/M/49	11	125	2	15/9	24	78	30	No	6	Discharge
5/F/68	14	91	2	5/13	18	68	20	No	5	Discharge
6/F/73	21	101	1	12	12	20	14	Yes (6)	10	Discharge
7/M/77	16	108	2	12/12	24	72	26	No	6	Discharge
8/F/59	10	83	2	9/4	13	48	15	No	4	Discharge
9/M/84	17	116	5	10/12/14/12/6	54	66	60	No	4	Exitus
10/M/66	12	144	10	5/5/9/5/10/10/10/3/11/3	71	180	80	No	11	Discharge
11/M/84	17	83	4	2/6/4/6	18	240	96	No	25	Discharge
12/F/73	19	64	13	5/10/8/10/3/10/10/10/10/8/10/8/8	110	600	180	No	30	Discharge
13/M/87	15	74	8	6/4/3/8/8/4/3/6	42	150	72	No	15	Discharge
14/M/77	10	123	18	2/9/8/10/3/7/3/12/9/9/3/8/8/9/9/12/9/4	134	489	229	No	27	Discharge
15/F/66	9	101	2	3/8	11	108	82	No	6	Discharge
16/M/73	13	116	14	6/2/2/10/7/9/11/10/7/10/10/10/5/10	109	198	94	No	10	Discharge
17/M/73	14	56	8	3/3/2/10/2/6/6/3	36	99	36	Yes (15)	21	Exitus
18/M/54	17	95	2	10/14	24	30	30	Yes (11)	19	Exitus
19/M/46	11	60	9	2/5/13/12/3/11/13/11/11	81	176	90	No	10	Discharge
20/M/53	10	95	3	8/10/10	28	80	42	No	6	Discharge
21/M/50	10	116	2	7/8	15	108	161	Yes (9)	17	Discharge
22/M/82	17	55	3	15/8/6	29	70	45	Yes (13)	23	Discharge
23/M/76	13	100	15	12/13/8/3/9/11/12/3/10/11/11/3/11/11/ 11	139	288	160	No	16	Discharge
24/M/69	13	132	3	3/11/10	24	30	30	No	3	Discharge
25/M/72	26	60	2	9/6	15	18	18	Yes (17)	18	Exitus
26/M/59	21	96	8	8/12/9/12/11/10/9/8	79	130	140	No	8	Discharge
27/M/71	14	95	6	10/3/12/12/4/8	49	104	140	No	7	Discharge
28/M/37	6	106	8	3/10/3/8/4/9/10/12	59	100	70	No	7	Discharge
29/M/59	10	67	5	3/6/3/3/11	26	86	42	No	6	Discharge
30/M/72	11	100	6	10/2/12/3/13/10	50	65	50	No	6	Discharge
31/M/61	10	113	3	8/11/11	30	72	20	No	4	Discharge
32/M/81	16	125	14	3/3/11/8/9/12/8/10/11/9/9/8/3/7	111	433	181	Yes (1)	19	Exitus
33/M/67	14	93	1	9	9	65	104	No	11	Discharge
34/M/70	12	68	6	11/4/11/11/10/11	58	86	62	No	7	Discharge
35/M/72	15	67	14	3/11/5/10/11/5/10/10/13/10/10/12/11/12	133	70	160	No	11	Discharge
36/F/76	17	106	5	3/12/9/9/10	43	80	58	No	5	Discharge
37/M/68	11	90	5	10/4/10/4/8	36	74	46	No	13	Discharge
38/M/84	14	71	3	7/10/9	26	96	118	No	7	Discharge
39/F/67	20	90	2	6/11	17	24	14	No	2	Discharge
40/M/63	16	90	4	7/7/6/5	25	96	25	No	6	Discharge
41/M/82	16	92	2	16/8	24	56	35	No	4	Discharge
42/M/54	12	66	9	12/12/5/11/3/12/4/10/11	80	100	90	No	5	Discharge
43/M/73	12	72	8	2/3/11/8/10/10/9/9	62	110	50	No	7	Discharge
44/M/69	18	68	9	2/14/11/9/10/10/10/10/11	87	104	94	No	9	Discharge
45/F/62	17	83	4	12/7/9/3	31	50	50	Yes (13)	24	Exitus
46/F/68	26	100	4	9/3/9/8	29	240	70	Yes (S)	Still	ICU
47/M/53	12	70	11	11/10/10/10	41	66	40	No	5	Discharge
48/M/48	13	64	2	9/18	27	33	24	Yes (9)	12	Discharge
49/M/66	15	147	3	14/9/10	33	110	40	No	8	Discharge
50/M/73	12	62	13	9/9/10/2/7/3/12/9/12/6/5/10/13	107	180	120	Yes (16)	25	Exitus
51/F/78	13	62	6	18/11/11/10/11/12	73	126	90	No	6	Discharge
52/F/65	11	120	4	3/13/10/3	29	40	65	No	4	Discharge
53/M/78	14	90	7	10/10/14/4/8/2/4	52	120	70	Yes (S)	Still	ICU
54/M/61	10	105	4	4/12/12/12	40	115	60	No	7	Discharge
55/F/75	23	100	4	6/9/8/3	26	72	48	Yes (8)	11	Exitus
56/F/45	6	132	1	10	10	32	18	No	9	Discharge
57/M/63	19	92	7	19/7/11/12/10/6/12	76	118	96	No	10	Discharge
58/M/45	8	80	11	4/14/8/3/11/3/10/3/10/10/8	84	336	240	Yes (S)	Still	ICU
59/M/64	10	104	8	7/9/8/7/7/7/10/10	65	192	70	Yes (S)	Still	ICU
60/M/50	17	114	1	17	17	18	20	Yes (S)	Still	ICU
61/F/82	15	118	6	10/5/10/10/3/8	46	164	96	Yes (S)	Still	ICU
62/M/71	15	65	12	4/8/9/12/11/3/5/10/4/11/10/10	97	260	192	No	18	Discharge
63/M/73	14	116	9	3/4/9/3/9/15/10/10/10	73	360	120	No	23	Discharge

Abbreviations: F: female; M: male; h: hours; d: days; APACHE II: Acute Physiology and Chronic Health disease Classification System II; FiO2: inspired oxygen fraction; PP: prone positioning; HFNO: high-flow nasal oxygen; DEX: dexmedetomidine; MV: mechanical ventilation; ICU: intensive care unit; (S): Still admitted in ICU.

Prior presentations

No.

Summary statement

In this prospective observational study including sixty-three non-intubated patients admitted to the ICU with moderate or severe ARDS by COVID-19, we showed that dexmedetomidine may be useful in combination with HFNO facilitating the acceptance of long periods of awake PP.

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Authors contributions

1. Conception of the study: Manuel Taboada
2. Study design: Manuel Taboada,
3. Data collection: All authors
4. Data análisis: Aurora Baluja, Manuel Taboada.
5. Drafting the manuscript: Manuel Taboada, Valentín Caruezo, Julian Alvarez.
6. Editing and approval of the manuscript: All authors

Declaration of Competing Interest

The authors declare the absence of conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110261.

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Manuel Taboada, M.D., Ph.D.*, Aurora Baluja, M.D., Ph.D., M.D., Laura Dos Santos, M.D., Irene González, M.D., Sonia Veiras, M.D. Ph.D, Valentín Caruezo, M.D., Alberto Naveira, M.D., Paula Mirón, M.D., Carmen Novoa, M.D., Patricia Doldán, M.D., Andrea Calvo, M.D., Ana Tubio, M.D., Salomé Selas, M.D., María Eiras, M.D., Adrián Martínez, M.D., Olga Campaña, M.D., María Teresa Rodríguez, M.D.[1], María Diaz-Vieito, M.D., Agustín Cariñena, M.D., Pablo Otero, M.D., Gumersindo Mariño, M.D., María Domínguez, M.D., Ignacio Muniategui, M.D., Francisco Aneiros, M.D., Julián Alvarez, M.D., Ph.D.

Department of Anesthesiology and Intensive Care Medicine, Clinical University Hospital of Santiago. Spain

* Corresponding author at: Department of Anesthesiology and Intensive Care Medicine, Servicio de Anestesiología y Reanimación del Hospital Clínico Universitario de Santiago de Compostela, Choupana sn, CP:15706, Santiago de Compostela (A Coruña), España.
E-mail address: manuel.taboada.muniz@sergas.es (M. Taboada).

[1] Department of Pharmacoloy, Clinical University Hospital of Santiago. Spain.