


ORIGINAL RESEARCH

Laryngeal complications after endotracheal intubation and prone positioning in patients with coronavirus disease 2019

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Abstract

Objectives: Laryngeal complications have been reported after endotracheal intubation and prone positioning in patients with critical coronavirus disease 2019 (COVID-19), but their association is unclear. In this study, we investigated the rate of laryngeal complications in patients with COVID-19 compared to an alternative condition (control group).

Methods: We retrospectively analyzed the data of 40 patients who underwent endotracheal intubation for either COVID-19 or an alternative condition (control group). Data on age, sex, body mass index (BMI), cardiovascular disease (CVD) risk factors, use of prone therapy, duration of endotracheal intubation, and duration from extubation/tracheostomy to laryngeal evaluation were collected from medical records.

Results: There were no significant differences in BMI, frequency of CVD risk factors, duration of endotracheal intubation, or duration from extubation/tracheostomy to laryngeal evaluation between the two groups. In the COVID-19 group, all patients adopted the prone position. In comparison, only one patient in the control group adopted the prone position. Significant differences were observed between the two groups regarding the incidence of vocal fold immobility and laryngeal granuloma.

Conclusion: Laryngeal complications were more common in the COVID-19 group than in the control group. Prone positioning may be a risk factor for these complications.

Level of Evidence: 4.

KEYWORDS

COVID-19, laryngeal granuloma, prone positioning, vocal cord paralysis

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1 | INTRODUCTION

At the beginning of the coronavirus disease 2019 (COVID-19) pandemic caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2), approximately 5% of patients with COVID-19 were classed as critical, requiring endotracheal intubation and mechanical ventilation.^{1,2} Vaccination against SARS-CoV-2 is reported to be highly effective for COVID-19. Severe COVID-19 is rare among individuals who have a complete vaccination record, with a severity rate is 0.015%.³ However, because of factors such as virus mutations, the number of infected individuals remains high, and there are still many patients at any one time with severe COVID-19 in Japan.⁴ COVID-19 causes acute respiratory distress syndrome (ARDS) in approximately 20% of hospitalized patients.² Because prone positioning improves outcomes in patients with ARDS by reducing lung compression and improving lung perfusion, it has been widely used in patients with COVID-19-associated ARDS.^{5,6} However, laryngeal complications, including vocal fold immobility, laryngeal/tracheal stenosis, and laryngeal granuloma after endotracheal intubation, have been reported after intubation and prone positioning in patients with COVID-19,⁷⁻¹³ and it has been suggested that prolonged intubation with prone positioning is associated with these laryngeal complications.⁷ However, little is known about the laryngeal complications that occur after intubation and prone positioning in patients with severe COVID-19. In this study, we investigated this issue.

2 | MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of Ehime University Medical Hospital (no. 2108028).

We treated 33 patients with COVID-19 who required endotracheal intubation and mechanical ventilation at our hospital between January 2021 and July 2021. Among these patients, patients who underwent laryngeal evaluation using a flexible endoscope after extubation or tracheostomy by otolaryngologists were included.

Patients who were treated with endotracheal intubation for respiratory failure, except for respiratory failure caused by COVID-19, in the intensive care unit between January 2018 and January 2021, and who underwent laryngeal evaluation using a flexible endoscope after extubation or tracheostomy by otolaryngologists, were included in this study as the control group. Patients who underwent lung surgery, cardiac surgery, or cranial surgery were excluded. Patients with airway burns were also excluded.

All patients were intubated by trained emergency physicians using video laryngoscopy. The endotracheal tube cuff pressure was maintained at 30–40 mmHg using cuff manometry in the control group and an automatic cuff pressure controller in the COVID-19 group.

Patient data, including sex, age, body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus, prone therapy, duration of endotracheal intubation, duration from extubation/tracheostomy

to laryngeal evaluation, and endoscopic laryngeal findings, were collected from patients' medical records.

The data are expressed as the mean \pm standard error of the mean. Each parameter was compared between the two groups using the Mann-Whitney *U* test or Fisher's exact test with JMP software for Macintosh (SAS Institute Inc., Cary, NC). A *p*-value of $<.05$ was considered statistically significant.

3 | RESULTS

Of the 33 patients with severe COVID-19 treated at our hospital, 16 patients who underwent laryngeal evaluation using a flexible endoscope were included in this study. Twenty-four patients, including patients with heart failure ($n = 8$), respiratory failure due to pneumonia ($n = 8$), septic shock ($n = 5$), or ARDS ($n = 3$), comprised the control group.

The clinical characteristics of both groups are summarized in Table 1. In the COVID-19 group, the age of the patients ranged from 36 to 82 years, with an average age of 60.4 ± 2.7 years. In the control group, the age of the patients ranged from 46 to 86 years, with an average age of 68.2 ± 2.5 years. The COVID-19 group was significantly younger than the control group ($p = .047$). BMI was 24.9 ± 1.0 in the COVID-19 group and 23.5 ± 2.0 in the control group; there was no significant difference in BMI between the two groups. All 16 patients with COVID-19 adopted the prone position, while only 1 patient (4.2%) in the control group adopted the prone position ($p < .001$). The number of patients with risk factors for cardiovascular disease (CVD), including hypertension, hyperlipidemia, and diabetes mellitus, was not significantly different between the two groups ($p = .19$, $p = .64$, and $p = .05$, respectively). The duration of endotracheal intubation and the duration from extubation/tracheostomy to laryngeal evaluation were not significantly different between the two groups ($p = .72$ and $p = .99$, respectively). Five patients (31.3%) in the COVID-19 group had unilateral vocal fold immobility (UVFI) (three cases on the left side and two cases on the right side), while one patient (4.2%) had left-sided vocal fold immobility (VFI). There was a significant difference between the two groups ($p = .03$). Laryngeal granuloma was observed in five patients (31.3%) in the COVID-19 group and in one patient (4.2%) in the control group ($p = .03$).

Figure 1 shows the size of the endotracheal tube. Among the male patients, 2 of 12 (16.7%) were intubated with an endotracheal tube with an internal diameter (ID) of 8.0 mm (outer diameter [OD] 11.8 mm) in the COVID-19 group, and 7 of 17 patients (41.2%) were intubated with an endotracheal tube with an ID of 8.0 mm in the control group. Among the female patients, all four were intubated with an endotracheal tube with an ID of 7.0 mm (OD 10.4 mm) in the COVID-19 group, and four of seven patients (57.1%) were intubated with an endotracheal tube with an ID of 7.5 mm (OD 11.2 mm) in the control group. Eight (50.0%) of 16 patients in the COVID-19 group and 10 (41.7%) of 24 patients in the control group underwent tracheostomy. The duration from intubation to tracheostomy was 12.3 ± 0.9 days in the COVID-19 group and 12.0 ± 1.7 days in the control

TABLE 1 Comparison of clinical characteristics between the COVID-19 group and the control group

| | COVID-19 group (n = 16) | Control group (n = 24) | p value |
|---|-------------------------|------------------------|---------|
| Sex (M/F) | 12/4 | 17/7 | >.99 |
| Age (years) | 60.4 ± 2.7 | 68.2 ± 2.5 | .047 |
| Body mass index | 24.9 ± 1.0 | 23.5 ± 2.0 | .07 |
| Prone positioning (n, %) | 16 (100%) | 1 (4.2%) | <.001 |
| Hypertension (n, %) | 4 (25.0%) | 12 (50.0%) | .19 |
| Hyperlipidemia (n, %) | 1 (6.3%) | 3 (12.5%) | .64 |
| Diabetes mellitus (n, %) | 4 (25.0%) | 14 (58.3%) | .05 |
| Duration of endotracheal intubation (days) | 9.6 ± 0.8 | 10.8 ± 1.0 | .72 |
| Duration from extubation to laryngeal evaluation (days) | 12.4 ± 3.6 | 10.0 ± 2.0 | .99 |
| Unilateral vocal fold immobility (n, %) | 5 (31.3%) | 1 (4.2%) | .03 |
| Laryngeal granuloma (n, %) | 5 (31.3%) | 1 (4.2%) | .03 |

Note: M, male; F, female.

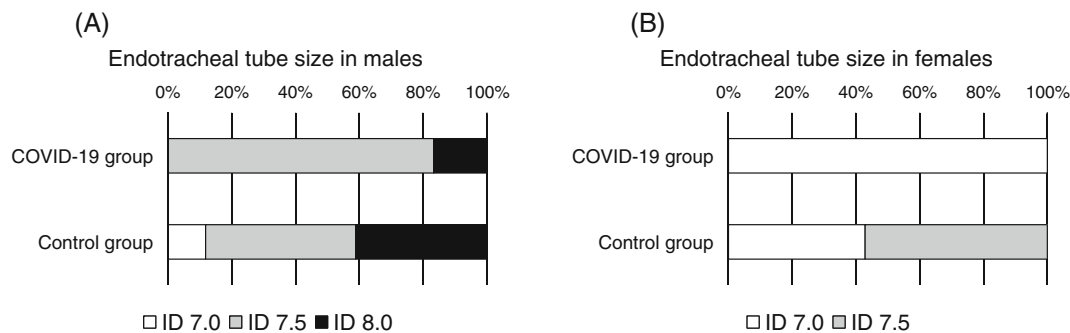


FIGURE 1 (A) Endotracheal tube size in male patients. An endotracheal tube with an internal diameter (ID) of 7.5 mm (outer diameter [OD] of 11.2 mm) was used most frequently in both groups. An endotracheal tube with an ID of 8.0 mm (OD of 11.8 mm) was less commonly used in the COVID-19 group than in the control group. (B) Endotracheal tube size in female patients. All patients with COVID-19 were intubated with an endotracheal tube with an ID of 7.0 mm (OD 10.4 mm), and 57.1% of patients in the control group were intubated with an endotracheal tube with an ID of 7.5 mm (OD of 11.2 mm)

TABLE 2 Comparison of clinical characteristics according to the presence or absence of unilateral vocal fold immobility

| | Unilateral vocal fold immobility | | p value |
|---|----------------------------------|------------------------|---------|
| | Yes (n = 5) | No (n = 11) | |
| Sex (M/F) | 3/2 | 9/2 | .55 |
| Age (years) | 64.6 ± 5.0 | 58.5 ± 3.3 | .46 |
| Body mass index | 23.8 ± 1.5 | 25.3 ± 1.2 | .57 |
| Duration of endotracheal intubation (days) | 9.6 ± 0.7 | 9.5 ± 1.1 | .91 |
| Duration from extubation to laryngeal evaluation (days) | 10.2 ± 6.1 | 13.5 ± 4.6 | .78 |
| Hypertension | 1 (20.0%) | 3 (27.3%) | >.99 |
| Dyslipidemia | 0 (0%) | 1 (9.1%) | >.99 |
| Diabetes mellitus | 2 (40.0%) | 2 (18.2%) | .55 |
| Endotracheal tube size | | | |
| Male (n = 12) | ID 7.5: 3 ID 8.0: 0 | ID 7.5: 7 ID 8.0: 2 | — |
| Female (n = 4) | ID 7.0: 2 | ID 7.0: 2 | |

Note: M, male; F, female.

| | Unilateral vocal fold immobility | | p value |
|---|----------------------------------|-------------|---------|
| | Yes (n = 5) | No (n = 11) | |
| Sex (M/F) | 4/1 | 8/3 | >.99 |
| Age (years) | 52.2 ± 4.4 | 64.2 ± 2.9 | .06 |
| Body mass index | 25.5 ± 0.7 | 24.6 ± 1.4 | .31 |
| Duration of endotracheal intubation (days) | 6.8 ± 1.0 | 10.8 ± 0.9 | .03 |
| Duration from extubation to laryngeal evaluation (days) | 10.6 ± 8.6 | 13.3 ± 3.8 | .23 |
| Hypertension | 1 (20.0%) | 3 (27.3%) | >.99 |
| Dyslipidemia | 0 (0%) | 1 (9.1%) | >.99 |
| Diabetes mellitus | 1 (20.0%) | 3 (27.3%) | >.99 |
| Endotracheal tube size | | | |
| Male (n = 12) | ID 7.5: 4 | ID 7.5: 6 | |
| | ID 8.0: 0 | ID 8.0: 2 | — |
| Female (n = 4) | ID 7.0: 1 | ID 7.0: 3 | |

Note: M, male; F, female.

TABLE 3 Comparison of clinical characteristics according to the presence or absence of laryngeal granuloma

group; there were no differences in the days from intubation to tracheostomy between both groups ($p = .59$).

Table 2 shows a comparison of clinical characteristics according to the presence or absence of UVFI among patients in the COVID-19 group. Sex, age, BMI, duration of endotracheal intubation, duration from extubation to laryngeal evaluation, and CVD risk factors were not significantly different.

Table 3 shows a comparison of clinical characteristics according to the presence or absence of laryngeal granuloma among patients in the COVID-19 group. The duration of endotracheal intubation was significantly shorter in patients with laryngeal granuloma than in patients without laryngeal granuloma ($p = .03$), while other factors were not significantly different between the two groups. Two patients had both UVFI and laryngeal granuloma.

4 | DISCUSSION

In this study, laryngeal complications, including UVFI and laryngeal granuloma, were observed more frequently in patients with severe COVID-19 than in control subjects. Although the mechanism underlying these findings is unknown, prone positioning may be associated with the occurrence of laryngeal complications after endotracheal intubation.

It has been reported previously that 7.9–76% of patients with severe COVID-19 have UVFI following endotracheal intubation.^{7–9} Our results, which demonstrated UVFI in approximately 30% of patients, were consistent with these previous reports. The reported incidence of UVFI after prolonged intubation ranges from 7% to 41% among patients without COVID-19.^{14–17} However, it has not previously been reported whether there is a difference in the frequency of UVFI between COVID-19 and other diseases requiring endotracheal intubation. In our study, the rate of UVFI after intubation was

significantly higher in patients with COVID-19 than in the control group. The duration of intubation, older age, risk factors for CVD, and the size of the endotracheal tube have been reported to be associated with VFI after endotracheal intubation.^{16–19} In this study, patients were younger in the COVID-19 group than in the control group. CVD risk factors, including BMI, hypertension, hyperlipidemia, and diabetes mellitus, did not differ between the two groups. The duration of intubation and the size of the endotracheal tube also did not differ between the two groups. Prone positioning was a factor that was significantly different between the two groups. It has been suggested that UVFI after endotracheal intubation is caused by recurrent laryngeal nerve paralysis (RLNP) due to compressive neural injury or arytenoid dislocation/subluxation.^{14,20,21} It was difficult to differentiate between these two diseases because we did not perform laryngeal electromyography. Thus, further studies are required to investigate whether UVFI after intubation and prone therapy are caused by RLNP or arytenoid dislocation.

Laryngeal granuloma was more frequently observed in the COVID-19 group than in the control group. It has been reported previously that the duration of intubation and the size of the endotracheal tube are risk factors for laryngeal granuloma after endotracheal intubation.¹⁶ Similar to UVFI, these factors did not differ between the two groups. Therefore, it is suggested that prone positioning is associated with the incidence of laryngeal granuloma. In our cohort, a shorter duration of intubation was associated with the incidence of laryngeal granulation in COVID-19 group. However, it is unclear why a shorter duration of intubation is related to laryngeal granulation. It has been reported that gastric reflux is suggested to be related to the incidence of laryngeal granulation.^{22,23} Therefore, other factors including acid reflux might be related to the incidence of laryngeal granulation.

Prone positioning has been used to treat severe hypoxemia in patients with ARDS,^{24,25} and it is commonly used for patients with

severe COVID-19.^{6,7} Adverse events associated with prone positioning include pressure ulcers, endotracheal tube obstruction, facial edema, enteral feeding intolerance, accidental extubation, and hemodynamic instability, among others.²⁶ However, laryngeal complications due to prone positioning are not well known. The mechanism of laryngeal complications caused by prone positioning is unclear. Rotation of the neck during prone positioning may exacerbate the pressure on the larynx due to the endotracheal tube or may dislocate the endotracheal tube and cause arytenoid dislocation. In addition, disturbance of mucosal microcirculation and nerve injury because of SARS-CoV-2 are potential causes of UVFI. It has been reported that early intervention for patients with postintubation laryngeal injury is associated with a favorable outcome compared with late intervention.²⁷ Otolaryngologists should be aware of these laryngeal complications after endotracheal intubation and prone positioning and should intervene earlier.

To date, an approach to prevent laryngeal complications after intubation and prone positioning in patients with severe COVID-19 has not been reported. However, laryngeal/tracheal stenosis was not observed in our cohort. The duration of intubation in the COVID-19 group was similar to that in the control group, and relatively shorter than that in previous reports that reported these laryngeal complications after intubation and prone positioning in patients with severe COVID-19.⁷⁻¹³ It has been recommended that tracheostomy is performed at least 10 days after intubation.²⁸ We have performed tracheostomies within 14 days to prevent severe laryngeal complications including laryngeal or tracheal stenosis. UVFI and laryngeal granulation can be treated conservatively, while laryngeal and tracheal stenosis require surgical procedures. Therefore, timely tracheostomy is important when intubation and prone positioning are prolonged.

There are several limitations in this study that should be noted. First, this study was retrospective, and the number of included patients was small. In a power analysis comparing laryngeal complications between the COVID-19 group and the control group, the power ($1 - \beta$) was 0.58. In addition, the number of included patients was too small in which to perform other statistical tests such as multivariate regression. A larger-scale, prospective study will be needed to clarify our observations. Second, because we could not assess the larynx using a flexible endoscope in all patients in the COVID-19 group, there was a risk of bias that the patients were enriched for those with laryngeal pathologies, and thus there is a possibility that the patients with COVID-19 in our cohort were not necessarily representative of the general population. However, some patients could not be evaluated with this approach because they were transferred to another hospital or because there was a lack of testing equipment, and thus this was not related to their symptoms. We could also not assess the larynx in all patients in the control group; therefore, there was also a risk of bias in this group. However, most prolonged intubated patients underwent larynx evaluation by flexible endoscopy before oral intake. Third, we could not follow up all patients with UVFI or laryngeal granuloma. Further studies on the outcomes of UVFI and laryngeal granuloma after endotracheal intubation in patients with severe COVID-19 are needed. In addition, laryngeal and tracheal stenosis were not

observed in our cohort; however, late laryngoscopic evaluation will be needed to confirm the absence of laryngeal or tracheal stenosis in the long term. Fourth, the influence of laryngeal inflammation caused by SARS-CoV-2 is still unknown. In this cohort, all patients in the COVID-19 group were treated by prone positioning therapy, while only one patient in the control group was treated using prone positioning therapy. Comparisons between the COVID-19 group and the control group without prone positioning are required to investigate the influence of laryngeal inflammation due to SARS-CoV-2 infection. In addition, because the proportion that required prone positioning differed between the COVID-19 group and control group, we should consider the possibility that systemic differences between COVID-19 and other diseases were involved.

5 | CONCLUSION

In this study, laryngeal complications, including UVFI and laryngeal granuloma, were more common in patients with COVID-19 than in the control group. Prone positioning may be a risk factor for laryngeal complications after endotracheal intubation.

ACKNOWLEDGMENT

We thank H. Nikki March, PhD, from Edanz (<https://jp.edanz.com/ac>) for editing a draft of this manuscript.

CONFLICT OF INTEREST

None declared.

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How to cite this article: Aibara S, Okada M, Tanaka-Nishikubo K, et al. Laryngeal complications after endotracheal intubation and prone positioning in patients with coronavirus disease 2019. *Laryngoscope Investigative Otolaryngology*. 2022; 7(6):1909-1914. doi:[10.1002/lio2.874](https://doi.org/10.1002/lio2.874)