The high risk of postintubation tracheal stenosis in patients intubated for organophosphate poisoning

Organik fosfor zehirlenmesi olan hastalarda yüksek postentübasyon trakeal stenoz riski

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Background: This study aims to reevaluate patients who developed postintubation tracheal stenosis with regard to the primary reason for intubation and therapy.

Methods: Between January 2001 and December 2006, 14 of 230 patients who underwent endotracheal intubation for various reasons in the intensive care unit (ICU) and then developed postintubation tracheal stenosis were analyzed retrospectively. All patients were examined with a neck and chest computed tomography (CT) scan, and tracheal anastomosis was performed. The resected stenotic tracheal rings were evaluated histopathologically.

Results: A total of 201 patients underwent endotracheal intubation due to general trauma (GT), and 29 of these were due to organophosphate poisoning (OPP). Fourteen of these patients developed tracheal stenosis, including nine with OPP and five with GT. The medical therapy and care were generally similar in both groups, except that high doses of atropine and/or pralidoxime were administered to the OPP patients. Diffused chronic active inflammation, fibrosis, and epithelial loss in the resected stenotic tracheal rings were more common in the OPP group than in the GT group.

Conclusion: The primary cause of intubation and the medical therapy employed may have an effect on postintubation tracheal stenosis.

Key words: Intensive care; postintubation; tracheal stenosis; tracheal surgery.

Amaç: Bu çalışmada entübasyon sonrası trakea stenozu gelişen hastalar, entübasyonun birincil nedeni ve tedavisine göre tekrar değerlendirildi.

Çalışma planı: Ocak 2001 - Aralık 206 tarihleri arasında yoğun bakım ünitesinde çeşitli nedenler ile endotrakeal entübasyon uygulanan 230 hasta arasından entübasyon sonrası trakeal stenoz gelişen 14 hasta retrospektif olarak incelendi. Hastaların tümü boyun ve göğüs bilgisayarlı tomografi taraması ile değerlendirildi ve trakeal anastomoz yapıldı. Rezeke edilen stenotik trakeal halkalar, histopatolojik olarak değerlendirildi.

Bulgular: Hastaların toplam 201'ine genel travma (GT), 29'una ise organik fosfor zehirlenmesi (OFZ) nedeni ile endotrakeal entübasyon uygulandı. On dört olguda trakeal stenoz gelişti, bu olguların dokuzu OFZ, beşi GT hastası idi. Organik fosfor zehirlenmesi olan hastalarda yüksek doz atropin veya pralidoksim tedavisi dışında, medikal tedavi ve bakım her iki grupta genel olarak benzer idi. Rezeke edilen stenotik trakeal halkalarda, yaygın kronik aktif inflamasyon, fibrozis ve epitel kaybı OFZ grubunda, GT grubundan daha fazla idi.

Sonuç: Entübasyonun birincil nedeni ve medikal tedavinin, entübasyon sonrası trakeal stenoz gelişimine etkisi olabilir.

Anahtar sözcükler: Yoğun bakım; postentübasyon; trakeal stenoz; trakeal cerrahi.

Although intensive care treatment has improved markedly over the last two decades, the development of tracheal stenosis is still a major problem associated with thoracic surgery and occurs at a rate of 11-16% of patients who have undergone intubation and tracheotomy.[1,2] Tracheal injuries occur frequently due to an improper or intubation, tube irritation, prolonged intubation period, or infection.[1] The primary cause of stenosis is ischemia due to the response of the mucosal membrane to pressure, and ischemia is usually followed by edema, ulceration, and necrosis in the tracheal tissue. In the granulation process of the damaged area, proliferation occurs with subsequent stenosis after the development of fibrous tissue.[2,3] With proper care, this risk can be decreased to 0.46%. [1] In addition to these preconditions, the primary reason for intubation is that it plays an important role in the development of tracheal stenosis. The purpose of this study was to reevaluate patients who had developed tracheal stenosis in their clinical course by focusing on the primary cause of their intubation and/or tracheotomy.

PATIENTS AND METHODS

Patients

From January 2001 to December 2006, 230 patients were followed up for endotracheal intubation due to general trauma (GT) or organophosphate poisoning (OPP) in the intensive care unit (ICU) of Ondokuz Mayıs University Faculty of Medicine Hospital in Samsun, Turkey. Of these 230 patients, 14 with tracheal stenosis were evaluated in this retrospective study. All patients were intubated in the emergency room, and for this procedure, 36-42 Fr polyvinyl chloride tubes were used for men and 32-34 Fr tubes were utilized for women, depending on the patient's body size. In long-term intubations, the cuff pressure was kept within the 28-32 cm H_2O to prevent tracheal damage. The same ICU staff followed up the patients. All 14 patients had previously undergone neck and chest computed tomography (CT) scans, and some had also had a virtual bronchoscopy. These patients were examined preoperatively with rigid bronchoscopes to determine the extent of the stenotic area, length of stenotic segment, and degree of inflammation. A cervical incision, partial sternotomy or right-side lateral thoracotomy was then performed as determined by the location of the stenotic area. The median follow-up period was two years. The causes of the stenosis were retrieved from the patient's files, and the frequency of tracheal stenosis development and histopathological changes which were observed in the resected stenotic trachea of the intubated GT and OPP

patients were compared. Student's t-test was used for the statistical analyses.

Histological assessment

The stenotic tissue segments were 2-5 cm in length and 1-10 mm in diameter. After fixation in 10% neutral buffered formalin for 24 hours, the tracheal segment was cut into serial transverse sections. Each section was embedded in a paraffin block, cut into histological sections 4-6 micrometers thick, and stained with hematoxylin-eosin (H-E) and Masson's trichrome (MT). In most of the stenotic sections stained with MT, the fibrotic area between the tracheal cartilage pericondrium and the superficial epithelium was measured by computer-aided planimetry using a microscope (Zeiss, Axiophot, Germany) with a color video camera system (Insight Diagnostic Instruments Inc., USA) and a morphometric image analysis system (Samba Technologies, France). The average thickness of sections were calculated in micrometers. Additionally, semiquantitative fibrosis was defined according to the following scale: 0= no fibrosis, 1= a few cells stained light green by MT without forming a distinguishable mass, 2= mass formed but with mild fibrosis, 3= moderate fibrosis, and 4= severe fibrosis in large areas with brilliant green as revealed by MT stain.

Types of inflammation were classified as acute, chronic, and active-chronic according to the cell types surrounding the arterioles. Polymorphonuclear leukocytes indicated acute inflammation, lymphocytes + plasmocytes indicated chronic inflammation, and polymorphonuclear leukocytes + plasmocytes + lymphocytes indicated active-chronic inflammation. Under light microscopy at high power (HPx10), the extent of inflammation was deemed to be diffused when the inflammation covered the whole magnified area and was considered to be focal when it was localized in a certain area. Immunohistochemically, CD 34 (mouse monoclonal antibody, Clone QBEnd/10, Lab Vision Corporation, Fremont, California, USA) was used as the primary antibody for the detection of vascularity. On the same areas, the number of capillaries was categorized as <3, 3-10 and >10 for sub-grouping the vascularity. Semiquantitative airway lining epithelial loss was defined according to the following scale: 0= no change; 1= <25% circumference loss; 2= 25-50% circumference loss; 3= 50-75% circumference loss; and 4= >75% circumference loss. The histological analyses were done by the same pathologist in a blinded model.

RESULTS

Of the 230 patients who underwent endotracheal intubation, 201 of these were attributable to GT and 29

Table 1. Patient numbers and postoperative histological scale

	Total number of patients	Tracheal stenosis	%	Inflammation (n)		Epithelial loss (n)	Fibrosis (n)
				DCA	FC	Scale 3-4	Scale 3-4
OPP	29	9	31.03*	8	0	7	8
GT	201	5	2.48*	0	4	1	1

DCA: Diffuse chronic active inflammation; FC: Focal chronic inflammation; OPP: Organophosphate poisoning; GT: General trauma; * p=0.001.

to OPP. Fourteen of the 230 patients developed tracheal stenosis, nine had OPP, and five had GT (Table 1). The probability of developing postintubation tracheal stenosis was statistically higher in the OPP patients than in the GT patients. Except for one, all OPP patients were female with a mean age of 23, and all GT patients were male with a mean age of 35. All 14 patients exhibited stridor and dyspnea.

All of the OPP cases were suicide attempts, and the patients had ingested various chemicals. In general, the GT patients were traffic accident victims. The medical therapy was similar for both groups, except that high doses of atropine (0.5-2 mg/kg/h) and/or pralidoxime (8-10 mg/kg/h) were administered to the OPP patients. In the ICU, the mean intubation period for the OPP patients was 20 days while it was 23 days for the GT patients. Two OPP patients and four GT patients underwent tracheotomies due to long-term intubation or acute respiratory distress. Decannulation could not be achieved in two patients with a preoperative tracheotomy. One female OPP patient could not be extubated and was operated on while intubated. Computed tomography revealed tracheal stenosis in all patients, and four patients underwent a virtual bronchoscopy. A preoperative endoscopic examination was performed on the stenotic area and neighboring tracheal mucosa to determine the extent of inflammation. The stenotic level was at the cricoid cartilage in one patient, first tracheal ring in five patients, second tracheal ring in four patients, third tracheal ring in three patients, and distal trachea in one patient.

Surgical technique

All 14 cases were intubated orotracheally or via the tracheostomy orifice for general anesthesia. Two cases needed preoperative endoscopic dilatation. The operative approaches employed were the following: cervical collar incision (n=11), cervical incision with partial median sternotomy (n=2), and right thoracotomy (n=1). The mean tracheal ring resection number was 6.63 (range 4-10 rings). In addition to postintubation stenosis, there was a separate stenosis area in the tracheotomy site of two patients. These patients required the resection of 8-10 rings.

Extensive mobilization was not required for tracheal resection and reconstruction. Anastomosis was performed on the cricoid cartilage in eight patients and between the tracheal ends in six patients. Resection and reconstruction were done according to the Grillo procedure.[4]

Patients were extubated at the end of surgical procedures. The mean hospitalization period was 15 days. One patient died due to nosocomial infection and terminal sepsis within the first postoperative month. Four patients underwent postoperative endoscopic dilatation due to stenosis in the anastomotic area. Restenosis was observed in patients who had tense anastomosis due to long-segment resection or in patients who necessarily underwent resection at a relatively early period after stenosis. Of the three OPP patients, one needed dilatation twice, one needed it three times, and one needed it six times. A tracheal stent was inserted in a patient who underwent dilatation six times. Pneumothorax occurred in two patients, and both underwent a tube thoracostomy. In the control CT at the sixth postoperative month, no complications were detected, and no problems have been observed since then.

Histopathologically, no statistically significant difference was observed in the inflammation, epithelial loss, or fibrosis between the two groups.

DISCUSSION

A protracted intubation period is the most common cause of tracheal stenosis.[1-3] However, in most patients who have undergone intubation, this does not develop. The general physical condition of the patient, local factors in the trachea, and duration of the intubation period are also responsible.[1] In the literature, four patients in a group of 65 patients underwent tracheal resection due to benign tracheal stenosis, and in another group of 54 patients, a patient who developed tracheal stenosis had to be intubated due to an attempted suicide with an unknown toxic material.[5,6] In other publications, the etiology of stenosis was most commonly reported as a tracheotomy or endotracheal intubation.[1,7] For this

reason, the involvement of OPP in the development of tracheal stenosis could not be established. Although all the patients were intubated under the same clinical conditions in the ICU, tracheal stenosis was more frequent in patients with OPP than in patients with GT. A significant association was found in the tracheal stenosis development between the two groups (p=0.001). Atropine, which is used in OPP therapy, has antimuscarinic effects via muscarinic receptors. These effects include diminishing the secretions of the respiratory tract which can induce tracheal stenosis. Thus, the primary reason for intubation and the resultant medical therapy may have a direct impact on these pathological progresses.

In OPP, symptoms develop because of the accumulation of acetylcholine at synapses.[8-10] Continuous electrical stimulation induced by acetylcholine causes muscarinic, nicotinic, and central nervous system (CNS) symptoms. The muscarinic symptoms include an increase in bronchial secretions, excessive sweating, epiphora, bronchoconstriction, miosis, diarrhea, and bradycardia,[8,10-12] and the nicotinic symptoms include progressive muscle weakness and paralysis. Paralysis of the respiratory muscles or diaphragm can also be observed. Dizziness, tinnitus, ataxia, dysphagia, and respiratory dysfunction are the symptoms of CNS.[8,10-13] Intubation is often inevitable in these patients. The clinical manifestations of OPP generally include muscarinic effects, and in OPP treatment, atropine is used for its antimuscarinic effects. Our clinical experience leads us to believe that the decrease in bronchial secretions induced by atropine can increase the damage due to intubation and contribute to the development of tracheal stenosis.

Organophosphate-based insecticides are widely used in gardens and in agriculture in Turkey. Poisoning with these readily available insecticides, either by accident or through attempted suicide, has been on the rise, and OPP is responsible for up to 40-60% of suicide attempts in African countries and up to 68% of attempts in Turkey due to their uncontrolled sales and widespread use. Because this type of insecticide is so common and so accessible, OPP has become a serious problem, especially in developing countries.[8]

The development of tracheal stenosis in the 31.03% of the patients who were intubated due to OPP in our study emphasizes how serious the situation is. More strikingly, the poisoning occurred mostly due to attempted suicide in our study, with eight out of the nine patients being females. Although no statistical significance could be established due to the small number of samples, in histopathological scale evaluations, there were distinct differences between the two groups (Table 1). While diffused chronic active inflammation was more common in OPP patients, focal chronic inflammation was observed in GT patients. Fibrosis and epithelial loss were more intensive in OPP patients than in GT patients. (Figures 1 and 2) Of the four patients who developed postanostomotic stenosis, three were OPP patients. No differences were observed in neovascularization and ulceration between the groups. We believe that experimental studies and studies with larger numbers of patients are needed to determine the role of medical therapy (including atropine) in the development of tracheal stenosis in OPP patients.

Resection and reconstruction in tracheal stenosis can be performed with reduced morbidity and mortality through precise preoperative assessment of the location

Figure 1. Moderate fibrosis along with lymphocyte and plasma cell infiltration in the submucosa of the stenotic trachea segment (H-E x 100).

Figure 2. Epithelial ulceration, fibrosis, and inflammation of the stenotic trachea segment (H-E x 200).

of the lesion, segmental length, and the general physical condition of the patient. Proper treatment and elimination of the primary etiology should be among the methods employed to prevent tracheal stenosis. Patients with OPP are more susceptible to tracheal stenosis than GT patients, and the increased risks involved in these cases should be considered when choosing appropriate treatment options.

Declaration of conflicting interests

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