Systematic Review to Define the Different Surgical and Non-Surgical Lines of Treatment for Reinke's Edema

Systematic Review Submitted for the Partial Fulfillment of the Master's Degree in Phoniatrics

By

Mira Nabil Abdo Saad
M.B., B.Ch.
Faculty of Medicine, Ain Shams University
Resident of Phoniatrics at Manchyet El-Bakry Hospital.

Under supervision of

Professor Dr.\ Aleyia Mahmoud El Shoubary
Professor of Phoniatrics
Phoniatrics Unit, Otorhinolaryngology Department
Faculty of Medicine, Ain Shams University

Professor Dr.\ Sabah Mohamed Hassan
Professor of Phoniatrics
Phoniatrics Unit, Otorhinolaryngology Department
Faculty of Medicine, Ain Shams University

Dr.\ Mona Sameeh Khodeir
Lecturer of Phoniatrics
Phoniatrics Unit, Otorhinolaryngology Department
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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To My Grandmother Soul

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Finally, I would like to dedicate this work to the ***soul of my grandmother***, whom I have missed a lot.

Mira Nabil

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List of Contents

List of Abbreviations

µm	Micrometer
CO_2	Carbon Dioxide
ECM	Extra Cellular matrix
GRBAS	Grade Roughness Breathiness Asthenia Strain
HA	Hyaluronic Acid
HAase	Hyaluronidase
Hz	Hertz
KTP	Potassium Titanyl Phosphate
LP	Lamina Propria
MAPLs	Minimal Associated Pathological Lesions
MPT	Maximum Phonation Time
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized Controlled Trials
SAM	Smith Accent Method
SD	Standard of Deviation
SLP	Superficial Lamina Propria
VFs	Vocal Folds
VHI	Voice Handicap Index

List of Tables

List of Figures

Introduction

Voice is the principal audible function of the vocal folds. It is the act of phonation which makes human speech suitable for audible communication. As the carrier wave for the speech signals, voice is one of the essential functions on which social life is based. Vocal disorders are therefore very conspicuous and distressing. Vocal disturbances are to be expected particularly when the vocal folds are affected. The smallest swelling on the free edge of the vocal fold can induce vocal disturbances with speaking as well as with singing **(Schrotter, 1893).**

In fact, any irregularity in length, width, thickness, specific weight, muscular development, position, insertion, motility and contractility, in short, any asymmetry in the physical properties of the vocal folds will affect the acoustic qualities of the voice. Irregularities can be regarded as primary disorders of the vocal folds or can be secondary to an underlying disease **(Arnold, 1958).** Primary disorders of the vocal folds can be either true neoplasms (malignant or benign) or pseudo-tumors (nodules, polyps, cysts and Reinke's edema) **(Jones et al., 1984)**. True benign tumors of the vocal folds are encountered infrequently **(Painter, 1990).** Many of the benign, non-neoplastic, non-inflammatory lesions of the vocal folds are

the minor associated pathological lesions which are also called "minimal associated pathological lesions" (MAPLs) **(Mossalam et al., 1986)**. According to **Kotby et al. (1989),** the main clinical features of these lesions are dysphonia, phonasthenic manifestations and specific micro-laryngoscopic appearances.

Reinke's edema is one of these MAPLs which are observed as diffuse spindle shaped translucent swelling of both vocal folds along their entire length with intact epithelium and causes varying degrees of dysphonia according to its duration, stage and severity **(Kotby and Barakah, 2016).**

There are several options for treating Reinke's edema that ranges from non-surgical conservative procedures which include voice therapy, steroid injection and hyaluronidase injection to the surgical procedures which includes micro-laryngeal phonosurgery, laser surgery using CO_2 laser, photoangilotic laser and microdebrider.

Aim of this work

The aim is to conduct a systematic review to define the different surgical and non-surgical lines of treatment of Reinke's edema to determine: What interventions are most effective for managing dysphonia associated with Reinke's edema, and how to select the best intervention for the different stages of Reinke's edema.

Anatomy of Reinke's Space

Reinke's space is a part of the vocal folds. It is a potential space between the lines of attachment of the mucosa to the submucosal layer of the vocal folds. This Space was first described by Reinke, in the mid-eighteen nineties, by injecting air and gelatin immediately under the mucosa, was able to create edema in a space. These results were published by Reinke in 1895 and 1897. Reinke emphasized that the subepithelial space of vocal folds, consisting of scattered connective fibrils, was confined on all sides by dense connective tissue which prevented further penetration of fluid **(Reinke, 1895 and 1897)**.

Although, Reinke was the first to describe this space, but he worked on a more superficially located layer than Hajek did in his initial experiments which Hajek reported on in 1891. The clinical entity of edema of the vocal folds had already been recognized by and predecessors like Bichat and Bayle but anatomical justification for accumulation of fluid in that subepithelial space was first found by Reinke **(Hajek, 1891)**.

The experiments of Reinke and Hajek have been repeated and corroborated completely **(Pressman 1956a and 1956b; Kosokovic et al., 1974).** Mayet in 1955 described a lamellar structure in the connective tissue of the conus elasticus where

the lamellas are connected to the basement membrane of the squamous epithelium of the vocal fold. The area between these two lines is consequently not connected directly with the conus elasticus **(Mayet, 1955 and 1961).**

The layer structure varies along the length of the vocal fold. The cover is thickest at the midpoint of the length of the membranous part of the vocal fold, and it becomes thinner towards the anterior and posterior ends. In females, it thickens with age **(Hirano et al., 1989).**

The microscopic picture of the vocal folds:

The vibratory margin of the vocal fold is much more complicated than simply mucosa applied to muscle or ligament. It consists of five layers as follow:

Layers of the vocal folds, (Figure, 1):

1. **The Epithelial Lining**
2. **Lamina Propria (LP):**
    a. Superficial LP (Reinke's Space)
    b. Intermediate LP
    c. Deep LP

    } Vocal Ligament

3. **Muscle** (Thyroarytenoid or Vocalis muscle)

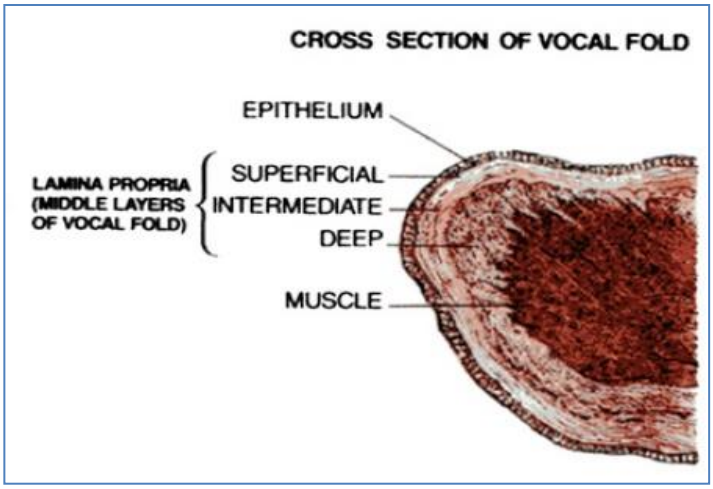

Figure 1: Cross section showing the layered structure of the vocal folds **(Sataloff, 1992).**

Reinke's Space as described by Kosokovic in 1974 is considered the superficial layer of the lamina propria (LP) of the vocal folds **(Figure, 2)** which is known as Reinke's space, is composed of loose areolar tissue and matrix. It contains few fibroblasts. It is like a mass of soft gelatin (very pliable). The anterior border of Reinke's space consists of an elastic membrane in the region of the anterior commissure where loose connective tissue ends, and firm connective tissue begins. The posterior border is the site where the perimysium of the vocal fold firmly adheres to the vocal process of the arytenoid **(Kosokovic et al., 1974).**

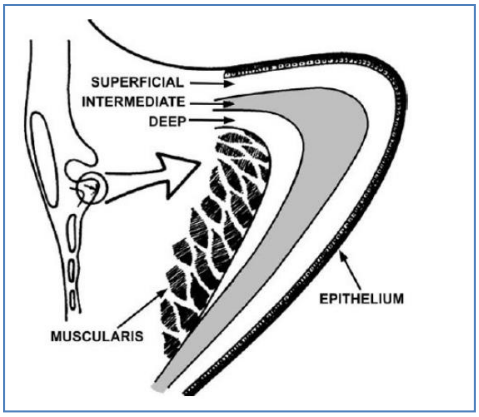

Figure 2: The ultra-structure of the vocal fold **(Nigel, 2008).**

Reinke's space is covered superficially by the epithelial lining of the vocal folds which is a thin lubricated epithelium covering the vocal folds forms the area of contact between the vibrating vocal folds and acts somewhat like a capsule, helping to maintain vocal fold shape. The epithelium lining most of the vocal tract is pseudo-stratified, ciliated, columnar epithelium, typical respiratory epithelium involved in handling mucous secretions. The vibratory margin of the vocal fold is covered with stratified squamous non keratinized epithelium, better suited to with stand the trauma of vocal fold contact. The basement membrane is a multilayered, chemically complex structure. It gives rise to Type VII collagen loops that surround Type III collagen fibers in the superficial layer of the lamina propria. Knowledge of the basement membrane has already been important in changing surgical technique. Additional

research is likely to show its great importance in other matters, such as the ability to heal following trauma, possibly the development of certain kinds of vocal fold pathology, and probably in histopathologic differential diagnosis **(Sataloff et al., 2007).**

Deep to Reinke's space are the intermediate layer of lamina propria, deep layer of the lamina propria and the Vocalis muscle. The intermediate layer of lamina propria contains a higher concentration of elastic fibers. It is like a bundle of soft rubber band (pliable). This layer is thickened at the anterior and posterior ends of the vocal folds known as anterior and posterior macula flava providing protection to the vocal folds from mechanical damage. Although variations along the length of the membranous vocal fold are important in only a few situations, the surgeon should be aware that they exist. Particularly striking variations occur at the anterior and posterior portion of the membranous vocal fold **(Hirano et al., 1989).**

Anteriorly, the intermediate layer of the lamina propria becomes thick, forming an oval mass called the anterior macula flava. This structure is composed of stroma, fibroblasts, and elastic fibers. Anteriorly, it inserts into the anterior commissure tendon, a mass of collagenous fibers that is connected to the thyroid cartilage anteriorly, the anterior macula flava

posteriorly, and the deep layer of the lamina propria laterally. As Hirano has pointed out, this arrangement allows the stiffness to change gradually from the pliable membranous vocal fold to the stiffness of the thyroid cartilage **(Hirano, 1993)**.

Posteriorly, a similar gradual change in stiffness occurs where the intermediate layer of the lamina propria also thickens to form the posterior macula flava, another oval mass. It is structurally like the anterior macula flava. The posterior macula flava attaches to the vocal process of the arytenoid's cartilage through a transitional structure that consists of chondrocytes, fibroblasts, and intermediate cells **(Hirano et al., 1987).**

The Deep layer of the lamina propria is composed primarily of collagenous fibers some of them get inserted into the Vocalis muscle. It is like a bundle of cotton thread (stiff layer) and is rich in fibroblasts. The intermediate and deep layers of the lamina propria constitute the vocal ligament and lie immediately below Reinke's space **(Nigel, 2008)**.

The Vocalis muscle makes up the body of the vocal fold and is one of the intrinsic laryngeal muscles. It forms the main body of the vocal fold and lies lateral and deep. Its fibers run parallel to the direction of the vocal fold. The Vocalis muscle is in fact a portion of thyroarytenoid muscle. When contracted, it is something like a bundle of stiff rubber bands **(Nigel, 2008)**. It