DISSERTATION ON

A STUDY ON ROLE OF ADJUVANT STEROID THERAPY IN PATIENTS WITH SINONASAL POLYPOSIS

Submitted in partial fulfillment of the requirements for

M.S.DEGREE BRANCH -IV OTORHINOLARYNGOLOGY

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UPGRADED INSTITUTE OF OTORHINOLARYNGOLOGY

MADRAS MEDICAL COLLEGE

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CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON ROLE OF ADJUVANT STEROID THERAPY IN PATIENTS WITH SINONASAL POLYPOSIS**" submitted by **Dr. VINOD JOSE KAKKANATT,** appearing for Part II M.S.E.N.T.. Branch IV Degree examination in March 2009 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation entitled "**A STUDY ON ROLE OF ADJUVANT STEROID THERAPY IN PATIENTS WITH SINONASAL POLYPOSIS** " is done by me at the Madras Medical College and Government General Hospital, Chennai during 2007-2008 under the guidance and supervision of Prof. S. KULASEKARAN, M.S., D.L.O.

This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of regulation for the award of M.S. DEGREE IN OTORHINOLARYNGOLOGY (BRANCH–IV).

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CONTENTS

ROLE OF ADJUVANT STEROID THERAPY IN PATIENTS WITH SINONASAL POLYPOSIS

INTRODUCTION

Chronic rhinosinusitis with Sinonasal Polyposis is a common problem that exacts a high cost in terms of direct health care as well as lost productivity[1].The common pathophysiologic denominator for virtually all forms of Chronic RhinoSinusitis (CRS) is inflammation, for which extensive pharmacotherapy is available including topical corticosteroids, antibiotics, saline irrigations and systemic steroids. Unfortunately, not all patients are cured or achieve control of their symptoms even with maximal pharmacotherapy. In these patients who have failed medical management, endoscopic sinus surgery(ESS) has been demonstrated and is generally accepted to provide improved relief of symptoms and better quality of life[3].

ESS is a commonly performed procedure, with an estimated 1000 procedures performed annually in our institute-Upgraded Institute of Otorhinolaryngology in Madras Medical College in Chennai. Although there is some controversy as to the best or most appropriate surgical technique for treating patients with Chronic Rhinosinusitis with Sinonasal polyposis (CRSwP)[5] most

surgeons will recommend that these patients undergo polypectomy[6], complete ethmoidectomy, and middle meatal antrostomy, with or without frontal sinusotomy or sphenoidotomy. However, there is significant variability and a lack of standardization or guidelines[4] with respect to the preparation and peri-operative pharmacotherapy regimen and management for patients undergoing ESS for CRSwP.

In particular, some surgeons advocate the use of preoperative systemic steroids, citing such advantages as facilitation of the surgical procedure by reducing edema, polyp load, and bleeding. The theoretic advantages of peri-operative steroids often cited include reduced edema and scarring postoperatively as well as suppression of the intrinsic inflammatory disease to permit better healing and better outcomes[2]. Relevant to this discussion is the fact that systemic steroids have been well described to have a litany of potential side effects, ranging from nuisance short-term problems such as mood disturbance and fluid retention, to moderate effects such as gastric irritation, to devastating side effects such as osteonecrosis of the femoral head[12]. Therefore, given that some surgeons advocate the use of peri-operative systemic steroids whereas others do not. The study design developed to assess surgical outcomes is placebo-controlled and seeks to assess specific surgical outcomes[7] at the time of surgery as well as subjective and objective outcomes in the short and intermediate postoperative period.

In this study 50 cases of chronic rhinosinusitis with sinonasal polyposis is taken.25 cases were given peri-operative systemic steroids and the rest 25 were given placebo drugs peri-operatively. Operative and clinical data were collected and analyzed critically.

AIMS OF THE STUDY

The primary objective of the study is to assess the effect of peri-operative systemic corticosteroids on both subjective and objective outcomes in patients undergoing ESS for treatment of CRSwP. The primary measure of subjective change is the Sinus Symptom Questionnaire (SSQ) from the Lund-McKay staging system.[13] The measure of objective change is the Lund-Kennedy Endoscopy Scale (LKES).[14] Consequently, the primary objective of the study can be stated as three specific sub-objectives, as follow.

Objective 1.

To assess the effect of peri-operative prednisone versus placebo with respect to operative parameters of the technical aspects of surgery-

a) duration of surgery

b) amount of blood loss during surgery

c) health of mucosa

d) disease clearance,that is the no.of sinuses opened

Objective 2.

To assess the effect of peri-operative prednisone versus placebo with respect to changes in the six subscales of the SSQ.The parameters include-

a)facial pain

b)headache

c)nasal block

d)nasal discharge

e)olfactory disturbances

f)overall discomfort.

Objective 3.

To assess the effect of peri-operative prednisone versus placebo with respect to changes in the total LKES-Lund-Kennedy Endoscopy Score post-operatively at 6 months.The parameters include-

a) post op scarring

b) post-op crusting

c) recurrent polyps

REVIEW OF LITERATURE

CHRONIC RHINOSINUSITIS:

Epidemiology

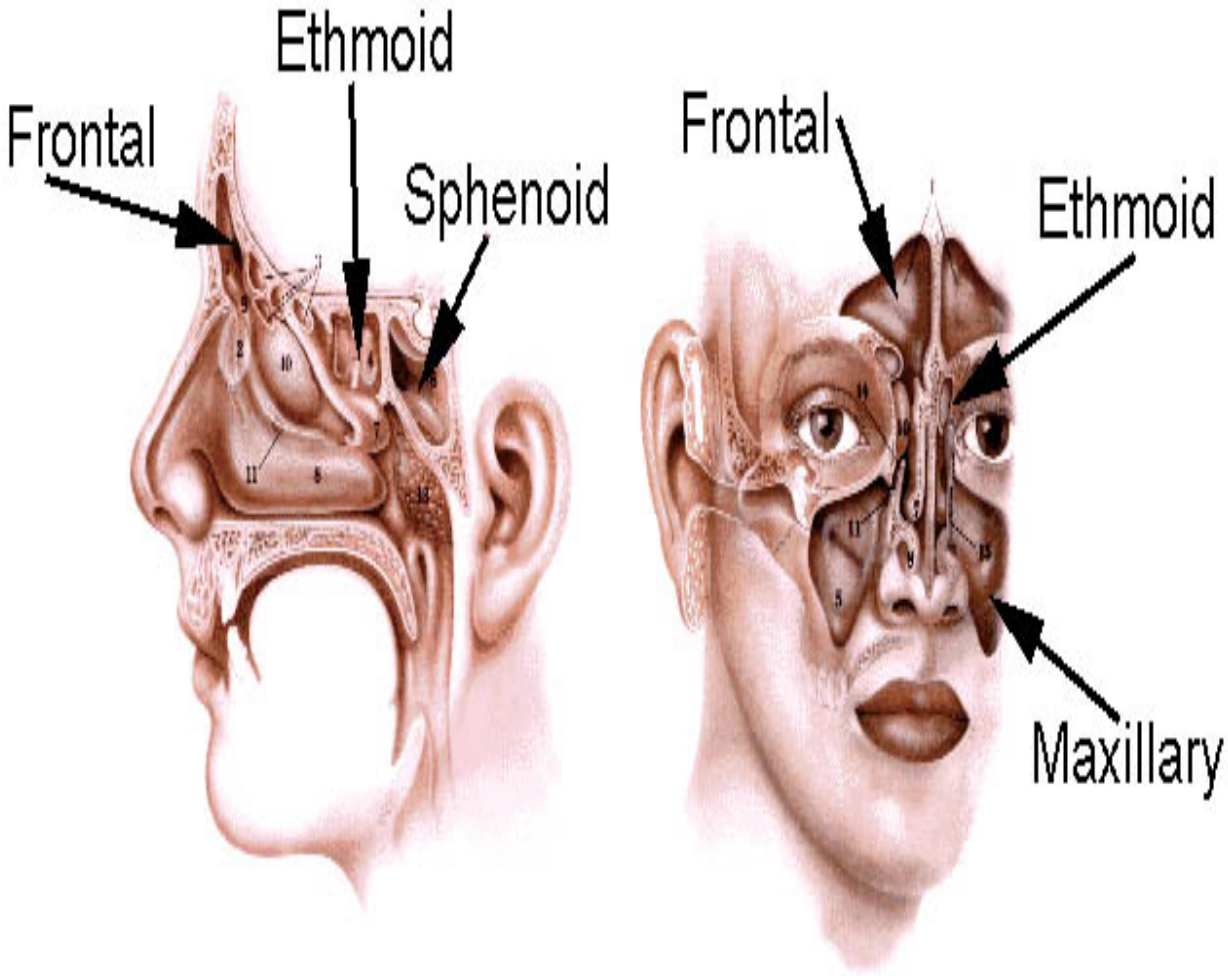
Chronic Rhinosinusitis with Sinonasal Polyposis is an inflammatory disease of the sinonasal tract that is of multifactorial etiology and complex classification. It occurs spontaneously in isolation but also is a relatively common co-manifestation of diseases such as chronic asthma[7], allergic rhinitis[7], cystic fibrosis[8], and inflammatory bowel[8] disease.

Traditionally discounted as a relatively benign condition, it has warranted increasing attention in recent years as awareness has grown of the significant societal impact it has. This impact relates not only to its relatively high prevalence, for example, affecting up to 16% of adults in the United States, 17%in the United Kingdom, and 13.5%in Canada, 22% of patients in India, 24% of patients in our Out Patient Department, but also to the significant effect it has on patient quality of life and the economic burden it places on society, both in terms of direct health care costs and indirect costs secondary to loss of productivity.

In one study, 22 adult patients were studied prospectively. CRS caused an average of 4.8 days of missed work per 12-month period. The overall yearly economic cost of CRS was estimated at$1,539 per patient. These costs amount to

billions of rupees in direct costs each year in addition to the estimated 250,000 endoscopic ethmoidectomies performed each year in the United States[10]. Thus, CRS is a common disease that exacts a significant toll on society in terms of direct costs and lost productivity, for which hundreds of thousands of patients undergo surgical treatment each year.

ANATOMY OF THE PARANASAL SINUSES. .



MAXILLARY SINUS

Structure

The adult maxillary sinus is a pyramid which has a volume of approximately 15 ml (34x33x23mm). The base of the pyramid is the nasal wall with the peak pointing toward the zygomatic process. The anterior wall has the infraorbital foramen located at the midsuperior portion with the infraorbital nerve running over the roof of the sinus and exiting through the foramen. This nerve can be dehiscent (14%). The thinnest portion of the anterior wall is just above the canine tooth--the canine fossa. The roof is formed by the orbital floor and transected by the course of the infraorbital nerve. The posterior wall is unremarkable. Behind this wall is the pterygomaxillary fossa with the internal maxillary artery, sphenopalatine ganglion and the Vidian canal, the greater palatine nerve and the foramen rotundum. The floor, as discussed above, varies in its level. From birth to age nine the floor of the sinus is above that of the nasal cavity. At age nine the floor is generally at the level of the nasal floor. The floor continues to sink as the maxillary sinus pneumatizes. Because of the close relationship with the dentition dental disease can cause maxillary infection, and tooth extraction can result in oral-antral fistulae.

Vascular supply

Branches of the internal maxillary artery supply this sinus. These include the infraorbital (as it runs with the infraorbital nerve), lateral branches of the sphenopalatine, greater palatine, and the alveolar arteries. Venous drainage runs anteriorly into the facial vein and posteriorly into the maxillary vein and jugular vs. dural sinus systems.

Innervation

The maxillary sinus is innervated by branches of V_2. Specifically, the greater palatine nerve and the branches of the infraorbital nerve.

Related structures

Nasolacrimal duct

The nasolacrimal duct drains the lacrimal sac and runs from the lacrimal fossa in the orbit down the posterior aspect of the maxillary vertical buttress and empties in the anterior aspect of the inferior meatus. The duct lies very close to the maxillary ostium. On average it lies 4mm-9mm anterior to the ostium.

Natural ostium

The natural maxillary ostium is located at the superior aspect of the medial wall of the sinus. Intranasally, it is usually in the posterior half of the ethmoid

infundibulum, or behind the lower 1/3 of the uncinate process. The posterior edge of the ostia is continuous with the lamina papyracea, thus a reliable landmark for the lateral limit of surgical dissection. The ostium size averages 2.4 mm but can vary from 1 to 17mm. The ostium is much smaller than that actual bony defect, as mucosa fills this area and defines the extent of the opening. 88% of maxillary ostium are hidden behind the uncinate process and therefore cannot be visualized endoscopically.

Anterior/Posterior Fontanelles/Accessory Ostium

Two bony dehiscences of the lateral nasal wall/maxillary sinus medial wall exist (sometimes there is one large bone dehiscence. These are usually covered by mucosa. In some individuals the anterior or posterior fontanelles may be patent which results in an accessory ostium. They are nonfunctional ostia and serve to drain the sinus only if the natural ostium is blocked and intrasinus pressure/gravity moves material out of the ostium. Accessory ostium are usually found in the posterior fontanel.

ETHMOID SINUSES

Structure

Posterior and anterior cells combined have a volume of 15 ml (3.3x2.7x1.4cm). The ethmoids are shaped like a pyramid and are divided into

multiple cells by thin septa. The roof of the ethmoids is composed of multiple important structures. The roof slopes both posteriorly (angle of 15 degrees) and medially. The anterior 2/3 of the roof is thick and strong and is composed of the frontal bone and the fovea ethmoidalis. The posterior 1/3 is higher laterally and slopes down medially to the cribiform plate. The junction between the lateral dense bone and the plate is one-tenth as strong as the lateral roof. The difference in height between the lateral and medial roof is variable, but can be as much as 15-17mm. The posterior aspect of the ethmoid cells borders on the sphenoid sinus. The lateral wall is the lamina papyracea of the orbit.

Vascular supply

The ethmoid sinuses are supplied by blood flow originating from both the external and internal carotid arteries. The Sphenopalatine artery as well as the ophthalmic artery (which branches into the anterior and posterior ethmoid arteries) supply the sinus. Venous drainage follows arterial supply and thus can track infection intracranially.

Innervation

Both V_1 and V_2 innervate this region. V_1 supplies the more superior aspect with V_2 innervating the inferior regions. Parasympathetic innervation is via the

Vidian nerve. Sympathetic innervation is via the cervical sympathetic ganglion and follows the arterial vasculature to the mucosa of the sinuses.

Related structures

Basal Lamella (Ground Lamella) of the Middle Turbinate

This structure forms the separation between the anterior and posterior ethmoid cells. It is the attachment of the middle turbinate and runs in three different planes in its course from anterior to posterior. The anterior most portion is vertical and inserts in the crista ethmoidalis and skull base. The middle third is oblique with insertion in the lamina papyracea. The final third runs horizontal with insertion in the lamina papyracea. The space under the middle turbinate is termed the middle meatus into which the anterior ethmoids, frontal sinus, and maxillary sinus drain. Surgical damage to the anterior or posterior portions of the middle turbinate may destabilize this structure and anteriorly risks disruption of the cribiform plate.

Anterior vs. posterior Ethmoid cells

The anterior cells are those anterior to the basal lamella. They drain into the middle meatus via the ethmoid infundibulum. They include the agger nasi cells, the ethmoid bulla and any other anterior cells. The posterior cells drain into the

superior meatus and border on the sphenoid sinus. They are generally fewer in number and larger than the anterior cells.

Agger nasi cell

The cell is found in the lacrimal bone anterior and superior to the junction of the middle turbinate with the nasal wall (often described as the bulge in the lateral nasal wall where the middle turbinate attaches). It is hidden behind the anterior most aspect of the uncinate process and drains into the hiatus semilunaris. It is the first cell to pneumatize in the newborn and is prominent through childhood. There can be from one to three cells. The posterior wall of the cell forms the anterior wall of the frontal recess. The roof of the agger nasi cell is the floor of the frontal sinus, and is therefore, an important landmark for frontal sinus surgery.

Ethmoid Bulla

This is the most constant landmark for surgery. It lies above the infundibulum and its lateral/inferior surface and the superior edge of the uncinate process forms the hiatus semilunaris. It is usually the largest of the anterior ethmoid cells. The anterior ethmoid artery usually courses across the roof of this cell. Suprabullar and retrobullar recesses may be formed when the ethmoid bulla does not extend to the skull base. The suprabullar recess is when there is a cleft between the roof of the ethmoid bulla and the fovea. The retrobullar space is

formed when there is a cleft between the basal lamella and bulla. This retrobullar space opens into what is known as the "hiatus semilunaris superior."

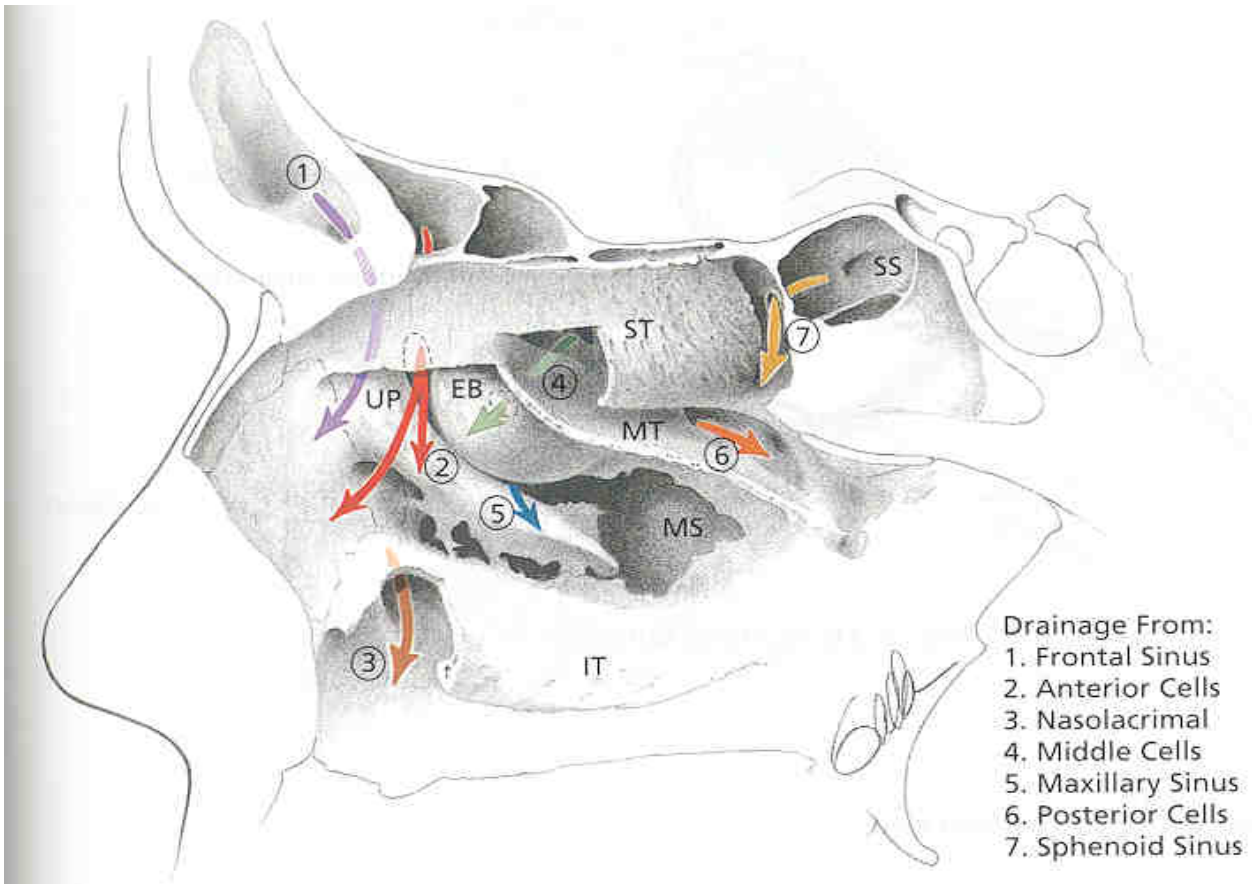
Ethmoid infundibulum

The development of the infundibulum precedes that of the sinuses. This recess, into which the anterior ethmoid sinuses, maxillary sinus and frontal sinus drain, is formed by multiple structures. The anterior wall is formed by the uncinate process, the medial wall is the frontal process of the maxilla and the lamina papyracea. It runs anteriorly in continuity with the frontal recess to its posterior limit where the uncinate process attaches to the lamina. The opening above the recess is known as the hiatus semilunaris. The maxillary sinus is found in this area.

Anterior/Posterior Ethmoid Arteries

The anterior and posterior ethmoid arteries arise from the ophthalmic artery in the orbit. The anterior artery crosses the medial rectus and penetrates the lamina papyracea. The artery then courses across the roof the ethmoid sinus in a thin bony mesentery (usually dehiscent), eventually supplying the cribiform plate and anterior septum. This artery is usually large and singular and may drape inferiorly into a sinus cell. Its position closely corresponds to the position of the more medial structure, ethmoidal fovea. The posterior artery crosses the medial rectus,

penetrates the lamina papyracea and courses through the posterior ethmoid cells (usually corresponding with the anterior wall of the posterior-most cell) to the septum. It supplies the posterior ethmoid sinuses, part of the superior and middle turbinates and small amount of the posterior septum. This artery is usually smaller and branched. It can be dehiscent and drape down within the sinus cells. Its position is associated with the position of the optic nerve near the orbital vertex. Because the development of these structures predate the sinuses their relation to the ethmoid cells can vary. Their association with the fovea and optic nerve remain constant. .



OSTEOMEATAL COMPLEX AND DRAINAGE OF PARANASAL SINUSES

FRONTAL SINUS

Structure

The volume of the sinus is approximately 6-7 ml (28x24x20mm). Frontal sinus anatomy is highly variable, but generally there are two sinuses which are funnel shaped and point upward. The depth of the sinus is the most surgically significant dimension as it determines the limitations of surgical approach. Both frontal sinuses have their ostia at the most dependant portion of the cavity (posteriomedial). Many feel this is the reason that these sinuses are rarely involved with infectious disease. Both the anterior and posterior walls of this sinus are composed of diploeic bone. However, the posterior wall (separates the frontal sinus from the anterior cranial fossa) is much thinner. The floor of the sinus also functions as a portion of the orbital roof.

Vascular supply

The frontal sinus is supplied by the ophthalmic artery via the supraorbital and supratroclear arteries. Venous drainage is via the superior ophthalmic veins to the cavernous sinus and via small venulae in the posterior wall which drains to the dural sinuses.

Innervation

The frontal sinus is innervated by branches of V_1. Specifically, these nerves include the supraorbital and supratrochlear branches.

Related structures

Frontal recess

The frontal recess is the space between the frontal sinus and the hiatus semilunaris into which the sinus drains. It is bounded anteriorly by the agger nasi cell and superiorly by the frontal sinus, medially by the middle turbinate, and laterally by the lamina papyracea. The cavity resembles a dumbbell as the frontal sinus narrows to the sinus ostium/channel and then opens again into the wider frontal recess. Depending on the extent of ethmoid pneumatization, this recess can become tubular resulting in a much longer narrowing of the dumbbell. Anomalous structures, such as the sinus lateralis (posterior to the frontal recess at the skull base) and frontal bulla (anterior to the recess at the base of the frontal sinus) may be mistaken as the frontal sinus during sinus surgery.

ISPHENOD SINUS

StructureIn the late teen years the sinus reaches its full size with a volume of 7.5 ml (23x20x17mm). Pneumatization of this sinus, like that of the frontal sinus, is very variable. Generally these are bilateral structures located at the posterosuperior aspect of the nasal cavity. Pneumatization can extend as far as the clivus, the sphenoid wings, and the foramen magnum. The walls of the sphenoid vary in thickness with the anterosuperior wall and roof being the thinnest (.1 to 1.5 mm). The other walls are thicker. The thinnest part of the anterior wall is 1cm from the fovea ethmoidalis. The position of the sinus and, therefore, its anatomic

relationships depend on the extent of pneumatization. The sinus can sit far anterior to, just anterior to, or immediately under the sella tursica (conchal, presellar, sellar/postsellar). The most posterior position can place the sinus just adjacent to vital structures such as the carotid arteries, optic nerves, maxillary branch of the trigeminal nerve, the Vidian nerve, the pons, sella tursica, and the cavernous sinus. These structures are often identified as indentions on the roof and walls of the sinus. A small percentage will have dehiscence of bone over such vital structures as the optic nerve and carotid arteries. Care must also be taken when removing sinus septa as these may be in continuity with the carotid and optic canal and can result in death and blindness.

The sphenoid sinus ostium drains into the sphenoethmoidal recess. The ostium is very small (.5-4mm) and is located about 10mm above the sinus floor. A 30 degree angle drawn from the anterior nasal floor approximates the location of the ostium on the posterosuperior nasal wall. It is noted to be close to the midline at the junction of the upper 1/3 and the lower 2/3 of the anterior sinus wall. It is generally medial to the supreme/superior turbinate, and is only a few millimeters from the cribiform plate. This ostium, like that of the maxillary sinus, has a much larger bony dehiscence which is narrowed by a membranous septum.

Vascular supply

The posterior ethmoid artery supplies the roof of the sphenoid sinus. The rest of the sinus is supplied by the sphenopalatine artery. Venous drainage is via the maxillary veins to the jugular and pterygoid plexus systems.

Innervation

The sphenoid sinus is supplied by branches from both V_1 and V_2. The nasociliary nerve (from V_1) runs into the posterior ethmoid nerve and supplies the roof. The branches of the sphenopalatine nerve (V_2) supply the floor.

Related structures

Sphenoethmoidal recess

The sphenoethmoid recess is a space behind and above the most superior turbinate. The boundaries of this space are formed by multiple structures. The anterior wall of the sphenoid sinus forms the posterior aspect. The nasal septum and cribiform plate form the medial and superior aspects. The anterolateral extent is determined by the most superior turbinate. The space opens into the nasal cavity inferiorly. The posterior ethmoid cells, as well as the sphenoid sinus empty into this region.

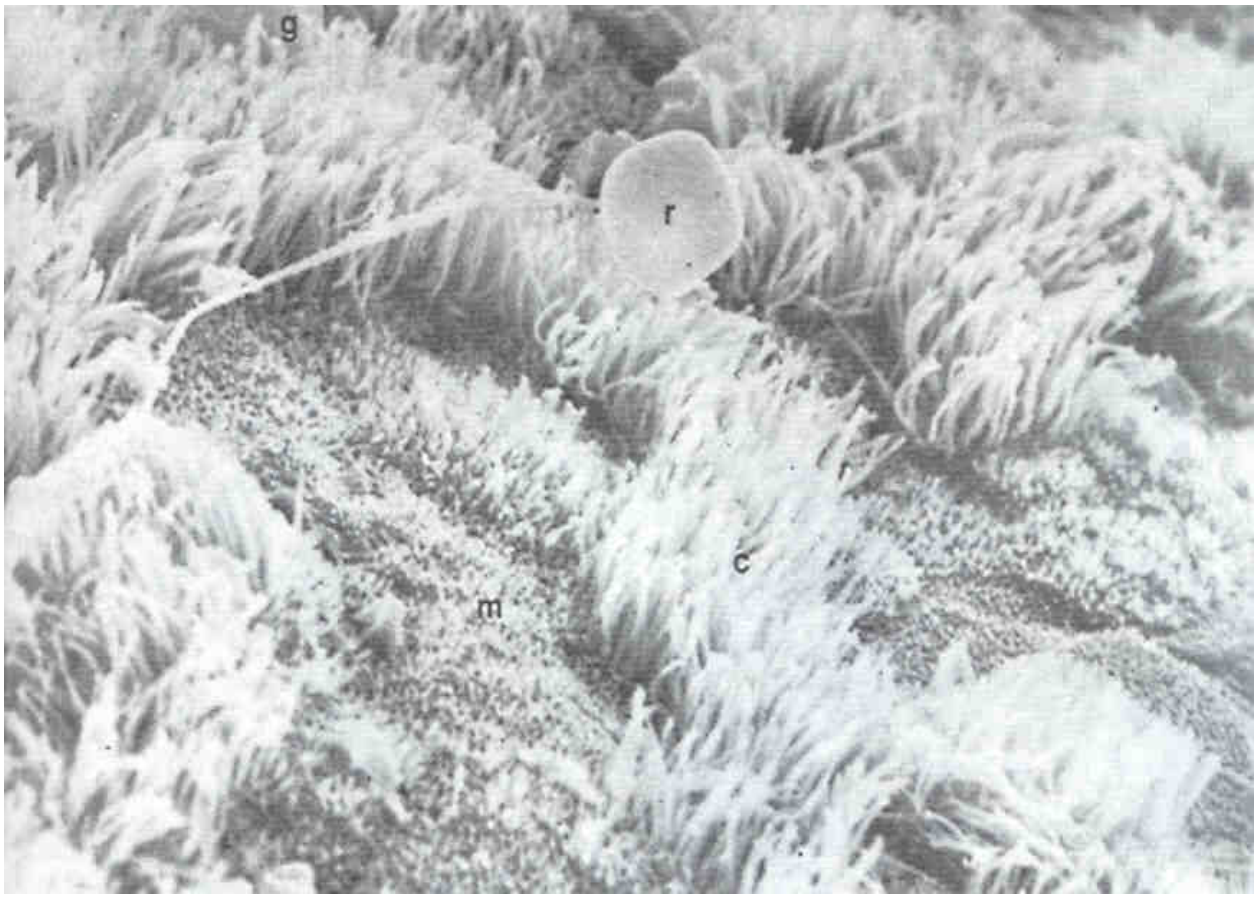
Sphenoid rostrum

This structure is simply the midline projection of the anterior sphenoid sinus wall. It articulates with the perpendicular plate and the vomer.

Onodi cell

As discussed above, these cells are ethmoid cells which are located anterolateral to the sphenoid sinus. Vital structures such as the carotid artery and optic nerve may run through this cell. These structures are often dehiscent. This requires careful dissection in this area and good preoperative radiographic examination to avoid poor outcomes.

MICROSCOPIC ANATOMY. .



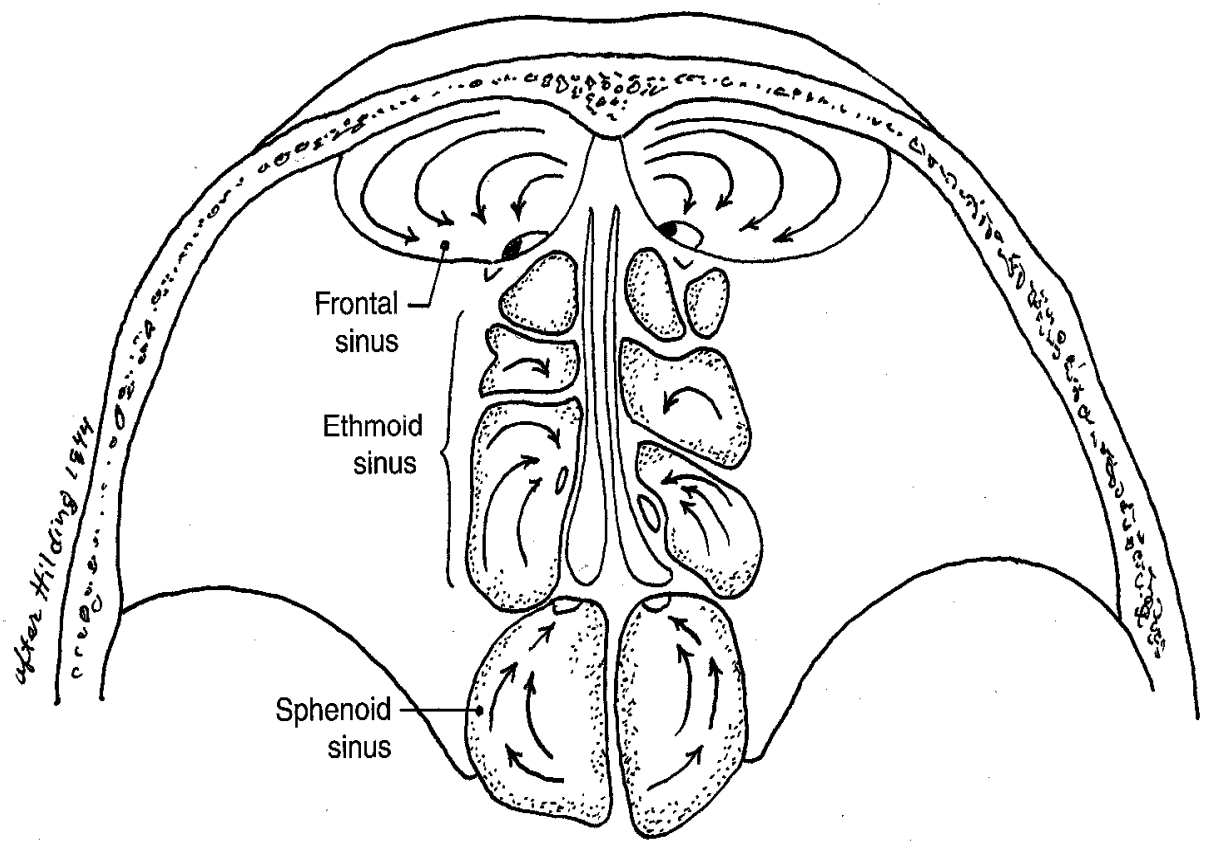
The sinuses are lined with pseudostratified ciliated columnar epithelium which is in continuity with the mucosa of the nasal cavities. The epithelium of the sinuses is thinner than that of the nose. There are four basic cell types. These include

ciliated columnar epithelial cells, nonciliated columnar cells, basal cells, and goblet cells. The ciliated cells have 50-200 cilia per cell with the usual structure of 9+2 microtubules with dynein arms. Experimental data shows these cells to beat at 700-800 times a minute, moving mucus at a rate of 9 mm/minute. Nonciliated cells are characterized by microvilli which cover the apical aspect of the cell and serve to increase surface area (likely to facilitate humidification and warming of inspired air). It is interesting to note that there is an increased concentration (up to 50%) at the sinus ostium. The basal cell's function is unknown. They vary in size, shape and number. Some have theorized that they serve as a stem cell which can differentiate as needed. Goblet cells produce glycoproteins which are responsible for the viscosity and elasticity of mucus. They are innervated by the parasympathetic and sympathetic nervous system. Thus, parasympathetic stimulation induces thicker mucus with sympathetic stimulation leading to more watery mucus secretion.

The epithelial layer is supported by a thin basement membrane, lamina propria, and periosteum. Both serous and mucinous glands tract down into the lamina propria. Anatomic studies have shown a general paucity of goblet cells and submucosal glands in the sinuses compared to the nasal mucosa. When comparing the sinuses, the maxillary sinus has the highest density of goblet cells. The ostia of

the maxillary, sphenoid, and anterior ethmoid sinuses seem to have an increased number of submucosal serous and mucinous glands.

MUCOCILIARY CLEARANCE. .



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The ciliated cells in each sinus beat in a specific direction. A resulting pattern of mucus flow results. Since many of the sinuses develop in an outward and inferiorly fashion, the ciliated mucosa often moves material against gravity to the sinus' exit. This means that mucus produced just adjacent to a sinus ostia, if it is on the afferent side, will travel around the entire sinus cavity, often against gravity, before exiting the ostia. This is one reason that creation of accessory ostia

at sites outside the physiologic ostium will not significantly improve sinus drainage. In fact, this sometimes results in mucus draining from the natural ostia reentering the sinus via the newly created opening and cycling through the sinus again. Hilding was the first that described each sinuses' mucus flow patterns, and his observations are still valid today. Later researchers described a phenomenon of stagnation which occurs when two ciliated surfaces come into contact (particularly applicable at the osteomeatal complex). This disrupts mucociliary mucus clearance and can result in sinusitis. Clearance of the disease is accomplished when this clearance mechanism has been restored.

SINUS FUNCTION

The physiology and function of the sinuses has been the subject of much research. Unfortunately, we still are unsure as to all the functions of these air-filled spaces. Multiple theories of function exist. These include the functions of warming/humidification of air, assisting in regulation of intranasal pressure and serum gas pressures (and subsequently minute ventilation), contributing to immune defense, increasing mucosal surface area, lightening the skull, giving resonance to the voice, absorbing shock, and contributing to facial growth. The nose is an amazing humidifier and warmer of air. Even at seven liters/minute of airflow, the nose has not reached its maximal ability to perform this function. Nasal humidification has been shown to contribute as much as 6.9 mm Hg on serum pO2.

Although the nasal mucosa is best adapted to perform this task, the sinuses contribute to mucosal surface area and warming ability. Some researchers have shown that mouth breathers have a decreased end-tidal CO2 which may increase serum CO2 and contribute to sleep apnea.

Because of the sinuses' copious mucous production they contribute heavily to the immune defense/air filtration performed by the nose. The nasal and sinus mucosa is ciliated and functions to move mucus to the choanae and the stomach beyond. The thickened superficial layer of nasal mucus serves to trap bacteria and particulate matter in a substance rich with immune cells, antibodies, and antibacterial proteins. The underlying *sol* layer is much thinner and serves to provide a thinner substrate in which the cilia are able to beat; their tips essentially grabbing the superficial layer and pushing it in the direction of the beat. Unless obstructed by disease or anatomical variance, the sinuses move mucous through their cavities and out of their ostia toward the choane. The most recent research on sinus function has focused on the molecule Nitrous Oxide (N2O). Studies have shown that the production of intranasal N2O is primarily in the sinuses. N2O has been shown to be toxic to bacteria, fungi, and viruses at levels as low as 100 ppb. Nasal concentrations of this substance can reach 30,000 ppb which some researchers have theorized as the mechanism of sinus sterilization. N2O has also been shown to increase ciliary motility.

The physiology and function of the paranasal sinuses is a subject that reflects the complexity of their anatomy. Continued research may likely reveal that all of these functions are part of a bigger, more involved picture than is now apparent.

Etiology of CRS

The precipitating cause of CRS remains elusive in many cases. As stated above, it frequently is seen in association with chronic asthma, with rhinitis occurring in approximately 75%of allergic asthmatics and asthma developing in 20%of those with seasonal allergic rhinitis[11]. Moreover, co-morbidity with asthma is associated with worse endoscopic evidence of rhinosinusitis and a less satisfactory response to endoscopic surgical management

Sampter's triad consists of nasal polyposis, asthma and aspirin intolerance. A common thread through asthma and polyposis is the presence of eosinophilia, which, similar to asthma, is associated both with more severe endoscopic evidence of sinusitis and a poorer response to treatment. Eosinophilia also is associated with nasal polyposis, both with and without CRS[15]. CRSwP, inturn, is associated with greater symptoms and overall worse disease than CRS without polyposis. The above described findings have led many authors to conclude that these seemingly disparate respiratory tract inflammatory conditions are, in many cases, actually manifestations of one common systemic disease.

One currently popular theory regarding the association between CRSwP, asthma, and eosinophilia is that a chronic inflammatory response occurs in response to bacterial superantigens. Also, more than one research group recently has identified the presence of bacterial biofilms within the sinuses, which may serve as a trigger for the chronic inflammatory response[16].

In cases of CRS without polyposis, chronic bacterial infection has been implicated as an etiologic factor. In contrast with acute bacterial rhinosinusitis, a higher incidence of Staphylococci has been described in CRS, including methicillin-resistant Staph aureus . However, numerous other bacteria have been cultured from the sinuses of patients undergoing endoscopic treatment of CRS, including the more common organisms such as Haemophilus influenzae, Streptococcus pneumoniae[25],and Moraxella catarrhalis[25].Other common pathogens, particularly in patients who have undergone previous surgery, include Pseudomonas aeruginosa and hemolytic streptococci. Moreover, one group has identified a higher prevalence of Helicobacter pylori than expected among individuals with nasal polyposis[16].

In contrast, other studies have failed to support a bacterial role in CRS causation. In one of these studies, positive cultures at the time of surgery were no different between patients with and without polyposis, and in the absence of gross

purulence visible endoscopically, some authors question the utility of antibiotics at all [25].

Antibiotics do appear to have some beneficial effect in the management of non-infectious CRS, but this generally pertains to them macrolide agents, which have been suggested to possess significant anti-inflammatory attributes. This anti-inflammatory role for macrolides has held variable degrees of favour in recent years.

Fungal infections commonly are associated with local and systemic eosinophilia. These findings have led investigators in recent years to suggest a role for fungi in the pathogenesis of CRS and nasal polyposis. These authors have found fungus to be ubiquitous on sinonasal culture using highly sensitive techniques and propose the theory that the afflicted patient populations react in an exaggerated fashion to these fungal antigens as compared with nonafflicted people. Again, however, the evidence is inconclusive and debate continues[25].

Other risk factors for the development of CRS are air pollution and chronic cigarette use. Other diseases associated with sinonasal polyposis include

- ✓ cystic fibrosis[25]
- ✓ allergic fungal sinusitis[25]
- ✓ Kartagener's syndrome-bronchiectasis, situs inversus & ciliary dyskinesis [25]

- ✓ Young's syndrome-sinopulmonary disease & azoospermia [25]
- ✓ Nasal mastocytosis[25] and
- ✓ Churg-Strauss syndrome[25].

Pathophysiology of CRS with Polyposis

As stated above, the mechanisms by which CRS and nasal polyposis develop are not entirely understood. However, considerable evidence suggests that both conditions result from chronic inflammation with resultant tissue hyperplasia[18].

Stammberger evaluated nasal polyps in 200 consecutive patients undergoing functional endoscopic sinus surgery. He noted that 80% polyps originated from the middle meatal mucosa, uncinate process and infundibulum. In 65%, polyps originated from the ethmoidal bulla and hiatus semilunaris and from the frontal recess in 48%. Polyps were found inside the bulla in 30%[3].

Nasal mucosa particularly in the region of osteomeatal complex becomes oedematous due to collection of extra-cellular fluid causing polypoidal change. Polypi which are sessile in the beginning become pedunculated due to gravity and excessive sneezing especially in allergic patients[3].

Nasal polyps usually have a respiratory epithelium with ciliated columnar and goblet cells. Squamous metaplasia can occur due to exposure and repeated trauma. Gross edema will lead to artifact when polyps are processed under electron microscopy.[3]

As the polyp shrinks the surface epithelium is lost to a variable extent and is described as “cobble-stones”. There is apparent thickening of basement membrane. The submucosal tissue is grossly edematous and contains few blood vessels and occasional nerve fibres.The cellular infiltrate is mainly plasma cells, small lymphocytes, macrophages and most striking feature is eosinophilia[3]. Eosinophils are found in 90% of polyps, the majority of the remaining cells in other polyps are neutrophils. Sensitized eosinophils are important in the initiation of mucosal edema in patients with aspirin hypersensitivity. In fact, eosinophilia often is apparent, both systemically and locally, within inflamed nasal mucosa and within polyps themselves. However, eosinophilia is not always present.

In one study in which biopsies were obtained from the inferior turbinates of 14 patients with nonallergic CRS versus 10 healthy controls, significant increases (P .05) were detected in numbers of CD3, CD4, and CD8 Tcells and Bcells in the nasal mucosa of patients with CRS[25].

In another study, 29 adults with refractory chronic sinusitis underwent functional ESS (FESS) after standard preoperative computed tomography (CT). Six patients with normal sinus mucosa served as control subjects. Patients were subdivided into two groups according to their dominant pathologic features: 16 had polypoid mucosa and peripheral eosinophilia, and 13 had glandular hyperplasia. The numbers of eosinophils, and of T and B lymphocytes in the lamina propria,

were significantly higher in patients with polypoid mucosa and eosinophilia versus those with glandular hyperplasia and versus normal control subjects, whereas the differences between patients with glandular hyperplasia and control subjects were insignificant.

Although the overall inflammatory reaction was relatively modest, nasal polyposis was more prevalent in patients with polypoid mucosa and eosinophilia; likewise, CT revealed significantly more extensive disease in these patients versus those with glandular hyperplasia. It can be concluded from this evidence that most patients with polyposis appear to have a more intense, and potentially systemic, inflammatory response associated with inflammatory cells, including eosinophils.

Results from these two studies suggest that there may be more than one overall mechanism by which CRS and nasal polyposis develop. At least one such mechanism is associated with significant eosinophilia, immunoglobin E production, and atopy. Another appears to be non-allergic, associated more with T-lymphocyte and neutrophil predominance. Various subsets of T lymphocytes appear to be more important than others in the pathologic process of CRS, with or without nasal polyposis. The number of CD4 cells consistently was higher than the number of CD8 cells, and CD4T-helper cells appeared to be especially predominant [25] in the initiation and regulation of inflammation

In another study involving 12 patients with CRS and polyposis, both local and systemic influx of CD4 lymphocytes was evident in response to Staphylococcal exotoxins[25], including inflammation within the polyps themselves, prompting these and other investigators to conjecture that CD4 cells present Staphylococcal or other infectious super-antigens as an initiating and propagating step in the development of CRS and associated polyps. Eosinophilia also has been observed as a response to Staphylococcal super-antigens, and both eosinophils and T lymphocytes appear in the setting of a diverse array of cytokines so as to accentuate and perpetuate the inflammatory response.

Recent research suggests that a chemokine called[25] RANTES (regulated on activation, normal T-cell-expressed, and secreted), a member of the CC chemokine family with chemotactic activity directed primarily toward eosinophils and T lymphocytes, may be very important in the recruitment of eosinophils and T lymphocytes into the nose in patients with CRS and nasal polyposis. Several additional chemokines such as eotaxin and monocyte chemotactic proteins have also been implicated as contributing factors in the development of eosinophilia in CRSwP

Hyperplasia of tissue, secondary to the local inflammatory response, results in a variety of the symptoms and complications of CRS, including polyposis.

Mucin [25] gene up-regulation probably is responsible for the mucus hypersecretion that can be so clinically prominent and problematic.

It can thus be seen from the previous summary that CRS is a complex disease with multiple proposed etiologies. Significant progress is being made with respect to our understanding of the molecular and immunopathologic mechanisms that underlie this disease, the common denominator of which is an intense, perpetuated inflammatory process, which drives the formation of polyps and hyperplastic mucosa. It is this inflammatory process[26] that is also the target of virtually all forms of therapy currently available to clinicians treating patient with CRS.

Clinical Presentation of Disease

CRS, with or without nasal polyposis, is associated with a myriad of clinical symptoms that commonly include facial pain or pressure; facial congestion or fullness; nasal congestion or obstruction; rhinorrhea; hyposmia or anosmia; low-grade fever; chronic cough; headache; halitosis; fatigue; dental pain; and ear pressure or pain[21].

Of these various symptoms, the most common major symptoms are nasal obstruction, observed in 94% of patients; facial congestions-(85%); and nasal discharge (82%); the most common minor symptom is headache, observed in 83%.

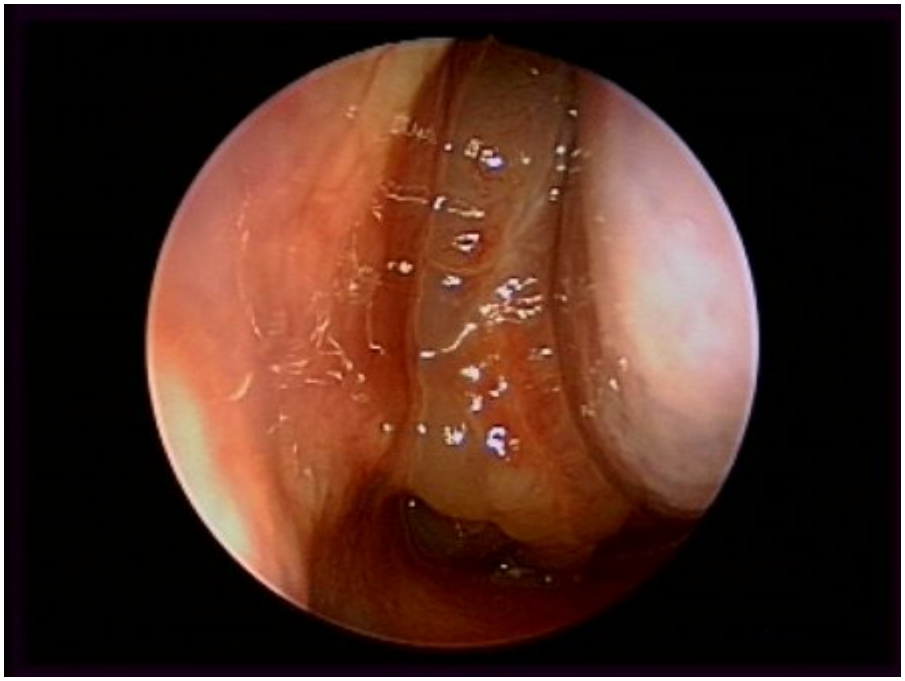


Fig 7 : Endoscopic Picture of Sinonasal Polyps

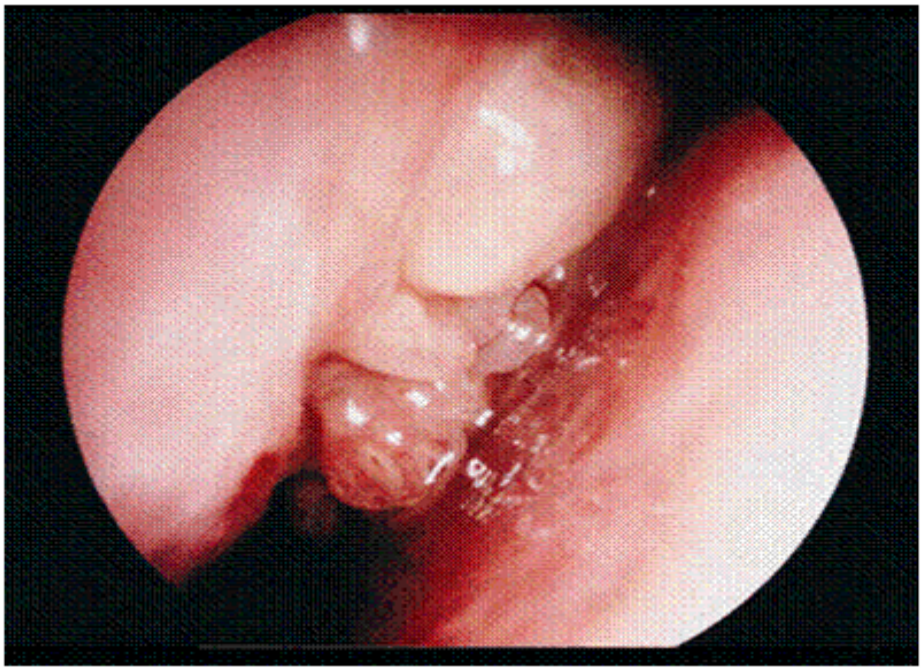
1. 

Fig 8 : Endoscopic Picture of Sinonasal Polyps

The Rhinosinusitis Consensus Research Definitions and Clinical Trial Guidelines list four different categories of sinusitis: recurrent acute sinusitis; CRSwP; CRS without polyposis; and classic allergic fungal sinusitis. Consequently, different sets of classification criteria have been created, primarily distinguishing acute bacterial rhinosinusitis from other types of rhinosinusitis[22]. Both include lists of major and minor symptoms, and both have requirements for at least two major criteria or one major and two minor criteria for a diagnosis of probable rhinosinusitis.

Both criteria sets include purulent anterior nasal drainage and purulent posterior drainage as major symptoms. Most of the other symptoms listed above are given largely as minor criteria for acute rhinosinusitis or some as major and others as minor criteria for rhinosinusitis, acute or chronic. This paper and research study focus on CRS rather than acute or allergic fungal sinusitis and, in particular, on CRSwP[25].

Nonsurgical Management of CRS and Nasal Polyposis

ESS or FESS generally is reserved for patients with CRS, with or without nasal polyposis, who are refractory to maximal medical management. However, this subgroup constitutes the minority of patients. Most patients respond to one or a combination of treatments that may include-Maximal Medical Therapy(MMT) with antihistamines, nasal decongestants, antibiotics, and corticosteroids-both

topical and systemic, Mast cell stabilizers, Mucoevacuants, Leukotriene antagonists, immunotherapy and other supportive management like optimal nutrition, steam inhalation, nasal irrigation, allergic desensitization and avoiding environmental ancitants[4].

Of these, antibiotics and corticosteroids have warranted the greatest research interest. Although the microbiology of purulent CRS is well documented, the treatment of this condition is not easily based on solid evidence. There is fairly solid evidence that endoscopically guided cultures can be helpful in identifying offending organisms in CRS ,and using this information[23] to direct antimicrobial therapy is a commonly accepted practice.

The most recent guidelines addressing the issue of therapy selection and duration still recommend 4to 6weeksof uninterrupted therapy for CRS. When chosen for use, a variety of different antibiotic regimens have been touted as effective, including amoxicillin/clavulanicacid , the macrolides (such as clarithromycin), ciprofloxacin and newer fluoroquinolones and trimethoprim/sulfamethoxazole[24]. Although usually taken orally, some treatment regimens warrant intravenous or intranasal delivery of these drugs.

However, in general, clinical trials involving antibiotics have been small, or noncontrolled, or of short duration, and relapse rates have been as high as 89%. Moreover, the use of antibiotics is not without the risk of complications.

Intravenous antibiotics are prone to a variety of catheter related complications, albeit in a small minority and all antibiotics carry the risk of drug reactions and the development of resistance. In patients who have failed more traditional medical regimens, potentially including CRS associated with chronic purulence, selective irrigation of the sinuses with a solution containing antibiotics and corticosteroids has shown potential.

Perhaps the most interesting and novel evidence supporting the benefit of antibiotics involved a study of mucociliary clearance in patients treated with antibiotics for CRS.

The respiratory tract is lined by an epithelium comprising mucus producing cells and ciliated cells that serves as the first line of defense in the upper and lower respiratory tracts. Failure of mucociliary clearance is associated with chronic or recurrent respiratory tract infection[25]. Prolonged antibiotic use can help to restore mucociliary system function.

Although antibiotics are generally thought to be of benefit through their antimicrobial properties, which reduce bacterial infection and its associated host inflammatory response, considerable work has examined the anti-inflammatory/immunomodulatory effects of the macolides, an effect that may be more important in CRS than their antimicrobial effect. Clarithromycin, in particular, has been demonstrated to have a variety of immunosuppressant effects,

including in vitro reduction in the cellular production[25] of transforming growth factor-beta and nuclear factor-kappa B and of interleukin-5, interleukin-8, and granulocyte-macrophage colony-stimulating factor. In fact, some authors are currently recommending macrolide therapy as a standard part of maximal medical therapy prior to considering a patient as a candidate for ESS.

Further evidence supporting the value of immune- modulating therapy in CRS comes from a recent pilot study involving the use of interferon (IFN)-gamma.

In that study[25], 10 patients with treatment resistant CRS who had been treated with exogenous IFN- gamma (50g/m2) were evaluated by retrospective assessment of clinical outcomes compared with clinical and laboratory findings before IFN-gamma treatment. Prior to treatment, all 10 patients had been suspected of having deregulated IFN-gamma production. CRS in these patients was reported to be better controlled in all nine patients who received exogenous IFN-gamma for longer than 3 months.

Thus it has been concluded that exogenous IFN-gamma maybe a therapeutic option in a subset of patients with treatment resistant CRS and evidence of deregulated IFN-gamma production. However, the greatest evidence both for the role of inflammation in the development and perpetuation of CRS and nasal polyposis and for the benefits of immune-modulating therapy stems from the

apparent effectiveness of corticosteroids in the treatment of both conditions occurring singly or in combination.

Corticosteroids in Medical Management of CRS and Nasal Polyposis

The evidence that topical corticosteroids have a beneficial effect in CRS and nasal polyposis is quite compelling.

As early as 1994, a study of 11patients[25] with CRS and nasal polyposis who had been treated for 1 month with the topical nasal steroid budesonide, 200 to 400 g/day, and compared them with 10 untreated patients. Overall, it was found that most eosinophils in the examined nasal tissues were in the stoma layers and that the proportion of activated eosinophils was significantly lower in polyps from steroid-treated patients. Also, in the polyps from treated patients, the superficial stoma layer and deep stoma layer both contained significantly fewer CD3, CD4, and CD8 T lymphocytes.

Subsequently, the benefit of various preparations of topical corticosteroids, such as betamethasone sodium phosphate nasal drops and beclomethasone dipropionate, fluticasone propionate, and budesonide nasal sprays, for CRS and nasal polyposis has been demonstrated in several randomized, placebo-controlled trials.

The mechanism by which they work appears to be multifactorial, the effect being initiated by their binding to a specific cytoplasmic glucocorticoid receptor.

At a cellular level, this results in a reduction in the number of antigen-presenting cells, in the number and degree of activation of Tcells, in number of mast cells, and in the number and degree of activation of eosinophils[25].

Topical corticosteroids are of use in the primary treatment of nasal polyps when they are of a small or medium size, but surgery is generally required for larger polyps because of the resultant nasal obstruction and limited access for topical preparations.

Corticosteroids[25] also have been suggested to reduce the need for ESS. Another study of 54 patients scheduled for ESS because of severe nasal polyposis, CRS, or both were included in a 12-week, double-blind, placebo- controlled study. Half of the subjects were randomized to receive fluticasone propionate nasal drops (FPND) in a concentrated form. Use of intranasal steroid spray was stopped at least 4 weeks before randomization. Signs and symptoms were recorded before, during, and at the end of the treatment period. At the end of the study, a CT scan was performed, and the need for operation was reassessed by means of a standardized scoring method. ESS no longer was required in 13 of 27 steroid-treated patients.

This study provides evidence of effectiveness for topical steroids delivered in an alternate form but did not provide effective management in all cases. Despite ample evidence that topical corticosteroids have efficacy in the preoperative

medical management of rhinosinusitis, only recently have investigators started to look at the potential benefit of intranasal steroids postoperatively. The results have been mixed.

One question that remains to be answered, and which is the focus of this paper, is the role of systemic corticosteroids peri-operatively in patients undergoing ESS. As discussed in the following section, ESS is believed to be a highly successful procedure, but it is associated with complications and a relatively high rate of recidivism, both of which might be alleviated, at least to some degree[25], by the concurrent application of the potent anti-inflammatory properties corticosteroids induce. Also, in the following section, the value and merits of systemic steroids in the management of CRSwP will be discussed.

Endoscopic Sinus Surgery

ESS, sometimes called FESS, was first described in the North American scientific literature by Kennedy in 1985. It was touted as an effective way of re-establishing ventilation and mucociliary clearance of the sinuses, primarily by means of endoscopic removal of hypertrophic tissue and bone from key areas of the anterior ethmoid and middle meatus. In addition, sphenoethmoidectomy was possible while preserving the middle turbinate.

The technique afforded the advantage of excellent visualization, with relatively minimal trauma, bleeding, and overall morbidity, so much so that, in 1994, Maran wrote, "Endoscopic nasal surgery has become the single major

Fig 9 : Endoscopic Picture of Sphenoid Polyps

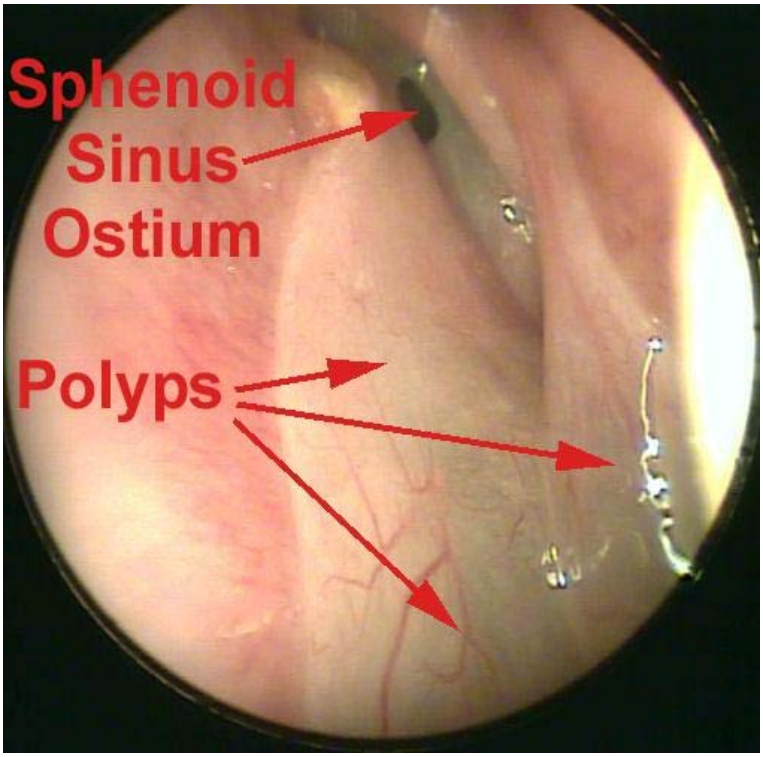
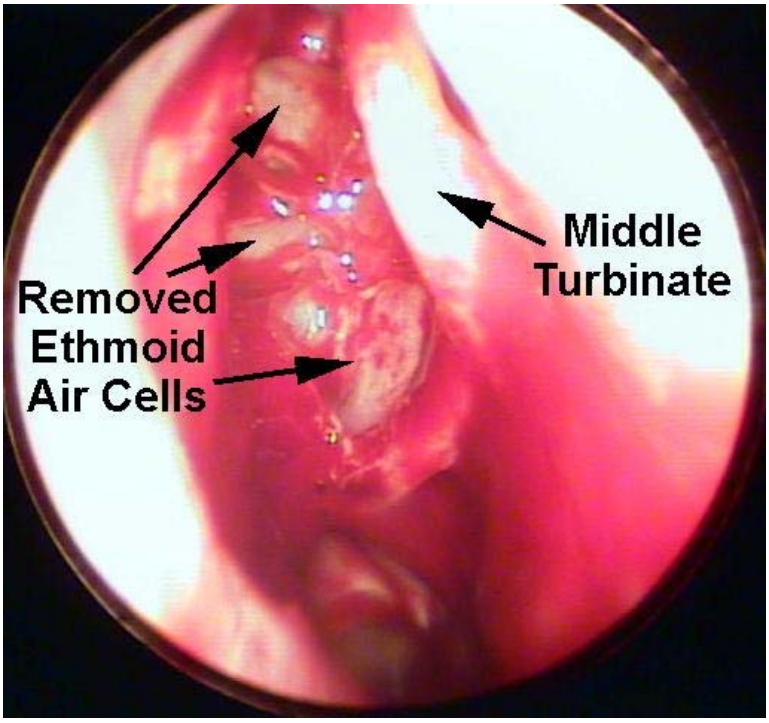


Fig 10 : Per operative picture Ethmoidectomy



advance in the specialty of otolaryngology since the introduction of the operating microscope and middle ear surgery".[25] Since that time, there have been numerous clinical studies demonstrating both the short-term and long-term benefits of ESS. These studies have documented improvement in a variety of parameters, from specific symptoms such as olfaction, to general health and quality of life. ESS even appears to benefit the asthma that commonly accompanies CRS.

Various studies demonstrated that[25] ESS was more effective at producing healthy sinus cavities than the radical Caldwell-Luc surgery. More recent studies have compared ESS in combination with various preparations of corticosteroids versus corticosteroids alone. There is evidence of the effectiveness of systemic steroids in the treatment of CRSwP and reinforces the widely held management principle that patients are only considered candidates for ESS when they have

failed maximal medical therapy, generally including systemic steroids. The benefit of ESS in CRS, with or without polyposis, largely is accepted.

Most endoscopic sinus surgeons only would consider a patient to be a candidate for ESS after they have failed maximal medical therapy, in its current state of the art. As surgeons, we are always cognizant that the procedure itself is not without risks, and once the decision has been made that a patient will benefit from ESS, the surgeon always considers the potential downside of the intervention, in particular the potential complications.

Complications of ESS generally include potential orbital injuries, such as hematoma or extraocular muscle injuries, osteitis, and skull base injuries[25]. All of these complications, fortunately, are rare in experienced hands.

Nonetheless, one of the potential advantages of peri-operative corticosteroids would be to reduce preoperative and intraoperative swelling and polyp load as well as reduce the degree of inflammation and, theoretically, blood flow or loss, thereby improving visualization of the surgical field and facilitating surgery and disease clearance. The use of corticosteroids peri-operatively, however, is unproven and not without potential risks of its own.

Peri-operative Management for ESS

Peri-operative medical therapy in patients undergoing ESS is believed by many to be important, although there is considerable variability in actual practice based on published and survey data. Although many surgeons believe that routine

post-operative care including endoscopic debridement optimizes surgical outcomes, the evidence is conflicting.

In fact, in one study[25], 95.5% of 45 patients with refractory CRS achieved at least a 50% reduction in symptoms, despite a complete absence of post-operative care other than nasal douching with hypertonic saline after the 10th postoperative day. Consequently, the general consensus appears to be that some peri-operative management is indicated.

A significant body of literature exists examining various aspects of peri-operative management, especially of postoperative management. These studies include clinical trials examining the effectiveness of peri-operative antibiotics; mitomycinC (MMC)[25]; nasal packing; various wound dressing materials; the use of post-operative debridement; and counseling regarding cessation of smoking cigarettes. These studies have provided conflicting results.

With respect to MMC, for example, Chungetal[25]., in a study of 55 patients undergoing bilateral ESS in whom a pledget soaked with 1 mL 0.04 mg/mL MMC randomly was applied to the infundibulum of one side and a similar pledget soaked in saline was applied to the other, unilateral adhesions were observed only in 3.6%of the MMC sides versus 14.5%of the saline sides, a result that almost achieved statistical significance (P .058). Conversely, in view of the unknown long-term risks of administering an antineoplastic agent for non-neoplastic disease, this therapy has not gained wide popularity.

Peri-operative Corticosteroids for ESS

As already indicated, corticosteroids, in one form or another, often are part of standard medical management, and this often is continued throughout the peri-operative period and beyond in patients undergoing ESS. However, this is not without risks because systemic corticosteroids not only reduce inflammation, they also generally impair immune responses, delay wound healing, and predispose patients to a variety of potentially serious side effects, some of which may occur acutely.

The rationale for their use in the peri-operative period, also as stated earlier, is that reduced inflammation in the operative field would intuitively be anticipated to improve visualization, reduce bleeding and related surgical complications, and result in improved healing, with less inflammation and less scarring. This all is unproven, however, which is the principal motivation behind the current study.

Mechanisms by Which Corticosteroids Work

Cortisone first was isolated from adrenal tissue by Mason et al. in the 1930s. It was Hench et al., however, who sparked interest in corticosteroids as a potential therapeutic agent, when they discovered their potent anti-inflammatory effects, a discovery that won these investigators a Nobel Prize in 1950. Unfortunately, it soon was discovered that the therapeutic use of corticosteroids

was associated with a myriad of potential side effects, many quite unpleasant and many others potentially disfiguring or serious.

After years of trial and error, the current state of the art for steroid use is to use as low a dose as possible, for as short a time as possible. Nonetheless, their use continues, in some instances, because they are life or limb saving. Moreover, many conditions, by their very nature, require the chronic use of corticosteroids. Until very recently, for example, chronic use of corticosteroids was the only therapeutic option available for patients with polymyalgia rheumatica and giant cell arteritis[25].

There is no question that, except for treating patients who are adrenal insufficient, the therapeutic benefits of corticosteroids almost exclusively stem from their potent anti-inflammatory and immunosuppressant effects. These effects certainly are what are thought to be of advantage in the treatment of CRS and nasal polyposis.

The specific mechanisms by which corticosteroids work in general, or in particular in CRS and nasal polyposis, are unclear. What is known is that corticosteroids have a large variety of anti-inflammatory and immunosuppressant effects that inhibit both cascades at virtually all levels. They inhibit the migration of neutrophils and monocytes; presentation of antigen by macrophages to lymphocytes; lymphocyte proliferation, activation, and differentiation, and cytokine production and action. Virtually all species of lymphocytes appear to be

sensitive to these inhibitory effects, including the T-lymphocyte subsets that appear to be predominant in CRS.

Recalling that CRS and nasal polyposis are both often associated with significant local and occasional systemic eosinophilia, corticosteroids also are potent inhibitors of eosinophils and have been used clinically to treat a variety of chronic inflammatory disorders associated with eosinophilia, including asthma, eosinophilia-myalgia syndrome, eosinophilic fasciitis, eosinophilic esophagitis, Churg-Strauss syndrome, hypereosinophilic syndrome, and chronic eosinophilic pneumonia. The primary advantages of corticosteroids in the management of CRS and nasal polyposis, therefore, are their potent anti-inflammatory and anti-immune effects, their easy delivery, and their generally very low monetary cost.

As stated earlier, the mucosal edema, friability, and tissue hypertrophy present in CRS and nasal polyposis may contribute to decreased visualization within the surgical field, more significant bleeding, and an increased risk of surgical mishaps. Consequently, reducing this swelling/tissue hypertrophy potentially could improve both the ease of the operation and the ultimate outcome. In addition, reduced inflammation in the post-operative period may improve longer-term surgical outcomes. That corticosteroids can be delivered intranasal by a variety of means, including sprays and drops, facilitates their use, reduces the risk of systemic side effects (especially if used in low doses and for shorter periods of time), and, likely, improves patient compliance.

Risks of Corticosteroid Use

For all their many uses and potentially life-saving effects, perhaps only narcotics and cancer chemotherapeutic drugs inspire more trepidation than corticosteroids, and justifiably so. The list of potential corticosteroid related side effects is long and filled with many theoretically concerning effects, including[25]

- ✓ Cushing's syndrome
- ✓ weight gain
- ✓ truncal obesity
- ✓ hypertension
- ✓ various disfiguring skin changes
- ✓ diabetes mellitus
- ✓ increased risk of infections, including opportunistic infections
- ✓ myopathy
- ✓ osteoporosis
- ✓ peptic ulcer disease
- ✓ hyperlipoproteinemia and atherosclerosis
- ✓ mood and mental changes
- ✓ pancreatitis
- ✓ osteonecrosis.

There are also a litany of short- term, nuisance side effects such as

- mood disturbances
- gastric irritation
- fluid retention
- increased appetite

which are reversible with cessation of the medications. With respect to their shorter, peri-operative use, however, perhaps the side effects of greatest relevance and potential concern are

1) impaired wound healing

2) immunosuppression with resultant increased infection risk

3) osteonecrosis, particularly avascular necrosis of the femoral head in old age patients (hip)

Delayed wound healing-

That cortisone causes detrimental effects on wound healing became evident as early as 1950and 1951, when several different research groups published the results of their studies. This is not surprising given the various skin manifestations observed with Cushing's syndrome, including skin atrophy and striae

. The mechanisms of impaired wound healing appear to relate to the catabolic effects of cortisone and its analogs. These catabolic effects include protein breakdown; decreased new protein synthesis in various tissues including

skin, muscle, bone, and connective tissue; and the inhibition of DNA synthesis and cell proliferation in various cell lines including fibroblasts. These all results in delayed formation of scar tissue and delayed epithelialization, an effect that can persist for up to 9 weeks, after the drug has been withdrawn[25].

There are, however, potential mechanisms by which this impairment in wound healing can be, at least partially, reversed, including the use of vitamin A, anabolic steroids, growth hormone, and the tetrachlorodecaoxygen anion complex. Despite this, the effect of intranasal steroids[25] on wound healing never has been studied, nor have any studies addressed the potential effects of corticosteroids on wound healing in ESS. In fact, there are theoretic advantages to some impairment in wound healing with respect to the common dilemma of synechiae formation post-ESS.

Increased risk of infection-

Corticosteroids primarily benefit humankind because of their anti-inflammatory and immunosuppressive effects. However, as stated earlier, these effects are not targeted at anyone facet of the immune system or inflammatory pathway.

Corticosteroids globally inhibit both, which, at least theoretically, should result in an increase in the risk of infections. In fact, such an increase risk has been documented. This is worthy of some consideration in the post-operative period,

both because of the increased risk of infections post-operatively and because of the adverse healing effects that wound infections cause.

As pertains to ESS, one recent study undertook intraoperative cultures from the nasal vestibule, middle meatus, ethmoid lining, and peripheral blood during and after ESS in patients with CRS. The study found that approximately 30%of the patients had sterile sinuses, 50%had coagulase-negative staphylococci, and the remainder had a mixed group of "nonpathogenic"organisms. Anaerobes were conspicuously rare. In addition, blood cultures were positive in 7% of cases and were consistent with an organism already identified at the operative site.

Whether an increase in infection risk would occur with the use of intranasal steroids is not clear. In general, lower doses of corticosteroids do not appear to increase infection risk, and the short-term, peri-operative use of these medications in an otherwise immunocompetent host does not intuitively appear risky. So far, virtually all the research demonstrating an increased infection risk caused by corticosteroids was performed on patients with autoimmune rheumatic diseases, which are, in themselves, associated with significant alterations in immune status, even untreated, and with an increased risk of infections. That the same level of risk would occur in patients with CRS, even at higher doses of steroids, is unlikely, but not known.

One should recognize that, although relatively little intranasal drug[25] is absorbed systemically, at least compared with oral preparations, nonetheless, there is some absorption via this route, a phenomenon that has led to the development of several intranasal delivered drugs for the treatment, for example, of refractory migraines. Moreover, even if the amount of steroid delivered systemically is relatively small and unlikely to precipitate systemic or peripheral infections, nonetheless, the risk of local infection and its effect on clinical outcome cannot be completely ignored.

Nevertheless, it can be generally summarized that topical intranasal steroids likely have an eligible risk of immune suppression, something that may not be the case with systemic steroids.

Osteonecrosis-

Avascular necrosis of the hip is one of the classic, acute catastrophic consequences of corticosteroid use, most commonly at higher doses. Unlike osteoporosis, which only develops after at least 3 months of therapy and usually only after much longer than that, osteonecrosis has been observed as early as 7 days after initiation of steroid therapy, albeit only very rarely and generally only with higher doses. Moreover, steroid-induced osteonecrosis can involve both hips or several other joints as well, with involvement particularly in the femoral heads and condyles, the humeral heads. Osteonecrosis of the hip has been subdivided into five clinical stages, numbered from 0 to IV, as part of the Association Research Circulation Osseous international classification criteria.

Early detection is important, most easily by means of magnetic resonance imaging(MRI). Treatment includes immediate cessation of steroids and supportive measures. Although traditional thinking holds that osteonecrosis develops secondary to a hypercoagulable state with impaired fibinolysis, recent evidence has suggested that corticosteroid induced adipogenesis in bone marrow may contribute to osteonecrosis and that the statin class of cholesterol lowering medications may be helpful in preventing steroid induced osteonecrosis. Unfortunately, many patients with hip disease ultimately require total hip arthroplasties. Patients with involvement of other joints sometimes require joint fusion.

When corticosteroids are considered in the context of short-term use in patients with CRSwP, the literature does give one cause for reflection. To date, there are no data on the risk of osteonecrosis[25] with intranasal use of steroids or with ESS. Clearly, systemic steroids have significant advantages in many disease states including CRS, but this is counterbalanced by the not insignificant associated side effects. Common sense on the part of clinicians as well as published recommendations propose that systemic corticosteroids be used in situations where the indications are solid, the evidence for their efficacy is accepted if not proven, and the medical co morbidities are taken into account.

MATERIALS AND METHODS

Patient Selection

The patient population chosen for study was that with CRSwP. This is the patient population within the Chronic Rhinosinusitis population that tends to be the most recalcitrant with respect to the recurrence of both objective and subjective findings postoperatively. It is also the population in which some surgeons are likely to use peri-operative systemic steroids[7,11].

Diagnostic Criteria

Consistent with the most recent definitions recommended for clinical research into rhinosinusitis,[15] the study population included patients with symptoms of mucopurulent nasal drainage, nasal obstruction and decreased sense of smell for greater than 12 weeks duration. Patients all underwent **diagnostic nasal endoscopy** to confirm the presence of nasal polyposis bilaterally as well as **computed tomography (CT) scanning** to confirm bilateral mucosal disease. No further sub-classification beyond CRSwP was performed, consistent with the current definitions and guidelines for research regarding patients with rhinosinusitis.[15]

Period of Study

June 2007-November 2008

In Upgraded Institute of Otorhinolaryngology

Inclusion Criteria

- Adult patients (over 18 yrs of age) scheduled to undergo ESS for treatment of their disease were offered the opportunity to participate in the study.
- Upper age limit was 60 years.

To become candidates for ESS, the patient either had to have failed maximal medical therapy. Maximal medical therapy for patients with CRSwP included prolonged trials of topical therapy for more than 3 months. Topical therapy was defined as intranasal steroids given twice daily and saline irrigations. Antibiotics in the form of a 4 to 6 week course were used as appropriate as based on the endoscopic findings and endoscopically guided culture results rather than on an empiric basis.

Exclusion Criteria

- ✓ Age < 18 years
- ✓ Age > 60 years

- ✓ Patients with Diabetes Mellitus
- ✓ Patients with Hypertension
- ✓ Patients with immunocompromised status and mucociliary disorders were excluded.
- ✓ Patients with allergic fungal rhinosinusitis (AFRS) were excluded from the study. This was done preoperatively based on the classic endoscopic findings of allergic mucin and the presence of classic CT scan findings. Presence of classic allergic mucin with Charcot-Leyden crystals and fungal hyphae constituted the diagnosis of AFRS, and the patient was not included in the study population

. **Experimental Design**

To assess the impact of peri-operative systemic steroids on surgical outcomes in patients with CRSwP, a randomized, placebo-controlled study was designed. Once patients were determined to meet the inclusion criteria for the study, they were randomized to receive either placebo or systemic steroids for 7 days preoperatively and 14 days postoperatively and then stopped in a tapering dose. The dose used was 30 mg taken as the entire daily dose in the morning .The moderate dose chosen (30 mg) for this study was believed to be sufficient for effective clinical activity and to mitigate the potential undesirable short-term side effects associated with higher doses (e.g., 50-60 mg). Active medication and

placebo-multivitamin tablets- were externally identical in terms of tablet preparation. Patients continued the medication after surgery for 2 weeks. Both the cases and placebo group were given topical steroids post-operatively. Follow-up done in the post-op period till 6 months.

Surgical Technique

ESS was performed using the Messerklinger technique as described by Kennedy.[16] Mucosal preservation and preservation of normal structures was attempted in all cases. All the cases were attempted to give maximum disease clearance. Packing materials were used as necessary for hemostasis or stenting and generally consisted of Merocel and Ivalon sponges when used. Decongestant Otrivin (xylometazoline) drops were advised for 3-5 days post-operatively. All patients were placed on nasal douching and saline sprays post-operatively as well as postoperative antibiotics for a period of 2 weeks. They resumed their topical intranasal steroid sprays after nasal douching .

Data Collection Points

Baseline surgical data collected with the help of anaesthetist and surgeon

Patients were routinely seen on postoperative days 2 to 4 for removal of the packing or stenting materials. They were then seen at 2weeks postoperatively for endoscopic inspection and debridement of the ethmoid cavities. Patients were

insisted to have regular follow up. Data were collected post-operatively during the follow-up and at the end of 6 months.

Sample Size

A sample size of 50 has been taken.

25 cases and 25 controls

Ethics Approval

Institutional Ethical Committee ,Government General Hospital & Madras Medical College, Chennai reviewed the experimental design and protocol as well as the letter of information and the consent form. Full approval of the board was granted under protocol number K.Dis.No.16328P &D3/Ethics/Dean/GGH/08. All patients were given information outlining the experimental protocol and all patients signed a consent form prior to entering the study.

Data Collection

Data were first collected regarding the surgery itself and its relative difficulty including the health and state of the sinonasal mucosa. In terms of postoperative data, two additional primary outcomes were identified, namely, subjective assessment of the impact of the disease on the patient (i.e., symptoms) as well as objective data in the form of nasal endoscopy.

Operative Data

Duration of the procedure and estimated blood loss, were all recorded. Also noted at the time of surgery was the health of the nasal and turbinate mucosa. A 3-point scale (healthy 1, inflamed/erythematous 2, severely inflamed/ friable3) was used for this measurement. Finally, the disease clearance and the no.of sinuses opened is estimated by the surgeon.

Subjective Outcomes

In choosing a subjective grading scheme, the historically reliable, disease-specific Lund-MacKay SSQ was used[13] The reasoning for this choice was reproducibility, reliability and demonstrated validity. In addition ,the results are easy to interpret and record with minimal burden to the study participant. It was also believed to be useful for assessing disease activity overtime and thought to be responsive to change.[15] Thus, a visual analogue scale (VAS) that measures from 0 (symptom not present) to 10 (extremely severe) was used to assess the six symptoms of nasal blockage/congestion, headache, facial pain, olfactory loss, nasal discharge/postnasal drip, and overall discomfort.

Objective Outcomes

Nasal endoscopy was included as the single most important outcome measure of disease activity in this study. The objective nature of the assessment

with direct inspection of the sinus cavities helped to avoid the potential unreliability of patient symptoms as an estimate of the disease, particularly in the early stages of recurrence. Nasal endoscopy is an excellent way to assess disease presence and severity. The Lund-Kennedy nasal endoscopy scoring system was used.[14] Crusting and scarring including synechiae formation are graded as absent (0), mild (1), or extensive (2). Mucosal edema when severe will lead into or border on polypoid change. Polypoid change would be scored as whether present or absent.

Statistical Analysis

All data were collected and entered into a standard statistical package . Standard demographic summaries were generated, and routine comparisons were made using both univariate chi-square test.

OBSERVATION AND RESULTS

The current study is a randomized, placebo-controlled study examining the effect of peri-operative systemic steroids on surgical outcomes in patients undergoing ESS for treatment of CRSwP. Both subjective and objective outcomes measures were used. The primary objective of the study was to assess, in a detailed fashion, the effect of the steroids on these subjective and objective outcomes.

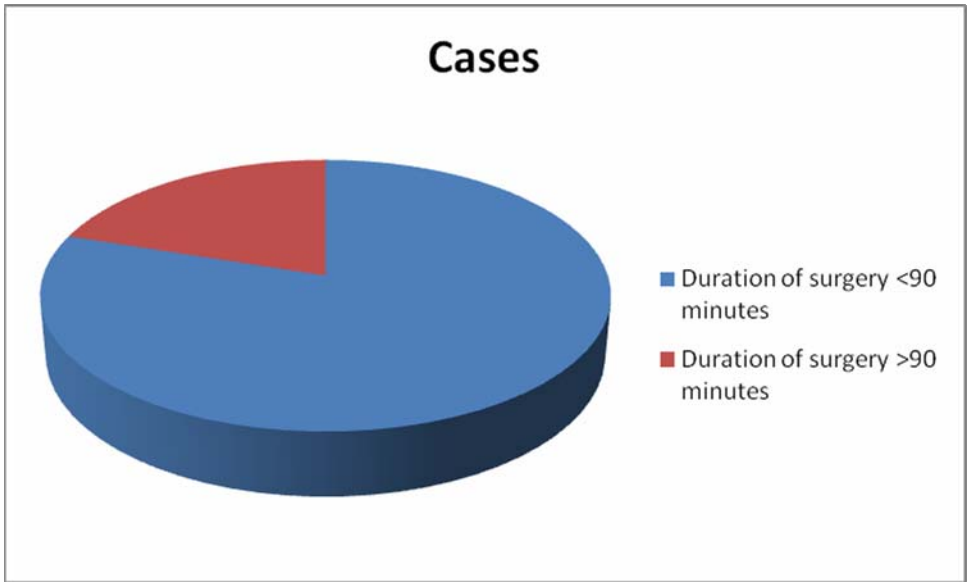
.Impact of Systemic Steroids on Technical Aspects of Surgery

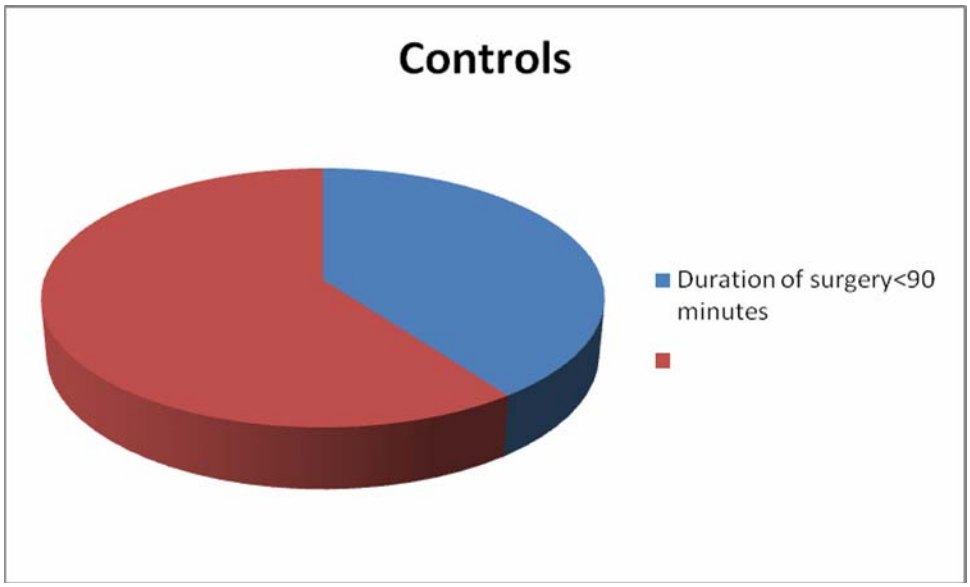
A frequent justification for the use of systemic steroids preoperatively in patients undergoing ESS for treatment of CRSwP is that it will facilitate the surgery.[11] The rationale includes less bleeding, better visualization, and less trauma to the tissues. This study therefore sought to provide some evidence to support

what is, at best, expert opinion only and not uniformly practiced.[7] The findings of this study demonstrate that there is a clinically significant difference detected in the technical difficulty of surgery.

In this study, the median value of duration of surgery in the test group is 60 minutes where as in the placebo group it is 110 minutes as shown in table1.Mean average in the test group is 70 minutes where as in placebo group it is 97.6 minutes

1. Duration of Surgery-fig :1&2





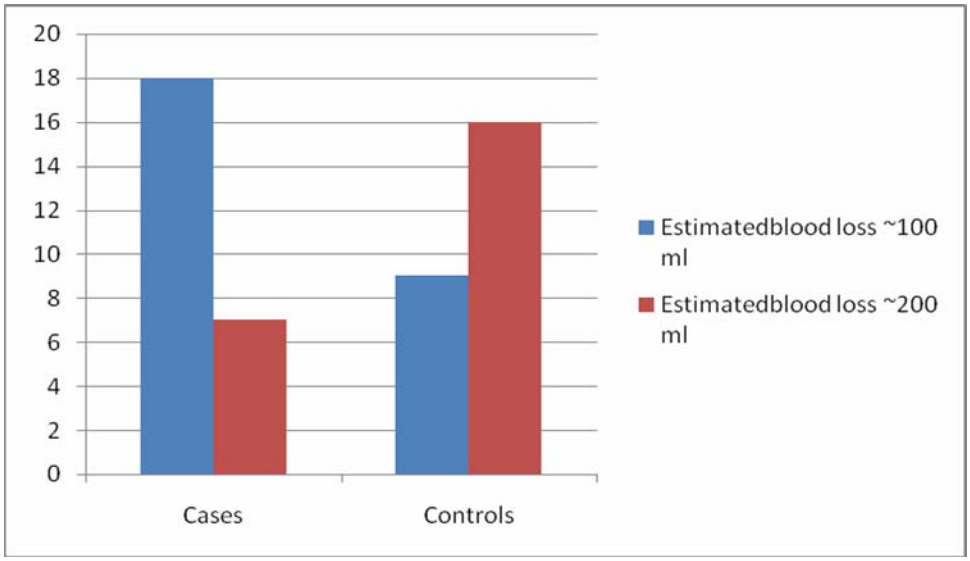
Test	minimum	40
	maximum	120
	median	60
Control	minimum	55
	maximum	130
	median	55

The use of peri-operative steroids has dramatically reduced the amount of blood loss during surgery. The mean average of amount of blood loss in the test group is 128 ml where as among the placebo group it is 164 ml. The bloodless field might have had significant influence on decreasing the duration of surgery as already seen in table 1. In the test group only 28% had severe (~200ml) blood loss using surgery where as in placebo group 64% had severe bleeding on table as shown below. .

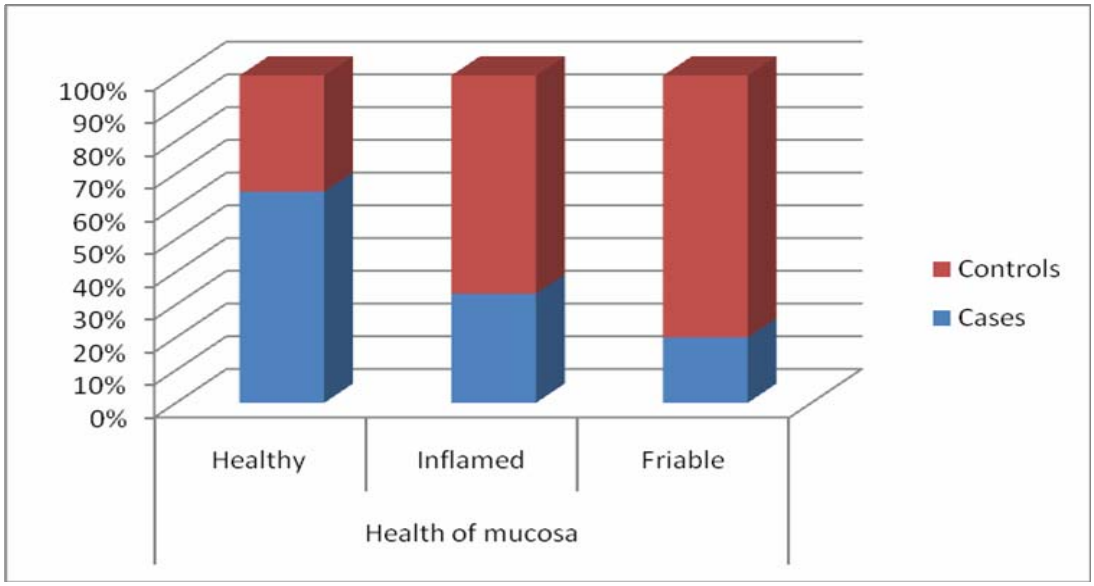
Table 2: Blood loss

Test/control			Frequency	Percent	Valid Percent	Cumulative Percent
test	Valid	100	18	72.0	72.0	72.0
		200	7	28.0	28.0	100.0
		Total	25	100.0	100.0	
control	Valid	100	9	36.0	36.0	36.0
		200	16	64.0	64.0	100.0
		Total	25	100.0	100.0	

2. Estimated Blood Loss-fig :3



3. Health of Mucosa-fig :4



Furthermore, patients who did not receive preoperative systemic steroids were far more likely to have sinonasal mucosa rated as friable in32% cases, inflamed mucosa in 24% cases and healthy mucosa in 44% cases. On the contrary

in the test group sinonasal mucosa were rate as friable in only 8% cases, inflamed mucosa in 12% cases and healthy mucosa in 80% cases. This is shown in table 3.

Table 3: Health of mucosa

Test/control			Frequency	Percent	Valid Percent	Cumulative Percent
test	Valid	healthy	20	80.0	80.0	80.0
		inflamed	3	12.0	12.0	92.0
		friable	2	8.0	8.0	100.0
		Total	25	100.0	100.0	
control	Valid	healthy	11	44.0	44.0	44.0
		inflamed	6	24.0	24.0	68.0
		friable	8	32.0	32.0	100.0
		Total	25	100.0	100.0	

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These differences were rated as significantly important clinically and this might have contributed to the operative ease during surgery in test group. This gross difference shows the anti-inflammatory efficacy of steroids in cases of sinonasal polyposis.

It is to be noted that maximum disease clearance could only be given in cases treated peri-operatively with steroids. All the sinuses-Maxillary, Ethmoids, Frontal and sphenoid sinuses-were cleared of the disease in all the cases in test group. In the placebo group, all sinuses could be opened only in 20% cases as

shown in table 4 .

Table4: No. of Sinuses opened

Test/control			Frequency	Percent	Valid Percent	Cumulative Percent
test	Valid	8	25	100.0	100.0	100.0
control	Valid	4	13	52.0	52.0	52.0
		6	7	28.0	28.0	80.0
		8	5	20.0	20.0	100.0
		Total	25	100.0	100.0	

In all the other cases in placebo group, surgeon was not satisfied about the disease clearance. In those cases surgery was restricted only to maxillary and ethmoid sinuses due to absence of adequate visualization and severe bleeding.

Finally, it is noteworthy that the two variables, duration of surgery, blood loss , mucosal health and the disease clearance which can be linked.

Impact of Steroids on Subjective Outcomes (Symptoms)

The impact of ESS on subjective outcomes for both groups was demonstrated in this study to be clinically significant at 6 weeks postoperatively.

Test/control			Facial pain score	Headache score	Nasal block	Nasal discharge	olfactory disturbance	overall discomfort	total score
test	N	Valid	25	25	25	25	25	25	25
		Missing	0	0	0	0	0	0	0
	Median		8	6	9	9	7	7	45
	Minimum		8	6	9	9	7	5	45
	Maximum		8	6	9	9	7	7	45
control	N	Valid	25	25	25	25	25	25	25
		Missing	0	0	0	0	0	0	0
	Median		4	4	4	4	4	4	20
	Minimum		4	4	4	4	4	4	20
	Maximum		6	6	6	6	6	6	30

operatively has only a median score of 2 for nasal block where as the placebo group showed a median score of 8.This is shown in table 5. This can be explained well with the complete disease clearance in the test group.

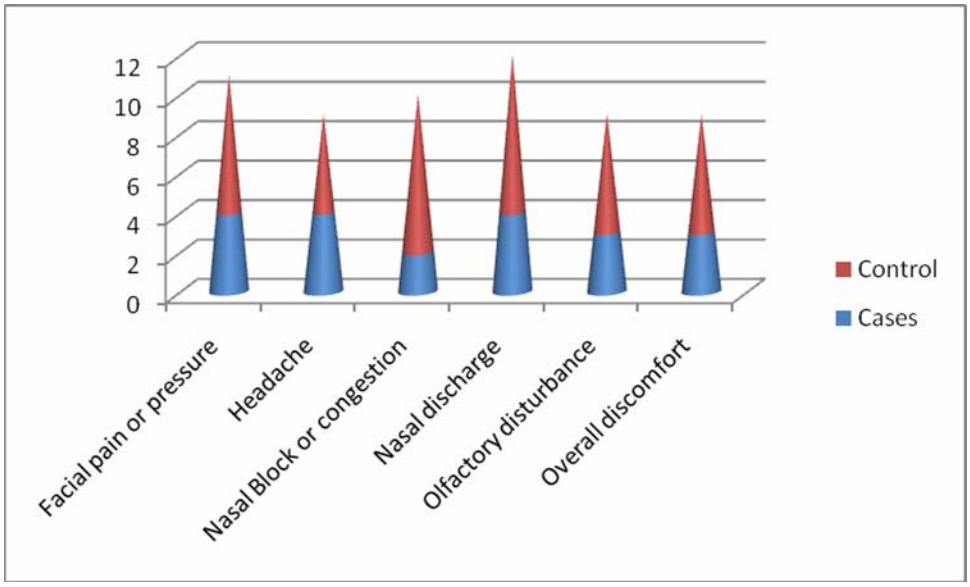
This difference could also be appreciated in the improvement of olfactory disturbance and over-all discomfort score note in the test group. As shown in table 5, median score for olfactory disturbance is 3 in the test group where as it is 6 in the placebo group. The same is seen with over-all discomfort score. This can also b explained well with the complete disease clearance in the test group and also the absence of post-op scarring, crusting and recurrence which is described later

There is also noticeable difference in the median score of facial pain among the test and the placebo group. As shown in table 5 it is 4 in the test group where as it is 7 in the placebo group. The same difference would be seen with median score for nasal discharge .It is 4 in the test group and 8 in the control group. This is shown in table 8.

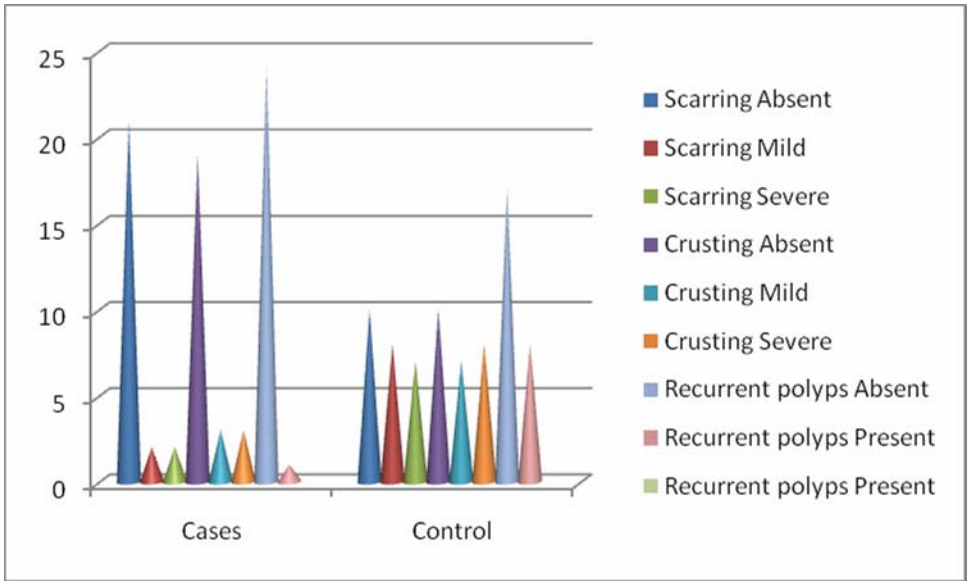
The only symptom score which does not show much difference between test group and placebo group is median score for headache. It is 5 in the placebo group and 4 in the test group. This is shown in table 5. This may b due to intermingling or blending of other causes of headache.

And the total symptom score shows significant difference among both groups. Median total symptom score in the test group is 20 where as the total

3. Subjective outcome-Visual Analogue Scoring-fig :5



4. Objective Outcome-Lund Kennedy Endoscopic Scoring-fig :6



symptom score among the control group is 40 .This proves the efficiency of peri-operative administration of steroids in the subjective outcome.

Impact of Steroids on Objective Outcomes (Endoscopy)

With use of the Lund-Mackay endoscopic scoring system to compare patients, there were significant improvements noted at most time points for the prednisone group but not for the placebo-treated groups. Thus, the patients receiving prednisone had clinically significant healthier cavities.

In the test group post-operative scarring and synechiae formation is absent in 84% cases where as there was scarring in the placebo group in 60% cases. This is shown in table 6.

Table 6: post-op scaring

Test/control			Frequency	Percent	Valid Percent	Cumulative Percent
test	Valid	absent	21	84.0	84.0	84.0
		mild	2	8.0	8.0	92.0
		severe	2	8.0	8.0	100.0
		Total	25	100.0	100.0	
control	Valid	absent	10	40.0	40.0	40.0
		mild	8	32.0	32.0	72.0
		severe	7	28.0	28.0	100.0
		Total	25	100.0	100.0	

:

This impact is due to the anti-inflammatory effect of corticosteroid peri-operatively. The less tissue injury due to healthy mucosa an less duration of surgery among the test group might also have contributed to decrease the incidence of scarring.

The same effect is seen with post-operative crusting also. This is shown in table7. In the test group there was no crusting in 76% of cases where as there was noticeable crusting in 60% of the placebo group. This also shows the efficacy of anti-inflammatory action of steroids.

Table 7: post-op crusting

Test/control			Frequency	Percent	Valid Percent	Cumulative Percent
test	Valid	absent	19	76.0	76.0	76.0
		mild	3	12.0	12.0	88.0
		severe	3	12.0	12.0	100.0
		Total	25	100.0	100.0	
control	Valid	absent	10	40.0	40.0	40.0
		mild	7	28.0	28.0	68.0
		severe	8	32.0	32.0	100.0
		Total	25	100.0	100.0	

The incidence of recurrence is also more among the placebo group. Recurrent polyps were seen in 4% of cases in the test group where as it was 32% in the placebo group as shown in table 8.

Table 8: Recurrent polyps

Test/control			Frequency	Percent	Valid Percent	Cumulative Percent
test	Valid	absent	24	96.0	96.0	96.0
		mild	1	4.0	4.0	100.0
		Total	25	100.0	100.0	
control	Valid	absent	17	68.0	68.0	68.0
		mild	8	32.0	32.0	100.0
		Total	25	100.0	100.0	

The recurrence was assessed at the end of 6 months. If an endoscopic follow-up is done at 2 years or later this value might increase. The increase recurrence rate among the placebo group can be attributed to the incomplete clearance of the disease as already explained in table 4.

Fig 11: Post-op Picture

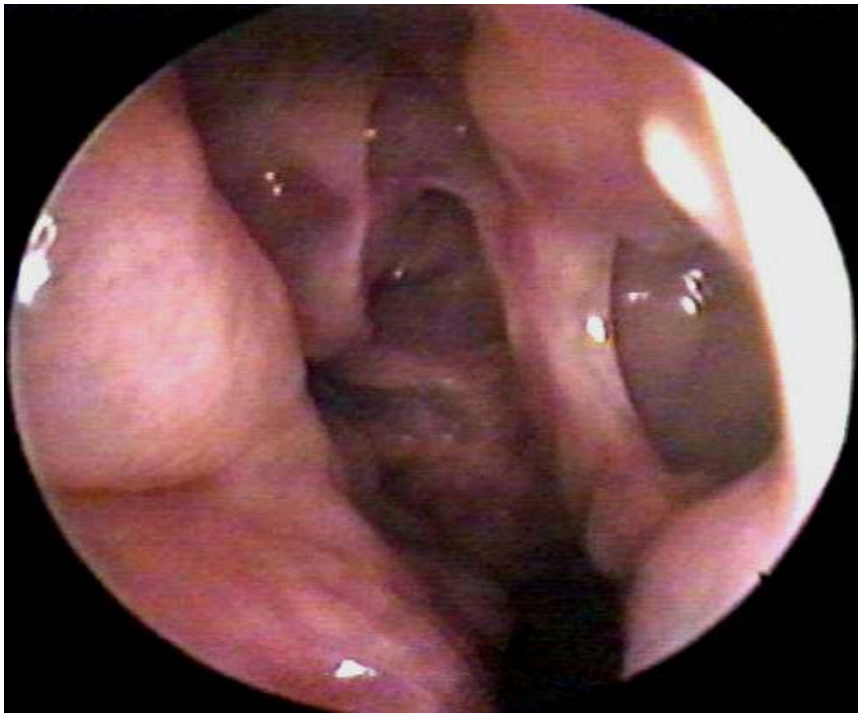
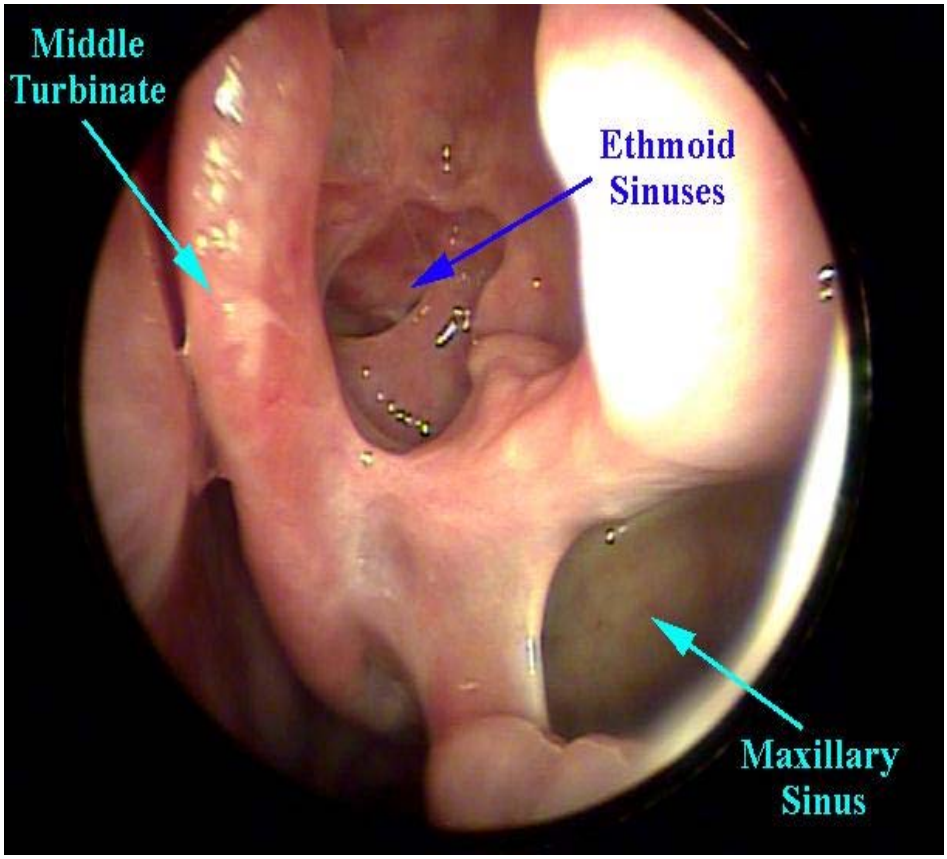


Fig 12 : Post-op Picture after 6 months



DISCUSSION

The treatment of Chronic Rhinosinusitis with Sinonasal Polyposis is Endoscopic Polypectomy. This has been well proven over many years. But the role of corticosteroids an its administration is debatable over many years. In this study this debate has taken into the topic of study.

Systemic steroids can be given as tablets –prednisolone –as we administered in this study or as depot injections. The total glucocorticoid dose in a depot injection corresponds to about 100 mg prednisolone. When given orally the dose is 30 mg prednisolone daily for 3 weeks. However controlled dose effect studies are not available.

Lildholt[3] has described that a short course of systemic steroid is equally effective as simple polypectomy with a snare and it may serve as medical polypectomy. This study also proves the above observation. In severe disease requiring endoscopic surgery, pre-operative use of steroid will considerably facilitate surgery. This is proven in this study. Adverse effects from this therapy cannot be expected to be severe and may be outweighed by increased quality of life in patients with severe disease an abolished fashion[3]

Intranasal steroids are by far the best documented type of treatment for Sinonasal polyposis. There are at least 16 placebo controlled studies and they have

all shown a significant effect. Some patients do not respond to topical steroids. This may be due to inadequate intranasal distribution of spray in a very blocked nose. Here comes the importance of Endoscopic polypectomy.

Intranasal steroids an systemic steroids will not eliminate the polyps, but the treatment clearly reduces the size and decrease the inflammatory activity of mucosa and thus facilitate surgery. On the other hand, an effect on polyps in the middle meatus cannot be expected as only a small fraction of spray reaches the middle meatus. So these critical areas should be opened during surgery to facilitate good ventilation of the sinuses. In this study in the placebo group, the number of sinuses opened surgically was actually lower than planned, an effect not observed with the prednisolone group. As noted by the surgeon, this difference was not caused by the absence of disease in the unopened sinuses, but rather was limited by technical issues primarily related to visualization and bleeding. With respect to the health of sinonasal mucosa as assessed at the time of surgery, there was a significant difference between groups, with the placebo group having a much higher incidence of friable an inflamed mucosa compare with the test group.

Controlled studies have shown that topical steroids can delay the recurrence of polyps after surgery. However the effect is partial especially in cases of pronounced inflammatory activity.

CONCLUSION AND SUMMARY

Based on the data collected and analyzed in this study, several conclusions can be drawn as related to the study objectives.

First, pretreatment with systemic steroids appears to confer the advantages of facilitating surgery, by opening up all the diseased sinuses; and clearing the disease and improving the health of the sinonasal mucosa and minimizing the bleeding thus decreasing the duration of surgery. Therefore, in the context of evidence-based practice, there is sufficient evidence to support the preoperative administration of systemic steroids to all patients undergoing ESS for CRSwP.

Second, treatment postoperatively with systemic steroids results in better symptom relief especially nasal obstruction, loss of smell, facial pain, nasal discharge, headache and overall discomfort.

Third, the treatment with systemic steroids in the immediate post-operative period results in endoscopically healthier sinus cavities in the short term, an outcome of relevance if the goal of sinus surgery for these patients is to achieve an endoscopically healthy sinonasal cavity in the long term. Thus, in the practice of surgeons who provide intensive postoperative care for patients post- ESS, including debridement and medical therapy, as based on the endoscopic findings,

there is evidence to support administering systemic steroids in the postoperative period in an effort to optimize the initial endoscopic appearance of the cavities

Lastly, the peri-operative administration of adjuvant steroids are also beneficial to prevent the post-operative complications like post-op scarring, synechiae formation, post-op crusting and to prevent recurrence.

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ABBREVIATIONS

- CRS → Chronic RhinoSinusitis
- ESS → Endoscopic Sinus Surgery
- CRSwP → Chronic Rhinosinusitis with Sinonasal Polyposis
- V_1 → Ophthalmic branch of Trigeminal Nerve
- V_2 → Maxillary branch of Trigeminal Nerve.
- pO_2 → Partial pressure of Oxygen
- CO_2 → Carbon Dioxide
- N_2O → Nitrous Oxide
- FESS → Functional Endoscopic Sinus Surgery
- CT → Computed Tomography
- RANTES → Regulated on Activation, normal T-cell expressed , and secreted
- MMT → Maximal Medical Therapy
- IFN → Interferon
- MBP → Major Basic Protein
- MMC → Mitomycin C
- MRI → Magnetic Resonance Imaging
- AFS → Allergic Fungal Sinusitis
- SSQ → Sinus Symptom Questionare
- VAS → Visual Analogue Scale
- LKES → Lund Kennedy Endoscopic Scoring