Letter to the Editor

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Efficacy of Early Prone Positioning Combined with Noninvasive Ventilation in COVID-19

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The role of prone positioning (PP) in the improvement of the oxygenation in patients with acute respiratory distress syndrome (ARDS) is well known. PP contributes to the improvement of the oxygenation by recruitment of collapsed alveoli, redistribution of inflation/ventilation, and by alteration of chest wall elastance (1). It is mainly recommended and applied in intubated patients with severe ARDS (PaO_2/FiO_2<100 mmHg) (1,2). There is a paucity of data regarding the efficacy of PP in combination with non-invasive ventilation (NIV). Ding L and colleagues recently showed the beneficial role of PP when combined with NIV. They demonstrated the PaO_2/FiO_2 increased in more than 75% of patients under NIV when PP was applied and the PaO_2/FiO_2 increment was more significant in severe patients, in whom NIV finally failed (3). Gattinoni et al. (4) and Marini and Gattinoni (5) highlighted the atypical features of ARDS in coronavirus disease 2019 (COVID-19) and suggested the PP might facilitate the oxygenation in COVID-19 patients mainly through redistribution of pulmonary perfusion. Although the data regarding the efficacy of NIV in the setting of ARDS remained still non-conclusive, an early trial of NIV has been suggested to be helpful in selected subpopulation of patients with pneumonia e.g. COVID-19 (5-7).

We prospectively evaluated the efficacy of prone positioning in combination with NIV therapy in COVID-19 patients admitted to our intensive care unit (ICU) wards at Massih Daneshvari Hospital from 26 February to 25 April 2020. The COVID-19 patients with a body mass index (BMI) less than 18 or greater than 30 and those requiring emergent intubation or already intubated have been excluded from the study. A random allocation sequence was generated. The patients were assigned by head nurse to one of the treatment groups; the NIV or NIV+PP groups. The allocation sequence was concealed until the moment of assignment. The institutional ethics review board approved this study (IR.SBMU.NRITLD.REC.1399.009).

Our study aimed to determine whether the use of PP could improve the measures of SpO_2 and PaO_2/FiO_2 in ICU-admitted COVID-19 patients and/ or could decrease the need for intubation.

The diagnosis of ARDS was made based on the Berlin criteria of ARDS. All patients received an early trial of NIV using CPAP or BiPAP S/T mode (Philips Respironics V680 ventilator and Philips Respironics Trilogy 202 portable ventilator) via total face mask or Helmet masks. The ventilatory support was turned to the invasive mechanical intubation at earliest signs of NIV failure when one of the following was emerged: Respiratory rate more than 40 per minute, loss of consciousness,

$PaCO_2$ > 50 mmHg, unstable hemodynamic status, PaO_2/FiO_2<50 mmHg. PP was applied 30 minutes every 4 hours. Moreover, an additional 30-minutes PP session was applied when SpO_2 fell under 82%.

During the study period, a total of 254 ARDS patients with a confirmed diagnosis of COVID-19 were admitted to our ICU wards. Out of these, 116 patients were early intubated, 63 patients treated by high flow nasal cannula (HFNC) and 75 patients received NIV. Among the latter, 45 patients received NIV in combination with PP. The characteristics of the patients treated by NIV, either with (NIV+PP group) or without PP (NIV group), are summarized in Table 1. Two groups were matched according to the demographic characteristics, underlying diseases and disease severity scores (SOFA and APACHE II scores). There was not a significant difference between SpO_2 and PaO_2/FiO_2 measures of two groups at the time of admission.

Table 1. Demographic Characteristics and Underlying Disease of all Patients

Items	NIV(n=30)	NIV+PP(n=45)	P-Value
Sex(male)	23(73.3)	29(64.4)	0.521
Age			0.724
<50	6(20.0)	7(15.5)	
50-70	15(50.0)	26(57.8)	
>70	9(30.0)	12(26.7)	
SOFA	9.4±4.0	9.6±3.5	0.446
APACHE II	21.3±5.0	23.6±5.7	0.218
BMI	28.2±3.0	27.3±4.2	0.103
Underlying Disease			
DM	10(33.3)	12(26.6)	0.589
IHD	2(6.6)	4(8.8)	0.326
CRF	0(0.0)	2(4.4)	0.661
Lung disease	3(10.0)	3(6.6)	0.530
Inadequate nutrition	1(3.3)	1(2.2)	0.899
HTN	5(16.6)	9(20.0)	0.779
Therapy Method			0.115
Favipiravir	20(66.7)	33(73.3)	
Actemra	6(20.0)	7(15.5)	
Hemoperfusion	7(23.3)	11(25.0)	
Plasmapheresis	6(20.0)	8(17.8)	

Our primary outcome measure was the PaO_2/FiO_2 at the end of the last NIV or NIV+PP session on the first day of intervention (post SpO_2 and post PaO_2/FiO_2). As secondary outcomes, we assessed the length of ICU stay and the need for intubation at the end of the study. The application of NIV resulted in a significant increase of PaO_2/FiO_2 in mild (p=0.038) and moderate (p=0.048) subgroups of patients treated with NIV alone, but not in patients with severe ARDS (p=0.192). However, PaO_2/FiO_2 significantly increased in all three subgroups of patients who received NIV in combination with PP (Figure 1). Although the mean of the SpO_2 and PaO_2/FiO_2 does not show significant difference among patients with severe ARDS in NIV and NIV+PP groups at admission, this measure showed a significant difference 24 hours after ICU admission (p=0.003). In addition, the application of NIV combined with PP resulted in a significantly shorter length of ICU admission (8.6 vs. 14.4, p=0.046). The need for intubation (22% vs. 40%, p=0.082) and the rate of mortality (20% vs. 33%, p=0.152) were though lower in the NIV+PP group, and failed to reach the statistical significance (Table 2).

To the best of our knowledge, this is the first study evaluating the role of PP in combination with NIV in COVID-19. The presented results are strongly in favor of the use of PP in combination with NIV in critically ill patients with COVID-19,

especially those with severe ARDS. The application of simple non-costly treatment approaches e.g. PP at the time of pandemics are of special importance, as pandemics usually result in overuse of ICU beds and strain on available resources.

Table2. Clinical characteristics and outcomes of patients in the success group

	NIV(n=30)			NIV+PP(n=45)		
	Mild(n=11)	Moderate(n=10)	Severe(n=9)	Mild(n=23)	Moderate(n=17)	Severe(n=5)
Pre Pao_2/FIO_2	213.4±14.9	150.7±17.7	79.6±13.3	233.1±15.7	138.4±18.5	76.9±13.0
Post Pao_2/FIO_2	247.3±18.7	178.5±17.4	92.0±17.4	261.4±18.0	174.1±18.8	132.2±19.0
P-value (Pre vs. Post)	0.038*	0.048*	0.192	0.033*	0.028*	0.009*
P-value (Post NIV vs. Post NIV+PP)	0.439	0.674	0.003*	0.439	0.674	0.003*
Pre SPO_2	91.8±2.1	87.7±1.7	50.8±1.9	87.3±2.0	69.8±1.5	53.7±1.4
Post SPO_2	97.6±1.8	95.4±1.6	82.2±1.7	98.1±1.6	96.3±1.7	98.4±1.4
P-value (Pre vs. Post)	0.119	0.041*	<0.001*	0.017*	<0.001*	<0.001*
P-value (Post NIV vs. Post NIV+PP)	0.846	0.501	<0.001*	0.846	0.501	<0.001*
ICU length of stay (Days), P-value		14.4±3.9, 0.046*			8.6±3.0, 0.046*	
Need to Intubation, n(%), P-value		12(40.0), 0.082			10(22.2), 0.082	
$ Need to Intubation, n(%)	2(18.2)	4(40.0)	6(66.7)	1(4.3)	6(35.3)	3(60.0)
ICU mortality, n(%), P-value		10(33.3), 0.152			9(20.0), 0.152	
ICU mortality, n(%)	2(18.2)	3(30.0)	5(55.6)	1(4.3)	6(35.3)	2(40.0)

*Significant at level 0.05

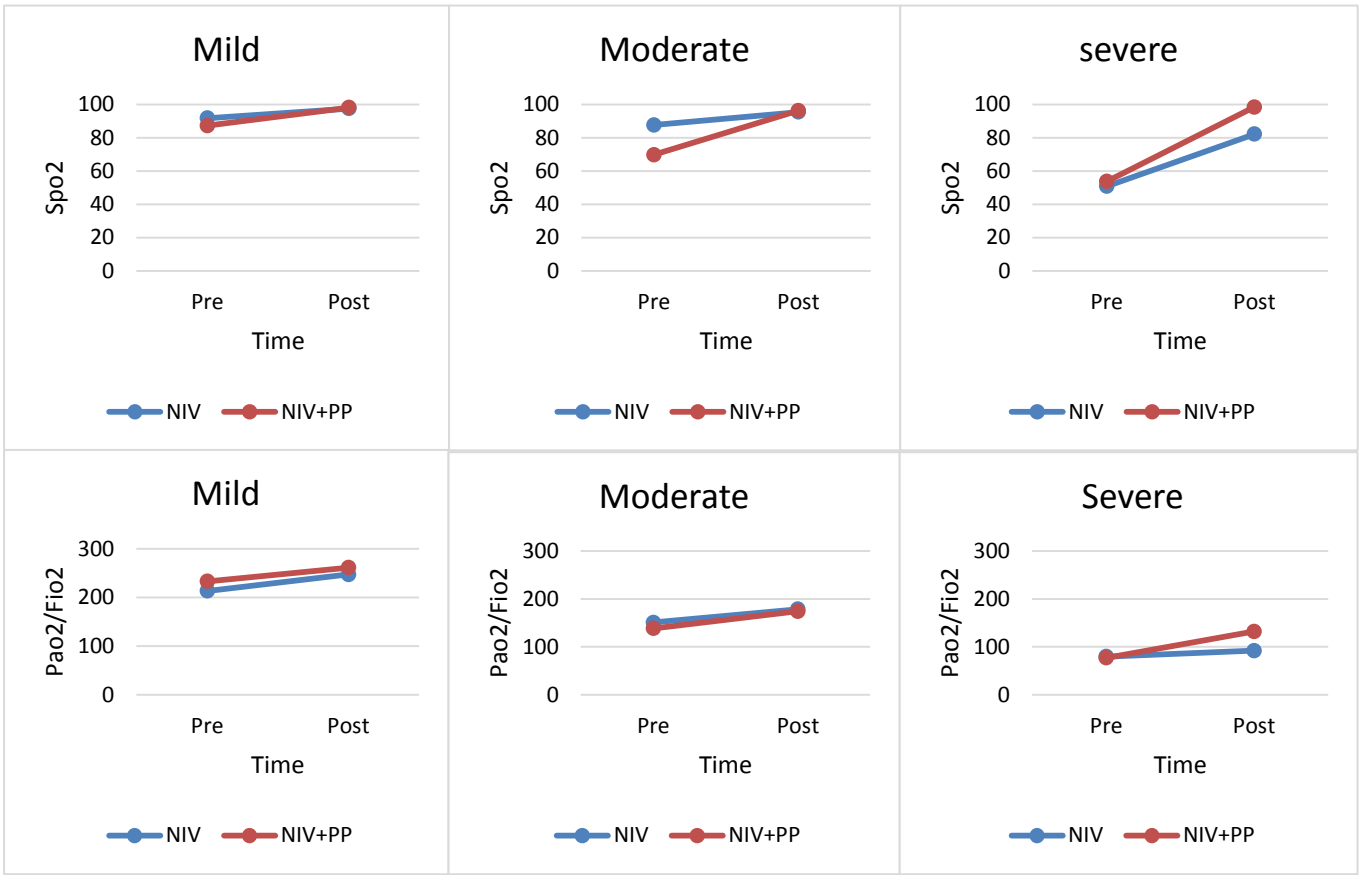

Figure 1. Comparison of SpO_2 and PaO_2/FiO_2 of each ARDS subgroups between NIV and NIV+PP treatment groups

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