Introduction

Chronic rhinitis is a common condition affecting over 20% of the population. [1]

Since patients with rhinitis form a heterogeneous group, until now there has been no universally accepted definition for the different entities. An attempt to take into consideration the pathophysiological mechanisms classified rhinitis in *allergic*, *infectious* and *other forms*. [2]

Other forms include the idiopathic rhinitis (IR, also referred to as intrinsic, in former times vasomotor rhinitis), a diagnosis of exclusion which has not been as extensively investigated as allergic rhinitis. [3]

Idiopathic rhinitis is a type of non-allergic rhinitis caused by improper functioning of the nasal mucosa. Idiopathic rhinitis has no cytologic evidence of inflammation and is associated with symptoms such as nasal obstruction, rhinorrhea, urge to sneeze and nasal pruritus. According to the World Health Organization (WHO) definition, idiopathic rhinitis is a case of allergic rhinitis (AR) that occurs for more than 4 days per week and lasts for more than 4 consecutive weeks. In many cases, the condition does not respond favorably to existing management protocols and is not mitigated by avoiding allergens. [4]

Various pharmacologic options including intranasal corticosteroids, oral and topical antihistamines, decongestants, intranasal cromolyn, intranasal anticholinergics, and leukotriene receptor antagonists have been widely used for the treatment of chronic rhinitis. (5)

However, few of these conventional methods lead to significant symptom relief for this reason, novel therapeutic methods have to be developed. Botulinum toxin A (BTA) is a neurotoxin with metalloproteinase activity that inhibits the release of acetylcholine from the presynaptic nerve endings at the neuromuscular and neuroglandular junctions. (6)

Botulinum toxin type A (BTA) has been injected in the nasal mucosa in patients with IR and allergic rhinitis to reduce nasal fluids, BTA has been injected in the nasal mucosa of the lower and middle turbinate mucosa for allergic and IR by different authors, resulting in a significant and up to 8 weeks lasting reduction of nasal hypersecretion. (7)

Aim of the Work

Systematic review of the clinical trials, in order to look in to the controversy of efficacy of using botulinum toxin locally in cases of NANIR to improve rhinorrhea and sneezing.

Review of Literature

The external nose and nasal airway are the outer most part in the respiratory system, The growth of a nasal airway is preceded by the formation of an olfactory placode from ectoderm in the 5-mm embryo.[8]

The nasal cavity is divided into two halves by the nasal septum, which grows to separate the nasal cavity in the 19-mm embryo. The three bony shelves-nasal turbinates or conchae-that project from the lateral wall of the nasal cavity develop as outgrowths from the lateral wall between the 7th and 12th weeks of embryonic growth. The paranasal sinuses develop in the embryo as outgrowths from the nasal cavity. The ethmoidal, sphenoidal, maxillary, and frontal sinuses are rudimentary at birth and slowly grow so that they are well developed by the seventh or eighth year of childhood. Slow growth continues until puberty. [9]

The anatomy of the nose is shown in (fig-1 and fig-2). Two separate airways begin at the nostrils (i.e., anterior nares) and are divided by the nasal septum until the posterior nares, where the airways unite and join the nasopharynx. The external nose is formed from bone and cartilage and surrounds the nasal vestibule, which is lined with stratified squamous epithelium and hair. The nasal vestibules are trumpet-shaped orifices; each narrow from approximately 90 mm2 at the nostril to a slit of 30 mm2 that separates the nasal vestibule from the main nasal cavity. [9]

The narrowest point of the nasal airway is at the junction between the nasal vestibule and the main nasal cavity, just anterior to the tip of the inferior turbinate called the nasal valve. (10)

The nasal valve is the narrowest point of the whole airway from nostril to alveoli if the total cross-sectional area at each level of the airway is considered. At the junction of the nasal valve and the main nasal cavity, the cross-sectional area of the airway abruptly expands to about 130 mm^2, and at this point, the airflow bends through almost 90 degrees. The main airflow is directed around the inferior turbinate, with the major airflow traveling close to the floor of the nasal cavity between the inferior turbinate and the nasal septum. With normal nasal breathing, relatively little airflow is directed upward toward the middle and superior turbinates, although sniffing is believed to direct more air toward the olfactory region in the upper part of the nasal cavity.

A coronal section through the nasal cavities (see fig-1 and fig-2) shows that the turbinates occupy much of the nasal cavity. The nasal airway is surrounded by the paranasal sinuses, which consist of the maxillary, frontal, sphenoidal, and ethmoidal sinuses. The anatomy of the paranasal sinuses varies, especially in the ethmoidal region, where many cells join to form the sinuses. The paranasal sinuses communicate with the nasal cavity through small ostia of 2 to 6 mm in diameter, and this restricted access means that there is very slow exchange of air between the sinuses and the nasal cavity. The function of the nasal sinuses has been the source

of much speculation.[11]

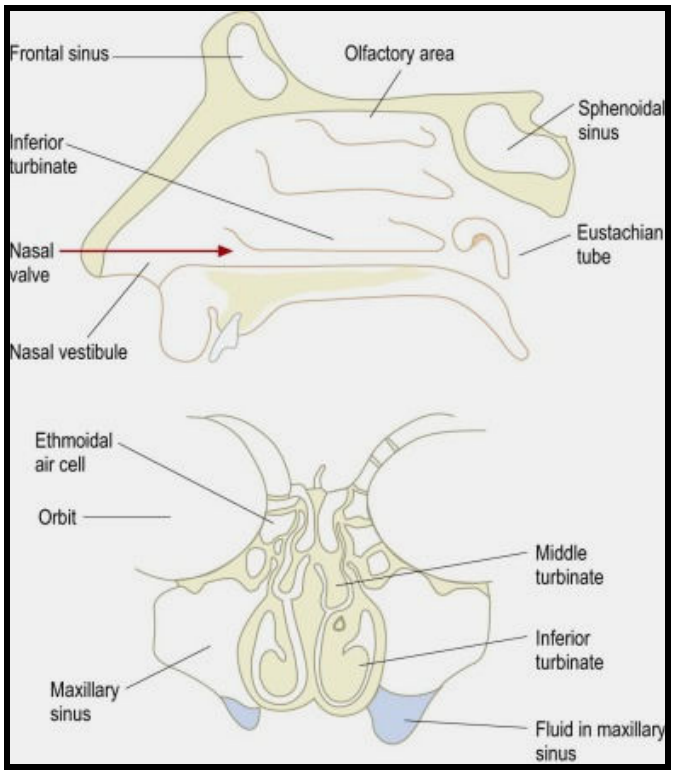

Figure (1): Coronal and sagittal view of the nose.[12]

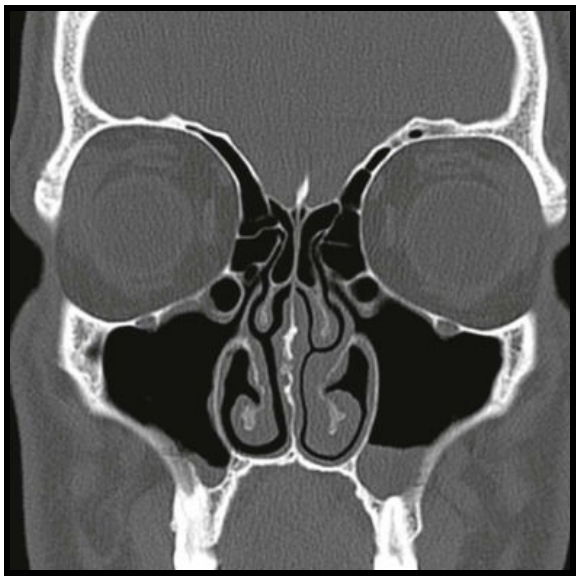

Figure (2): CT scan of paranasal sinus coronal view.[12]

Histology:

The epithelium of the nasal airway comes into direct contact with the inspired air. The physical, chemical, and biologic characteristics of the air have great potential for causing damage and infection. The epithelium of the nose is directly exposed to the external environment, and it acts as an air conditioner and as the first line of defense against toxic and infectious agents in the inspired air. The nose is lined by three distinct types of epithelium: a stratified squamous epithelium in the nasal vestibule and nasopharynx, a pseudostratified ciliated columnar epithelium in the main respiratory area of the nasal cavity, and a specialized olfactory epithelium with ciliated receptor cells in the olfactory area.[13]

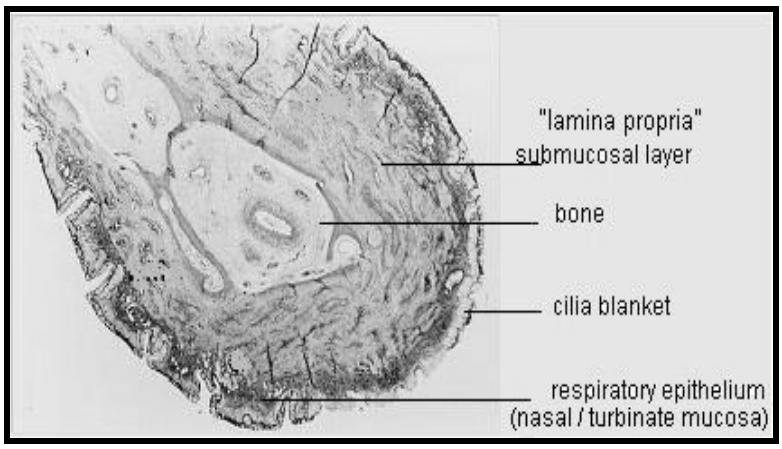

Figure (3): Cut section in Inferior turbinate showing histology. [14]

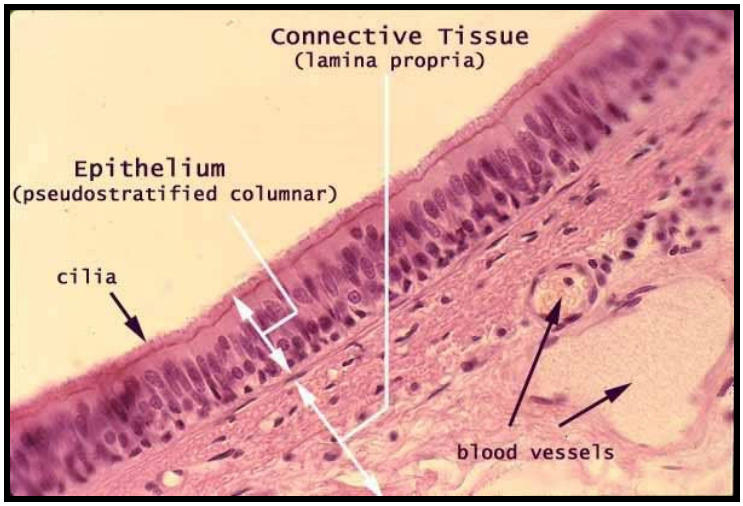

Figure (4): Nasal respiratory epithelium. [14]

Nasal fluid and nasal clearance:

Nasal fluid is a mixture of elements derived from glands, goblet cells, capillary plasma transudate, and cellular debris. The relative contributions of these different elements to the blanket of mucus overlying the nasal epithelium vary among individuals. Nasal fluid acts as an interface between the air we breathe and the delicate epithelium of the nasal cavity. The respiratory epithelium continuously clears secretions through the beating action of cilia, which is an important respiratory defense mechanism. Nasal fluid is derived from four sources in the respiratory area of the nasal cavity. [15]

1. Seromucous glands within the nasal epithelium.
2. Goblet cells distributed along the surface of the nasal epithelium.
3. Exudation of plasma from capillaries and veins within the nasal epithelium.
4. Secretions and cellular debris from leukocytes and epithelial cells.

MICROVASCULAR ANATOMY OF THE NASAL MUCOSA

The lamina propria in the nasal mucosa is rich in blood vessels. They differ from the vasculature in the tracheobronchial tree in three ways. First, there are venous sinusoids in the nose. Second, there are arterio-venous anastomoses in the nose. Third, the nasal vasculature shows cyclical changes of congestion, giving rise to the nasal cycle. *(16)*

Arterioles:

The arterioles are conspicuous by an absence of the internal elastic membrane, so that the endothelial basement membrane is continuous with the basement membrane system of the smooth muscle cell. In addition, porosity of the endothelial basement membrane has been described as a characteristic of nasal blood vessels. As a result of these structural characteristics, the subendothelial musculature of these vessels may be influenced more readily by agents, such as mediator substances, hormones and drugs, circulating in the blood stream, than are blood vessels elsewhere. (17)

Capillaries

The capillaries are either superficially below the surface epithelium or surrounding the glands, capillaries are fenestrated so play important role in evaporation and conditioning of inspired air.(18)

Venous sinusoids:

Large venous cavernous sinusoids, mainly localized to the inferior turbinates, are characteristic of nasal mucous membrane. They are normally found in a semi-contracted condition resulting from sympathetic nerve-mediated smooth muscle tone. The cavernous sinusoids are regarded as specialized vessels adapted to the functional demands of the nasal airway with respect to heating and humidification of inhaled air. When they distend with blood the mucosa will swell and tend to block the airway lumen, in part (normal) or completely (in disease). [17]

Postcapillary venules:

It is through the walls of postcapillary venules that extravasation of plasma takes place during inflammation of the mucosa, by the opening of gaps in the intercellular junctions between the endothelial cells. This will lead to an increase in interstitial liquid volume and pressure, and the latter will tend to force plasma-like liquid through into the lumen as exudate. The humoral mediators that cause extravasation of plasma are many, and include histamine, bradykinin, various prostaglandins, and sensory nerve neuro peptides such as substance P. [16]

***Arterio-venous anastomoses*:**

Blood can bypass the capillary bed via arteriovenous anastomoses. Approximately 60 % of blood flow is shunted through arteriovenous anastomosis and the actual blood flow per

cubic millimeter is greater than muscle, brain or liver.[19]

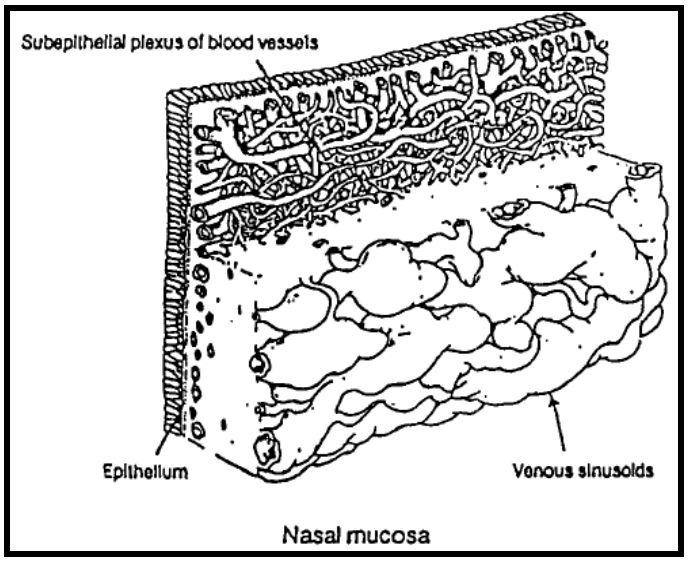

Figure (5): Diagram of the nasal vascular beds. A major obstructive mechanism of the nasal passages in filling of venous sinusoids (sinuses). The epithelium and the subepithelial plexus of micro vessels are actively involved through the plasma exudation process, both in normal mucosal defense and in inflammatory airway diseases, such as rhinitis.[20]

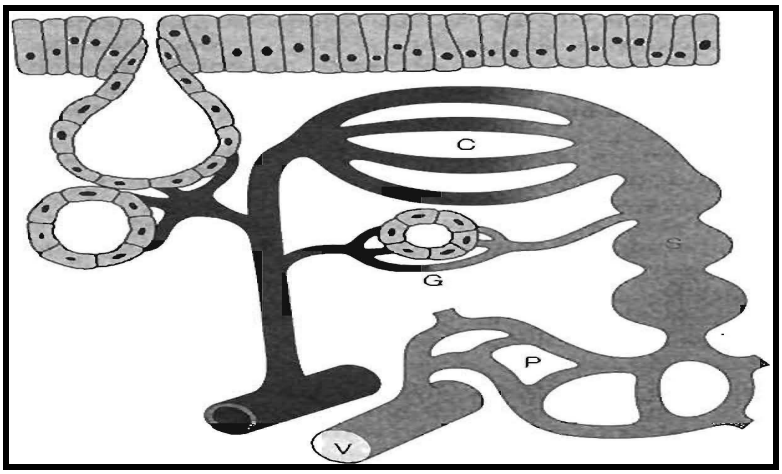

Figure (6): Schematic representation of the blood supply of the turbinates. **A**: arteriole; V: venule; **C**: capillaries; **G**: interstitial glands; P, venous plexus; S, venous sinusoids. [19]

Nervous and autonomic control of nasal mucosa and vascularity:

Nasal mucosa is supplied by sensory, sympathetic and parasympathetic innervations. The olfactory and trigeminal nerves predominantly supply the sensory innervation of the nose. The ophthalmic and maxillary branches of the trigeminal nerve contain sensory nerves from the nasal mucosa and vestibule, and supply the sensations of touch, pain, temperature and itching as well as the appreciation of nasal airflow. *(18)*

These sensory nerves which consist of both myelinated and non-myelinated fibres, and contain non-adrenergic non-cholinergic peptidergic nerves, are also responsive to chemical stimuli and account for the initiation of sneezing and nasal hypersecretion through reflex pathways. The unmyelinated fibres are slow conducting and, in the vast majority, belong to the nociceptor, C-fiber type. Sensory neural responses are conducted centrally on afferent pathways and give rise to the recognition of the sensory neural response as, for example, pain or itch. Sensory C fibres from the trigeminal ganglion contain the tachykinins, substance P (SP), neurokinin A (NKA), as well as calcitonin gene-related peptide (CGRP). In addition, gastrin-releasing peptide has also been identified in the human nasal mucosa, and more recently urocortin, a member of the corticotropin releasing factor (CRF) neuropeptide family. (21)

Immunohistochemical analysis reveals that these neuropeptide containing nerves are present in nerve endings around the sphenopalatine ganglion cells, around blood vessels, and beneath or within the epithelium. Receptors for these neuropeptides are also found in a similar distribution, colocalized to neural ganglia, glands as well as arterial and venous blood vessels. [22]

It is probable that in the normal nose these neuropeptides exert a fine-tuning role in the regulation of glandular secretion and vascular tone. Activation of sensory neurons by irritants and locally released inflammatory mediators induces both vasodilatation and micro-vascular leakage. This is considered to occur through stimulation of local axonal reflexes and modification of ganglionic neurotransmission. [18]

Both parasympathetic and sympathetic nerve fibers supply the efferent neural pathways to the nasal mucosa. The parasympathetic system largely regulates nasal glandular secretion, while sympathetic fibers regulate nasal flow and the state of engorgement of the venous erectile tissue. The primary parasympathetic postganglionic neurotransmitter is acetylcholine which acts on the muscarinic (M) receptors. The sympathetic nerves reach the nasal mucosa via the superior cervical ganglion and are distributed to the nasal blood vessels via the nerves of the pterygoid canal (vidian nerve) and by branches of the trigeminal nerve. The primary neurotransmitter is noradrenaline, this has vasoconstrictor actions through actions on α-adrenergic receptors.[23]

Although the primary sympathetic response is vasoconstriction, it has been suggested from animal models that b1- and b2-adrenergic receptors are also present on the vasculature of the nasal mucosa, and that their stimulation results in vasodilatation of resistance vessels and increase in blood flow. In addition, it has been indicated that b-adrenoreceptors have an influence on glandular activity. [23]

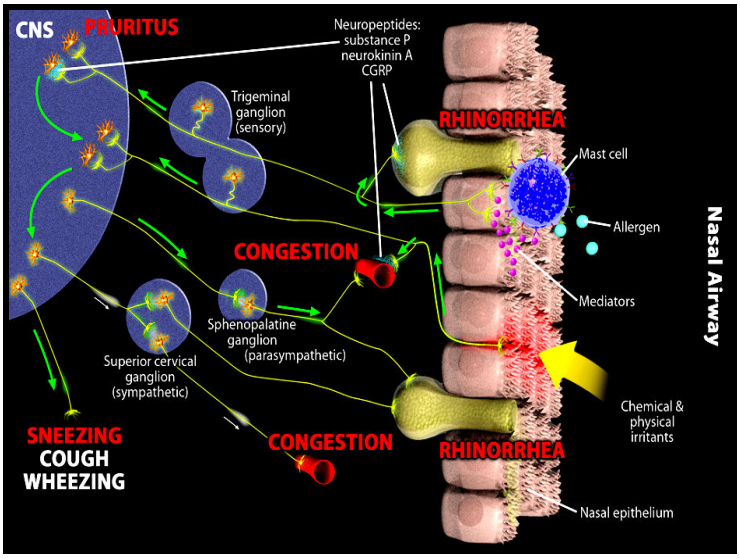

Figure (7): Generation of nasal symptoms through neural pathways. [24]