Post-intubation Laryngeal Disorders in COVID-19 Patients: A Prospective Study.

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Abstract

Objective: To investigate post-intubation laryngeal complications in severe COVID-19 patients. Methods: From September 2020 to April 2021, consecutive patients presenting with laryngological symptoms following severe COVID-19 infection and related intubation were included. Demographic, age, gender, comorbidities, symptoms, intubation duration, tracheostomy features, and laryngeal findings were collected. Videolaryngostroboscopy findings were analyzed by two senior laryngologists in a blind manner. Results: Forty-three patients completed the evaluations. The intubation duration was <14 days in 22 patients (group 1) and >14 days in 21 patients (group 2). The following abnormalities were found on an average post-intubation time of 51.6 days: posterior glottic stenosis (N=14), posterior commissure hypertrophy (N=19) or laryngeal diffuse edema (N=10), granuloma (N=8), laryngeal necrosis (N=2), vocal fold atrophy (N=2), subglottic stenosis (N=1) and glottic flange (N=1). Sixteen patients required surgical treatment (N=17 procedures). The number of intubation days was significantly higher in patients with posterior glottic stenosis (26.1 ± 9.4) compared with those presenting posterior commissure hypertrophy (11.5 ± 2.9) or granuloma (15.1 ± 5.8; p<0.001). Fourteen patients required surgical management. Conclusion: Prolonged intubation used in severe COVID-19 patients is associated with significant laryngeal disorders. Patients with a history of >2-week intubation have a higher risk of posterior glottic stenosis.

Introduction

Coronavirus disease 2019 (COVID-19) is a worldwide infection that led to more than 236,000,000 cases and 4,800,000 deaths as October 5, 2021.[1] According to world regions, less than 20% of COVID-19 were severe-to-critical disease, which is defined as a condition with severe acute respiratory distress requiring mechanical ventilation.[2] The proportion of survivors after severe or critical COVID-19 ranges from 20 to 62% regarding studies.[3] Survivors may keep neurological and systemic postdischarge complications, e.g. breathlessness, psychological distress or cognitive impairments.[4] The mid-to-long term otolaryngological complications of COVID-19 were poorly investigated at the exception of olfactory and gustatory dysfunctions.[5] Recent studies reported swallowing disorders at post-intensive care unit (ICU) discharge,[6] while others reported laryngeal injuries post-tracheostomy.[7]

The aim of this study was to investigate post-intubation laryngeal complications in severe COVID-19 patients.

Methods

Subjects and setting

From September 2020 to April 2021, patients presenting to our laryngology unit with severe-to-critical COVID-19 infection and intubation histories were consecutively included. Patients consulted for voice or swallowing disorders that developed in the few weeks/months after the COVID-19 hospitalization. The COVID-19 infection had to be confirmed through RT-PCR or serology. The patients with the following exclusion criteria were excluded from the analysis: asthma and use of inhaled corticosteroids, neurological or psychiatric illness, previous history of neck surgery or trauma, malignancy, history of head and neck radiotherapy and tracheal stenosis. The Hospital IRB reviewed and approved the study (ref.202201). A waiver of informed consent of study participants was granted because participant data were protected and anonymized.

Epidemiological, clinical and laryngological outcomes and treatments

The following epidemiological and clinical data were collected: demographic information; age; gender; comorbidities; dates/features of documented COVID-19 infection, hospital stay; intubation and tracheostomy; general, voice, swallowing and airway complaints; medical and surgical required treatment and follow-up. The decision of percutaneous tracheostomy was made by intensive care physicians in case of prolonged intubation (>14 days).

The laryngological examination was performed by a senior laryngologist (SH, MC, LCB or JRL) with a videolaryngostroboscopy (XION GmbH, Berlin, Germany). The conclusion of the videolaryngostroboscopy examination was reviewed by a second senior laryngologist in a blind manner according to the initial conclusion. The following laryngeal disorders were considered in the diagnosis: laryngopharyngeal reflux (LPR), laryngeal diffuse edema, posterior commissure hypertrophy, laryngeal necrosis, granuloma, posterior glottic stenosis, subglottic stenosis, and posterior glottic diastasis. The Bogdasarian-Olson classification for stenosis of the posterior glottic membrane,[8] and the McCaffrey staging system[9] for subglottic and tracheal strictures were used to characterize laryngeal lesions. Patients with a suspicion of LPR and lack of response to medical therapy combining diet, proton pump inhibitors and alginates, benefited from a 24-hour hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH). According to the laryngeal disorders, the following medical treatments included antibiotics, corticosteroids, proton pump inhibitors (PPIs) and alginate. Patients with no improvement of lesion with medical treatment benefited from surgical treatments, i.e. CO_2 laser posterior transverse cordotomy, placement of Montgomery-type laryngeal calibration tube, laser flange (scare), or vocal fold fat injection.

Statistical methods

Statistical analyses were performed with the Statistical Package for the Social Sciences for Windows (SPSS version 24.0; IBM Corp, Armonk, NY, USA). Depending on the outcomes and distribution, the following tests were used to compare outcomes between two groups of patients (patients with a history of <2-week tracheostomy and those with a >2-week tracheostomy): Chi-square and Mann-Whitney U Test. The relationship between patient epidemiological and clinical features was investigated with Spearman analysis and multivariate analysis. A level of significance of $p<0.05$ was used.

Results

Forty-three patients with a history of severe-to-critical COVID-19 completed the evaluations. Patients consulted in our laryngology unit on average 51.6 ± 30.2 days after their hospitalization in intensive care units (UCI, range: 2-5 months). The mean age of cohort patients was 59.0 ± 11.3 yo. There were 10 females (23.3%) and 33 males (76.7%). Twenty-two patients were intubated less than 2 weeks (Group 1), while 21 were intubated more than 2 weeks (Group 2), respectively. The epidemiological and clinical features of patients are described in Table 1. Patient groups were comparable regarding gender proportion, mean age, tobacco history, comorbidities and symptoms. The most prevalent comorbidities included hypertension, diabetes and obesity (Table 1). The mean intubation duration was 9.9 ± 3.7 days in group 1, while patients of group 2 were intubated during 26.3 ± 6.8 days. In our medical center, the position of patients in the ICU bed were changed daily (stomach/back). There were 3 and 5 tracheostomies in groups 1 and 2, respectively. The mean duration of tracheostomy decannulation was 34.9 ± 22.0 days. One patient was not decannulated at the time

of the consultation.

Dysphonia (100%), dyspnea (44.1%) dysphagia (20.9 %), and neck pain (9.3%) were the most prevalent symptoms (Table 1). The videolaryngostroboscopy examination reported posterior commissure hypertrophy, posterior glottis stenosis, laryngeal diffuse edema and granuloma as the most prevalent laryngeal abnormalities in patients (Table 2). Figure 1 reported some laryngeal findings of patients. Two laryngeal examinations were considered as normal by the judges. The proportions of posterior commissure hypertrophy and laryngeal edema were significantly higher in group 1 compared with group 2 ($p<0.001$), while posterior glottic stenosis was more prevalent in group 2 compared with group 1 ($p<0.001$). The posterior commissure hypertrophy occurred concurrently to another abnormality in 16 cases, e.g. diffuse laryngeal edema (N=8), granuloma (N=5), bilateral vocal fold insufficiency (N=2), and posterior glottic stenosis (N=2). According to the classification of Bogdasarian,[12] the posterior glottic stenoses of group 1 were type 3 and 4, while the posterior glottic stenoses of group 2 were type 2, 3, and 4 in 1, 6, and 5 cases, respectively. Patients with posterior glottic stenosis, laryngeal necrosis and subglottic stenosis benefited from neck and chest CT-scan, which did not find another respiratory abnormality. Patients with a history of tracheostomy developed posterior glottic stenosis (N=4), laryngeal edema (N=4) associated with granuloma in two cases.

The surgical approaches performed in patients are reported in Table 2. Laryngeal necroses and posterior glottic stenoses were treated with corticosteroids and antibiotics, which led to effective results in 7 cases. Patients with posterior commissure hypertrophy, laryngeal diffuse edema and granuloma received antireflux diet, PPIs and alginate. Two patients with lack of improvement of posterior commissure hypertrophy and laryngeal erythema benefited from HEMII-pH, which confirmed the LPR diagnosis. Surgical treatment was proposed to patients who did not improve symptoms and findings posttreatment. The following surgical approaches were performed in 16 patients: granuloma laser excision (N=4), Montgomery-type calibration tube placement (N=4), dilatation (N=3), laser posterior transverse cordotomy (N=2), laser flange resection (N=1), and vocal fold fat medialization (N=1). One patient benefited from concurrent posterior transverse cordotomy and laser excision of granuloma. All patients benefited from speech therapy prior and after treatment. The number of intubation days was significantly higher in patients with posterior glottic stenosis (26.1 ± 9.4) compared with those presenting posterior commissure hypertrophy (11.5 ± 2.9) or granuloma (15.1 ± 5.8; $p<0.001$). Hypertension and diabetes were not associated with the development of any laryngeal injury.

Discussion

The relationship between COVID-19 and laryngeal disorders was initially observed in an epidemiological study in which 26% of COVID-19 patients reported dysphonia throughout the clinical course of the disease.[10] The potential laryngeal reach by the virus was supported in basic science studies reporting significant angiotensin converting enzyme-2 (ACE2) expression in vocal fold and laryngeal tissues.[11]

In the present study, we observed a high prevalence of laryngeal injuries in patients with a history of severe-to-critical COVID-19 and intubation. Depending on the intubation duration, the most common findings included posterior commissure hypertrophy and laryngeal edema, posterior glottic stenosis, and granuloma. Some recent studies reported similar laryngeal injuries in patients with a post-COVID-19 history of intubation.[12,13] Naunheim *et al* . observed vocal fold immobility (40%), posterior glottic stenosis (15%), subglottic stenosis (10%), laryngeal edema (10%), LPR (10%) and posterior glottic diastasis (10%) in a cohort of 20 adults with a history of post-COVID-19 intubation.[12] In the same way, Neevel*et al* . reported substantial prevalence of vocal fold motion impairment (50%), early glottic injury (39%), subglottic/tracheal stenosis (22%), and posterior glottic stenosis (17%) in 24 patients who required endotracheal intubation for a severe COVID-19.[13] Rouhani *et al.* showed that 19% of COVID-19 patients with a history of tracheostomy in intensive care unit had vocal fold immobility and subglottic stenosis at 2-month postdischarge.[7] More recently, Felix *et al* . observed laryngotracheal lesions in 40% of patients with a history of post-COVID-19 intubation, including posterior glottic or subglottic stenosis (17%), granuloma (16%) and hypermia of glottis (6%).[14] In the study of Felix *et al* ., 60% of patients had normal laryngeal examination.[14]

Whatever the intubation indication, the laryngeal injuries observed in this study are known to arise after endotracheal intubation. The majority of lesions developed in the posterior laryngeal region, which may be due to the greatest pressure and trauma from the endotracheal tube during prolonged intubation in prone position.[12]The influence of prone position seems to be an important factor according to studies that reported the development of laryngeal injuries only 3 days post-intubation.[15] The mean delay of the development of symptoms (dysphonia, dysphagia or dyspnea) in our patients was 3 months post-intubation, which corroborate the findings of previous studies.[14]

The mechanisms underlying the high prevalence of laryngeal injuries post-COVID-19 intubation remain poorly understood. The COVID-19 infection is associated with endothelial dysfunction, systemic prothrombotic state, microvascular injury, mucosa necrosis, and healing process impairments.[16] In that way, it seems conceivable that the ACE2-related infection of laryngeal cells by the virus may lead to a local inflammatory reaction, which may weaken the laryngeal tissues. However, to date, this hypothesis remains not demonstrated. Moreover, it is unclear if COVID-19 is associated with a higher prevalence of post-intubation laryngeal injuries than other diseases.

The two most prevalent lesions in our study were posterior glottic stenosis and posterior commissure hypertrophy/laryngeal edema. Interestingly, we observed that the duration of intubation was a predictor of the development of posterior glottic stenosis. This observation support the findings of Hillel *et al* . who reported that duration of intubation, ischemia, and diabetes mellitus were significant risk factors for the development of posterior glottic stenosis.[17] Similar studies corroborated the relationship between the duration of intubation and the development of posterior laryngeal lesions.[18,19] An additional potential factor that may increase the laryngeal inflammation is reflux. COVID-19 patients commonly require moderate to high positive end-expiratory pressure,[20] which may increase the stomach pressure and the back flow of gastric content into the laryngopharyngeal cavity. The deposited pepsin into the laryngeal tissue may, therefore, decrease the defense mechanisms of laryngeal mucosa,[21] increasing the risk of injuries and lesions. The posterior commissure hypertrophy and laryngeal diffuse edema are furthermore two prevalent findings associated with LPR.[21] From a pathophysiological standpoint, the development of posterior glottic stenosis is related to ulceration of mucosa and cartilage, inflammation with granulation, and fibrous contraction,[22] which are related to the endotracheal tube pressure. As granulation tissue matures, it may assume the smooth, regular, and round shape of a granuloma,[23] which are moreover found in the present study in 13.8% of patients.

Many comorbidities may be associated with the development of laryngotracheal injuries, including type 2 diabetes mellitus, obesity, hypertension, cardiovascular disease, or smoking.[24] In the present study, we did not observe such association, but our cohort was not statistically powered to detect differences between subgroups of patients. The high prevalence of hypertension, cardiovascular disease and diabetes were just related to the inclusion of severe-to-critical COVID-19 patients in whom these conditions have a critical impact on the infection severity form. Tracheotomy is commonly considered as a relevant factor in the reduction of the occurrence of laryngeal lesions.[25] In our study, the patients who benefited from tracheostomy reported similar proportions of laryngeal injuries than those who had no tracheostomy, which is attributed to the delay between the intubation and the tracheostomy decision (>14 days). Indeed, in our hospital, this delay was due to the greater risk of contaminating health professionals during an early procedure.

The management of laryngeal injuries may involve medical and surgical approaches. Only 16 patients benefited from surgical approaches after medical therapy failure, corresponding to 39% of cases. The high prevalence of posterior commissure hypertrophy, granuloma and diffuse laryngeal edema may explain this high rate of medical therapy success.

The present study has several limitations. The small sample size and the lack of control group evaluating the prevalence of post-intubation laryngeal injuries in patients without COVID-19 history are the most important limitations. Moreover, we did not assess some important ICU outcomes, including the tube size or the lung pressure of mechanical ventilation device, which may have a significant impact on the development of laryngeal injuries. Finally, we did not have sufficient follow-up to determine the mid-to-long term effectiveness of surgical procedures.

Conclusion

Prolonged intubation used in severe COVID-19 patients is associated with significant laryngeal disorders including laryngeal edema, posterior glottic stenosis, granuloma, laryngeal necrosis or vocal fold insufficiency. Patients with a history of >2-week intubation have a higher risk of posterior glottic stenosis, which may be managed medically or surgically. Future studies are needed to determine whether COVID-19 infection is associated with a higher risk of laryngeal injuries than other intubation causes.

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Summary/Key points

-At the start of the pandemic, many COVID-19 patients were intubated more than 14 days in intensive care units.

-A long intubation period (> 14 days) was associated with tardive laryngeal lesions.

-COVID-19 patients who were intubated >14 days mainly reported posterior glottic stenosis, posterior commissure hypertrophy or laryngeal diffuse edema, and granuloma 51.6 days after the hospital discharge.

-A long period of intubation was associated with a high risk of posterior glottic stenosis.

- Prolonged intubation used in severe COVID-19 patients during the pandemic is associated with significant laryngeal disorders.

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Table 1: Epidemiological and clinical features of patients.

	Group 1: <2 w	*Group 1*: >2 w	
	intubation (N=22)	intubation (N=21)	p-value
Mean age (yo)	60.2 ± 11.6	57.9 ± 11.2	NS
Gender			
Male	16 (72.7)	17 (81.0)	NS
Female	6 (27.3)	4 (19.0)	
Comorbidities			
Hypertension	14 (63.6)	16 (76.2)	NS
Type 2 diabetes mellitus	11 (50.0)	9 (42.9)	NS
Dyslipidemia	6 (27.3)	6 (28.6)	NS
Obesity	4 (18.2)	6 (28.6)	NS
Heart failure	1 (4.5)	6 (28.6)	-
Obstructive sleep apnea	1 (4.5)	3 (14.3)	-
Chronic tobacco	8 (36.4)	10 (47.6)	NS
Tobacco (pack-year)	19.3 ± 3.5	15.7 ± 3.5	NS
Intensive Care Unit features			
Intubation duration (days)	9.9 ± 3.7	26.3 ± 6.8	<0.001
Tracheostomy (N, %)	3 (13.6)	5 (23.8)	NS
Laryngology Unit symptoms			
Dysphonia	22 (100)	21 (100)	NS
Dyspnea	5 (22.7)	14 (66.6)	NS
Dysphagia	3 (13.6)	6 (28.5)	NS
Neck pain	1 (4.5)	3 (14.2)	NS

Table 1 footnotes : Abbreviation: NS=non-significant; w=week.

Table 2: Laryngeal disorder findings and treatments.

	Group 1: <2 w	*Group 1*: >2 w	
Outcomes	intubation (N=22)	intubation (N=21)	Total
Laryngeal disorders (N of findings)	N=32	N=26	N=58
Posterior commissure hypertrophy	15 (15.4)	4 (15.4)	19 (32.8)
Isolated posterior commissure hypertrophy	*2 (13.3)*	*0 (0)*	-
Concurrently to another abnormality	*13 (86.7)*	*4 (100)*	-
Posterior glottic stenosis	2 (6.3)	12 (46.2)	14 (24.1)
Unilateral ankylosis	*1 (50)*	*5 (41.7)*	-
Bilateral ankylosis	*1 (50)*	*7 (58.3)*	-
Laryngeal diffuse edema	9 (28.1)	1 (3.8)	10 (17.2)
Granuloma	5 (15.6)	3 (11.5)	8 (13.8)
Laryngeal necrosis	0 (0)	2 (7.7)	2 (3.4)
Normal	1 (3.1)	1 (3.8)	2 (3.4)
Subglottic stenosis	0 (0)	1 (3.8)	1 (1.7)
Posterior glottic flange	1 (3.1)	1 (3.8)	2 (3.4)
Vocal fold atrophy	1 (3.1)	1 (3.8)	2 (3.4)
Treatments (N of procedures)	N=5	N=12	N=17
Granuloma laser excision	4 (80.0)	1 (8.3)	5 (29.4)
Montgomery-type calibration	1 (20.0)	3 (25.0)	4 (23.5)
Posterior glottic stenosis	*1 (100)*	*3 (100)*	-

	Group 1: <2 w	*Group 1*: >2 w	
Laser posterior transverse cordotomy	0 (0)	3 (25.0)	3 (17.6)
Posterior glottic stenosis	-	*3 (100)*	-
Dilatation	0 (0)	3 (25.0)	3 (17.6)
Laryngeal necrosis and fibrosis	-	*1 (33.3)*	-
Severe laryngeal edema and dyspnea	-	*1 (33.3)*	-
Subglottic stenosis	-	*1 (33.3)*	-
Laser flange resection	0 (0)	1 (8.3)	1 (5.9)
Vocal fold fat injection		1 (8.3)	1 (5.9)
Vocal fold atrophy		*1 (100)*	-

Table 2 footnotes : Abbreviations: w=week.

Figure 1: Laryngeal Abnormalities associated with Post-COVID-19 intubation.

Figure 1 footnotes : Laryngeal findings associated with a post-COVID-19 history of intubation included posterior synechia (A), posterior glottic stenosis (B), laryngeal necrosis (C), or granuloma (D).