Awake Prone Position in Patients with COVID-19: A Case Control Study

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Abstract

Background: Hypoxemic respiratory failure is a common manifestation in COVID-19 and is associated with a higher morbidity and mortality rate.

Methods: We conducted a prospective observational study of patients admitted with COVID-19 with hypoxemia, treated with or without prone position (PP) along with standard care.

Results: A total of 98 patients with COVID-19 treated with awake PP were compared with 98 patients treated with standard of care alone. The mean age of the patients was 55.9 ± 13 years. The common co-morbid were HTN, DM and IHD. The median length of hospital stay in cases (with PP) and control (no PP) was 8 days (IQR 4 - 7) and 7 days (IQR 5 - 11) respectively. The use of awake PP did not reduce the risk of invasive ventilation (8.1% patients in PP vs. 3.1% in control group). "Overall mortality was 10.3%, 7.2% with PP and 13.3% with standard of care respectively (p-value 0.16)".

Conclusion: Awake PP is a safe therapeutic option for patients with COVID-19. However, its benefit in terms of avoidance of endotracheal intubation, decrease duration of hospital stay and mortality are not clearly defined.

Keywords: *COVID-19; Prone Position; ARDS; Pandemic; SARS-CoV-2*

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is an emergency across the globe, as its rapid transmission and the high mortality rate has caused severe disruptions. Since the first reported case of COVID-19 in Wuhan, Hubei province, China on December 31, 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected 130,422,190 people and killed 2,842,135 people worldwide as of April 5, 2021, according to the World Health Organization (WHO). Although some areas of the world are experiencing a drop in case counts, other areas are facing a resurgence in cases which has raised concerns on the prevention and management of this disease and has opened new gates of research to explore the hidden mysteries [1].

The clinical experience thus far has demonstrated significant diversity in the trajectory of SARS-CoV-2 infection, spanning patients who are asymptomatic to those with severe, and critical disease forms, leading to high mortality [2]. A major cause of the morbidity and mortality of the illness is an acute viral pneumonitis, characterized by worsening hypoxia, which, if untreated, can progress, eventually leads to acute respiratory distress syndrome (ARDS) and respiratory failure [3]. The underlying pathogenesis of ARDS is exaggerated immune response that causes alveolar injury, severe hypoxemia, multiorgan failure and is associated with significant-high mortality [4].

Prone position (PP) has been used for the last many years for the management of ARDS for patients on mechanical ventilation. The proposed mechanism that improves hypoxemia with prone ventilation is improved V/Q (ventilation/perfusion) matching, better tidal volume distribution, change in pleural pressure and improved pulmonary secretion drainage [5,6]. Data from randomized control trials

and meta-analysis has strongly supported the early use of PP ventilation and showed a survival benefit in patients with ARDS [7,8]. This has led to widespread use of PP ventilation in mechanically ventilated patients with COVID-19 and has shown favorable outcomes [9].

Awake pone position showed marked improvement in hypoxemia with the reduced rate of intubation in patients with COVID-19 [10,11]. Even though patients experienced improved oxygenation with conscious prone positioning, an increase in the requirement for invasive ventilation is still reported in the literature for a different part of world [12,13]. Several studies have been published related to the use of awake PP in COVID-19 but data is limited to case report or case series, retrospective or prospective cohort with small sample size. Even though associated with improvement in hypoxemia, its impact on clinical outcomes such as survival, need for ICU admission has not been very well defined [14].

Data from published studies related to awake PP in COVID-19 patients with hypoxemia is sparse and conflicting. Considering the urgency to explore therapeutic options that can help in the management of patients outside ICU and can avoid ICU transfer especially in resource-poor settings, many clinical trials are underway. While results of clinical trials are awaited to draw any definitive conclusion, we would like to share our experience with awake PP ventilation in non-intubated patients with hypoxemia from LMIC.

Materials and Methods

This single-centre, observational study was conducted at Aga Khan University Hospital (AKUH), Karachi, Pakistan between July 1st 2020 and August 31st 2020. AKUH is a joint commission international (JCI) accredited, one of the largest (740 bedded) tertiary care university hospitals in the country.

In our study, we included all adult patients (18 years or above) who were admitted with severe and critical COVID-19 and received awake PP early on after admission as part of their treatment strategy along with the standard of care and were compared with those who received standard of care alone based on existing local guidelines. Patients who received PP with invasive mechanical ventilation were excluded.

COVID-19 was diagnosed by a nasopharyngeal or oropharyngeal swab for SARS-CoV-2 using real-time reverse transcription-polymerase chain reaction (RT-PCR). The severity of disease was graded according to the National guidelines of management of COVID-19 established by the Ministry of Health, Pakistan.

The protocol for awake proning was adopted from previously published studies on awake proning [15]. The respiratory therapist and nursing staff help the patients for PP. The assessment for initiation, frequency, and duration of each session of proning was based on the primary physician's decision. Along with demographic data, clinical features and CXR findings, PaO_2/FiO_2 (PF) ratio were recorded before the initiation of the prone position. The primary outcome was the avoidance of intubation and secondary outcomes were in-hospital mortality and the length of hospital stay.

This study received approval from the Aga Khan University Ethics Review Committee (ERC Reference Number: 2020-4782-11061, Date; 15-Jun-2020).

Statistical analysis

The analysis was performed using SPSS (Statistical Package of Social Sciences) version 19. Continuous variables with normal and non-normal distributions were reported as mean ± SD and median [inter-quartile range (IQR)], respectively. The frequency (%) of demographic and clinical factors was assessed and stratified by case and control group. Independent samples t-test or Mann-Whitney U test was used to observe the mean difference between the case and control group. Similarly, a chi-square test was used to observe the association between patients admitted with COVID-19 and received PP with those who received standard of care. The patient's PF ratio was assessed through paired t-test to see the changes from baseline to discharge among the study groups. All p-values were based on two-sided tests and significance was set at a p-value less than 0.05.

Results

A total of 98 patients who received prone position along with the standard of care were compared with 98 patients in the group treated with standard of care alone. The mean age of the study population was 55.9 ± 13 years and there was no difference in both groups. There was male predominance in both case and control groups (73% vs. 70%). The most frequent comorbid conditions were hypertension (48%), diabetes mellitus (46.4%), ischemic heart disease (14.8%), and chronic kidney disease (8.2%). Fever (85.2%), shortness of breath (69.9%) and cough (69.4%) were common presenting symptoms in all patients included in the study. However, myalgia (p-value < 0.001), shortness of breath (p 0.001) and diarrhea (p-value 0.001) were more common in patients who received PP (Table 1). Critical COVID-19 was present in 50% of the patients treated with PP while 35% of patients managed with standard of care only had the critical disease.

	Total; n = 196	[1]Cases; n = 98	[2]Control; n = 98	p value
Age (years)	55.9 ± 13.0	56.1 ± 12.3	55.7 ± 13.7	0.81
[3]SCU; days				
Median [4](IQR)	4.0 (2 - 7)	4.0 (2 - 7)	4.0 (2 - 7)	
Ward stay; days				
Median (IQR)	2.0 (0.13 - 4.0)	3.0 (1.8 - 5.0)	1.0 (0 - 3.0)	
Gender Male Female	143 (73) 53 (27)	73 (74.5) 25 (25.5)	70 (71.4) 25 (25.5)	0.62
DM	91 (46.4)	42 (42.9)	49 (50)	0.31
HTN	94 (48)	49 (50)	45 (45.9)	0.56
[5]IHD	29 (14.8)	13 (13.3)	16 (16.3)	0.54
[6]CLD	4 (2.0)	1 (1.0)	3 (3.1)	0.31
[7]CKD	16 (8.2)	6 (6.1)	10 (10.2)	0.29
Asthma	9 (4.6)	2 (2.0)	7 (7.1)	0.08
[8]CVA	5 (2.6)	4 (4.1)	1 (1.0)	0.17
Malignancy	6 (3.1)	1 (1.0)	5 (5.1)	0.21
Immune state	7 (3.6)	4 (4.1)	3 (3.1)	0.99
Smoker	9 (4.6)	4 (4.1)	5 (5.1)	0.99
Symptoms Fever	167 (85.2)	89 (90.8)	78 (79.6)	0.02
Cough	136 (69.4)	71 (72.4)	65 (66.3)	0.43
Myalgia	27 (13.8)	23 (23.5)	4 (4.1)	< 0.001
Runny nose	2 (1.0)	2 (2.0)	0	0.49
Sore throat	17 (8.7)	10 (10.2)	7 (7.1)	0.44
Dyspnea	137 (69.9)	79 (80.6)	58 (59.2)	0.001
Nausea	18 (9.2)	7 (7.1)	11 (11.2)	0.32
Vomiting	9 (4.6)	4 (4.1)	5 (5.1)	0.99
Abdominal pain	3 (1.5)	3 (3.1)	0	0.24
Diarrhea	11 (5.6)	11 (11.2)	0	0.001
Headache	4 (2.0)	4 (4.1)	0	0.12
Confusion	2 (1.0)	2 (2.0)	0	0.49
Radiological findings Unilateral	23 (11.7)	11 (11.2)	12 (12.2)	0.82
Bilateral	171 (87.2)	86 (87.8)	85 (86.7)	0.83
Consolidation	7 (3.6)	7 (7.1)	0	0.01
Interstitial infiltrate	4 (2.0)	1 (1.0)	3 (3.1)	0.62
Pleural effusion	3 (1.5)	3 (3.1)	0	0.24
Cavitation	5 (2.6)	1 (1.0)	4 (4.1)	0.36
Multilobar involvement	87 (44.4)	87 (88.8)	0	< 0.001
Tocilizumab	70 (35.7)	43 (43.9)	27 (27.6)	0.01
Remdesivir	14 (7.1)	14 (14.3)	0	< 0.001
NIV used	107 (54.6)	63 (64.3)	44 (44.9)	0.006

Table 1: *Baseline characteristics of patients with COVID-19 treated with or without awake prone position.*

1. Cases: Patients with COVID-19 treated with prone position ventilation with standard of care, 2. Control: Patients with COVID-19 treated with standard of care alone, 3. SCU: Special care unit, 4. IQR: Interquartile range, 5. IHD: Ischemic heart disease, 6. CLD: Chronic liver diseases, 7. CKD: Chronic kidney disease, 8. CVA: Cerebrovascular accident.

The median duration between admission and initiation of PP was 3 (1 - 6) day. The mean days of proning were 4 days (IQR 2 - 6). The minimum numbers of hours of awake PP tolerated by any patient were 2 hours and maximum numbers of hours were 16 per day. No major complication related to awake PP was reported and PP was tolerated by all patients.

There was a significant increase in PF ratio from baseline to discharge in patients who were treated with PP (< 0.001) and only 8 out of 98 patients required intubation. Although the mean PF ratio at the time of admission was significantly low in patients treated with awake PP as compared to the control group (p-value 0.001) both groups have shown significant clinical improvement in PF ratio (Table 2).

	[1]Cases		[2]Control	
	Baseline	**Discharge**	**Baseline**	**Discharge**
[3]PF ratio				
Median (IQR)	214.5 (152.7 - 331.5)	396.5 (288.2 - 523)	310 (137.7 - 427.2)	457 (376 - 533)
p value	< 0.001		< 0.001	
PF ratio	275.9 ± 181.3	408.1 ± 176.6	297.3 ± 179.1	454.4 ± 161.8
p value	0.91		< 0.001	

Table 2: *Comparison of PaO$_2$/FiO$_2$ at base line and at time of discharge between case and control group.*

1. Cases: Patients with COVID-19 treated with prone position ventilation with standard of care, 2. Control: Patients with COVID-19 treated with standard of care alone, 3. PF ratio PaO$_2$/FiO$_2$.

The median length of hospital stay in patients with PP was 8 days (IQR 4 - 7) and control 7 days (IQR 5 - 11). The median length of stay in special care was comparable in both group (4, IQR 2 - 7) but ward stays once shifted out of special care was longer in the patients who received PP (3 days vs 1 day, IQR 1.8 - 5 vs. 1 - 3) although this difference did not reach statistical significance. The use of awake PP did not reduce the risk of intubation and invasive ventilation as 8 (8.1%) patients in PP group and 3 (3.1%) in control group required intubation.

The overall mortality rate was 10.3%. 7.2% with PP and 13.3% with standard of care respectively (p-value 0.16)". Compared to cases managed with PP, mortality was higher in the control group but was not statistically significant (p-value 0.16). The causes of mortality were ARDS (65%), septic shock (30%) and multi-system organ failure (10%) but ARDS was more common in the control group (p-value 0.02) (Table 3).

Mortality	Total; n = 20	[1]Cases; n = 7	[2]Control; n = 13	p value
	20 (10.3)	7 (7.2)	13 (13.3)	0.16
Cause of death				
[3]ARDS	13 (65)	2 (28.6)	11 (846.6)	0.02
Septic shock	6 (30)	3 (42.9)	3 (23.1)	0.61
[4]MODS	2 (10)	1 (14.3)	1 (7.7)	0.99

Table 3: *Outcomes of patients with COVID-19 treated with or without awake prone position ventilation.*

1. Cases: Patients with COVID-19 treated with prone position ventilation with standard of care, 2. Control: Patients with COVID-19 treated with standard of care alone, 3. ARDS: Acute respiratory distress syndrome; 4. MODS: Multi-organ dysfunction syndrome.

Discussion

Awake prone position ventilation was found to be a safe and effective measure in patients with COVID-19 suffering from hypoxic respiratory failure but we did not find any difference in primary and secondary outcomes i.e. avoidance of intubation, length of hospital stay and mortality in both groups of patients managed with and without conscious prone position.

Even though the mean PF ratio at the time of admission was significantly low in patients treated with awake PP as compared to the control group (p-value 0.001) in this study but both groups showed significant clinical improvements in PF ratio. Awake prone position is found to be associated with improved oxygenation, may lead to avoidance of intubation in patients with hypoxic respiratory failure and has gained widespread acceptance all over the world during the current pandemic of COVID-19 [10]. Prospective observational studies have shown that awake prone positioning improved the oxygenation of COVID-19 patients with ARDS but a significant number of patients still require intubation [16,17]. Awake PP is considered to be a safe intervention that can easily be performed therefore can be initiated even in small healthcare facility and even at home. This can reduce the patient burden of large tertiary care centres already overwhelmed with an influx of patients with more critical illnesses in the current crisis [18-20]. There is conflicting data about the efficacy of PP as a measure that can avoid invasive ventilation, it may prevent or delayed intubation therefore invasive mechanical ventilation should not be deferred when indicated [21].

The overall mortality was 10.3% in this study with higher mortality observed in the group treated with standard of care alone but this difference did not reach statistical significance. Our results are in accordance with a recently published multicenter trial (preprint) which showed no difference in mortality and hospital stay in patients with COVID-19 treated with standard of care vs awake prone position ventilation [22]. Although considered to be a safe and feasible manoeuvre,41% of COVID-19 patients treated with awake PP required intubation and mortality was 12% in a study done by Solverson and colleagues [23]. Similarly, results of other studies did not demonstrate any decrease in the need for intubation and mortality in patients with COVID-19 related hypoxic respiratory failure treated with oxygen therapy, HFNO and PP [24,25]. In a retrospective cohort study, hypoxic patients with COVID-19 were followed up to 15 days and no beneficial effects like reduction in mortality, avoidance of intubation and transfer to ICU were observed in patients treated with awake PP in comparison to control group [26].

We did not find any complication related to awake PP and all patients tolerated the procedure well. The commonly reported complications of conscious proning were general discomfort, backache, musculoskeletal pain, facial swelling and dislodgement of devices [23,27].

Previously published data on the use of awake PP in COVID-19 is limited to case series or observational studies, small sample size with inconsistent results and majority lacked control groups. Our observational study is distinctive as it has included a comparative group to assess the effectiveness of awake PP in terms of mortality and the need for invasive ventilation.

Prone position may be beneficial for patients with COVID-19 in terms of prevention of invasive mechanical ventilation and improvement in oxygenation but its efficacy is still not well established [28,29]. Results of large multicenter prospective randomized clinical trials are needed to draw on meaningful conclusion.

The interpretation of our results was limited by observational study design that will require a future prospective randomized controlled trial to identify potential subgroups of the patient's population that might get benefit from conscious prone positioning once they developed hypoxic respiratory failure with COVID-19. Currently, there is a lack of substantial evidence on the effectiveness of awake PP in COVID-19 patients with hypoxemia. Good quality studies with a large sample size are needed to ascertain the contribution of awake PP in improving hypoxemia in patients with ARDS and identify those who might gain benefit from this cost-effective maneuver. This will help in the management of patients in low resource settings and will help in the modification of treatment protocol in early ARDS and

COVID-19. The true value of awake PP once established can be utilized in the management of ARDS in a wider patient population with diverse etiologies.

Now, awake PP should be considered as an adjunctive therapeutic option in patients with COVID-19, especially in countries with over-burdened poor quality healthcare infrastructure settings where awake PP might be the only option available for management of hypoxemia due to lack of availability of enough intensive care facilities. However, reservations are associated with the effectiveness of awake PP with COVID-19 ARDS and invasive or NIV should not be delayed once indicated.

Conclusion

Awake prone ventilation appears to be a safe intervention that can be utilized in small centres, medical wards and even at home for the management of patients with COVID-19 with less severe hypoxemia, which can delay the progression of respiratory deterioration. However, its benefit in terms of avoidance of endotracheal intubation, the need of invasive mechanical ventilation or decreased duration of hospital stay are not clearly defined and require further high-quality studies to generate robust evidence.

Conflict of Interest

The authors have no conflict of interest.

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