Predictors of Treatment Success in Awake Prone Positioning for Non-Intubated COVID-19 Patients With Acute Hypoxemic Respiratory Failure

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Introduction

Prone positioning is known to reduce mortality among patients on mechanical ventilation with moderate-to-severe ARDS.[1] When extrapolating data about these patients with ARDS, awake prone positioning is touted as a low-risk intervention that can be performed outside the ICU. Studies show that awake prone positioning is feasible and effective in improving oxygenation in subjects with COVID-19 related pneumonia who are not intubated.[2,3] In our recently published multi-center randomized controlled meta-trial, we found that awake prone positioning significantly reduced the composite outcome of intubation or death within 28 days of enrollment for subjects with COVID-19 and with acute hypoxemic respiratory failure supported by high-flow nasal cannula (HFNC) oxygen therapy.[4] The early identification of patients at high risk of failure of awake prone positioning may help avoid delayed intubation, which might ultimately improve outcomes. However, predictors of awake prone positioning success remain largely unknown. Thus, we aimed to explore predictors of awake prone positioning success in subjects who were not intubated.

Methods

This was a post hoc analysis of the American data set from the meta-trial.[4] Subjects assigned to the awake prone positioning arm and receiving awake prone positioning for ≥30 min were included. Additional data, including subject response to awake prone positioning on the second and third days of enrollment, had been prospectively collected in the American data set only were analyzed and reported. Treatment success was defined as a subject being discharged from the hospital alive without invasive ventilatory support after 28 days of enrollment. In this trial, the subjects were required to be in the prone position until intubation or death or until HFNC was discontinued based on predetermined criteria of S_{pO_2} of 92–95% on HFNC flow at 40 L/min and F_{IO_2} of 0.4. The original multi-center randomized controlled trial was registered in clinicaltrials.gov (NCT04325906) and approved by all the

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Drs Li, Mirza, and Vines conceived the idea. Drs Li, Kaur, Mirza, Scott, Mogri, Trump, and Morris, Mr Elshafei, and Ms Jackson implemented the study. Drs Li, Vines, Mirza, Trump, and Mogri supervised the study. Drs Mirza, Kaur, and Li conducted data analysis. Drs Mirza, Li, Vines, Kaur, Trump, and Mogri interpreted the data. Dr Mirza drafted the manuscript. Drs Li and Vines provided critical edits. All the authors reviewed the manuscript for important intellectual content and approved the final manuscript.

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Table 1. Subject Baseline Characteristics and Outcomes

Characteristics and Outcomes	Treatment Success ($n = 65$)	Treatment Failure ($n = 43$)	P
Age, mean ± SD y	60 ± 12	64 ± 11	.09
Men, *n* (%)	44 (68)	25 (58)	.41
BMI, mean ± SD kg/m^2	30.4 ± 4.9	29.6 ± 5.3	.40
Comorbidities, *n* (%)			
Chronic lung disease	4 (6)	7 (16)	.11
Chronic cardiac disease	12 (19)	11 (26)	.47
Cancer	2 (3)	6 (14)	.057
SOFA, median (IQR)	3 (2–4)	3 (2–4)	.60
S_{pO_2}/F_{IO_2} at study enrollment, median (IQR)	156.7 (129.3–183)	134.3 (111.3–156.7)	.005
S_{pO_2}/F_{IO_2} at study enrollment, mean ± SD	159.6 ± 35.6	140.4 ± 39.3	.01
ROX index at study enrollment, median (IQR)	6.74 (5.05–8.1)	5.11 (3.99–7.46)	.02
Time from hospital admission to enrollment, median (IQR) h	16.1 (4.1–41.5)	18.7 (7.9–46.2)	.51
Time from HFNC to enrollment, median (IQR) h	2.5 (0–14)	2 (0.6–12.5)	.84
Awake prone positioning initiated within 1 h of enrollment, *n* (%)	40 (61.5)	33 (76.7)	.10
HFNC duration, median (IQR) d	4.2 (2.1–7.2)	6.9 (2.5–11.5)	.037
Total days that needed to prone, median (IQR) d	3.9 (1.9–7.1)	6.6 (2.5–11.9)	.009
Average prone positioning duration, median (IQR) min/d	101 (41–469)	258 (103–478)	.12
Antivirals, *n* (%)	44 (68)	33 (77)	.39
Systemic use of steroids, *n* (%)	45 (69)	32 (74)	.67
Received NIV, *n* (%)	5 (8)	20 (47)	<.001
Hospital LOS, median (IQR) d	10.7 (8.5–14.9)	24.5 (17.6–42.5)	<.001
ICU LOS, median (IQR) d	5.0 (2.1–7.0)	21.8 (17.2–35.5)	<.001

BMI = body mass index
SOFA = Sequential Organ Failure Assessment
IQR = interquartile range
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
LOS = length of stay
ROX= S_{pO_2}/F_{IO_2}/breathing frequency

participating hospitals' ethics committees (approval 20032604-IRB01 in the leading hospital).

Continuous variables were reported as mean ± SD or median (interquartile range [IQR]) and compared by using the Student *t* test or the Mann-Whitney test. Categorical variables were reported as proportions and compared by using the chi-square test or the Fisher exact test. Binary stepwise logistic regression was carried out to determine the impact of age, cancer, S_{pO_2}/F_{IO_2} at study enrollment, ROX index (S_{pO_2}/F_{IO_2}/breathing frequency) at study enrollment, mean daily duration of awake prone positioning, and S_{pO_2}/F_{IO_2} improvement on day 2 on the likelihood of treatment success. The accuracy of the variables to predict treatment success was assessed by calculating the area under the receiver operating receiver operating characteristic curves. Statistically significant independent variables were maintained in the model. A two-sided $P < .05$ was considered statistically significant. Data analysis was conducted by using SPSS 26.0 (SPSS, Chicago, Illinois).

Results

From April 2, 2020, through January 26, 2021, 112 subjects were enrolled in the awake prone positioning group. Four subjects were excluded from this analysis due to being in the prone position for <30 min. One hundred eight subjects (69 men) were included, with a mean age of 62 y, of whom 65 (60%) had treatment success. Compared with the treatment failure group, the subjects in the treatment success group had a higher median (IQR) S_{pO_2}/F_{IO_2} (156.7 [129.3–183] vs 134.3 [111.3–156.7]; $P = .005$) and median (IQR) ROX index (6.7 [5.1–8.1] vs 5.1 [4.0–7.5]; $P = .02$) at study enrollment, whereas no other significant differences in age, sex, body mass index, Sequential Organ Failure Assessment scores, and treatments were found between the groups (Table 1).

In the first awake prone positioning session, S_{pO_2}/F_{IO_2} and ROX index were significantly improved in both treatment success and failure groups (Fig. 1), and the improvement of S_{pO_2}/F_{IO_2} was similar in both groups (treatment success vs failure, 14.3 [2.9, 33.6] vs 7.5 [2.2, 40.8]; $P = .48$). However, only the subjects in the treatment success group had a significant improvement of S_{pO_2}/F_{IO_2} and ROX index with awake prone positioning on the second day and a significant improvement of S_{pO_2}/F_{IO_2} on the third day. The median (IQR) S_{pO_2}/F_{IO_2} improvement to awake prone positioning on the second day was greater in the treatment success versus the treatment failure group (12.0 [3.3–31.0] vs 3.9 [0.5–12.0]; $P = .003$). Compared with the treatment

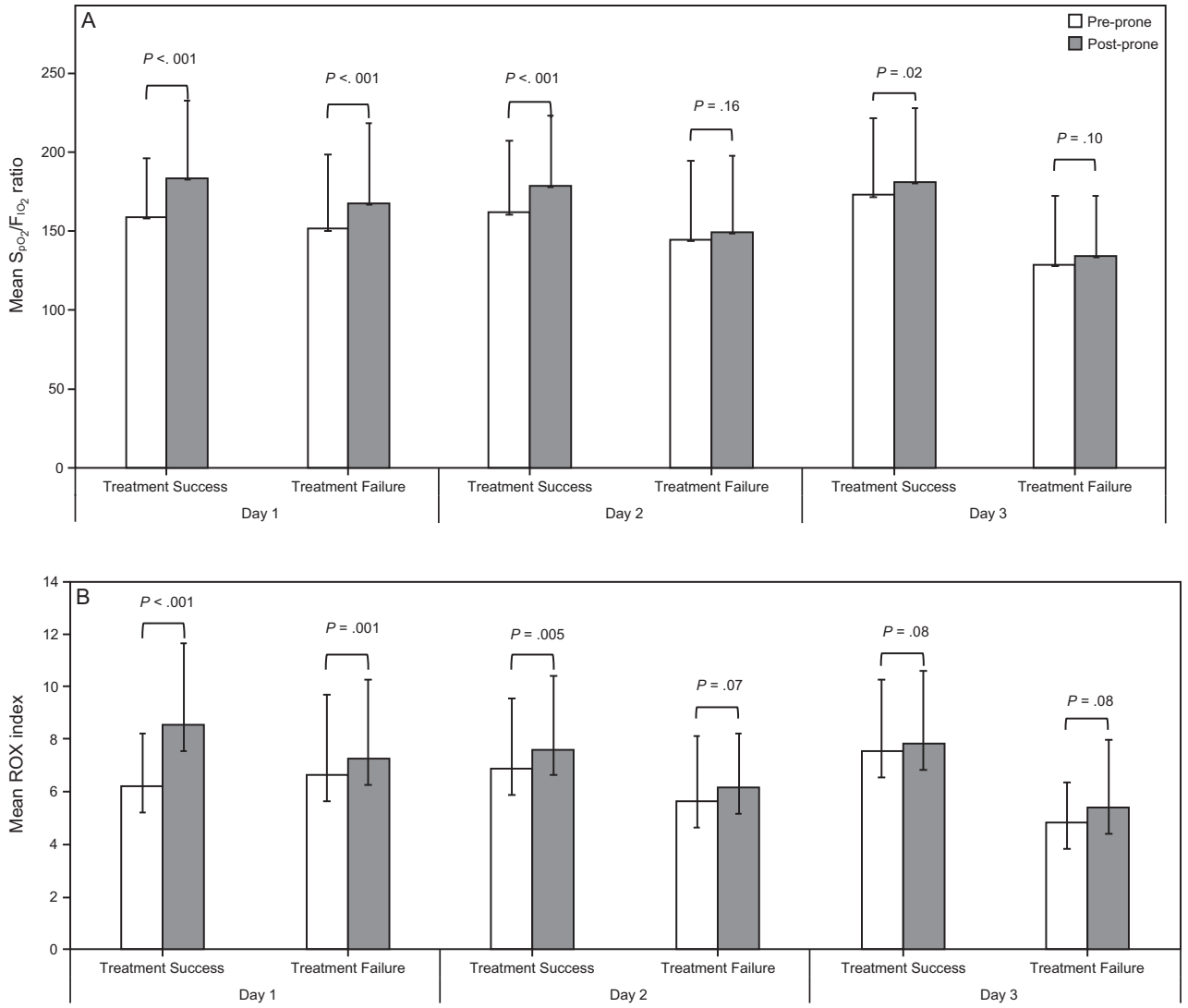

Fig. 1. Oxygenation response to awake prone positioning in the first 3 days between treatment success and failure groups. In the first day, subjects' S_{pO_2}/F_{IO_2} (A) and ROX index (B) significantly improved after awake prone positioning in both treatment success and failure groups. However, in the second day, only the subjects in the treatment success group had significant improvement of S_{pO_2}/F_{IO_2} and ROX index after awake prone positioning. Similarly, on the third day, S_{pO_2}/F_{IO_2} still significantly increased after awake prone positioning in the treatment success group but not in the treatment failure group. ROX= S_{pO_2}/F_{IO_2}/breathing frequency.

failure group, the subjects in the treatment success group had a shorter median (IQR) HFNC duration (4.2 [2.1–7.2] d vs 6.9 [2.5–11.5] d; $P = .037$) and a shorter median (IQR) need-to-prone days (defined as the duration from study enrollment to HFNC discontinuation or intubation/death) (3.9 [1.9-7.1] vs 6.6 [2.5–11.9]; $P = .009$), but similar time spent on awake prone positioning at the daily average in the need-to-prone days (Table 1).

Logistic regression analysis identified that higher S_{pO_2}/F_{IO_2} at study enrollment (odds ratio [OR] 1.022, 95% CI 1.007-1.037; $P = .004$) and S_{pO_2}/F_{IO_2} improvement to awake prone positioning in the second day (OR 1.051, 95% CI 1.016-1.087; $P = .004$) were associated with treatment success. The optimum cutoff value identified by drawing receiver operating characteristic curves for S_{pO_2}/F_{IO_2} at study enrollment was 150, with a sensitivity of 0.646 and specificity of 0.674; whereas the cutoff value for S_{pO_2}/F_{IO_2} improvement to awake prone positioning in the second day was 11.5, with a sensitivity of 0.532 and specificity of 0.763. More subjects with S_{pO_2}/F_{IO_2} at study enrollment of $\geq$ 150 had treatment success than did subjects with S_{pO_2}/F_{IO_2} at study enrollment $<$ 150 (75% vs 44%; $P =$ .002). The subjects in the treatment success group had less use of noninvasive ventilation (8% vs 47%; $P < .001$), shorter median (IQR) ICU stay (5.0 [2.1–7.0] d vs 21.8 [17.2–35.5] d; $P < .001$), and shorter median (IQR) hospital stay (10.7 [8.5–14.9] d vs 24.5 [17.6–42.5] d; $P < .001$) versus the treatment failure group.

Discussion

In this study, we found that significant improvements in S_{pO_2}/F_{IO_2} at day 2 and higher pre-prone S_{pO_2}/F_{IO_2} were possible predictors of awake prone positioning treatment success among subjects with COVID-19 induced acute hypoxemic respiratory failure. We found a higher S_{pO_2}/F_{IO_2} and ROX index before awake prone positioning in the treatment success group compared with the treatment failure group. This suggests a less-severe degree of respiratory failure in the treatment success group. Alternatively, this suggests that, within the inclusion group, the subjects with a higher S_{pO_2}/F_{IO_2} and ROX index benefitted the most from awake prone positioning because these subjects were potentially earlier in the spectrum of inflammation at the point of intervention. This is in accordance with analysis of our recently published data that suggests that early awake prone positioning had greater benefit than late awake prone positioning,[5] which might imply a therapeutic window for subjects to benefit from awake prone positioning.

The prognostic value of subject responses to prone positioning during the first prone session for subjects with ARDS who were intubated was explored by van Meenen et al.[6] When using changes in oxygenation, dead space, and driving pressure, they found no significant differences between survivors and nonsurvivors. In our previous study that evaluated subjects with ARDS induced by COVID-19 and who were intubated, we found significant improvements in oxygenation during the first prone session in the subjects who survived and in those who died or were placed on extracorporeal membrane oxygenation.[7] However, survivors continued to respond to prone positioning during the second and third prone positioning sessions compared with no significant improvements among those who died or needed extracorporeal membrane oxygenation. The aforementioned results agree with the findings in our current study, which demonstrated that continued response to awake prone positioning on day 2 predicts treatment success. The treatment success group may still be in the exudative phase with diffuse alveolar damage, which could respond to awake prone positioning.[8] This hypothesis needs to be validated in future studies.

Given the poorer outcome in the group with $S_{pO_2}/F_{IO_2} < 150$ before awake prone positioning, close monitoring for response to awake prone positioning is needed for those subjects. Also, it is particularly important to assess their response to awake prone positioning on day 2, which might help decide the need for intubation. In addition, because a daily duration of awake prone positioning for at least 8 h/d was found to be associated with treatment success,[4] efforts should be made to improve the tolerance of awake prone positioning among patients with pre-prone positioning $S_{pO_2}/F_{IO_2} < 150$, with the goal of avoiding intubation. The sample size of this post hoc analysis that examined the awake prone positioning subgroup might not be powered to comprehensively investigate predictors of awake prone positioning treatment success. This may explain why the ORs were marginally associated with treatment success for both S_{pO_2}/F_{IO_2} at enrollment and S_{pO_2}/F_{IO_2} improvement to awake prone positioning on day 2. The smaller sample size might also explain the poor sensitivity and specificity for the cutoff values. Studies with a larger sample size are needed. In addition, we only enrolled subjects with COVID-19 and acute hypoxemic respiratory failure supported by HFNC. Thus, our findings cannot be applied to those with mild hypoxemia treated by invasive oxygen therapy or patients with acute hypercapnic respiratory failure. Our findings also cannot be generalized to patients without COVID-19.

Pre-prone positioning oxygenation and oxygenation responses to awake prone positioning on the second day were associated with treatment success for subjects with COVID-19 and acute hypoxemic respiratory failure supported by HFNC. Further clinical trials are needed to confirm these findings. Closely monitoring patients with $S_{pO_2}/F_{IO_2} < 150$ using HFNC before awake prone positioning, especially their response to awake prone positioning on the second day, may be helpful in identifying their need for intubation.

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