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Laryngotracheal Stenosis

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Literature Review

Introduction

Idiopathic subglottic stenosis (ISS) is defined as a narrowing of the airway at the area lying directly below the vocal cords, which is encompassed by the cricoid cartilage (Damrose, 2008). Women have been found to be predominately affected by ISS, with ISS tending to affect women in the range of 20 to 50 years of age (Dedo & Catten, 2001; Poetker et al., 2006, Valdez & Shapshay, 2002). ISS has no identifiable cause, with the diagnosis of ISS made only after other etiologies have been ruled out (Gnagi et al., 2015).

Whereas ISS has no identifiable cause, acquired subglottic stenosis (AS) is related to various etiologies, such as systemic inflammatory conditions, trauma, prolonged intubation, or previous tracheostomy (Gnagi et al., 2015). A remaining important etiology of AS is postintubation subglottic stenosis (PITS) (Keshava, Weingarten, & Grosu, 2013). An increased occurrence of PITS has been found to occur in women, with the prevalence within the age range of 30 to 60 years (Al-Qadi, Artenstein, & Braman, 2013; Chen et al., 2001; Poetker et al., 2006; Zias et al., 2008).

The increased incidence of subglottic stenosis in women has been recognized by an ENT-otolaryngologist at a tertiary care center in central Illinois. Specifically, the ENT-otolaryngologist has noticed the prevalence of PITS more often in perimenopausal/menopausal women. The ENT-otolaryngologist has requested the problem be further investigated, and evidence-based recommendations made.

Aim Statement

The aim of this project is to provide awareness regarding the incidence of PITS, including the heightened incidence in perimenopausal women. The review of literature will review current evidence for understanding subglottic stenosis, identification of factors that potentially aid in the identification of at-risk patients, and preventative measures to ensure good patient outcomes post-intubation. By the Spring 2020, the evidence found in the literature, including recommendations for the care of at-risk populations, will be presented to the anesthesia personnel at the previously mentioned midwestern tertiary care center.

Search Strategy

Databases. Academic Search Complete. CINHAL Plus With Full Text. Cochrane Database of Systemic Reviews. Medline Complete. PubMed. ScienceDirect

Keywords. The primary words searched were subglottic stenosis, laryngotracheal stenosis, idiopathic subglottic stenosis, acquired subglottic stenosis, and post-intubation subglottic stenosis. Secondary words included the words female, women, menopause, and perimenopause. No specific limitations were applied. Variations between the primary words listed and the secondary words were used to reveal roughly over 100 relevant articles. The articles chosen to review were narrowed down based on inclusion of upper airway anatomy and/or physiology, risks factors, and prevention strategies.

Results

Anatomy and physiology of the upper airway.

Structures and functions. The upper airway consists of the nose, mouth, pharynx, larynx, trachea, and main-stem bronchi (Butterworth, Mackey, & Wasnick, 2013). The pharynx stretches from the base of the skull to the point of the cricoid cartilage (Heiner & Gabot, 2014). The pharynx serves as a common passageway for the digestive and respiratory systems

(Sherwood, 2010). The three components of the pharynx include the nasopharynx, oropharynx, and hypopharynx.

Two tubes, the trachea and esophagus, extend from the pharynx. The larynx is located at the entrance of the trachea (Sherwood, 2010). The larynx begins with the epiglottis and ends at the cricoid cartilage. The cartilages and muscles of the larynx function in a complex manner to accomplish the following: protect the lower airway from aspiration, provide patency between the hypopharynx and trachea, provide protection through gag and cough reflexes, and allow for phonation (Heiner & Gabot, 2014).

The trachea arises at the inferior border of the cricoid cartilage and extends to the carina (Heiner & Gabot, 2014). The posterior aspect the trachea is membranous. The anterior aspect consists of cartilaginous rings. At the level of the carina, the trachea divides into the right and left main-stem bronchi (Butterworth, Mackey, & Wasnick, 2013). The bronchi function to warm and humidify inspired air, passing to the alveoli (Heiner & Gabot, 2014).

Blood supply to the larynx and trachea. The larynx blood supply originates from the external carotid, which branches into the superior thyroid artery. The superior thyroid artery gives rise to the superior laryngeal artery, which supplies the supraglottic region of the larynx. A terminal branch of the inferior thyroid artery, the inferior laryngeal artery, supplies blood to the infraglottic region of the larynx (Heiner & Gabot, 2014). The inferior thyroid artery supplies blood to the proximal trachea and esophagus. The lower trachea, carina, and bronchi gain blood supply from branches of the bronchial arteries, which arise directly from the aorta (Tong & D’Amico, 2012).

Knowledge of the blood supply to the larynx and trachea is critical in understanding the pathogenesis of intubation-related injuries. When pressure from an ETT surpasses capillary pressure, the microcirculation in the mucosa and mucoperichondrium is disrupted (Benjamin et al., 2008). Furthermore, tracheal mucosal pressures exerted by the cuffs on ETTs can result in hypoperfusion, with resultant tracheal mucosal damage (Sultan et al., 2011). The implications of the aforementioned factors have on the development of subglottic stenosis will be discussed in greater detail later in the literature review.

Gender differences and sex hormones. Women have narrower airways, shorter tracheas, and a weaker pars membranosa compared to men (Cardillo et al., 2010; Miñambres et al., 2009). The pars membranosa is the membranous portion of the trachea, located posteriorly (Kakodkar, Schroeder, & Holinger, 2012). The average tracheal length in the adult varies from 10 to 15 cm, with men generally having longer tracheas than women (Tong & D'Amico, 2012). The small larynx and trachea in adult women, as well as weakness of the membranous portion of the trachea, may predispose women to intubation-related injuries (Divatia & Bhowmick, 2005).

Respiratory function is known to be influenced by hormones, with phases of the menstrual cycle having a potentially greater impact (Macsali et al., 2013). Sex hormones are believed to have a protective effect on airways and the drive to breathe. Progesterone increases the tone of the upper airway muscles and increases the chemoreceptor response to hypoxia and hypercapnia, thereby stimulating respiration. (LoMauro & Aliverti, 2018).

Estrogen receptors are seen in the larynges of males and females, both in normal and pathological states (Damrose, 2008). Estrogen has been linked to wound healing. One proposed mechanism for wound healing is that estrogen suppresses neutrophil accumulation, thereby increasing levels of fibronectin with subsequent collagen deposition and wound contraction (Valdez & Shapshay, 2002). Another proposed mechanism of estrogen's role in wound healing suggests that estrogen increases transforming growth factor β1 (TGF-β1) from fibroblasts, promoting early extracellular matrix production, which ultimately leads to fibrosis and deposition of collagen types I and III (Ashcroft et al., 1997; Chau et al.,1998). Estrogens, although can lead to effective wound healing, can also trigger a mechanism of hypertrophic scarring (Ashcroft et al., 1997).

The two major subclasses of estrogen receptors, (ERα) and (ERβ), have been found with differing expression within tissues, which may attribute to variances in wound healing between sexes (Hardman et al., 2008). Research has indicated that patients with venous stasis disease, having a specific variant in the ERβ receptor, can be predisposed to tissue ulceration (Ashworth et al., 2005). Other research has concluded an imbalance between ERα, ERβ, and progesterone may lead to inappropriate inflammation, thereby potentially increasing susceptibility to upper airway stenosis. These associated hormonal changes appear to play a role in the grade of stenosis and associated receptor patterns (Fiz et al., 2018). Additionally, these imbalances in estrogens and progesterone occur during menopause (LoMauro & Aliverti, 2018).

Laryngotracheal stenosis.

Laryngotracheal stenosis (LTS) is defined as luminal compromise at the laryngeal, subglottic, or tracheal level, that can lead to life-threatening extra-thoracic limitation in pulmonary ventilation (Gelbard et al., 2015). The most common site of obstruction in patients with LTS is the subglottic larynx, accounting for approximately 50% of all stenoses (McCaffrey, 1992). Subglottic stenosis, a type of lesion associated with postintubation tracheal stenosis (PITS), is a narrowing of the airway that occurs distal to the vocal cords, within the cricoid cartilage, typically as a result of cricothyroidostomy or an oversized endotracheal tube (ETT) (Wain, 2009). Generally, subglottic stenosis is the result of mechanical trauma from endotracheal intubation (Valdez & Shapshay, 2002).

Patients developing subglottic or tracheal stenosis following a tracheostomy, or within two years of intubation are defined as having an iatrogenic etiology of injury (Gelbard et al., 2015). Acquired subglottic stenosis (AS) is another term the author frequently found in the literature that described intubation-related subglottic injuries. Idiopathic subglottic and tracheal stenosis (ISTS) has no identifiable cause and is diagnosed only after other etiologies have been ruled out (Gnagi et al, 2015). Other LTS etiologies include: autoimmune, and polytrauma (traumatic) (Gelbard et al., 2015).

Idiopathic versus iatrogenic stenosis.

Idiopathic stenosis. ISS occurs predominately in women, with a proposed contributing factor being related to estrogen receptors (Dedo & Catten, 2001; Koshkareva, Gaughan, & Soliman, 2007; Valdez & Shapshay, 2002). ISS has an increased incidence of occurring in perimenopausal women, affecting women primarily ages 20 to 50 years of age (Dedo & Catten, 2001; Valdez & Shapshay, 2002). Other proposed mechanisms related to the development of idiopathic subglottic stenosis (ISS) include gastroesophageal reflux (GERD), presence of mycobacterial infections, and an intense episode of coughing (Damrose, 2008; Jindal et al., 1994; Blumin & Johnston, 2011). There appears to be a correlation between female dominance in ISS and extraesophageal reflux (Poetker et al., 2006).

Iatrogenic stenosis. The frequency of LTS as a result of endotracheal intubation ranges from 1 to 11 per cent (Koshkareva, Gaughan, & Soliman, 2007). Pressure-related loss of regional flow leading to necrosis is the fundamental mode of damage leading to post-intubation stenosis (PITS) (Wain, 2009). PITS can occur in the area between the level of the ETT tip up to the subglottic and glottic area (Zias et al., 2008). Cuff over-inflation, inappropriately sized tubes, and sudden movements of the tube are the major mechanisms contributing to injury (Medina et al., 2009). The incidence of PITS appears to be more common in females (Al-Qadi, Artenstein, & Braman, 2013; Hawkins, 1977; Zias et al., 2008; Zubairi et al., 2010). Comorbidities associated with iatrogenic LTS include an increased incidence of GERD, obstructive sleep apnea (OSA), tobacco use, hypertension, and type II diabetes mellitus (DMII) (Gadkaree et al., 2017). The exact contribution of every possible risk factor to the development of airway injury associated with subglottic stenosis is difficult to establish (Poetker et al., 2006). Nonetheless, the fact still remains that women are predominately affected by this tracheal pathology (Dalar et al., 2013).

Misdiagnosis.

The literature has implicated potential misdiagnosis occurring in both idiopathic and iatrogenic cases. Individuals are often incorrectly treated for disorders such as asthma, chronic bronchitis, or respiratory and circulatory insufficiency (Papla et al., 2003). In as many as 44% of patients, PITS is not diagnosed at initial presentation (Spittle & McCluskey, 2000). Symptom onset of LTS after intubation have been found to range between 32 days to three months post-extubation (De, 2008; Sarper et al., 2005).

The etiology of LTS is often difficult to determine because patients present to a wide variety of physicians and are treated several times before going to a specialized surgeon (Lorenz, 2003). Patients present with symptoms of dyspnea on exertion, chronic cough, stridor, hoarseness, and shortness of breath (Gnagi et al., 2015). Diagnosis of PITS is usually not made until the residual tracheal lumen is practically closed (Brichet et al., 1999). Therefore, patients who report a history of intubation, coupled with a history of progressive dyspnea or wheezing unresponsive to bronchodilators, should always be considered as a potential diagnosis of tracheal stenosis (Spittle & McCluskey, 2000).

Furthermore, the pathogenesis behind ISS remains speculative (Valdez & Shapshay, 2002). The following statement, in addition to the abundance of evidence regarding misdiagnosis/delay in diagnosis in both idiopathic and iatrogenic cases of LTS, leads the author to question if a relationship exists between the two defined etiologies. Gnagi et al. (2015) concluded from a 160-participant survey comparing patients' experiences with AS versus ISS, and found no statistically significant differences in symptoms or historical factors between the two.

Cuff over-inflation and endotracheal tube size as causes of LTS.

Cuff over-inflation. An endotracheal tube cuff (ETTc) is meant to ensure adequate ventilation and reduce leakage of inhalation agents as well as air (Liu et al., 2010). When ETTc pressure exceeds the tracheal wall capillary pressure, the microcirculation in the mucosa and mucoperichodrium is interrupted (Benjamin & Holinger, 2008). The mucosa and integrity of the airway wall structure is eventually lost as ischemia and necrosis occurs. The injury resulting from ischemia begins within the first few hours following intubation, and results in a web-like fibrosis within three to six weeks (Wain, 2009). At ETTc pressures exceeding 22 mm Hg tracheal mucosa blood flow begins to decrease, and when the pressure reaches 30 mm Hg tracheal mucosa blood flow decreases markedly (f). Research has indicated that less than one third of anesthesia providers inflate the ETTc within 20 to 40 cm H_20 (Sengupta et al., 2004; Stewart et al., 2003).

ETTc pressure should be regularly measured after endotracheal intubation; however, this is not done in most hospitals (Garcia, Guerrero-Romero, & Rodriguez-Moran, 2001). Most clinicians estimate the ETTc pressure by palpation of the pilot balloon, corresponding with experience level (Liu et al., 2010). In anesthesia practice, ETTc pressure is generally measured through cuff palpation, or through cessation of an audible leak around the cuff (Kahn et al., 2016). Yet, studies have indicated the inability of anesthesiologists, anesthesia residents, and staff of critical care units to accurately determine ETTc pressure by palpation of the pilot balloon (Fernandez et al., 1990; Ganner, 2001).

***Endotracheal tube size*.** The larger the outside diameter of the ETT, the more significant the pressure on the mucosa and cartilage (Benjamin & Holinger, 2008). Although a larger diameter ETT can have an effect on both sexes, research has suggested women are more susceptible to injury. Gelbard et al. (2015) found through a 15-year chart review, conducted at Vanderbilt University, revealed that an iatrogenic cause was the most common etiology for LTS. Of the patients grouped as having an iatrogenic cause, 69% were female. Oversized ETTs, in the smaller female trachea, were concluded as the contributing cause. Frequent use of oversized ETTs is seen with the increased rates of intubation-related complications in women and children (Coordes et al., 2011).

Evidence within the literature has suggested the appropriately sized ETTs related to gender. In a study by Karmakar et al. (2015) the recommended ETT size for men of shorter stature as a 7.0- or 7.5-mm, with an increase in size appropriate for taller men. The recommended ETT size for women was a 6.5 to 7.0mm sized tubes (Karmakar et al. (2015). Based on findings in a prospective cross-section study, Coordes et al. (2011) recommended using a 7.0mm for average-sized women, based on a weight of 72.6 ± 14.8 kg, and 8.0mm for average-sized men, based on a weight of 84.2 ± 14.6 kg. Most researchers concur that ETT size should be chosen based on the anticipated airway diameter and ventilatory needs of the patient, however, consider variability in the size of ETTs used by different providers and institutions (Schiff, 2017). Therefore, there is a need for ETT appropriate size (Schiff, 2017).

Prevention and Recommendations

Post-procedural ETT-related complications can be reduced through proper control of ETTc pressure by a manometer, even in procedures lasting only a few hours (Liu et al., 2010). ETTc pressures are recommended to be maintained between 20 to 30 cm H_20 or less, and the recommended cuff pressure range for the laryngeal mask airway (LMA) is 40 to 60 cm H_20 or less (Ashman, Appel, & Barba, 2017). When the ETTc pressure exceeds 25 cm H_20, reassessments should be conducted regularly in order to identify changes in the minimal occlusive volume (MOV) and allow for subsequent decreases in the ETTc pressure (Sultan et al., 2011).

Women, though having smaller tracheas, are more likely to receive proportionally larger ETTs then men, therefore increasing their risk for stenosis (Schiff, 2017). Several recommendations to determine appropriate ETT size are found in the literature. Butterworth, Mackey, and Wasnick (2013) recommend the internal diameter of the oral endotracheal tube to be between 7.0 mm to 7.5 mm for women. Farrow, Farrow, and Soni (2012) recommended fitting the tracheal tube based on the purpose. They concluded that during anesthesia procedures smaller tubes may be acceptable, whereas if an intensive care unit (ICU) admission is expected then the general rule to use 8.0 mm for women and 9.0 for males is reasonable (Farrow, Farrow, & Soni, 2012).

In recent years, anesthesia providers began placing tubes 1-2mm smaller. This trend was driven by the observation that ventilator pressures were insignificantly impacted during anesthesia. The practice is maintained because of the perceived decrease in sore throat and hoarseness, ease of insertion, and less tracheal damage. However, in the ICU, the ETT is a conduit for airway management by clearing airway secretions and safe passage of fiberoptic bronchoscopy when indicated (Farrow, Farrow, & Soni, 2012).

Studies have found health care personnel tend to increase the ETT size in obese patients (D'Anza, Green, & Knight, 2015; Halum et al., 2012). Zias et al. (2008) found in a retrospective chart review that 66% of the cases of post tracheostomy and PITS were classified as being obese. In another retrospective study, Cavaliere et al., (2007), discuss obesity as being a coexisting condition of 14% of the PITS cases. This study suggests a correlation between the use of larger ETTs in the obese population, as a risk factor for the development of PITS. The research evidence indicates tracheal diameter does not change with weight, but instead the tracheal diameter and size of the ETT should be selected based on height (Schiff, 2017).

Literature also reveals proposed pharmacologic methods for the prevention of subglottic stenosis. Cetin et al. (2012) found through an experimental study on rabbits that early inhibition of cyclooxygenase-2 (COX-2), as evidenced by prostaglandin E2 (PGE2) levels in subglottic mucosa secretions, resulted in reduced stenosis and fibrosis. In a randomized, single-blinded, experimental study on rabbits conducted in New-Zealand, Mitomycin-C in a dose of 0.4 mg/ml showed to have no effect on the prevention of post-extubation subglottic stenosis (Kumar, Ravikuma, & Thanka, 2017).

In a systematic review of literature Hirshoren & Eliashar (2008), concluded that while Mitomycin could be considered as an adjunct to the prevention and treatment of subglottic stenosis, it should still be considered as an unproven treatment. The study recommended the use of antibiotics, steroids, and intensive anti-reflux treatment in the modulation of subglottic stenosis. However, the study concluded that the data was conflicting on the role of the aforementioned medication in the prevention of subglottic stenosis.

Anesthesia providers must conduct a thorough preoperative assessment on every patient under their care, and recognize patients who may be at risk for subglottic stenosis (Rodriguez, 2010). "The risk factors that predispose patients to the development of post-intubation tracheal stenosis include prolonged intubation, traumatic intubation, history of previous intubation or previous tracheostomy, corticosteroid usage, advanced age, female sex, estrogen usage, severe respiratory failure, severe reflux disease, Wegener's granulomatosis, sarcoidosis, obstructive sleep apnea and previous radiation therapy for oropharyngeal and laryngeal cancer" (Kastanos, as cited in Zubairi, 2010, p. 1).

In order to prevent a case of unanticipated subglottic stenosis, the anesthesia provider should be suspicious to any patient presenting with a history of prolonged endotracheal intubation, as it places the patient at risk for subglottic stenosis (Rodriguez, 2010). With the prevalent occurrence of misdiagnosis of subglottic stenosis, the anesthesia provider should be aware of the associated symptoms, and screen for the symptoms during the preoperative assessment. Symptoms of ISS include shortness of breath, dyspnea on exertion, stridor, hoarseness, or chronic cough (Valdez & Shapshay, 2002). However, for the patient to be symptomatic at rest, the airway cross-sectional area must decrease to less than 30% patency (Wain, 2009).

Conclusion

Laryngotracheal stenosis has been linked to several etiologies. Two significant etiologies discussed in the literature include idiopathic and iatrogenic, with post-intubation tracheal stenosis as a form of iatrogenic. Iatrogenic injury from endotracheal tubes (ETTs) and /or tracheostomy tubes remains the most common cause of subglottic stenosis (Gadkaree et al., 2017). Adult women, with ages ranging from 20 to 60 years of age, have been found to be predominately affected by the etiologies defined as idiopathic and iatrogenic (Al-Qadi, Artenstein, & Braman, 2013; Chen et al., 2001; Dedo & Catten, 2001; Poetker et al., 2006; Valdez & Shapshay, 2002; Zias et al., 2008).

The proposed mechanisms contributing to the development of PITS, such as ETTc pressure and ETT size, will aid in outlining recommendations in the prevention, specifically in women. The pharmacological measures for the prevention of subglottic stenosis remains unclear to their effectiveness.

The literature demonstrates health characteristics associated with patients who have developed PITS. The etiology behind ISS appears to be relatively unclear, but predisposing health characteristics, some very similar to PITS, seem to be evident in the literature. Secondary to the misdiagnosed/undiagnosed occurrences in both cases of PITS and ISS, as well ISS being a diagnosis of exclusion, the author sees the benefit of including characteristics associated with both classes of subglottic stenosis the screening tool.

Conceptual Framework

The Stetler Model will be used to guide the proposed project. The Stetler Model can best be described as a prescriptive, practitioner-oriented model (Stetler, 1994). The model is intended to "mitigate some of the human frailties of decision making and thus to facilitate appropriate, effective, and pragmatic utilization; raise the consciousness of potential users; and increase the role of critical thinking in professional practice" (Stetler, 1994, p. 25).

The Stetler model consists of six phases: preparation, validation, comparative evaluation, decision-making, translation/application, and evaluation (Stetler, 1994). The preparation phase began with the identification of the issue by an ENT-otolaryngologist, at the Midwestern tertiary care center for project implementation. The evidenced-based research attained through the review of literature comprises the validation phase. The validation phase identifies research studies that support the project. The validation phase leads to the evaluation phase through reviewing research evidence and translation of the research findings into a teaching module, in the form of a PowerPoint presentation, which will be presented to the facility stakeholders.

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