Research Square

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A Study of Various Risk Factors Affecting Tracheal Wall Microstructure in Intubated Patients

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Abstract

INTRODUCTION:

Trachealstenosis is one of the complications associated with endotracheal intubation. This study aimed to reveal the effects of various risk factors associated with endotracheal intubation on tracheal microstructure.

OBJECTIVE:

To study the effects of various risk factors associated with endotracheal intubation on tracheal microstructure. This includes all intubated patients with various underlying conditions irrespective of the duration of intubation, mainly in anticipation of prolonged intubation.

METHODS:

A prospective study was conducted on 50 critically ill intubated patients. The tracheostomy operation was performed on individual patients who were not intubated for more than 10 days. A part of the anterior tracheal wall was removed and subjected tohistopathological examination (HPE) to assess inflammation, mucosal ulceration, submucosal gland damage, perichondrial changes, cartilage necrosis, squamous metaplasia and fibrosis.

RESULTS:

Significant changes in histopathological findings were found as the duration of intubation increased. Additionally, significant findings in histopathology were found in patients with any of these risk factors, such as diabetesmellitus (DM), organophosphorus poisoning (OPP), steroid use, and gastroesophageal reflux disease (GERD) ($P < 0.05$).

CONCLUSION: This study revealed that various risk factors associated with endotracheal intubation can cause significant changes in tracheal microstructure. More studies with large samples are needed to determine the histopathological changes leading to laryngotracheal stenosis.

INTRODUCTION

Laryngotracheal stenosis (LTS) is a life-threatening condition with fixed, extra thoracic restrictions in pulmonary ventilation[1]. The complexity of the treatment options makes this condition a surgical challenge. The incidence of laryngotracheal stenosis ranges from 0.1 to 30% in prolonged intubated patients[2]. Endotracheal intubation is a procedure that is frequently necessary among severely ill patients and may be performed by less experienced residents. This may be life-saving, but several adverse events have been recognized. These include damage to the larynx and trachea from prolonged endotracheal intubation[3]. The utilization of high-volume and low-pressure cuffed tubes in the ICU remarkably reduces the incidence of postintubation tracheal stenosis[4]. Usually, when the cuff pressure exceeds the mucosal

capillary pressure, the mucosa between the cuffed endotracheal tube and the underlying cartilages develops ischemia within the first few hours of intubation[5]. Factors that predispose patients to tracheal injury include age, female sex, anatomical characteristics, fragility of the upper airway mucosa, gastroesophageal reflux disease, and other risk factors, including the presence of a nasogastric tube[6]. Various studies have been published regarding endotracheal intubation and other factors leading to LTS. Studies on the histopathological evaluation of the trachea after endotracheal intubation are limited. Although endotracheal intubation may cause LTS, its effects on the microstructure of the trachea are not clearly known. This study aimed to reveal the effects of endotracheal intubation and various risk factors associated with endotracheal intubation on tracheal microstructure.

OBJECTIVES

To study the effects of endotracheal intubation and various risk factors associated with endotracheal intubation on tracheal microstructure. This includes all intubated patients with various underlying conditions irrespective of the duration of intubation, mainly in anticipation of prolonged intubation.

MATERIALS AND METHODS

This was a prospective study conducted by the Department of Otorhinolaryngology and Department of Pathology with the approval of the ethics committee of the Karnataka Medical College and Research Institute, Hubballi. (This institute mainly caters to the rural population, which includes dry arid land, with a major occupation being farming. The issue of crop loss due to scarce rain pushes farmers to the verge of attempting suicide with organophosphate poisoning). Informed consent was obtained from all the patient attenders and conscious patients. Fifty individuals (38 men and 12 women) who were intubated for various reasons composed the study group. Patients were included irrespective of their age, and the mean age of the study group participants was 41.50 ± 14.41 years. The lowest and highest ages were 18 and 68 years, respectively. All consecutive eligible intubated patients were included in the study. Patients with a history of previous endotracheal intubation or tracheostomy were excluded from the study. A detailed history was obtained from patient attenders, treating doctors and the nursing team. Important aspects of history include age, sex, primary diagnosis for which intubation was performed, such as OPP with respiratory distress, history of DM, GERD, duration of intubation, size of the endotracheal tube used, cuff pressure and volume, use of Ryle's tube, intubation performed by anaesthetists, physicians or junior residents, whether the patient was conscious during intubation, history of repeated intubation, steroid use during treatment, and hypotensive episodes while on treatment. Endotracheal intubation tubes were taped securely close to the lips. The support arms suspend ventilator tubing to avoid transmission of gravitational forces to the artificial airway. Suctioning was performed as often as necessary with a sterile, gloved technique using various types of disposable plastic catheters. Patients were followed prospectively from the time of endotracheal intubation and were examined daily. Tracheostomy was planned after discussion with the treating physician starting from postintubation day 1 for road traffic accident patients with insecure upper airways to day 10 for those who required long term artificial

ventilation. Tracheotomy was performed with sedation via propofol in the intubated patient, and the strap muscles were separated vertically and retracted laterally via blunt dissection at the midline. The thyroid isthmus was identified and divided between two clamps or retracted; finally, the trachea was visible. The cricoid cartilage and tracheal rings were determined; then, the pretracheal fascia was divided, and the trachea was opened using a No. 11 blade. A part of the anterior tracheal wall was removed and sent for HPE. Posterior tracheal wall sampling was not included because of the possibility of tracheoesophageal fistula secondary to compromised vascularity. The samples were fixed in 10% neutral buffered formalin for 24 h and then processed and embedded in paraffin wax blocks. Four-millimeter-thick serial sections were cut and stained with hematoxylin-eosin. In addition, Masson's trichrome staining was performed on other sections to verify fibrosis in the subepithelial region. The specimens were microscopically examined for specific findings, such as inflammation, mucosal ulceration, the presence of submucosal glands, squamous metaplasia, perichondrial changes, cartilage necrosis, and fibrosis.

RESULTS

The most common cause for which endotracheal intubation indicated was Organophosphorus poisoning (12, 24%).The next most common diagnosis was a road traffic accident (RTA) (9, 18%) and other causes included alcoholic liver disease (3, 6%), snakebite (3, 6%), chronic kidney disease (3,6%), cerebrovascular disease (3,6%), bronchopneumonia (3,6%), tubercular meningitis (2,4%), alcohol withdrawal (2,4%) and 10 other individual causes.

Various risk factors in the study population included comorbidities, events that occurred during the course of the intubated period, and the size of the endotracheal tube used. The distributions of these risk factors are shown in Table 1.

Table 1
Distribution of various risk factors in the study population

Risk factor	Frequency (%)
DM	11 (22)
GERD	13 (26)
OPP	12(24)
Conscious during intubation	34 (68)
Repeated intubation	12 (24)
Difficult intubation	7 (14)
Endotracheal intubation size (mm)	
7	6 (12)
7.5	22 (44)
8	22 (44)
Steroid administered	10 (20)
Hypotension episode	12 (24)

The duration of intubation is an important risk factor for the development of LTS. One RTA patient underwent tracheostomy within a few hours of intubation. Most patients underwent intubation on day 3, and 2 patients underwent intubation on day 10. The details of the duration of intubation are presented in Table 2.

Table 2
Distribution of patients according to the duration of intubation

Duration (days)	Frequency (%)
1	1 (2)
2	4 (8)
3	10 (20)
4	9 (18)
5	7 (14)
6	4 (8)
7	7 (14)
8	4 (8)
9	2 (4)
10	2 (4)

Cuff pressure and volume measurements were the same in all patients, and all the patients had feeding tubes in situ.

The desired findings were analyzed in the post tracheostomy specimen of the anterior tracheal wall, which revealed inflammation on the first day of intubation. On the second day, there was mucosal ulceration and damage to the submucosal glands, which also extended to the third day with perichondrial changes and squamous metaplasia. On the fourth day, necrosis of the cartilage was evident, with the appearance of fibrous tissue, and fibrosis was clearly observed on the sixth day. Figure 1 shows the various findings with respect to the duration of intubation.

A Pearson correlation between the duration of intubation and histopathological findings was performed, which revealed a statistically significant **positive correlation** ($p < 0.05$).

Patients with DM were found to be 6.63 times more at risk of developing mucosal ulceration upon intubation, which was statistically significant ($p < 0.05$). Patients with a history of GERD were significantly more likely to have fibrosis ($p < 0.05$). Patients who were intubated with 8mm endotracheal tubes had 5.85 times more mucosal ulceration than those who were intubated with 7 and 7.5mm endotracheal tubes ($p < 0.05$). Figure 2 shows the distribution of patients according to the size of the endotracheal tube used. Patients with organophosphorus poisoning and steroid use were more likely to have perichondrial changes on histopathological examination ($p < 0.05$).

DISCUSSION

Endotracheal intubation is associated with various complications in the long term. One important and dreadful complication is LTS.

In general, various changes occur to any epithelial surface in response to trauma, as does the trachea mucosa, ranging from mild inflammation to fibrosis. Currently, rather than direct damage to the tracheal wall, various other risk factors are responsible for disturbing the microcirculation of the trachea.

Weymuller Jr reported that inflammation is usually associated with congestion and soft tissue edema within hours of intubation[7]. In addition, long-term ischemia leads to necrosis of the mucosa, which in turn leads to superficial ulcers and deeper ulcers with exposure of the underlying cartilage, followed by partial or complete damage to the tracheal rings with loss of structural integrity of the affected tracheal segment[7]. Moreover, if the tube was in situ for two days or more, most of the patients had marked ulceration at one or more sites. In addition, the ulceration with the cuff begins on the anterior wall and is maximal throughout its course. This is due to the unyielding cartilages that are found in the anterior two-thirds of the tracheal wall. The posterior wall is more yielding and more mobile with no cartilage, and the soft cushion of the esophagus lies posteriorly[8]. Minor or moderate epithelial erosions usually heal by regeneration and re-epithelialization, but if healing is incomplete, the epithelium may be replaced by squamous metaplasia[9]. The creation of an intratracheal zone of the squamous epithelium in the ciliated epithelium can be expected to impair the removal of these secretions from the airways. This, in turn, may significantly increase the frequency and duration of acute and chronic infections[10]. A proliferative phase with re-epithelialization often begins at the same time that secondary infection, perichondritis and further ulceration expose more cartilage. Following cartilage necrosis later in the chronic phase of healing, lymphocytes and macrophages accumulate at the margins and base of the erosions, fibroblasts become active, and scar tissue formation begins[9]. In our study, on the first day of intubation, there was inflammation on the second day, there was mucosal ulceration and damage to the submucosal glands, which extended to the third day, with perichondrial changes and squamous metaplasia. On the fourth day, necrosis of the cartilage was evident, with the appearance of fibrous tissue, and fibrosis was clearly observed on the sixth day. The histopathological findings revealed that the proportion of various above mentioned histopathological changes increased with the duration of intubation and was statistically significant.

The comorbidities may have influenced the duration of intubation indirectly and did not seem to have a direct influence on the presence of tracheal complications[11]. In-addition, one study reported that patients with diabetes mellitus and/or cardiovascular disease may have microvascular occlusion that contributes to the regional ischemia caused by endotracheal tube cuff pressure[9]. In our study, patients with diabetes were found to be nearly 7 times more at risk of developing mucosal ulceration upon intubation, which was statistically significant.

Basoglu A et al noted that fibrosis and epithelial loss were more common in OPP patients than in general trauma patients. The clinical manifestations of OPP generally include muscarinic effects, and in OPP treatment, atropine is used for its antimuscarinic effects. Atropine exerts its antimuscarinic effects via

muscarinic receptors. These effects include diminishing the secretions of the respiratory tract, which can induce tracheal stenosis[12]. In the present study, patients with organophosphorus poisoning had a significantly greater risk of perichondrial changes. We did not find any significant difference in histopathological findings with respect to fibrosis.

It is well-known that if patients receive steroids at large doses, their healing response to the irritative process is reduced. Steroids, because of their effect on wound healing, have been reported to be predisposing factors for the development of tracheal stenosis[8]. Our results also revealed that patients who were on steroids had significantly greater perichondrial changes.

Stiles PJ has also revealed that laryngopharyngeal reflux resulting from spilling over the larynx with gastric acid and pepsin adds to local injury, delays healing, and predisposes patients to infection[8]. The stasis of secretions may be further aggravated by the loss of the mucosal surface, impairment of mucociliary clearance and excessive secretions. Reflux in critically ill patients is common, and anti-reflux therapy should be routine[9]. Our findings also revealed that the incidence of fibrosis was significantly greater among patients with GERD.

El Din MH correlated the tube size and histopathological findings[10]. He reported that patients with a tube size of 6 mm experienced inflammation and erosion of the epithelium. Patients with a tube size of 7 mm exhibited inflammation, erosion of the epithelium, and ulceration, and more severe damage, such as atrophy of the submucosal glands, necrosis of the cartilage, and metaplasia, was observed in patients who were intubated by 7.5mm. Patients who were intubated with a tube size of 8mm had metaplasia, necrosis of the cartilage, and fibrosis. In another work by Rangachari et al, the determination of the tube size of an adult patient was usually based on the physician’s assessment of neck morphology and the external features of the larynx[11].

Excessive inflation of the endotracheal tube cuff results in high pressure on the tracheal wall, thus affecting blood perfusion of the tracheal mucosa and resulting in ischemic necrosis of the tracheal mucosa[13]. The blood supply of the trachea is complex. Tracheal cartilage seems to depend on diffusion from the submucosal capillary plexus on the luminal aspect for nutrition. There was no major capillary plexus on the external surface of the trachea. Thus, intraluminal compression of the tracheal mucosa leaves the underlying cartilage essentially devoid of nutrition and highly susceptible to ischemic necrosis[14].

Generally, when the cuff pressure exceeds the mucosal capillary pressure (30 mm hg), the mucosa between the cuffed tube and the underlying cartilages develops ischemia within the first few hours of intubation. The cuff restricts the flow of blood through the tracheal tissues, thus causing ischemic damage. High-volume, low-pressure cuffs are useful for reducing the incidence of these problems. We found that patients intubated with an endotracheal tube size of 8 mm had 5.85 times more mucosal ulceration than did those intubated with sizes of 7 and 7.5 mm. In our study patients, the standard cuff volume used was 7ml, and the cuff pressure was maintained between 15 and 26 mmHg.

Various studies have revealed many risk factors that can promote the effects of endotracheal tubes on the tracheal wall, such as trauma caused during intubation, the need for reintubation, the presence of infection during intubation[15], multiple intubations, traction and movement of the tube[13], difficult intubation due to abnormal anatomy, and intubation by an unskilled operator[16,9], inadequate patient sedation and less cooperation on the part of the patient, and the level of cognitive function in patients with central nervous system injuries has also recently been shown to be associated with the exacerbation of laryngotracheal injury[11].

In intubated patients, the frequent occurrence of long periods of hypotension associated with compensatory vasoconstriction, which is sometimes enhanced by the use of vasoconstrictor drugs, is of particular importance. In these patients, the circulation to the tracheal mucosa is grossly deficient. They will increase local ischemia[8]. Many factors such as hypotension, Ryle's tube usage, conscious level of the patient, repeated intubation, difficult intubation, cuff pressure and cuff volume, did not significantly influence the magnitude of HPE injury.

CONCLUSION

As the duration of intubation increases, damage to the tracheal microstructure is aggravated in intubated patients. Not only the duration of intubation but also various other factors, such as underlying comorbidities in intubated patients, such as DM, GERD, medical conditions for which intubation is performed, such as OPP, medical treatment like steroid use, and endotracheal tube size are important. More studies with different age groups and larger sample sizes are needed to determine the effects of various risk factors or LTI in intubated patients.

Declarations

Author Contribution

Jijo john and Somanath wrote the main manuscript text and Kadeeja and Raveendra prepared the figures and tables and editing.All authors reviewed the manuscript.

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Figures

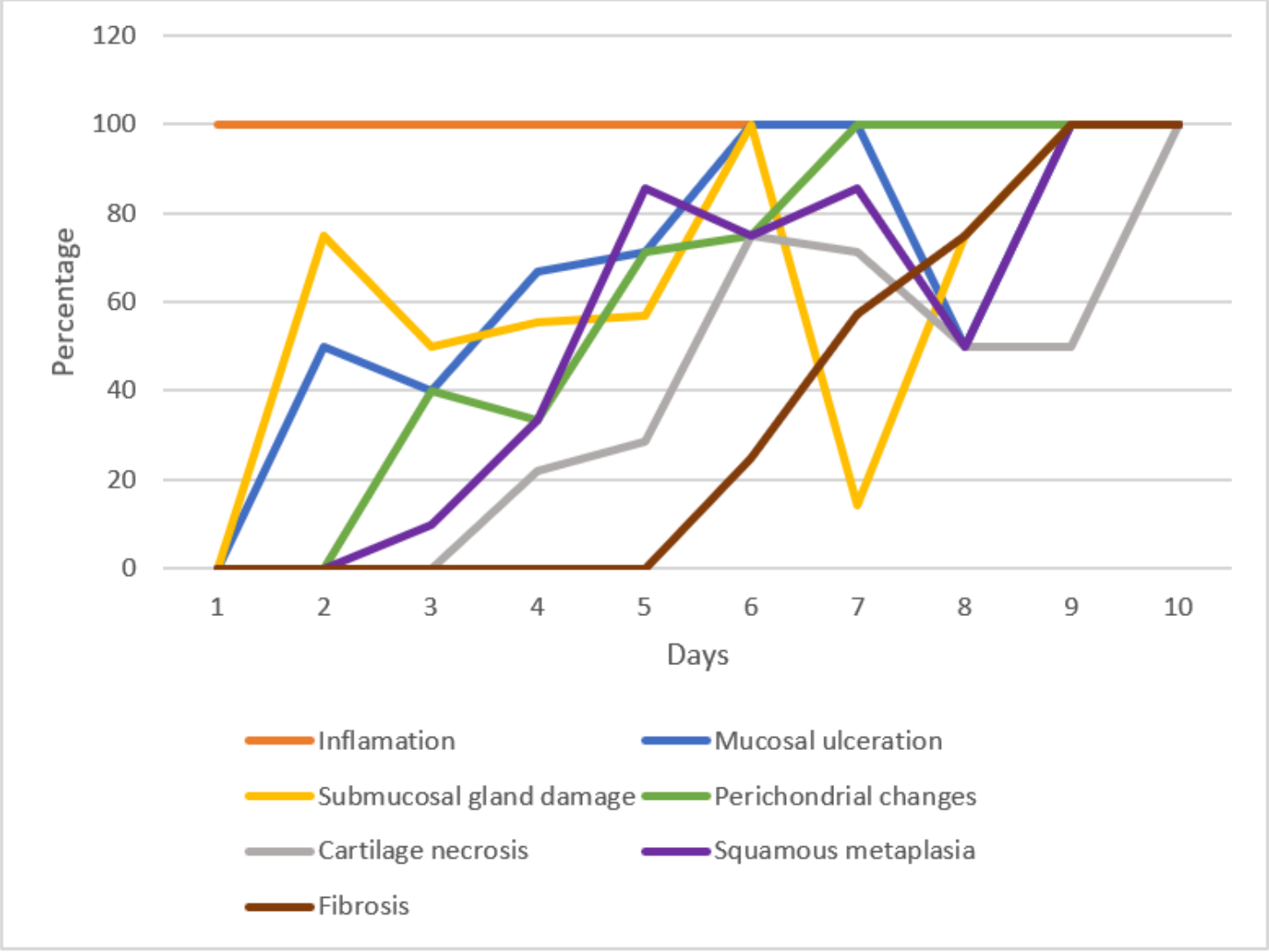


Figure 1

Histological findings based on the duration of intubation

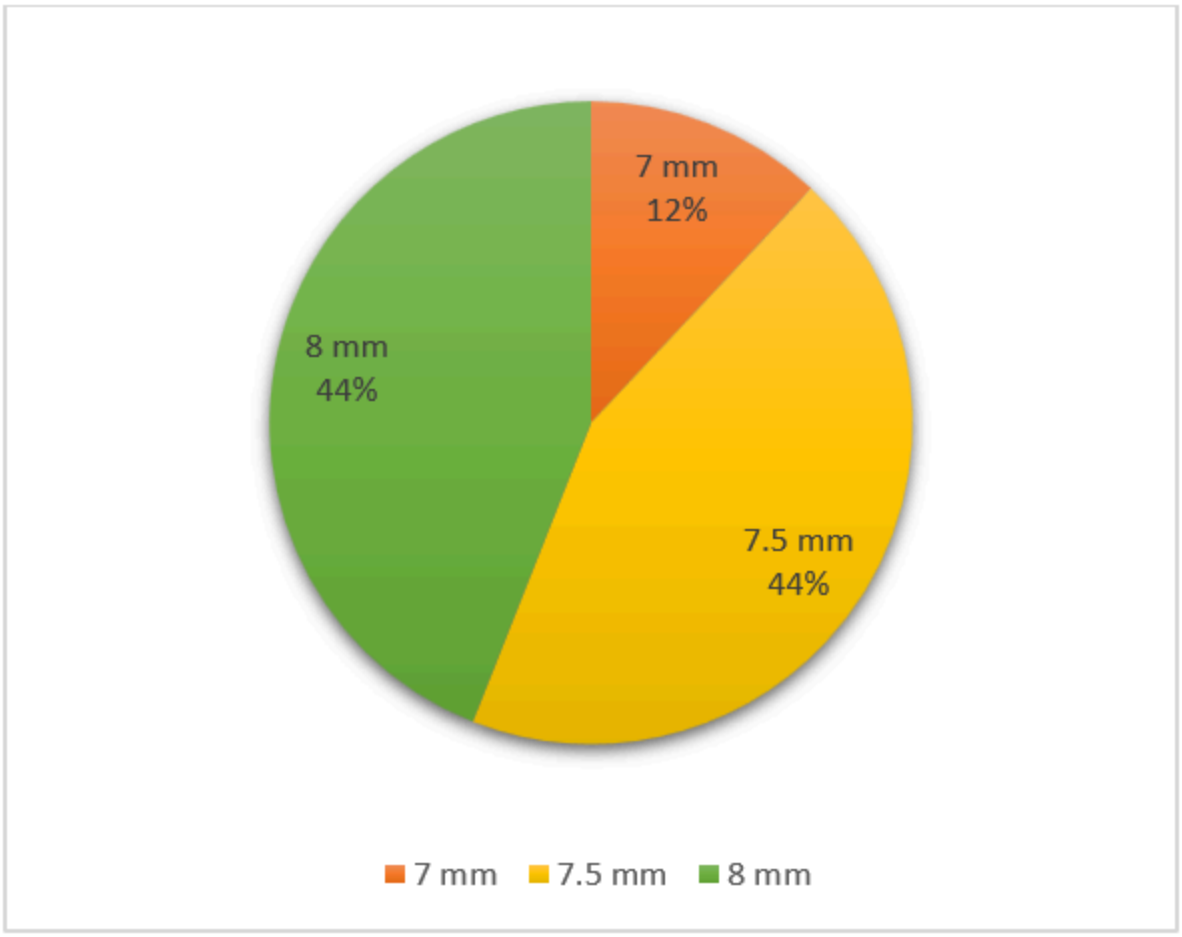


Figure 2

Distribution of patients according to the size of the endotracheal tube