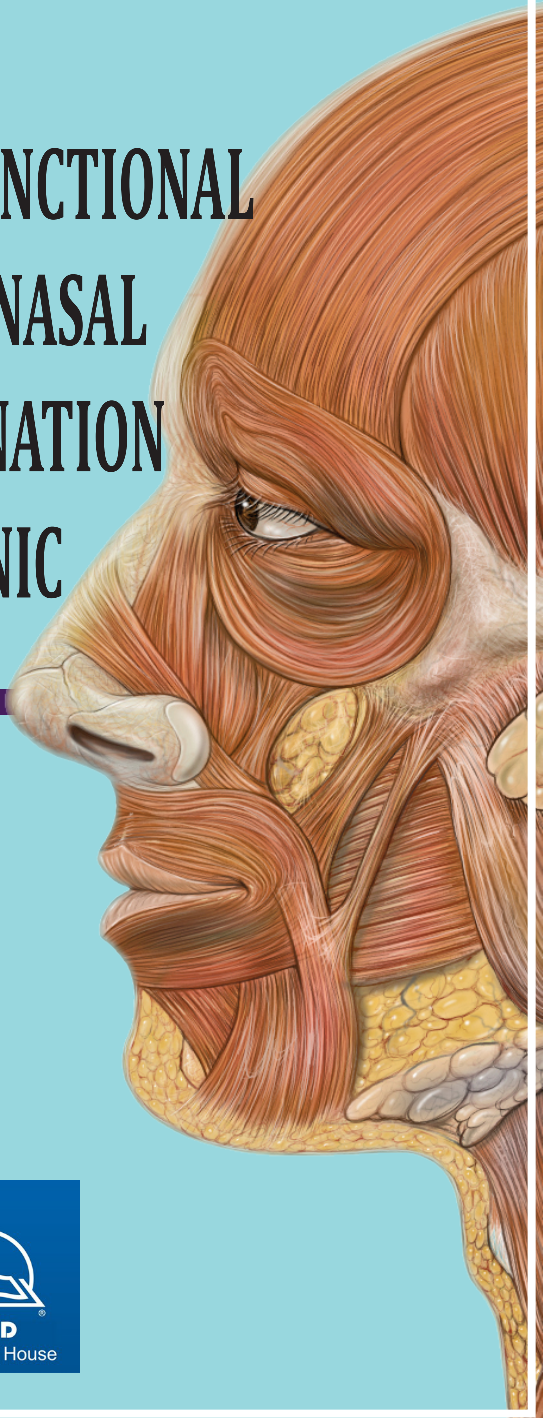
STRUCTURAL AND FUNCTIONAL EVALUATION OF THE NASAL MUCOSA AND EXAMINATION OF PLACE IN THE CLINIC



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Preface

First of all, this book, which we have done, has been made in order to provide better service to the patient and to improve his treatment in line with research and studies. Thus, in the past years, many methods have been introduced and good results have been obtained as a result of post-traumatic complications of the healing of the nasal mucosa. As a result of the advancement of new technologies and medicine, it has been observed that positive results are obtained in the treatments applied to the wounds in the sinus mucosa and nasal mucosa. In addition, by developing new treatment models, it offers a great treatment method in airway epithelial regeneration as a result of treatment, especially as a result of alternative treatment methods such as stem cells and other regenerative medicine models. This study we have done will contribute to patient satisfaction and more positive results, as well as being able to move to a higher level by developing newer technologies.

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Introduction

Nasal cavities are complex anatomical structures with different functions, characterized by high variability among individuals. Its main function is to humidify and warm the inhaled air, to filter and ventilate the paranasal sinuses, but it also has a very important role in smell and speech. The nasal cavity can change the airflow according to the variations in the shape and morphology of the nasus, but these changes are cause significant problems in the lower respiratory tract. In addition disturbances in the nasal airway can also alter other homeostasis balancing systems such as sleep and the circulatory system (1). For this reason, it has gained importance to examine the anatomical differences of the nasal cavities with imaging techniques. In particular, computed tomography and cone-beam computed tomography provided significant support in this regard. Diverse forms of these changes can cause obstruction in the drainage pathways from the paranasal sinuses and sinusitis. That is, changes in the middle turbinate play a role in the pathogenesis of the phlogistic processes of the paranasal sinuses. Moreover, inadequacies in recognizing anatomical differences can cause surgical complications. Identifying and knowing these anatomical structures and their relationships with neighboring structures is important for determining treatment options. Nasal cavity is a bilateral structure located symmetrically of the face, bordered by the hard palate below, the maxillary sinuses and nasal septum and mucosa on the side, and the ethmoid and sphenoid bones cranially. In the sagittal plane, the nasal cavity with the midline septum divides into an oriented bilateral space.

Nasal cavities are needed to moisten and warm the inhaled air. The nose is adjacent to the body of the frontal bone superiorly, the nasal bone and ethmoid bone anteriorly, and the sphenoid bone posteriorly. The process of the maxilla anteriorly and the horizontal plate of the palatine bone posteriorly form the lower part of the nasal cavities. The lateral walls of the nose are formed by the ethmoid, palatine, pterygoid process of the sphenoid bone, the medial surface of the lacrimal and maxillary bones, and the lower nasal concha (2). The structures that form the lateral and upper walls of each nasal cavity in the inferomedial direction are called conchae. The turbinates are usually in three pairs: inferior turbinates (maxillary), middle and superior turbinates (ethmoturbinal). The fourth turbinate, which is rarely observed, is located at the top and is also called the Santorini turbinate. This turbinate is located on the posterior upper part of the nasal lateral wall and on the lateral margin of the sphenoid sinus. The development of the turbinates proceeds through the endochondral ossification of the cartilage progenitors, which can be observed in the eighth week. These structures divide each nasal cavity into pathways to form the nasal passages (Fig. 1). Generally, the lower turbinate is the largest and the upper turbinate is the smallest (3). The inferior nasal passage lies below the inferior nasal concha and is the point where the nasolacrimal duct opens; The middle nasal tract provides drainage of the frontal, anterior ethmoid and maxillary sinuses. The superior nasal passage connects with the posterior ethmoid and sphenoid sinuses through a sphenoid-ethmoid depression located posterior to the superior turbinate, lateral to the nasal septum. The maxillary sinuses connect with the middle nasal passage through the mouth. The middle turbinate is an important turning point for the definition of the anatomical structures in the lateral wall of the nasal cavity, and anatomical and variational knowledge is important in sinus surgery.

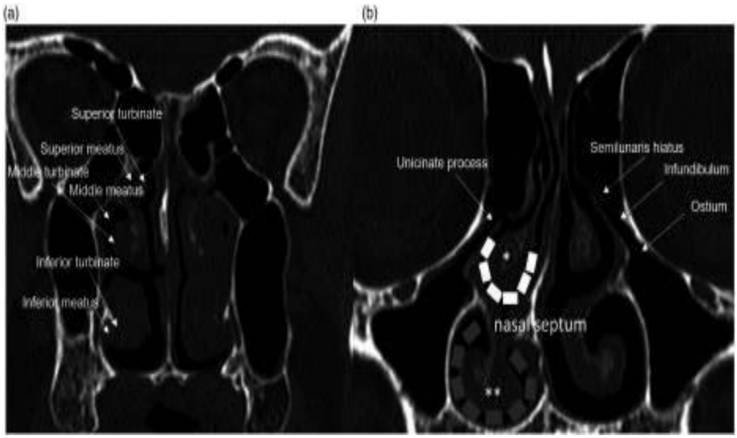

Figure 1. Conchae and meati. (a) Nasal polyposis in the left nasal cavity. Middle and inferior turbinates on the right; inferior meatus partially hypertrophied. (b) White line: middle and gray line inferior meatus; asterisk: middle turbinate; two star: inferior turbinate (4).

While the olfactory mucosa is usually located in the upper turbinate, the middle and lower turbinates are rich in vascular capillaries and are lined by respiratory mucosa with venous sinusoidal structures that warm, humidify and filter the inhaled air. It also changes the airflow resistance. Under the control of the sympathetic nervous system, they are constantly stimulated by environmental factors and endogenous stimuli, as a result they swell and shrink. This process is called the 'nasal cycle'. It is characterized by obstruction of the nasal cavities. Various inflammations, allergies or polluted air cause airway obstruction as a result of swelling of the turbinate tissue in response. During periods of hormonal changes such as pregnancy or premenstrual period, long or temporary obstruction of the turbinate tissues can be observed.

The nasal septa divides the nasal cavities into right and left (Figure 2), consisting of a total of 5 parts as complex bone and cartilage components: rectangular cartilage, vertical plate of ethmoid bone, vomer, nasal crests of maxillary bones and palatine bone. The vomer and ethmoid bone form the bony posterior part of the septum. Nutrition of the nasal cavities is provided by the branches of the internal maxillary artery and the internal carotid artery (5). Nervous stimulation is carried out by the olfactory, ophthalmic and maxillary branches of the trigeminal and facial nerves.

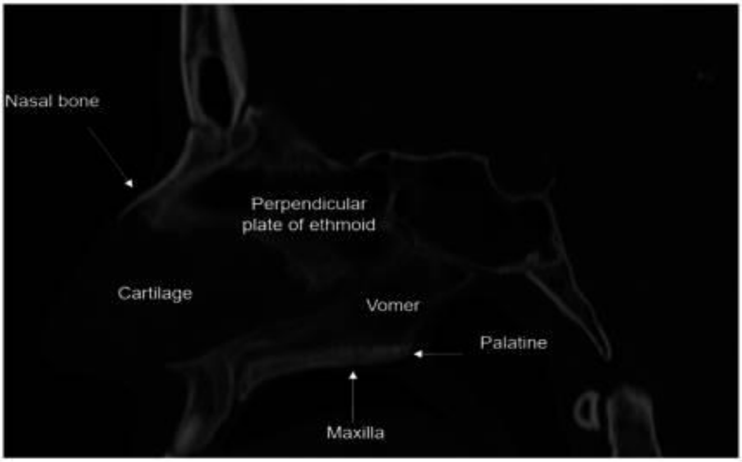

Figure 2. The nasal septum consists of cartilages anteriorly, vomer bone posteriorly, the vertical plate of the ethmoid bone, and the maxillary crest (4).

Nasal septum

The septal contour towards one side of the nasal cavity results in nasal septum deviation (Figure 3), and this can be noticed in more than 50% of patients. It can occur as a right or left-sided or S-shaped curvature. The incidence of this condition varies between 14.1% and 90.4%. Septal deformities are much more common than septal curvature.

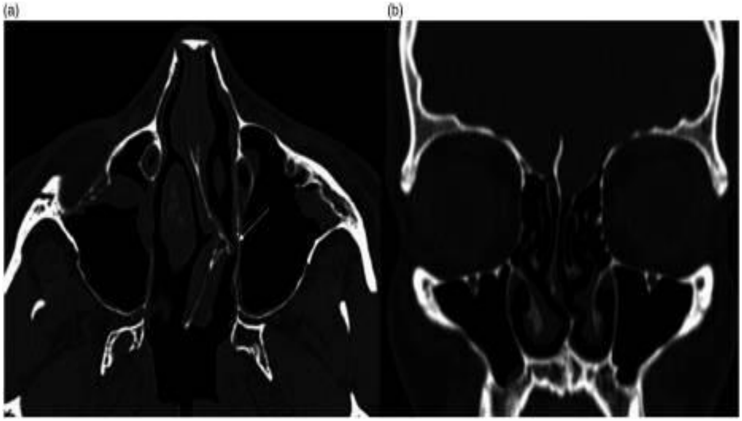

Figure 3. (a) Left-sided septal deviation originating from bone (white arrow) contacting the medial wall of the left maxillary sinus and (b) S-directional septal deviation (4), axial views.

According to the results of maxillary sinus CT scan performed in 594 patients, left-sided deviations were observed more frequently than right-sided deviations (43.9% vs 36.4%). The prevalence of septal deviations defined by the S-curve was 18.5% higher in males. Dorso-ventral deviation was observed in 10.9% of the cases, caudal-rostral deviation was observed in 7.6%. In another study involving 150 patients, 63.3% of cases with nasal septum deviation had conchal abnormalities, concha bullosa being the most common variation (45.3%), followed by paradoxical middle turbinate (8.7%) and pneumatized upper turbinate (9.3%). has been reported. According to the results obtained, the incidence of concha bullosa was found to be higher in patients with nasal septum deviation compared to the current literature (5). Nasal septum deviations may be congenital or due to different traumas, including minor trauma or birth trauma at an early age. Deviations can be mild and asymptomatic. When a deviation is severe, it can identify obstructive symptomatology by re-directing exhaled air through the nasal cavity. In addition, septal deviation may worsen the obstruction or cause hypoplasia of the ipsilateral turbinates by increasing hypertrophy of the contralateral inferior turbinate and middle turbinate bullosa.

Nasal septum pneumatization

Septal pneumatization is one of the rarely observed cases among septal deformations (Figure 4). Its incidence can vary between 0-4%. In some cases, pneumatization may narrow the spheno-ethmoidal recess, restricting access to the sphenoid ostium. Pneumatization of the vertical plate originating from the ethmoid bone has also been reported in cases of nasal septal mucocele.

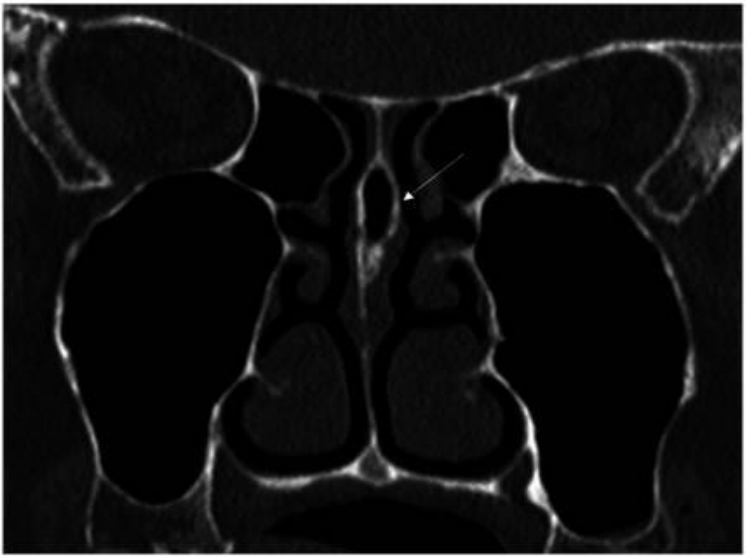

Figure 4. Nasal septum pneumatization (arrow) (4).

Septal spur

Septal spur may be associated with septal deviation without significant side-to-side differences in 34% of septal deviations (Figure 4), or may also occur with a normally aligned septum on the left side, with a frequency of 5.8%, which is more frequently reported. Spurs formed between the septum and the adjacent nasal wall are often due to hypoplasia of the middle turbinate or its relationship with the accessory ostium of the sinuses. In a study conducted with patients whose rhinogenic contact point was sensitive to headache, it was reported that patients with septal spurs had very intense and prolonged pain sensations, and headache frequency. Therefore, it has been suggested that due to the pressure between the mucosal surfaces in the small area of the septal spur, it determines more intense pain sensation than septal deviation and concha bullosa, and this is related to the release of substance P and neuropeptides from the local mucosa.

Concha Bullosa

Concha bullosa results from the pneumatization of the turbinates or the presence of an air cell in the turbinates. Its incidence varies between 14 - 53.6% in the population. Data on the exact mechanism are not clear and it has been reported that the formation of concha bullosa may occur as a result of a deviated septum or compensatory changes that regulate airflow in the individual anatomical structure.

The expression 'middle turbinate turbinate bullosa' refers to the pneumatization of the inferior bullous portion, while the pneumatization is referred to as 'Grunwald cells' or 'lamellar bullae' when there is a vertical lamellar limitation above the osteomeatal unit (Figure 5). Although pneumatization is frequently seen in the lower and upper turbinates, it is most commonly seen in the middle turbinate (Figure 6). There may also be unilateral or bilateral pneumatization. Pneumatized cavities provide passage to the corresponding nasal meatus. In a study conducted in South Korea, it was reported that inferior turbinate bullosa was seen only in males with an incidence of 1%. Moreover, it has been reported that unilateral concha bullosa is often associated with the protrusion of the nasal septum from the turbinate.

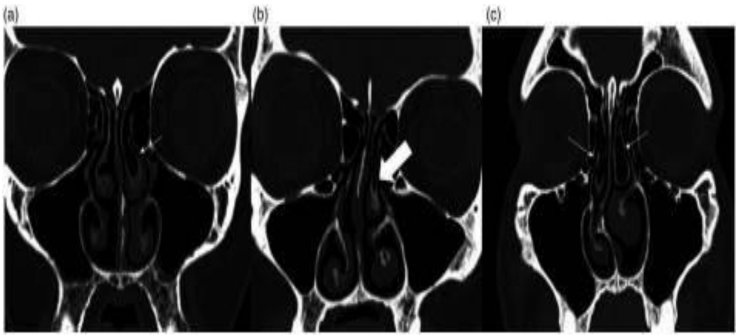

Figure 5. Left middle turbinate variant (a) concha bullosa (thin arrow), pneumatization with inferior bullosa. (b)

Grunwald cell (thick arrow), pneumatization above the vertical coverslip level. (c) Bilateral concha bullosa (arrows) (4).

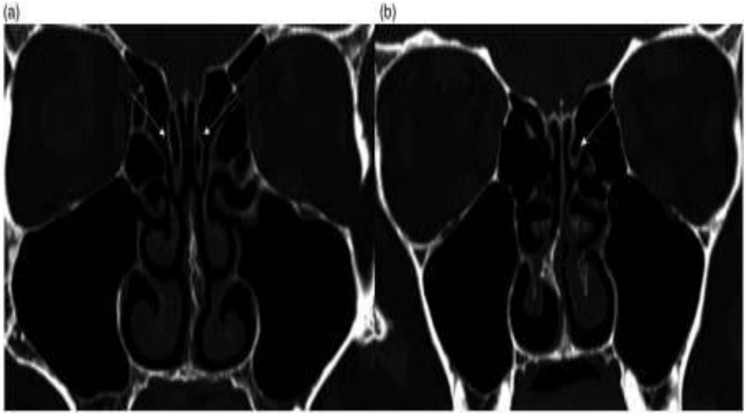

Figure 6. Pneumatization of both (a) superior turbinates and (b) left superior turbinate (white arrows) (4).

Segmentation Analysis

Surgical correction is frequently used to correct nasal obstruction. However, since approximately 1/3 of patients report poor or no improvement in their symptomatology after the operation, new techniques such as computational fluid dynamics (CFD) have been developed to estimate the benefits of the surgical operation. They rely on core segmentation procedures to produce an accurate model based on anatomical variants from CT and magnetic resonance imaging (Figure 7). Segmentation of nasal cavities from imaging datasets is a critical step. The anatomical complexity of these structures and their extensive connection to the ethmoid sinuses and pharynx airway components make segmentation of a single nasal cavity difficult without the manual intervention of an experienced surgeon. Nasal airway segmentation can also be used for surgical operation planning and evaluation of treatment options based on postoperative results.

Figure 7. Segmentation of nasal cavities with a three-dimensional semi-automatic segmentation software (ITK SNAP). (4).

Medially, the nasal septum divides the nasal cavities into two. The nose does not provide air exchange, but also removes particles in the inhaled air and volatile compounds dissolved in water. Thus, a contact area is created that allows only clean and humidified air to enter the lungs (6). The respiratory mucosa cleans, warms or cools the inhaled air and humidifies it to body temperature. In this cleaning process, the epithelium and the glands in the epithelium and deep venous sinusoids play an important role. These functions depend on local mucosal feedback systems, sensory and autonomic reflexes. The first structure that the inhaled air encounters is the vibrissae, which protects the nasal valve. The vibrissae are composed of the nasal septum, the lateral wall of the nostril, and the anterior end of the inferior turbinate. The area of the hole has a cross section from 30 to 40 mm2. From this area, air enters at 12 to 18 m/s in laminar flow, but is rapidly decelerated by turbulent flow of 2 to 3 m/s in the larger cross-sectional areas behind the valve. This change accounts for almost half of the total airflow resistance in the lungs. The deceleration deposits fine particulate material on the nasal mucus and promotes the dissolution of volatile water-soluble chemicals such as formaldehyde (7).

Mucus and Epithelium

The fluid covering the epithelium forms a layer approximately 10 to 15 µm thick. Its low viscosity in the sol phase allows synchronized ciliary movements to be more efficient. Highly viscous, heavily glycosylated acidic acid (with sialic acid and sulfate concentration), and mucins cross-linked by disulfide and their associated proteins form the gel phase of the mucus and coat the surface (8). In general, the mucus content consists of mucin, salt and 95% water. The pH of the mucus fluid varies between 5.5 - 6.5. Submucosal gland secretion and plasma proteins extravasated from the post-capillary venules of the lamina propria provide strong antimicrobial protection (Fiugre 8). Approximately 1-2 L of mucus secretion can be produced per day. The free water evaporates completely to humidify the inhaled dry breathing air. Heat is also lost during evaporation (enthalpy), which is monitored by mucosal cold sensors. The heat loss lost here is directly proportional to the air flow, so the cold sensitive nerve sensors here determine the extent of the airway opening by providing neural output. These sensory data are sent to the brainstem to provide breath-to-breath control of respiratory and inspiratory muscle activity and to play a regulatory role. In the heating and cooling generated by the autoregulation of the vessels in the mucosa and the counter current during inhalation and exhalation, the posterior nasal air temperature is maintained at approximately 30°C and 97% humidity, independent of inspired air temperature and humidity. Cilia provide coordinated collection of mucin. Starting 1-2 cm in front of the nostril, the cilia swing forward on the squamous epithelium lining the nostril, while they sweep backwards on the rest of the nasal mucosa. Pacemarkers in the maxillary sinuses ensure that the ciliary beat is directed upwards against gravity. Cilia make about 1,000 beats per minute and move mucus clumps at a rate of 3-25 mm per minute (9). Approximately 100% of particles larger than 4 µm in diameter are absorbed and swallowed before the posterior nasopharynx. Different epithelial cell populations secrete members of the lipocalin subfamily and proteins such as lipocalin 1, which is also expressed from the palate, lung, upper respiratory, nasal clone (PLUNC). These secretions bind bacterial polysaccharides and other lipids. Secretoglobins also contain Clara cell protein 6. They contain antimicrobial polypeptides, lacrimal proline-rich protein, cystatins and defensins. Regulatory proteins S100A8, eotaxin, interleukin-8 and other cytokines can be expressed in normal mucosa and induced under inflammatory conditions. It has been reported that the expression of lipocalin in murine olfactory epithelium changes as a result of prolonged exposure to octane (10). In contrast, lipocalin is reported to be downregulated by the olfactory binding protein. Goblet cells in the respiratory epithelium secrete mucin 5AC. The toxicity of leukocytes migrating through the epithelium or mucus may modulate cellular secretion and mucus content lining the epithelial surface due to changes in osmolarity and indirect effects of neurotransmitters released by axon response mechanisms.

Post Capillary Venules

In the respiratory epithelium, blood vessels lie beneath the epithelial basement membrane as perforated capillaries and capillaries. Important regions that regulate vascular extravasation are important for the regulation of leukocyte adhesion and diapedesis. There are inflammatory mediator receptors in endothelial cells that trigger local vasodilation and edema. Changes in the mucosa are quite minor and can only be evaluated by microstereometry. Countercurrent condensation of water from the air during exhalation can recover some of the water and energy that moistens the air during inhalation. The processes of neuropeptides on the vascular system are controversial because of their low innervation in the human nasal mucosa. Vascular autoregulation with nitric oxide and hydrogen sulfide (H2S) may play a role in supplying plasma water and proteins to the subepithelial lamina propria region for exudation of epithelial fluid.

Submucosal Glands

It opens into the tubulo-acinar glands through invaginated epithelial canals. Mucosal cells secrete "deleted malignant brain tumor"(11), which is mucin 5B, microsemino-protein-β, and a sialydated scavenger receptor glycoprotein. Mucosal cells are centrally located within the acini and are surrounded by more distant seromucous "demilunes". Serous cells form the transport site of locally synthesized IgA. Plasma cells in the mucosa produce Igα1 and Iga2 heavy chains and κ light chains. IgA heavy chains join by joining J chains to form dimers. The dimers bind to the polymeric immunoglobulin receptor.

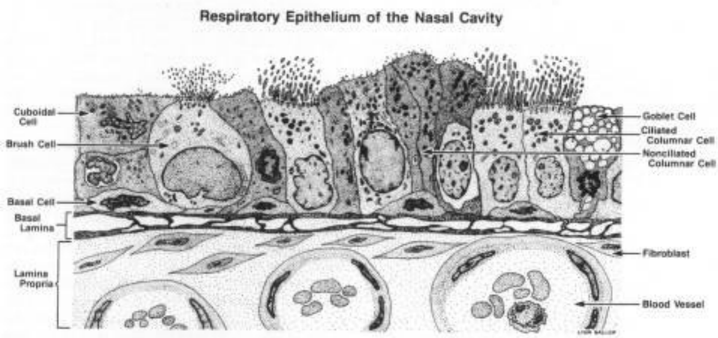

Figure 8. Respiratory Epithelium of the Nasal Cavity (12).

Due to the complex parts involved in the structure of the human nose, there have been variations in the shape and form of the nose. The different variations in muscle, skin and fat and their direct relationship to profile shape are not well established. Individual structural variations have been reported to form dermo-cartilaginous ligaments and lateral cartilages, but still anatomical variations of the nasal profile have not yet been fully documented. Anthropologists make a categorical classification of nose types by identifying some descriptive features and using the shape of the nose details (Figure 9). These nasal classifications include structures that reflect the surface features of the nose, such as the shape of the tip of the nose, the contour of the dorsum or root, and the underlying structures are not associated with this condition. Because variations in anatomical structures must be documented, it is difficult to find the needed anatomical information based on data obtained, especially when performing percent identification. Due to the anatomical complexity of the nose, its role in face recognition is great, and it also has an important feature for both forensic and surgical craniofacial reconstruction. These data add to our knowledge of nasal anatomy, but make no claim to be specific guidelines for nasal reconstruction.

Although the nose appears to be formed by the skull bones when viewed from the outside, it is supported by the soft tissue underneath. In its external profile, it consists of the root of the nose, dorsum, tip and columella, while the lateral wings of the nose consist of holes that join the ala and alar sulcus. These structures are supported by tissues that participate in the underlying nasal structure, such as bone, cartilage and muscle. The nasal skeleton is composed of the main nasal bones and processes of the maxilla. Anteriorly, the nasal spine protrudes from the floor of the nasal cavity medially superiorly to the maxilla and creates its variability in shape and length (13). Moreover, although few bones make up the nasal cavity, only the nasal bones, the maxilla, vomer, and ethmoid bones, support the nasal cartilaginous skeleton. Some small cartilage structures join this bone support structure along with several septql, bilateral alaris and lateral cartilages. The nasal septum supports other cartilage and soft tissues of the nose and strengthens the nasal framework by dividing the nasal cavity into two. The septum is formed by the fusion of the vertical plate of the vomer and ethmoid bone and the septal cartilage. The vomer forms the posterior and lower parts of the nasal septum and articulates with the ethmoid and septal cartilages. Anteriorly, the septal cartilage attaches to the anterior nasal spine below and the lateral cartilages above. The gray lateral cartilages are triangular and thicker where they attach to the anterior septal cartilage. They are continuous with the septal cartilage along the upper border and diverge anteriorly to allow movement during respiration. The lateral cartilages attach to the lower surface of the nasal bones and may also attach to the anterior ridge of the maxilla. However, some consider the lateral cartilages to be wing-like extensions of the septal cartilage. The position and shape of the alar cartilages are affected by the height of the nasal septum, but these cartilages do not attach directly to the maxilla. The unique shape of the medial and lateral shell of the alar cartilage, together with the interdomal fat pad, forms the columella, which forms the nasal tip and outer nostril walls. Between the lateral crura and the frontal process of the maxilla, there are small small alar cartilages in the intercartilaginous region under the lower edge of the upper lateral cartilages (14).

Among the nasal diseases, diseases accompanied by chronic inflammation and infection, such as rhinosinusitis, can significantly reduce the patient's quality of life. Rhinosinusitis is a very common disease affecting approximately 5-15% of the population. Antibiotics, nasal douches, steroids and nasal sprays are preferred to the patients in order to eliminate the infection, which are among the medical and alternative treatment options, to eliminate the inflammatory factors and to increase the regeneration and to return the mucosa to the normal respiratory epithelium. Another proven treatment is the successful use of endoscopic sinus surgery if conservative treatment fails in chronic rhinosinusitis and nasal polyposis.

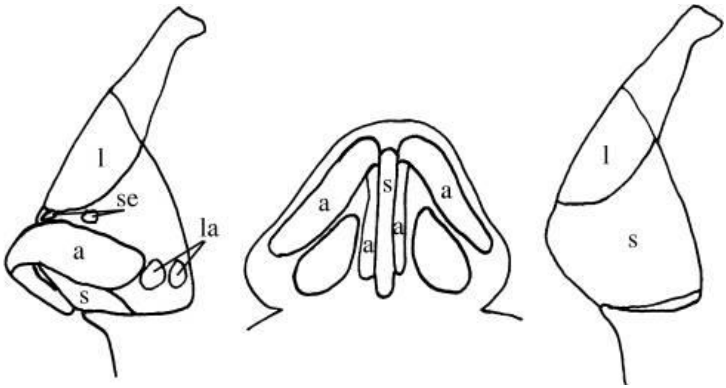

Figure 9. The cartilages that make up the nasal skeleton are septal cartilage (s), bilateral alar (a) and lateral cartilage (l), and smaller alar (la) and sesamoid cartilage (se) (15).

Nasal diseases, especially chronic inflammatory and infectious diseases led by rhinosinusitis, can significantly reduce the patient's quality of life. Rhinosinusitis is a common nasal disease that is common in approximately 15% of the population. Antibiotics, steroids, nasal sprays, and douches are often prescribed in treatments to administer to patients to eradicate infection, inhibit mechanisms that trigger inflammation, and revert the impaired nasal mucosa to normal, functional epithelium. Endoscopic sinus surgery is one of the preferred treatment options after cases where conservative treatment of nasal polyposis and chronic rhinosinusitis has failed (16). However, damage to the mucosa after surgical operations is an inevitable outcome, and these damages can result in very serious complications, especially in the frontal recesses, where they cause synechia, fibrosis, and adhesions. This may be due to a variety of factors that may result in mucosal metaplasia due to chronic inflammation or secondary injury from surgery that may compromise the regeneration of healthy tissues remaining. It has aroused interest in understanding the mechanisms of postoperative wound healing of the nasal mucosa with endoscopic sinus surgery in the otolaryngology clinic. What is known to date on wound healing is that it only concerns the repair of injured skin or cornea. Little is known about the basics of the physiological healing process of the nasal mucosa and wound healing (17). The scientific literature on healing of the nasal mucosa has been reviewed and discussed for the past ten years. In these studies, the basic mechanisms that play a role in nasal mucosa physiology and wound healing after nasal surgical treatment and the latest updates in treatment are presented.

Mucosal Regeneration

Nasal epithelial tissue consists of a pseudostratified columnar cell layer, which is the diffuse respiratory epithelium that is separated from the lamina propria by the basement membrane underneath. The different types of cells contained in the epithelium include: basal, goblet, ciliary and non-ciliary columnar cells. Healthy nasal mucosa ensures mucus production and transport by nasal epithelial cells, absorption of surface fluid, homeostasis, and immune responses compatible with the underlying circulatory system elements (17). Nasal mucosal injuries can occur after radiotherapy or surgery and as a result of chronic rhinosinusitis. Wound healing in the nasal mucosa following endoscopic sinus surgery consists of four distinct clinical stages of the healing process. Respectively, the surgical cavity must be cleaned immediately, mucosal passage is achieved, and tissue remodeling with complete epithelialization. In vivo nasal injury models using experimental animals such as rabbits and rats showed that wound healing in the nasal mucosa was physiologically related to the observed phases of hemostasis, inflammation, proliferation, and tissue remodeling (18).

Injury of the nasal mucosa causes severe bleeding. Therefore, the first thing to do in wound healing is to close the leakage that causes bleeding by activating the coagulation cascade and forming fibrin plugs. The first two weeks immediately after the surgery are very important. Because the blood accumulating in the nasal cavity can cause crusting. Approximately two weeks after the operation, the operative cavity is determined and the next healing phase is started. In the rabbit and rat model, crusting formation, which is similar to the morphology of nasal wounds, can be observed. After the homeostasis phase, the inflammatory phase occurs. The main purpose of this phase is to clear the infection in the wound area. In humans, a mucosal change is experienced 3-10 weeks after nasal surgery in response to removal of the mucosa. These changes may include fibrous hyperplasia causing fibrotic adhesions, edema of the mucosa, formation of vesicle and granulation tissue in epithelial cells, and mini-polyps. These changes are then suggested, leading to the nasal mucosa epithelialization. Experimentally, subepithelial edema and leukocyte infiltration were examined two days after injury in rats and three weeks after injury in rabbits (17). The proliferation phase follows the clearance of pathogenic material and dead immune-associated cells. Clearance of mucosal changes in humans is followed by epithelialization, which occurs after approximately 11-14 weeks. Increased subepithelial fibrosis and increased epithelial thickness were noted in rats, especially the day after the operation, while epithelial thickness in rabbits was reported to occur and peak four weeks after injury.

The final stage in wound healing is ensuring tissue integrity and remodeling of the epithelium. In this phase, in which the regeneration of the epithelial cells in the nasal mucosa is completed, the epithelial cells are completed with their differentiation into goblet and ciliated cells. Although this process takes some time in humans, changes in the nasal mucosa can be noticed approximately six months after the surgery. This situation was observed in experimental rat and rabbit models, where the differentiation of goblet cells and ciliary cells in the epithelium began on the 14th day and almost returned to normal on the 28th day. In a rabbit model, the number of ciliary cells has been reported to peak at week 5 after injury.

Endoscopic Sinus Surgery (ESS) and Postoperative Complications

ESS is a treatment method with low morbidity and high success rate in the treatment of chronic sinus diseases. The aim in ESS is to eliminate the existing pathology while preserving the normal anatomy and physiology as much as possible. While performing ESS, normal or reversible mucosa should be preserved as much as possible, and mucosal excision should be limited only to the severely diseased or non-recoverable mucosa at key points (18).

There are difficulties in the evaluation and comparison of surgical results in patients undergoing ESS. Various classifications have been made for these evaluations in the literature. But for today, the most valid method for evaluating the results of ESS; patients are asymptomatic postoperatively and their subjective complaints resolve. Success rates in ESS vary according to the presence/absence of anatomical variation, hyperplastic mucosa, suppuration, polypoid structures, and Acetylsalicylic acid triad. Success rates of ESS are reported to be between 80-95% in the literature. Presence of nasal polyposis is one of the factors that negatively affect the success results. The recurrence of nasal polyps in a short period of 3 years reduces the long-term success rates in patients with nasal polyposis. The recurrence rate of nasal polyps is reported to be 32% in the literature. Therefore, the success rate of ESS in patients with nasal polyps is lower than the success rate in chronic sinusitis (19, 20).

Intracerebral hemorrhage, cerebrospinal fluid CSF fistula, orbital hematoma, blindness, diplopia, severe hemorrhage, carotid artery injury, central nervous system defect, meningitis and brain abscess are the major complications of ESS. Among the minor complications, conditions such as synechia, lamina papyracea perforation, periorbital edema and ecchymosis, subcutaneous emphysema, epistaxis, subconjunctival hemorrhage, ostium stenosis and anosmia have been reported. Major complications are between 0-1% and minor complications are between 8-14% in the literature; the mean complication rate has been reported as 2-11% (21). Osteitis is bone thickening that occurs with inflammation. Damaged mucosa can also affect the viability of the bones that make up the nasal cavity. If chronicity occurs, the weakened vitality can eventually turn into osteoarthritis, which leads to thickening of the bone tissue. Strategies for treatment after osteitis, known as bone thickening, are few and unknown (22). Therefore, the importance of the management of recovery in post-operative nasal injuries has increased. Controlling post-operative bleeding, eliminating and preventing adhesions, accelerating the healing process. With the introduction of ESS into the routines of Otolaryngology, it has been possible to eliminate the pathological event or process by preserving the normal anatomy and physiology at the maximum level in most sinus diseases. Due to its high level of success and low morbidity rate in the treatment of patients with chronic or recurrent sinusitis, ESS is considered as the main surgical method.

Nasal Wound Healing

Numerous topical interventions and dressings are used to facilitate the healing of wounds in the nasal mucosa after invasive sinus surgery. The purpose of these interventions is primarily to prevent infection and reduce the occurrence of chronic inflammation, and intravenous antibiotics or steroids, nasal douches and nasal packings are used. Thus, an environment that will accelerate the healing process of the nasal mucosa is created and healing takes place.

Medical treatment

Systemic medications consist of steroids and antibiotics, which are used to reduce inflammation and infection that inhibit and stop wound healing following sinus surgery. They are usually administered orally or intravenously for postoperative management (23). Among the most commonly used corticosteroids are betamethasone and prednisolone. Controversy exists regarding preoperative systemic steroid use in ESS. However, recent systematic reviews and meta-analyses have revealed that steroids administered postoperatively may be associated with improvement and reduce the risk of recurrence, especially in patients with chronic rhinosinusitis with nasal polyposis. According to the results of Jorrisen and Bachert's research, it has been reported that the use of topical mometasone furoate sprays for 6 months after oral administration of 2 mg/kg of betamethasone daily for 7 days reduces the risk of sinusitis and accelerates postoperative recovery. In addition, it has been shown that oral administration of 30 mg/kg prednisone for 9 days postoperatively resulted in healthier sinus cavities (24). Wound recurrence was observed in a significant majority of harvests, even in the immediate post-operative period, although steroids were demonstrated in the majority of patients for wound healing and prevention of relapse. Moreover, it has been observed that long-term use of systemic steroids can lead to numerous side effects. Few studies have supported the use of antibiotics in patients after ESS. According to the results of three-week treatment with amoxicillin and clavulanate potassium, there was no significant difference in symptoms and endoscopic scores compared to the control. In another similar study, a randomized, double-blind controlled study with 250 mg oral amoxicillin for 4 weeks found no difference in improvement. In another follow-up study, they reported that a two-week course of amoxicillin and clavulanate improved nasal congestion and drainage only on the fifth day and improved endoscopic scores on the 12th day compared to other symptoms (25). Due to the emergence of bacterial resistance to the macrolide, the risks outweigh the benefits and it is recommended to reduce antibiotic use.

Nasal spray

Nasal spray is a method of delivering drugs, especially steroids, into the nasal cavities using an aerosol bottle. The main purpose of using nasal spray is to modulate the inflammatory phase that prevents wound healing after surgery. It is considered among the standard medical treatments for sinusitis not to recur after surgical operations. Beclomethasone dipropionate, the first aerosol corticosteroid, has been used topically in clinical practice since the 70s. There are many aerosol steroids available, including its preparations prednisolone acetate, mometasone furoate, triamcinolone acetonide, and fluticasone propionate. Meanwhile, different types of intranasal steroid sprays have been reported to have therapeutic efficacy after ESS. Two types of intranasal steroid sprays (fluticasone and budesonide) reported to reduce the incidence of polyposis in patients with chronic rhinosinusitis after ESS have been identified in clinical studies. Budesonide has been observed to be superior to fluticasone. The application of antibiotics and antifungals in topical nasal sprays has been accepted as the cornerstone of postoperative management after ESS. This is due to the old paradigm of rhinitis as a result of a microorganism infection in the postoperative sinus. Due to antibiotic-resistant microorganisms, both treatments have often been discredited for post-operative management following ESS.As technology evolves, nasal spray is used to deliver bioactive compounds such as the ECM component or the coagulation cascade component. In an in vitro skin wound healing model, the ECM protein hyaluronan has been shown to increase re-epithelialization. Administration of nebulized sodium hyaluronate to the nasal cavity has been shown to provide a faster recovery following ESS while maintaining patient comfort throughout the procedure.

The idea of introducing coagulation cascade components intranasally focuses on resolving the hemostasis phase to promote wound healing. In a prospective study comparing the application of aerosolized fibrin and non-absorbable nasal packing, it was revealed that fibrin spray improved adhesions, bleeding, crusting, granulation tissue formation, and frontal sinus ostium stenosis, as well as general relief after endoscopic surgery (26).

Alternative Treatment

Many cultural and religious methods have been described in the past for the treatment of nasal injuries. Considering the close relationship of the inspired airway with the external environment due to the function of the nasal mucosa, herbal medicines play an important role in the treatment of many nasal injuries.

Nasal Irrigation

The ancient Hindu practice of Ayurveda is thought to constitute the oldest source of nasal irrigation. Ayurvedic inscriptions list a number of personal hygiene practices called soucha. Among the soucha is jala neti, also known as a nasal irrigation practice. According to scripture, a higher state of meditation can be achieved by purifying the nose, as clean breathing can lead to clear thinking. The simplest method of cleaning the nose is to draw and blow water from the palms, which is also a step in the practice of Muslim wudu. Modern science has demonstrated the importance of nasal irrigation in enhancing wound healing of the nasal mucosa. Since the paranasal sinus mucosa is a continuation of the nasal cavity mucosa, infections of this region usually progress as rhinosinusitis. Therefore, applications for the treatment of these areas affect both inseparably. For centuries, physicians have argued that nasal irrigation has a place in the treatment of patients with sinonasal problems and have often prescribed 'physiological' or 'normal' saline solution. These solutions in different mixtures have been accepted as safe and effective by many physicians and are widely used all over the world, without any documentation of evidence of significant change in symptoms. However, some authors are against the excessive use of saline nasal drops, arguing that they prevent the normally necessary moistening of the nasal mucosa, dries the mucosa, disrupts the pH balance, and that even the use of high-density mixtures too often and for a long time has toxic effects on the nasal mucosa (27).

The exact mechanisms are still unknown, but experts mention the importance of nasal irrigations in direct cleaning of the nasal mucosa, regardless of the composition of the solution used. Washing solutions cause the mucus lining to soften and become dislodged. In addition, antigen and inflammatory mediators such as leukotrienes and prostaglandins that cause allergic reactions can also be removed in this way. Low concentrations of salt and isotonic solutions in the composition of saline solutions can affect the effectiveness of nasal irrigation, as they will immediately significantly reduce microbial antigens. On the other hand, it has been shown that hypertonic solutions can affect the microbial antigen concentration at a minimum level (27).

With the addition of ions such as sodium and chloride to the nasal irrigation, the integrity of the epithelial cells can be preserved and its function can be supported. In addition, by directly inhibiting the 5-lipoxygenase enzyme with the addition of magnesium, cell repair is promoted and eicosanoid metabolism, which will limit inflammation, is reduced. Magnesium also inhibits the exocytosis of eosinophils and, together with zinc, reduces apoptosis of cells in the respiratory epithelium (28).

Chinese medicine

Based on traditional Chinese medicine (TCM) theory, many herbal formulations are available to balance "Yin-Yang". The emergence of diseases is thought to be caused by an imbalance in theory. In Asian countries, especially in China, oral antibiotics containing medicinal plants are used together with nasal steroids as additional treatment after ESS. Studies are available to investigate the safety and efficacy of Zhu-Yuan decoction (ZYD) in postoperative care after ESS. In TCM theory, the ZYD method is used for the relief of medical symptoms. In the study, it was reported that ZYD application showed similar safety and efficacy with intranasal cortisone (29).

Propolis

Propolis, which is one of the materials used by bees to build their hives, has been synthesized by bees from plant resin and has been shown to have anti-inflammatory activity. In a study using experimental models and a nasal injury model, it was revealed that propolis reduced the inflammation of the wounds in the nasal mucosa and accelerated the healing. It has also been shown that propolis reduces the severity of inflammation and protects the function of both goblet cells and cilia in the nasal mucosa. The precise mechanisms of propolis in the healing of wounds in the nasal mucosa should be supported by further study, but it has been suggested that the healing is due to its immunostimulatory effect, where the cytokine secretory capacity is significantly increased over the course of treatment. In addition, propolis is known to cause a significant increase in ECM components in the first phase of wound healing. In another study conducted with caffeic acid phenyl ester, a bioactive component of propolis, it was revealed that wound healing in the nasal mucosa significantly increased (30).

Curcumin

It has been reported that turmeric has a special place among the most researched and known spices for its medicinal properties. In particular, curcumin has been shown to have anti-inflammatory and wound-healing aspects in skin wounds. In the rat nasal mucosa injury model, curcumin has been reported to reduce inflammation in the mucosa and accelerate wound healing. Among the reasons for this is that it inhibits the production of cytokines for the activation of macrophages and monocytes and reduces the inflammatory response in the nasal mucosa. In addition, it is known that curcumin increases vascularization more in diabetes models and improves it by organizing myofibroblasts and granulation tissue (31).

Tissue Engineering

Tissue engineering is a multidisciplinary approach regenerative medicine branch that has become a technology used in many fields in recent years, providing tissue repair and regeneration using stem cells, biomimetic scaffolds and bioactive molecules. This technology can be used to repair the nasal mucosa, and tissue engineering in the context of regeneration is promising as an application that will provide the formation of the nasal cavity, including cartilage and bone tissue.

Cell and Tissue Therapy

Efforts to defeat diseases and prevent aging from the existence of mankind to the present have been the attractive power of medicine until now. We are at the beginning of a new era in the field of health and biotechnology, and many medical applications that were unimaginable in the past decades are about to be realized in today's developments. Among these applications, the most remarkable developments that are in force today and that will show more effect in the near future are in the field of cells and cellular applications. The positive developments in the number and result of the researches add a new type of human cells and sources that can be used in treatment every day, and the increasing demands show the need for these cells and tissues.

In terms of wound healing, there are reports that it is effective on the healing of wounds in the skin and corneal epithelium made with stem cell technology. Kavuzlu et al. In their experimental rabbit model, they used an oil-derived mesenchymal stem cell layer to accelerate the healing of nasal wounds (32). The implanted mesenchymal stem cell layer yielded results that enabled the proliferation of cells with morphology similar to ciliary nasal epithelial cells. It has been mentioned that many different mechanisms are active, from growth factors to cytokines, from collagen production to angiogenesis in the wound area, that play a role in the healing process, that the microenvironment is created to increase and stimulate new epithelialization, and that it is important to increase the antioxidant effect through neutralization of reactive oxygen species.

Kardia et al. By using a technique similar to their study technique, cells with regeneration ability were tried to be used as an aerosol to the injured tissue. With this technique, they achieved a successful improvement in airway regeneration and repair by applying aerosolized allogeneic respiratory epithelial cells on an experimental rabbit model. The regeneration and repair process followed cell differentiation, migration, proliferation, and redifferentiation to regenerate respiratory epithelium. Rapid re-epithelialization of the injured epithelial area has been reported. In addition, it has been suggested that there are factors that induce and mediate respiratory epithelial repair in the release of compounds such as growth factors, cytokines, and chemokines that contribute to the repair process. Autologous tissue grafting is considered the gold standard in many surgical interventions. This method can also be used in burns and connective tissue injuries. The use of autologous grafts for nasal mucosal injuries has been shown to improve re-epithelialization in rabbits. Topdag et al. In light and scanning electron microscopy findings, it has been shown that the ciliary epithelium covers a larger area, has more mature and functionally more sophisticated cilia, and less hypertrophic epithelium is formed in the grafted tissue than in the ungrafted tissue (33).

Plasma Therapy

In studies on the use of plasma in medicine, some of the literature has suggested that it has many beneficial effects, including anti-inflammatory, anti-cancer, anti-microbial and even tissue regeneration. expanded. Although the content of plasma is complex, it is considered to be the fourth state of matter, consisting of partially ionized gases that also contain electrons, radicals, energetic photons, and ions.

Won et al. In their further studies, they examined the in vitro and in vivo therapeutic effects on nasal mucosa regeneration by converting plasma into a non-thermal plasma-treated solution (NTS) (34). NTS was prepared by treating solutions with non-thermal plasma via a plasma device. While the obtained NTS simultaneously increased cellular proliferation, migration and transition from epithelium to mesenchymal cells during the wound healing process, BEAS-2B had no adverse effects on human bronchial epithelial cells in terms of cytotoxicity.

In addition, another in vitro study using NTS in wound healing showed that it increased the activities of matrix-metalloproteinase (MMP)-2/MMP-9, one of the inducers of cell migration. To provide further evidence for this efficacy in the nasal mucosa injury model, which they projected into the in vivo model, they tested the right nasal septal mucosa after applying the wound model to the nasal mucosa by applying NTS-treated saline irrigation towards the nasal mucosa. The mean height of the newly formed tissue was compared with the control group using epithelial thickness and subepithelial index in the treated group. The histopathological results showed that NTS significantly increased epithelial thickness and epithelial proliferation, and significantly decreased the subepithelial index. This revealed that it caused a decrease in edematous changes in the tissue. It also showed that the group treated with NTS had more activity in terms of inflammatory cell infiltration compared to the control group. All these results documented the potential efficacy of plasma therapy in accelerating wound healing of the nasal mucosa (35).

Nasal Packing

Intranasal packing is mainly used to control bleeding after nasal septoplasty, turbinate and paranasal sinus surgery, and also to fix the cartilage and bone skeleton after surgery. Apart from these, intranasal packing also prevents post-surgical adhesions (36). However, there is no general standard regarding the indications of intranasal packing, the duration of packing and the type of material used. Telfa (non-tissue wound dressing, Kendall product), merocel (Absorbent, natural cellulose substance), glove finger and extraforated gauze are the materials used for intranasal buffering. While some surgeons remove the tampon on the same day, some can keep it for up to 5 days (37). Lubianca et al. (38) reported that they did not observe a statistical difference in terms of bleeding complications in patients who underwent intranasal packing between 1-24 hours and 24-48 hours in endonasal surgeries. Pain is the most common complication of intranasal packing. Thomas et al., in the pain scoring of 72 patients who underwent endonasal surgery with intranasal packing for 2 hours and 24 hours, found the pain score to be significantly lower in the 2-hour group compared to the 24-hour group (39). These complications may occur at different rates in different types of tampons.

Conclusions

Over the past years, many methods have been introduced and good results have been obtained as a result of post-traumatic complications of nasal mucosa healing. As a result of the advancement of new technologies and medicine, it has been observed that a positive result has been obtained in the treatments applied to the wounds in the sinus mucosa and nasal mucosa. In addition, as a result of alternative treatment methods, such as stem cells and other regenerative medicine models, it offers a great treatment method in airway epithelial regeneration as a result of treatment.

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