Respiratory Failure in COVID-19 with Awake Prone Positioning and HFNC Therapy: Aggravating Factors

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The combination of high-flow nasal cannula (HFNC) oxygen therapy and awake prone positioning (PP) was reported to improve the clinical outcome of patients with coronavirus disease 2019 (COVID-19) in respiratory failure. However, delay in intubation among patients treated with HFNC and awake PP has been linked to mortality. Our aim was to evaluate factors that indicated aggravation among patients with HFNC therapy and awake PP.

This cohort study was conducted from November 2020 to June 2021 at St. Marianna University School of Medicine, a tertiary facility with over 1000 beds. We included patients with COVID-19 who were treated with HFNC therapy and awake PP immediately after admission. The exclusion criteria were pregnancy, immunocompromise (receiving chemotherapy, human immunodeficiency virus infection, etc.), or starting intubation or palliative care within 1 day after admission. We included patients who signed Do Not Resuscitate (DNR) or Do Not Intubate (DNI) orders after admission because the standard of care for COVID-19 was the same as patients without a DNR/DNI order. The final cohort of 65 patients was divided into 2 groups: those with an event (those who were intubated or died, n = 18) vs. without an event (those who were survived without intubation, n = 47).

HFNC therapy and awake PP were performed in patients requiring oxygen (saturation of percutaneous oxygen [SpO2]/fraction of inspiratory oxygen [FiO2] < 200) and whose chest images showed bilateral ground-glass opacities. The awake PP protocol involved asking patients to remain in the PP for 2 hours, 3 times a day.

Results were corrected for patients’ characteristics, vital signs, blood test, treatment information, and clinical information. We compared between those with an event and those without an event using the Fisher exact test and Wilcoxon rank-sum test. We applied a strict cut-off p value of 0.005 due to the multiple comparisons. All analyses were performed using STATA/MP v15.1 (StataCorp LLC, College Station, TX, USA).

Table 1 shows the results. The median ROX index (with event, 6.02 vs. without event, 7.54), C-reactive protein (CRP) (with event, 12.7, vs. without event, 5.6), procalcitonin (with event 0.34, vs. without event, 0.09), and NT-pro-BNP (with event, 1108, vs. without event, 120) showed significant differences (all P < 0.005).

Our results showed a significantly lower ROX index in patients who had an event. The ROX index has been proposed as a tool to identify COVID-19 patients at high risk of intubation. Our results suggest that the ROX index may be a useful tool to evaluate the risk of intubation among COVID-19 patients treated with HFNC therapy and awake PP.

CRP and procalcitonin were significantly elevated among patients with an event. The normal procalcitonin level is < 0.5 ng/ml, and high levels can predict bacterial infection. Even though the procalcitonin levels were statistically significant between the 2 groups, it was almost within the normal range and clinically meaningless in the context of our study, however, CRP levels differed significantly between the 2 groups. NT-pro-BNP has been reported as independently associated with mortality among patients with COVID-19. In our study, patients with an event had significantly higher NT-pro-BNP levels. These results suggest that higher CRP and NT-pro-BNP may predict events in COVID-19 patients treated with HFNC therapy and awake PP.

In conclusion, our study showed that ROX index, CRP, procalcitonin, and NT-pro-BNP might be related to an event. Further investigations using a larger sample size are necessary to confirm the effect of our regimen.
Table 1. Comparison between coronavirus disease 2019 patients treated with HFNC\(^\dagger\) therapy and awake PPI who were intubated or died and patients who survived without intubation

| Patient characteristic | With events (intubated or died) \((n = 18)\) | | | | | | Without events (survived without intubation) \((n = 47)\) | \(P\) value |
|-----------------------|----------------------------------------|---|---|---|---|---|---|
| Age (years), median \((IQR)\) | 64.5 (61.0–75.0) | 81 (78.5–88.5) | 77 (64–82) | 68 (52–74) | 0.008 |
| Male sex, No. (%) | 8 (80.0) | 6 (75.0) | 14 (77.8) | 33 (70.2) | 0.542 |
| Body mass index, median \((IQR)\) | 26.4 (23.3–28.7) | 22.0 (19.9–26.3) | 24.4 (22.4–28.6) | 25.5 (22.8–28.0) | 0.758 |
| Smoking history, No. (%) | 3 (30.0) | 0 (0.0) | 3 (16.7) | 19 (40.4) | 0.085 |
| Comorbidities | | | | | |
| Chronic heart failure, No. (%) | 1 (10.0) | 0 (0.0) | 1 (5.6) | 3 (6.4) | 1.000 |
| Diabetes mellitus, No. (%) | 5 (50.0) | 2 (25.0) | 7 (38.9) | 20 (42.6) | 0.788 |
| Chronic obstructive pulmonary disease or asthma, No. (%) | 3 (30.0) | 2 (25.0) | 5 (27.8) | 7 (14.9) | 0.288 |
| Chronic kidney disease | | | | | |
| Without dialysis, No. (%) | 0 (0.0) | 1 (12.5) | 1 (5.6) | 6 (12.8) | 0.663 |
| With dialysis, No. (%) | 3 (30.0) | 1 (12.5) | 4 (22.2) | 1 (2.1) | 0.018 |
| Vital signs (after HFNC therapy) | | | | | |
| Heart rate (/min), median \((IQR)\) | 80 (74–90) | 88 (79–117) | 84 (77–103) | 77 (64–89) | 0.022 |
| Systolic blood pressure (mmHg), median \((IQR)\) | 126.0 (18.0–142.0) | 133.5 (112.5–151.5) | 127.5 (108.0–145.0) | 125.5 (118.0–135.0) | 0.792 |
| Diastolic blood pressure (mmHg), median \((IQR)\) | 67.0 (55.0–72.0) | 63.5 (57.0–77.5) | 65.5 (56.0–74.0) | 64 (56.0–72.0) | 0.587 |
| Respiration rate (/min), median \((IQR)\) | 28 (16–38) | 27 (22–29) | 25.5 (20.0–28.0) | 22.0 (20.0–25.0) | 0.273 |
| Body temperature \(^{\circ}\C\), median \((IQR)\) | 37.1 (36.4–37.3) | 37.1 (36.8–37.7) | 37.1 (36.6–37.4) | 36.8 (36.5–37.1) | 0.146 |
| Saturation of percutaneous oxygen \(\%\), median \((IQR)\) | 95.5 (92.0–97.0) | 92.5 (91.0–97.0) | 94 (91–97) | 96 (94–97) | 0.165 |
| Partial pressure of arterial oxygen/fraction of inspiratory oxygen, median \((IQR)\) | 160.0 (139.5–174.4) | 155.3 (104.1–200.7) | 157 (117.1–183.8) | 183.2 (160–228) | 0.016 |
| Bicarbonate (mmol/L), median \((IQR)\) | 5.52 (4.79–7.15) | 6.28 (5.17–7.82) | 6.02 (4.79–7.22) | 7.54 (6.67–10) | < 0.005 |
| Blood test results | | | | | |
| White blood cell count \((x10^{3}/\mu\text{L})\), median \((IQR)\) | 6950 (5800–9400) | 6950 (4900–12100) | 7800 (5500–10400) | 6600 (4000–9600) | 0.189 |
| C-reactive protein, mg/dL, median \((IQR)\) | 6.6 (4.1–12.9) | 14.9 (12.6–19.3) | 12.7 (6.9–16.7) | 5.6 (3.0–8.3) | 0.003 |
| Procalcitonin (ng/mL), median \((IQR)\) | 0.34 (0.21–0.64) | 0.43 (0.17–1.17) | 0.34 (0.21–0.64) | 0.09 (0.06–0.2) | < 0.001 |
| D-dimer (µg/mL), median \((IQR)\) | 0.8 (0.4–1.5) | 1.7 (0.9–3.3) | 1.1 (0.6–1.9) | 0.8 (0.6–1.9) | 0.691 |
| Ferritin (ng/mL), median \((IQR)\) | 650 (168–1440) | 347 (157–1005) | 470 (167–1272) | 724 (370–1335) | 0.291 |
| Creatinine (mg/dL), median \((IQR)\) | 1.09 (0.87–6.21) | 1.01 (0.73–2.28) | 1.05 (0.85–2.67) | 0.735 (0.6–1.08) | 0.034 |
| N-terminal pro-brain natriuretic peptide (pg/mL), median \((IQR)\) | 1275 (452–3994) | 1275 (485–6584) | 1108 (452–4510) | 120 (38–310) | < 0.001 |
| Interleukin-6 (pg/mL), median \((IQR)\) | 67.6 (42.4–112.2) | 82 (22.2–91.2) | 68.4 (34.6–91.2) | 30.9 (9.8–83.4) | 0.116 |
| Arterial blood gas (after HFNC therapy) | | | | | |
| Partial pressure of arterial oxygen \((mmHg)\), median \((IQR)\) | 99.8 (95.4–135.8) | 80.2 (72.5–89.5) | 94.8 (80.8–118.6) | 99.8 (82–114.0) | 0.655 |
| Bicarbonate \((mmol/L)\), median \((IQR)\) | 21.2 (20.2–22.1) | 22.9 (19.9–24.7) | 21.7 (19.9–23.5) | 23.3 (21.7–25.5) | 0.601 |
| Treatment | | | | | |
| Antibiotic, No. (%) | 4 (40.0) | 8 (100.0) | 12 (66.7) | 29 (61.7) | 0.780 |
| Remdesivir, No. (%) | 10 (100.0) | 8 (100.0) | 18 (100) | 44 (93.6) | 0.555 |
| Dexamethasone, No. (%) | 10 (100.0) | 8 (100.0) | 18 (100) | 47 (100) | 1.000 |
| Heparin, No. (%) | 10 (100.0) | 8 (100.0) | 18 (100) | 47 (100) | 1.000 |
| Tocilizumab, No. (%) | 3 (30.0) | 6 (75.0) | 9 (50.0) | 11 (23.4) | 0.069 |
| Clinical information | | | | | |
| Time from symptom onset to admission \((days)\), median \((IQR)\) | 7.5 (4.0–9.0) | 6.5 (2.5–7.5) | 7 (4–9) | 8 (7–10) | 0.070 |
| Admission from another hospital, No. (%) | 8 (80.0) | 3 (37.5) | 11 (61.1) | 30 (63.8) | 1.000 |

\(^\dagger\)High-flow nasal cannula

\(^\ast\)Prone positioning

\(^\ast\)Interquartile range
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References

1. Tonelli R, Pisani L, Tabbi L, et al. Early awake proning in critical and severe COVID-19 patients undergoing noninvasive respiratory support: A retrospective multicenter cohort study [published online ahead of print, 2021 Mar 22]. Pulmonology. 2021;S2531-0437(21)00077-5.

2. Colaianni-Alfonso N, Montiel G, Castro-Sayat M, et al. Combined non-invasive respiratory support therapies to treat SARS-CoV-2 patients: A prospective observational study [published online ahead of print, 2021 Jul 21]. Respir Care. 2021;respcare.09162.

3. Suliman LA, Abdelgawad TT, Farrag NS, Abdelwahab HW. Validity of ROX index in prediction of risk of intubation in patients with COVID-19 pneumonia. Adv Respir Med. 2021;89(1):1-7.

4. Deléaux I, André M, Colombier M, et al. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes?. Ann Rheum Dis. 2003;62(4):337-340.

5. Caro-Codón J, Rey JR, Buño A, et al. Characterization of NT-proBNP in a large cohort of COVID-19 patients. Eur J Heart Fail. 2021;23(3):456-464.