Endoscopic Surgery Versus Balloon Sinuplasty in Chronic Rhinosinusitis
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Endoscopic Surgery
Versus Balloon Sinuplasty
in Chronic Rhinosinusitis

ACADEMIC DISSERTATION
To be presented, with the permission of
the Board of the School of Medicine of the University of Tampere,
for public discussion in the Main auditorium of building M,
Pirkanmaa Hospital District, Teiskontie 35, Tampere,
on 21 October 2016, at 12 o’clock.

UNIVERSITY OF TAMPERE
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Endoscopic Surgery Versus Balloon Sinuplasty in Chronic Rhinosinusitis
To my father for motivating me to study medicine

Αφιερωμένο στον πατέρα μου, που μου μετέδωσε το πάθος του για την ιατρική
Rhinosinusitis (RS) is a common medical condition with substantial symptoms and a remarkable impact on the quality of life (QoL). The term RS is defined as the concurrent infectious and inflammatory processes that affect the nasal passages and the surrounding paranasal sinuses. Infection, mucosal hyperactivity and anatomical variation all contribute to some extent to the pathophysiology of RS. Chronic rhinosinusitis (CRS) is an inflammatory condition of the nasal passage and paranasal sinuses lasting for 12 weeks or longer. A key point of CRS is the persistent inflammation of the nasal and paranasal cavities. Symptoms of CRS vary in severity and prevalence. Surgery is reserved for patients who are refractory to medical treatment.

This aim of this thesis is to study the effects of balloon sinuplasty (BSP) and endoscopic sinus surgery (ESS) on the quality of life (QoL) of patients diagnosed with CRS. In a prospective randomized non blinded controlled trial, the clinical outcome and impact of both BSP and ESS treatment were assessed and compared separately. Acoustic rhinometry and rhinomanometry were used to assess nasal airway patency. Mucociliary clearance (MCC) was measured with an endoscope and gamma camera after 0.03 ml of saccharine, methylene-blue dye and human albumin labelled with Tc99m was introduced to the bottom of maxillary sinuses. Further, the pathology of the upper airway mucosa and the expression of matrix metalloproteinase-9 (MMP-9) protein was studied. In addition, changes in histopathology after treatment were evaluated and compared.

Adult patients with symptomatic isolated CRS or recurrent acute rhinosinusitis (RAR) without severe findings in the sinuses, as documented in a sinus cone beam computer tomography (CBCT) scan and clinical examination, were randomized in 2 groups: ESS and BSP. The main variables in this study were the Sinonasal Outcome Test-22 (SNOT 22), the rhino tests (acoustic rhinometry and rhinomanometry), MCC and the histopathology of the nasal mucosa. These parameters were analysed preoperatively and postoperatively after 3, 6 and 12 months. The study was carried out at the Department of Otolaryngology, Tampere University Hospital, Finland.
There was not only a subjective improvement in symptoms after surgery but also an objective improvement in the QoL of our patients seen as a decrease in the total SNOT 22 score (P < 0.05). There were no significant differences found between the ESS and BSP groups (P > 0.05). Based on rhinomanometry results, nasal airway resistance (NAR) decreased after treatment. With regard to adverse effects, BSP was noticeably associated with a lower risk of synechia. Neither of the treatment methods had any effect on MCC. As assessed by saccharine test, smoking was associated with a worse mucociliary transport rate. Methylene blue test results were correlated to the results from the saccharine test and Tc99m-labeled tracer technique separately.

Histopathological analysis of the nasal mucosa before treatment showed increased thickness of epithelium, absence of cilia, metaplastic changes of epithelium, hyperplasia of the mucosal glands, angiogenesis, remodelling of epithelium, thickened lamina propria (LP) and infiltration of the epithelium and mucosa by inflammatory cells.

Allergy was correlated with the hyperplasia of goblet cells and absence of cilia was associated with worse QoL. The number of inflammatory and goblet cells were linearly correlated preoperatively and after treatment. Amelioration of treatment was observed in both treatment groups. A strong positive association was found between the expression of matrix metalloproteinase-9 (MMP-9) in epithelium and the number of inflammatory cells in the nasal epithelium and mucosa. Hypertrophy of the mucosal glands, hyperplasia of blood vessels and mucosal edema were reduced after both treatments. These histopathological changes were more remarkable in the uncinectomy group. BSP was correlated with a higher number of inflammatory cells at 6 months after treatment (P = 0.05).

Both ESS and BSP had a positive effect on the QoL of patients and decreased NAR. Both surgical techniques seemed to be equally effective in the treatment of CRS. The less traumatic nature of BSP most likely explains the lower risk of developing adhesions postoperatively. Both techniques affected positively on mucosal inflammation but failed to recover mucociliary function.


Aikuiset potilaat, joilla oli joko krooninen tai toistuva rinosinuiitti, mutta lieviä tai keskivaikeita löydöksiä kartiokelatiotokonetomografiassa kuivissa (CBCT), satunnaisitettiin kahteen hoitoyhmään: tähystyskirurgiseen leikkaukseen (ESS) tai ulosvirtaukanavien pallolaajennuksiin (BSP). Päämuuttujina käytettiin ylähengitysteiden elämänlaatukyselyä (SN O T-22), rinometrisia mittauksia (akustinen rinometria ja rinomanometria), värekarvatoiminnan mittausta ja nenän limakalvon histologiaa. Nämä muuttuvat analysoitiin ennen hoitoa ja 3, 6 ja 12
kuukautta hoidon jälkeen. Tutkimus toteutettiin Tampereen yliopistollisen sairaalan korva-, nenä- ja kurkkutautien klinikassa.


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ABBREVIATIONS

ARS acute rhinosinusitis
ASA acetylsalicylic acid
BSP balloon sinuplasty
CBCT cone beam coronal tomography
CRS chronic rhinosinusitis
CRSSNP chronic rhinosinusitis without nasal polyps
CRSwNP chronic rhinosinusitis with nasal polyps
CSF cerebrospinal fluid
CT coronal tomography
ECM extracellular matrix
ESS endoscopic sinus surgery
GERD gastroesophageal reflux disease
H & E hematoxylin and eosin
HRQoL health-related quality of life
IgE immunoglobulin E
IL-5 interleukin 5
LP lamina propria
MCC mucociliary clearance
MIST minimally invasive sinus technique
MMP matrix metalloproteinase
NAR nasal airway resistance
OMC ostiomeatal complex
QOL quality of life
RAR recurrent acute rhinosinusitis
RAST radioallergosorbent test
RCT randomized controlled trial
RS rhinosinusitis
RSOM-31 rhinosinusitis outcome measure-31
SNOT-16 & SNOT-22 sino-nasal outcome test-16 & 22
SPSS Statistical Package for the Social Sciences
TGF-b transforming growth factor-beta
TIMP tissue inhibitors of metalloproteinase
INTRODUCTION

The upper nasal airway plays a crucial role in airway homeostasis by warming up, humidifying and filtering incoming air. A pseudostratified ciliated columnar epithelium lining covers the nasal cavities as well as the paranasal sinuses. [1] Mucociliary clearance (MCC) is a substantial element of the respiratory function that protects the sinuses against infection. Mucus functions as a modulatory factor of humidity and temperature on the respiratory tract. It also cleanses the nose and throat as it flushes out invading microorganisms and pollutants through its constant movement down the upper respiratory tract. There are millions of cilia that sweep back and forth on an average of 10 to 20 beats per second pushing the mucus along. MCC clears the sinuses of their secretions in less than 10 minutes. The mucus then drains from the nose to the throat in about 20 to 30 minutes. [1, 2]

Rhinosinusitis (RS) is a common medical problem with significant symptoms and a substantial impact on the quality of life (QoL). RS reflects the concurrent inflammatory and infectious processes that affect the nasal passages and the contiguous paranasal sinuses. Infection, mucosal hyperactivity and anatomical variation all contribute to some extent to the pathophysiology of RS. Recurrent acute rhinosinusitis (RAR) is diagnosed when four or more episodes of bacterial acute rhinosinusitis (ARS) occur per year, without signs or symptoms of RS between episodes. If symptoms last for 12 weeks or longer in addition to clinical evidence of inflammation or oedema of the middle meatus or ethmoid region and/or radiographic imaging confirms that paranasal sinus inflammation persists for more than 12 weeks, the patient has chronic rhinosinusitis (CRS). [3] Symptoms vary in severity and prevalence. Nasal obstruction is the most common symptom followed by facial congestion-pressure-fullness, discoloured nasal discharge and hyposmia. [4] [5]

A cornerstone of CRS is persistent inflammation of the nasal cavity of unknown cause. Consequently, diagnosing CRS requires documentation of the inflammation in addition to persistent symptoms. On some rare occasions, CRS may be suspected based primarily on objective findings (e.g., nasal polyps or radiological findings) when other conditions have been excluded. Histopathological study of inflamed mucosa shows, for example, mucus cell hyperplasia, oedema, thickened basal
membrane, infiltration of eosinophils and neutrophils, abnormal mucosal remodelling and loss of cilia. Chronic inflammation of the nasal mucosa is associated with decreased MCC. [6] A lack of ciliated epithelia or non-functional cilia are regarded as the most important reasons for impaired MCC. However, the basic causative mechanisms responsible for the clinical picture of the disease still remain unclear. Obstruction in the ostia is believed to be a consequence of chronic inflammation that eventually leads to pathological alterations in the maxillary sinus mucosa and MCC. Based on this theory, unblocking the natural ostia and improving the ventilation of the sinuses should restore the damaged mucosa.

The study of the histopathology of nasal epithelium has proposed the hypothesis that a group of several genes and proteins may be responsible for the chronic inflammatory changes and abnormal mucosal remodelling. Matrix metalloproteinases (MMPs) are a subgroup of a larger group of zinc-dependent endopeptidases. The MMP-family comprises more than 20 so far identified members and plays a role in the cleavage of extracellular matrix (ECM) in normal physiological processes. This process is crucial in, e.g., embryonic development, reproduction and tissue remodelling as well as in disease processes such as inflammation, arthritis and metastasis. MMPs have been identified in nasal epithelium and one of them, MMP-9, has been located in the seromucous glands and in polymorphonuclear cells. RS is a heterogeneous disease process. Primary treatment is conservative and multiple treatments and therapies are available that include antibiotics,[7-13] hypertonic and isotonic saline irrigations or sprays,[14-21] topical and systemic steroids, [13, 22-26] antileukotriene agents and [27-31] endoscopic sinus surgery (ESS). [3] Based on current evidence, the most common treatments for chronic rhinosinusitis without nasal polyps (CRSsNP) are saline lavage, intranasal steroids and long-term macrolide antibiotics.[32] Surgery is mainly indicated for patients who are recalcitrant to medical treatment. During the last decades, ESS has become the preferred method for the treatment of CRS. ESS is defined as the access and widening of the natural pathway of the sinuses using endoscopes through the nose. In the early 2000s, the balloon sinuplasty (BSP) technique was introduced in the field of rhinology. In practice, BSP is a minimally invasive tool in rhinology that is based on the concept of remodelling the anatomy of the paranasal sinus ostia without removing mucosal tissue or bone and consequently facilitating the drainage of the mucus that builds up in patients suffering from CRS or RAR. The procedure requires no cutting and no removal of bone and tissue, which differentiates it from ESS.
ESS and BSP seem to improve both the patients' symptoms and QoL. The use of BSP has so far been generally shown to be feasible and safe. [33] Mucociliary clearance, as assessed by saccharine test [34], does not seem to correlate with the Sinonasal Outcome Test -22 (SNOT-22) questionnaire score and QoL. [6] However, there are controversial data about the effect of endoscopic surgery on MCC. In the majority of previous studies, BSP was compared with a hybrid technique where the patients underwent a combination of ESS and BSP.[33] The study and comparison of these two techniques as separate entities is therefore of substantial importance.
2 REVIEW OF THE LITERATURE

2.1 Rhinosinusitis

2.1.1 Definition, symptoms and diagnosis

RS is typically classified as ARS and chronic RS based on symptom duration (12), (15). ARS is a common upper respiratory tract infection that involves inflammation of the nasal and paranasal sinus mucosa. [35] The infection may be mild, moderate or severe. The symptoms of a common cold typically resolve in less than 5 days. In cases of ARS, however, symptoms worsen after 5 days or persist for more than 10 days. In all cases, symptoms resolve in less than 4 weeks.

Patient history and clinical examination are essential for the diagnosis of ARS. The symptoms of ARS are nasal congestion, purulent discharge, fever, headache, facial pain/pressure, dental pain, postnasal drip, cough and tenderness around the sinus area. [4, 5, 35, 36]

Based on the European Position Paper on Rhinosinusitis and Nasal Polyps document, CRS is defined by the presence of two or more symptoms associated with findings in nasal endoscopic or coronal tomography (CT) scan. [36] A CT scan is therefore not always required to diagnose CRS. The persistence of symptoms for more than 12 weeks without any clinical improvement despite medical treatments supports the diagnosis of CRS.

CRS is subdivided into two categories according to the findings of nasal endoscopy: CRS with and without nasal polyps. Previously, these two groups were considered to be variations of one single disease. Indeed, nasal polyposis was considered to be the end point of the evolution of CRS without nasal polyps (CRSsNP). [36] Nowadays, there is strong evidence that CRS with nasal polyps (CRSwNP) or CRSsNP are completely disparate based on distinct inflammatory pathways, cytokine profiles and different tissue remodelling. Approximately 60% of all CRS cases are CRSsNP. CRSsNP is defined as the following: symptoms persist for >12 weeks and the presence of more than 2 of the following symptoms: a) anterior or posterior mucopurulent discharge b) nasal congestion c) facial pain/pressure and...
d) decreased sense of smell. Diagnosis is confirmed by objective documentation using nasal endoscopy (presence of purulence, edema, crust) or with CT scan findings. CRS is defined by chronic inflammation of the nasal and paranasal sinus mucosa, cytokine release and tissue remodelling that includes changes in the extracellular matrix (ECM), protein deposition and tissue structure. [37]

2.1.2 Epidemiology

RS is a heterogeneous group of diseases that affect one out of seven people in the United States. [5] The prevalence of CRS in Canada has been estimated to be 5% of the total population. [38] A higher percentage of 13% to 15.5% has been proposed for the United States [39] while CRS prevalence in Europe is estimated to be about 2.7% to 6.6% of the population. [40] CRS is not only one of the most common chronic diseases in developed countries, but it also substantially affects the QoL [41] and productivity of patients [42] and increases healthcare spending. [43]

The cost of treating CRS patients seems to be higher than the costs related to the treatment of bronchitis. [44] In the United States, it has been estimated that the annual cost of CRS treatment is six billion dollars. [45] Based on previous studies, CRS has been shown to affect certain factors of general health (social functioning, bodily pain) more than angina, chronic heart failure, chronic obstructive pulmonary disease or chronic back pain. [46, 47]

2.1.3 Aetiology

2.1.3.1 Acute rhinosinusitis (ARS)

Viruses account for at least 80% to 90% of the causative agents of ARS. ARS becomes a bacterial infection in about 0.5% to 2% of cases. [48] In these particular conditions, the so called "infernal trio" (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis infections) must be considered. [49] Anaerobes have been reported in up to 30% of cases. The pathophysiology of ARS involves interaction between a predisposing condition [allergic rhinitis (AR), immune deficiency and environmental factors], a viral infection and a consequent inflammatory response in the mucosal lining of the nose and paranasal sinuses. [50]
2.1.3.2 Chronic rhinosinusitis (CRS)

The role of the microorganisms in CRS has not been clearly defined. Infection or colonization of the sinus by bacteria or fungi may lead to a complex and aggressive inflammatory reaction. Bacterial infections in the paranasal sinuses are involved in acute exacerbations of CRS. The most commonly found bacteria are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis. However, other bacteria such as coagulase-negative staphylococci, Staphylococcus aureus, enterobacteriaceae, Corynebacterium spp, Pseudomonas aeruginosa and less commonly the gram-negative enteric bacteria have been identified. [51] Anaerobes (e.g., Propionobacterium spp, bacteroides, or peptococci) and microaerophilia streptococci (i.e. Streptococcus milleri) are mainly involved in odontogenic cases. These bacteria are rarely involved in ARS. [48, 52] [53] In cases of CRSsNP, there is a higher risk that medical treatment will not be as effective due to some "bacteriological" factors.

Gram-negative bacteria or methicillin-resistant Staphylococcus aureus are involved in CRS, and they tend to be resistant to empirically prescribed antibiotics. However, no significant bacteriological features have been observed between CRSwNP and CRSsNP. [54]

In some cases, the formation of biofilms on the sinonasal mucosa can be a challenge in the treatment of CRS. By forming biofilms, bacteria are able to more efficiently resist antibiotic treatment and persist as a low grade infection within the sinus mucosa. The precise role of biofilms in the pathogenesis of CRS is still vague, but they can explain the persistence of rhinorrhea and crusting even though the antibiotic has been proven to be active in vitro. [55, 56]

Local osteitis of the bone underlying the mucosa may have a possible role in the course of CRS by inducing persistent inflammatory changes in the surrounding mucosa. Concurrent osteitis can be found in one third to about half of all patients suffering from CRS using radiographic and pathological criteria, respectively. [57, 58]

The role of fungi in CRS has been argued since the first publication by Ponikau et al. [59] that advocated that fungi that normally colonize the nasal and paranasal cavities might initiate an inflammatory response characterized by an eosinophilic infiltration into the nose and sinuses, leading to the development of CRS. Fungal cultures of nasal secretions have been positive in as many as 202 (96%) of 210 consecutive CRS patients.

A combination of host and environmental factors seems to be the causative form of CRS. Such factors can be categorized into general (genetic factors and immune
deficiency), local (anatomic abnormalities, mucosal and bone inflammation) and environmental factors (air pollution, allergens, viruses, bacteria and fungi). [57]

The pathophysiology leading to CRS of the maxillary and frontal sinuses usually involves a sum of changes that lead to the obstruction of the ostiomeatal complex (OMC) that include mucosal swelling and inflammation, mucous stasis, impaired MCC and microbial infection. [1]

Among several different theories about the pathophysiology of CRS, inflammation, fungal-mediated hypersensitivity, bacterial biofilms, osteitis and superantigens have latterly emerged with novel therapies targeted towards each of these specific areas. [60]

The immune barrier hypothesis suggests that a multitude of potential defects in mechanical (epithelial) and immunologic (innate and adaptive) barriers contribute to CRS. Taken together, various defects in the immune barrier result in increased microbial colonization, accentuated barrier damage and a compensatory and damaging immune response.

2.1.4. Clinical features and quality of life

The signs and symptoms of RS can differ depending upon contributing factors and the overall duration. Signs and symptoms of ARS can be divided into three groups. The first group of major criteria (very important, frequent) comprises nasal congestion, purulent nasal discharge, facial pressure, hyposmia/anosmia, headache, halitosis, dental pain, toothache and cough. The second group of minor criteria comprises fever, facial pain and tenderness, fatigue, intractability and prolonged duration. The third group comprises symptoms that may alert the physician to the presence of complication and include the following: local extension, palpable frontal or malar masses and deformity, frontal swelling, orbital pain, periorbital edema, proptosis and ophthalmoplegia. [5, 36]

CRS is most likely present if these symptoms continue for more than 12 weeks. CRS can also have a considerable effect on health-related QoL (HRQoL). [37] Health utility values among patients with CRS have been reported to be comparable to those of many chronic diseases such as congestive heart failure, coronary artery disease and chronic obstructive pulmonary disease.
2.1.5. Staging and classification

Direct visualization of nasal mucosa or computer tomography (CT) scanning have been used as tools for the objective confirmation of inflammation in upper airway mucosa. Among others proposed, Lund-Mckay classification has been dominantly used. [61, 62] Nasal endoscopy using a rigid scope is preferred for the direct visualization of mucosa. However, in some cases, anterior rhinoscopy using an otoscope or nasal speculum may provide enough information. A crucial point of nasal endoscopy is the identification of nasal polyps because that will lead the clinician to rule out neoplasm in unilateral polyps, as well as to propose slightly different treatment strategies for bilateral polyps.

2.1.6. Endoscopic staging

Anterior rhinoscopy, after decongestion, is performed in an outpatient setting at baseline as well following intervention. Information about the presence of edema, discharge, crusting, scarring and polyps can then be assessed. Typically, anterior rhinoscopy is performed with a nasal speculum with specific attention being paid to the middle turbinate and the middle meatus. An otoscope may also be used instead, but it is suboptimal.

Even though, in some cases (i.e., large polyps or gross purulence), anterior rhinoscopy is sufficient, nasal endoscopy is superior in that it also allows a more expanded visualization of the posterior nasal cavity, nasopharynx, and often the sinus drainage pathways in the middle meatus and the superior meatus.

The advantage of nasal endoscopy is that it also provides the ability to review and assess posterior septal deviation, polyps or secretions in the posterior nasal cavity and polyps or secretions within the middle meatus or in the sphenoethmoidal recess. Additionally, samples of secretions and cultures may be taken during nasal endoscopy for later analysis.

Endoscopic evaluation is in principle an office procedure that can be performed using a flexible or rigid endoscope, typically after a topical decongestant and anaesthetic. Depending on anatomy and the physician's experience, nasal endoscopy provides a view of the nasal cavity, inferior turbinate, inferior meatus, middle meatus, uncinate process, hiatus semilunaris, maxillary ostia, anterior ethmoidal bulla, frontal recess, sphenoid recess, sphenoid ostium and the nasopharynx.

A diagnosis of CRS is supported when clinical examination reveals purulent mucus or edema in the middle meatus or ethmoid region, or polyps in the nasal
cavity or middle meatus. Diagnosis might be quite unclear when there are abnormalities such as neoplasms, soft tissue masses, foreign objects, tissue necrosis and findings consistent with autoimmune or granulomatous disease. A positive nasal endoscopy (pus or polyps) decreases the possibility of an incorrect diagnosis and a negative nasal endoscopy has a role in ruling out CRS. Persistent symptoms are not enough to make a diagnosis of CRS. The presence of inflammation has to be documented (polyps, edema or purulent mucus). [63, 64] Edematous mucosa has a lighter shade of pink or white. Nasal endoscopy should be the front-line clinical test for confirmation of CRS, while CT scanning maybe reserved for patients with a prolonged or complicated clinical picture. [65]

2.1.7. Imaging in CRS

The use of CT imaging has noticeably improved the imaging of paranasal sinus anatomy compared with plain sinus radiographs. CT imaging can help quantify the extent of inflammatory disease, based on decreased pneumatization of the paranasal sinuses, and improves diagnostic accuracy because CT image findings correlate with the presence or absence of CRS in patients with suggestive clinical symptoms. Even though CT findings may not necessarily correlate with symptom severity, correlation seems to improve when 3D-analysis is used. [66, 67] CT imaging of the paranasal sinuses (axial and coronal images) allows for adequate visualization of the OMC.

Furthermore, CT imaging is an objective method for monitoring CRS. Complimentary information such as mucosal abnormalities, sinus ostial obstruction, anatomic variants, and sinonasal polyposis are more accurately assessed with CT. Mucosal changes such as mucosal thickening are not specific and should therefore be interpreted in the context of clinical examination and nasal endoscopy. CT imaging in CRSwNP or CRSsNP is crucial in order to exclude aggressive infections or neoplastic disease that might mimic CRS or ARS. Bony destruction, extra-sinus extension of the disease process and local invasion raise suspicions of neoplasia. In cases of such suspicious findings, magnetic resonance imaging (MRI) should be ordered to differentiate between benign obstructed secretions and tumour and to assess for any spreading outside the nasal cavity and sinuses. [68-70] CT imaging of the paranasal sinuses should carry out preoperatively before ESS in patients with CRS or RAR.

In 1998, cone beam computed tomography (CBCT) was introduced as a new method for dental imaging. [71] CBCT was used primarily to evaluate bony anatomy and to screen for overt pathology of the maxillary sinuses prior to dental
implant treatment. The main indication for CBCT was dental implant treatment planning, and the majority of studies used a small field of view (fov) for imaging. During the last few years, CBCT has been proposed as a low-radiation-dose alternative to traditional CT for the evaluation of the paranasal sinuses. [72] Based on the results of a cross-sectional study, CBCT shows high accuracy, and CBCT findings strongly correlate with sinus endoscopy findings. When also taking into consideration its lower cost and lower radiation doses, CBCT seems to be a promising alternative method for the diagnosis and classification of CRS. [73, 74] It has been claimed that in the future, CBCT will become the reference method for sinus imaging following promising results in other fields of otolaryngology. [75]

2.1.8. Lund-Mackay staging

Lund-Mackay classification has been developed for the classification of patients with CRS. Based on CT findings, all sinuses as well as OMC are assessed as follows: for all sinus systems except for ostiomeatal complex: 0 = no abnormalities, 1 = partial opacification, 2 = total opacification. For the ostiomeatal complex 0= not occluded, 2= occluded. This classification has been validated and it is widely used around the world. [61, 62]

2.1.9. Microorganisms

2.1.9.1. Bacteria

Questions still remain about the role of bacteria in the pathophysiology of CRS. Both aerobes and anaerobes have been found in patients with CRS. However, bacteria were not only retrieved from the diseased side but also from the non-diseased contralateral side. [108] In a previous study with 114 patients with CRS, aerobes were isolated in 86% of patients while anaerobes were isolated in 8% of patients. In the same study, fungi were retrieved from 11% of patients. Staphylococcus aureus, coagulase-negative Staphylococcus and Streptococcus pneumoniae were the most frequent microorganisms. In 80% of cases, same pathogens were isolated from both the middle meatus and the maxillary sinus.
Similarly, among healthy individuals, coagulase-negative Staphylococcus, Staphylococcus aureus and Streptococcus pneumoniae were the most frequent isolates. [109] In a later prospective study by Araujo et al. with 134 CRS patients, 220 microorganisms were isolated. Staphylococcus aureus (31%) and coagulase-negative Staphylococcus (23%) were the most frequent microorganisms with a frequency of 31% and 23%, respectively.

Gram-negative or facultative microorganisms were isolated in about one third of patients. Anaerobes were found in 12% of patients. The majority of samples with positive cultures presented many or few white blood cells. In the control group, the most frequent microorganisms were coagulase-negative Staphylococcus (40%) and Staphylococcus aureus (18%). No anaerobes were retrieved in the control group. However, an important observation of the study was that there were few or no white blood cells in the control group. [110] A recent review study claims that Staphylococcus aureus and anaerobic organisms (Prevotella and Porphyromonas, Fusobacterium, and Peptostreptococcus spp.) are the most common isolates in CRS.

The formation of a biofilm in cases of CRS may play a significant role in the pathogenesis and persistence of CRS. [52] Finegold et al. found that infection with anaerobes is associated with more frequent recurrences of signs or symptoms of bacterial maxillary sinusitis. [111]

2.1.9.2. Fungi

The presence of fungi in human sinuses has been confirmed by cultures. Fungi can be found in both healthy and pathological mucosae. Fungi may cause a variety of pathology from non-invasive fungus balls to invasive refractory disease. [39, 112] The species Aspergillus and particularly Aspergillus fumigatus have been isolated from the majority of fungal sinusitis cases. Based on a recent review by Dr Fokkens et al., there is not sufficient evidence to suggest an improvement of CRS using antifungal agents. Further, the role of fungi in CRS appears to be less significant than was previously thought. [113]
2.1.10. Conditions associating with chronic rhinosinusitis without polyps (CRSsNP)

CRS is a heterogonous disease and some inherited genetic variations and medical conditions as well as environmental factors seem to be associated with CRS. Nevertheless, the processes that initiate and sustain the abnormal inflammation are still largely unexplained. [36, 39]

2.1.10.1. Ciliary impairment

Secondary and most likely reversible dysfunction of ciliary epithelium has been observed in CRS. [64] On the other hand, in cases of cystic fibrosis (CF), cilia are unable to transport the viscous mucous which leads to ciliary impairment and consequently to CRS. [76]

2.1.10.2. Allergy

Based on previous reviews, it has been suggested that allergy predisposes to CRS. The role and association of allergy to CRS still remains unclear, however. [77] The percentage of patients with a positive skin prick test has been found to be higher among patients with CRS. [78, 79]

2.1.10.3. Asthma

Previous studies support that inflammation of the upper and lower airways coexists and there is evidence that treatment of sinusitis also improves asthma symptoms. The updated ARIA document summarized the available evidence regarding the association between AR, asthma and CRS. [80] Based on imaging in patients with asthma, a high prevalence of abnormal sinus mucosa was found. [81, 82] Severe steroid-dependent asthma is associated with more severe symptoms and the radiological findings of CRS. [83]

2.1.10.4. Genetic factors

There is association of some gene expression pathways with mucosal inflammation or abnormal epithelial repair in CRS. However, part of the pathway and mechanism
remains unclear. Thus, it has not so far been possible to use this data in the treatment of CRS. [84, 85]

2.1.10.5. Gastroesophageal reflux disease (GERD)

There is some evidence to suggest an association between gastroesophageal reflux disease (GERD) and CRS. The omeprazole-responsiveness of rhinosinusitis symptoms implies a possible role for GERD in CRS pathogenesis. [86] Even though Helicobacter pylori DNA has been isolated from sinus samples in patients with CRS, a causative mechanism has not been confirmed. [87, 88]

2.1.10.6. Osteitis

Osteitis involves inflammatory changes in the underlying bone that may lead to refractory CRS, and it is associated with worse outcomes after ESS. [89, 90] Based on the findings of a study by Lee et al., the frequency of concurrent osteitis was 36% to 53% of patients with CRS using both radiographic and pathological criteria, respectively. No conclusions were drawn as to whether there is any causal relationship between osteitis and CRS. [57] In another study in patients with CRS, osteitis of bone underlying the sinus mucosa was correlated with the presence of bacterial biofilm in pathogenic mucosa. [91]

Based on animal and human models of CRS, the presence of inflammation and remodelling within the bone of the paranasal sinuses has been verified. Osteitis may spread to involve distant sites within the paranasal sinuses which has implications for the medical and surgical management of CRS and may contribute to CRS recalcitrant to management. [92]. It has been claimed that there is a high prevalence of osteitis among CRS cases which consequently affects the bony component of the sinuses. Among patients with extended radiological disease and undergoing revision surgery, the prevalence of osteitis is even higher. Further investigation is needed regarding the management, clinical implications and natural course of osteitis.[93]
2.1.10.7. Pregnancy

Nasal congestion is common during pregnancy. A study of 117 pregnant women revealed that 9% suffered from pregnancy rhinitis. [94] According to Sorri et al., bacterial ARS seems to occur more frequently among asthmatic pregnant women. [95] Allergic rhinitis usually pre-exists even though it may develop or be recognized for the first time during pregnancy.

Allergic rhinitis can be differentiated from pregnancy rhinitis by the presence of the associated symptoms of sneezing, nasal pruritus and watery rhinorrhea, in association with nasal congestion. [96] Based on a recent review by Lal et al., RS is treated during pregnancy with nasal corticosteroids as a maintenance treatment for CRS and with pregnancy-safe antibiotics for ARS and CRS exacerbations. However, there is a lack of an evidence-based treatment that is particularly optimized for pregnant women. [97]

2.1.10.8. Environmental factors

Based on the literature, tobacco smoking is associated with acute and chronic rhinitis. [98] [38] Tobacco exposure is one of the most studied risk factors for various airway diseases, including CRS. There is some evidence that suggests active cigarette smoking is more prevalent among patients with CRS. An occupational environment that is rich in airborne particles and vapours might also increase the risk of CRS even though it may be difficult in some cases to differentiate between CRS and conditions with similar symptoms such as occupational rhinitis. [46] [99]

Comorbid psychiatric conditions such as anxiety and depression seem to be correlated with a higher rate of CRS diagnosis and healthcare utilization associated with CRS. Lately, epidemiologic studies have pointed out possible underlying demographic factors that are associated with CRS. [46]

2.1.10.9. Anatomical variations

Anatomical variations such as concha bullosa and septal deviation have been proposed as potential risk factors for CRS. [100] However, later studies have claimed no association of anatomical variation with CRS symptoms [101] There have also been some studies that claim no association of septal deviation and CRS symptoms.
Nevertheless, the role of septal deviation in the development of CRS remains controversial. [102-105]

2.1.10.10. Immune dysfunction

Based on a retrospective study, a higher incidence of immune dysfunction was found among patients with refractory sinusitis. In the same study, 6.2% of patients had selective IgA deficiency which is much higher than the 0.3% incidence in the general population. [106]

In a recent retrospective study, the immune status of CRS patients was assessed by evaluating the responses to diphtheria and tetanus vaccines. After vaccination, CRS patients showed lower responses to diphtheria and tetanus toxoid than the controls. [107] Thus, these results suggest that immunological testing could be considered in patients with refractory sinusitis.

2.2 Treatment

CRS is considered to be an inflammatory disease with occasional acute exacerbations associated with infection. Treatment of an episodic acute infection with, for example, antibiotics while leaving the underlying condition untreated, will most likely be followed by exacerbations. Therefore, the priority should be the management of both the underlying cause and the contributing factors.

2.2.1 Antibiotics

Even though there is indication for the treatment of only acute bacterial exacerbations of CRS with antibiotics, general/family practitioners frequently prescribe antibiotics for CRS. Amoxicillin and amoxicillin plus clavulanic acid remain the antibiotics of choice [64, 65]. Confirmed infection by Pseudomonas aeruginosa is one clear indication to prescribe fluoroquinolone. Prolonged treatment with low-dose macrolides for 6 to 12 weeks has shown some anti-inflammatory effects especially in patients with low levels of IgE. [32, 114, 115]

In CRS cases, edema-related obstruction and impaired MCC result in a mucosa prone to bacterial infections. [1] Therefore, to ensure better long-term results,
treatment should target the underlying inflammatory disorder. The objectives of such treatment are to improve drainage, remove obstruction, promote mucociliary function, eradicate infection, reduce inflammation and prevent complications. Medical treatments for CRS are numerous and aim to reduce mucosal inflammation, remove mucus and modulate environmental triggers. The anti-inflammatory effect of macrolides seems to be clearer in a neutrophilic infectious disease such as cystic fibrosis. [116-119]

2.2.2 Maintenance Medical Therapies for CRS

2.2.2.1 Topical Corticosteroids

The use of corticosteroids for the treatment of CRS is based on their anti-inflammatory effect as well as their ability to reduce glycoprotein release from submucosal glands (i.e., thin mucus) and to decrease vascular permeability.

In conjunction with antibiotics, topically, intranasally or systemically administered glucocorticoids are the foundation of the treatment of CRS. This assertion is supported by strong evidence that is based on meta-analyses quantifying the findings from more than 40 randomized controlled trials (RCT)s. [7-12, 120]

A RCT in patients with CRSwNP showed that corticosteroids improved the patients' QoL and that the degree of reduction of polyps was directly associated with the degree of improvement in QoL. [13] Meta-analyses of studies on patients without nasal polyps revealed that topical corticosteroids were associated with improved symptom total scores and a greater proportion of symptom responders. [14]

Therefore, glucocorticoids seem to be effective in the treatment of CRSwNP or CRSsNP. [14, 16] However, these studies demonstrate only minor improvement without concomitant surgery. Some publications also suggest the use of topical steroids during the postoperative period to improve wound healing. [121]

2.2.2.2 Saline Irrigations

Sinonasal saline irrigations facilitate the removal of mucus and contribute to the restoration of normal MCC. The effect of hypertonic versus physiologic saline in
MCC and nasal patency has been studied in previous RCTs. Hypertonic saline was found to have no effect, but physiologic saline improved not only MCC but also nasal patency, as assessed by acoustic rhinometry. [19, 20]

However, another study suggested that hypertonic saline is better and it improved MCC. [122] Based on the findings of a study by Pynnonen et al., an increased volume of irrigation is more efficient than low-volume saline sprays. A further finding from the same RCT was that saline irrigation improved quality of life as assessed by SN O T questionnaire. [18] Wormald et al. compared different methods of nasal irrigation (nasal spray, nebulization with Rinoflow and nasal douching) and it was found that nasal douching is the most effective method in improving the symptoms of CRS. [21]

Other previous studies indicated that a combined treatment with saline irrigation and topical steroids is superior to saline irrigation alone in the treatment of CRS. [123] Another recent RCT showed that irrigation with either sodium chloride (NaCl) 6% or 0.9% improved QoL, as assessed by SN O T -20, in patients with cystic fibrosis and CRS. [124] There is an increasing body of evidence that supports the effectiveness of saline irrigation as a complimentary treatment of CRS. [14-18, 124]

The efficiency of nasal irrigation when baby shampoo, sodium hypochlorite or xylitol were added to saline solution has also been studied. Based on the results of these studies, there is some evidence that the addition of sodium hypochlorite or xylitol to saline solution may increase the efficiency of saline irrigation. [125, 126]

2.2.2.3 Leukotriene pathway antagonists

Leukotriene and their receptors have been found in patients with nasal polyps. [27] Cysteine leukotriene receptors locate in respiratory mucosa. Leukotriene antagonists bind to these receptors and thus inhibit the act of leukotriene D4, C4 and E4. Leukotriene antagonists also inhibit 5-lipoxygenase and, as a consequence, block the production of leukotrienes from arachidonic acid.

Consequently, there is a decreased recruitment of eosinophils, decreased vasodilation and decreased mucous secretion. [27, 32] Based on the findings of five RCTs, there is strong evidence that supports the use of a leukotriene antagonist (montelukast) in patients with CRSwN P. However, montelukast was not found to be superior to corticosteroids. Furthermore, no evidence grade is assigned for the use of leukotriene antagonists in patients with CRSsN P. [3, 27-31]
2.2.2.4 Antihistamines and Allergy Immunotherapy

AR has been associated with CRS. It is estimated that about 20% to 60% of patients with CRS also suffer from AR. Prevalence is higher in those patients with nasal polyps. Antihistamines reduce an allergen-induced Immunoglobulin-E(IgE)-mediated host response. Thus, treatment with antihistamines and allergy immunotherapy has been claimed to decrease vascular permeability, vasodilation and nasal secretions. [127, 128] Even though there is strong evidence about this association, it is still unclear whether allergy has a role in the pathophysiology of CRS and whether treating AR improves CRS-specific outcomes. [129]

However, based on one systematic review, 6 case series were analysed and it was concluded that allergy immunotherapy improves allergy-specific symptoms but has no consistent positive effect on sinus specific symptoms. [130] Thus, a C-II grade weak recommendation is designated to allergy immunotherapy for the specific management of chronic sinusitis. However, there is no grade of evidence for the use of oral antihistamines during the specific management of CRS. There is, however, some evidence that suggests that antihistamines and allergy immunotherapy might be beneficial for managing concurrent AR. [32, 131]

2.2.3 Intermittent or Rescue Medical Therapies for CRS

2.2.3.1 Systemic Corticosteroids

Systemic corticosteroids are mostly required in cases where patients have severe nasal polyposis or acute inflammatory exacerbations in order to treat acute mucosal inflammation. Based on the literature, oral corticosteroids are associated with reduced polyp size and improved symptoms and QoL. [13]

However, these improvements are not long-lasting. Unless a maintenance therapy with topical corticosteroids is added, the improvements will last no longer than 3 months. The effect of oral corticosteroids in patients with CRSsNP has been studied in controlled randomized studies. [13, 132]

There are studies that support the fact that oral corticosteroids are associated with improved olfactory and symptom scores. However, the best available evidence for patients with CRSsNP comes from prospective case series without control groups and with heterogeneous concurrent medical therapy protocols. [133, 134]
2.2.3.2 Short-term Oral Antibiotics (Nonmacrolide)

The target of short-term antibiotics in the treatment of CRS is to eradicate active infection by inhibiting bacterial cell wall formation, inhibiting bacterial folate synthesis and promoting bacterial DNA fragmentation. [32] Three previous RCTs indicated that antibiotics improve CRS to some degree; however, no difference was found between different regimes (cefotiam vs cefixime; amoxicillin/clavulanate vs ciprofloxacin and cefaclor vs amoxicillin). [135-137] The effect of doxycycline versus corticosteroids in the treatment of CRSwNP patients was assessed in another RCT, and doxycycline was not only effective in reducing polyp score but it also showed a more long-term effect than corticosteroids. [24]

2.2.3.3 Long-term Therapy

It has been suggested that macrolides have an anti-inflammatory effect in addition to an antimicrobiological effect. As a result, macrolides have been used in the treatment of patients with chronic lower airway diseases such as asthma and panbronchiolitis. Prolonged treatment with low-dose macrolide antibiotics have been evaluated as a therapy for CRS. [18, 32, 138, 139]

One RCT showed that three-month treatment with macrolides improved QoL, reduced the symptoms of CRS and improved MCC, especially in patients with CRSsNP and low levels of IgE. [115] The only RCT in patients with CRSwNP, showed no difference between macrolide therapy (azithromycin) and placebo. [140] Although the meta-analysis demonstrated an improvement in QoL at a single time point after starting macrolide therapy (24 weeks), the pooled RCTs contained a heterogeneous patient population (patients with CRSwNP and CRPsNP), and therefore the clinical significance of the improvement was questionable. Furthermore, the QoL improvement was not sustained 12 weeks after completion of the macrolide therapy. [139]

In summary, an A-II grade and recommendation is designated for the long-term use (>12 weeks) of macrolide therapy in patients without nasal polyps. Given the negative results from one RCT, a B-III grade and recommendation against use is designated for long-term macrolide therapy of patients with nasal polyps. [32, 114] According to the European position paper on rhinosinusitis, long-term treatment with antibiotics is recommended at the same level as ESS for the treatment of CRS. Additionally, long-term treatment with antibiotics may be used after surgery in patients with difficult-to-treat CRS. [36, 39]
2.2.3.4 Anti-Immunoglobulin-E (IgE) therapy

The role of IgE-mediated inflammation on the underlying pathophysiology of CRS remains unclear. [141] Anti-IgE therapy comprises the administration of a recombinant DNA-derived humanized IgG monoclonal antibody that binds free IgE and inhibits binding to mast cells and basophil receptors. Two RCTs included patients with serum IgE levels from 15 kU/mL through to 700 kU/mL and compared omalizumab with placebo. Omalizumab is a monoclonal antibody that specifically binds to free human immunoglobulin E (IgE). Unfortunately, both studies lacked statistical power and contained moderate estimates of bias. Thus, an A-II grade and recommendation is designated to anti-IgE therapy for CRSwNP and asthma, while no evidence grade or recommendation is assigned for anti-IgE therapy for patients with CRSsNP. [142, 143]

2.2.3.5 Anti-Interleukin 5 (IL-5) therapy

IL-5 therapy is defined by the delivery of a humanized IgG monoclonal antibody that binds free IL-5 and impairs eosinophilic-mediated inflammation. [32] Two RCTs in patients with nasal polyposis evaluated anti-IL-5 therapy (reslizumab and mepolizumab). Even though, reslizumab (1 mg/kg or 3 mg/kg) slightly reduced blood eosinophil levels, it did not have any positive effect on the symptoms of CRP compared with placebo. [144] There was an association of mepolizumab (2 injections of 750 mg received 28 days apart) with improved polyp scores in approximately 50% of patients compared with placebo, but the study did not evaluate patient-reported outcomes. [145] Based on a review by Rudmik et al., an A-II grade and recommendation is designated for anti-IL-5 monoclonal antibody therapy in patients with nasal polyposis. No grade of evidence or recommendation is assigned for anti-IL-5 therapy for patients without nasal polyps. [16]

2.2.3.6 Topical Antibacterials

There is not sufficient evidence to support any clear benefits of the use of topical antibiotics in patients with CRS. [8, 14] There are many controversies in the choice of antibacterial agent, dosage and delivery method which make the study of the efficiency of topical antibiotics more complicated. [14]
Two RCTs, which both utilized empiric therapy, failed to show any significant improvement in symptom, QoL and endoscopy scores compared with the non-treatment groups. [146, 147] Four systematic reviews evaluated topical antibiotics for CRSsNP. High-volume topical mupirocin irrigations may be an appropriate therapy in selected cases of recalcitrant disease with a sinus culture positive for Staphylococcus aureus.

It has been concluded that current usage evidence recommends against the use of topical antibiotic therapy delivered using nebulized and spray techniques in routine cases of CRS. Also, no grade of evidence or recommendation is designated for the use of topical antibiotics for the treatment of CRSwNP. [14, 139, 148, 149]

2.2.3.7 Topical Antifungals

In both CRS patients and healthy controls, nasal mucosa may be colonized by fungi. It has been proposed that an abnormal immunological response to fungi may cause CRS and that the eradication of fungi may resolve sinus disease.[32] The administration of amphotericin B topically in the paranasal mucosa by lavage or spray was previously studied in four RCTs. However, an analysis of these studies showed no benefit of topical amphotericin B compared with placebo for patients with CRSsNP. [14, 150-153]

2.2.3.8 Immunomodulators

A group of CRS patients recalcitrant to conventional treatment was studied in a RCT and the effectiveness of filgrastim, a recombinant human granulocyte colony-stimulating factor, was tested. Nevertheless, no significant improvement was observed. [154] On the other hand, a pilot study with interferon gamma showed some promising results in treating refractory CRS, but the number of patients was too small to provide evidence to justify such treatment. [155] The following illustration (illustrated by George Bizakis) depicts the proposed mechanisms of action for chronic sinusitis medical therapies.
The diagram illustrates the mechanisms of action for different treatments in respiratory diseases. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and decrease inflammation. Corticosteroids reduce cytokine production and decrease allergic responses. Macrolides act by inhibiting RNA polymerase II and reducing inflammatory mediator production. Epinephrine and beta-agonists relax smooth muscle and relieve bronchospasm. Saline irrigation clears respiratory pathogens and allergens. Macrolides increase ciliary clearance. Antihistamines block histamine receptors and reduce allergic reactions. The diagram shows the interactions between these treatments and their effects on various cellular processes.
2.2.4 Surgical treatment

The main goal of surgical treatment has been the improvement of the ventilation of the sinuses through the natural ostia. Taking into consideration that the pathophysiology and clinical course of CRS has been shown to be heterogeneous, treatment should be individualized. Sinus surgery may be considered in patients with RAR.

Surgery is reserved for patients who are refractory to medical treatment and patients with an anatomic obstruction resulting in CRS. The understanding of the anatomical and functional complexity of the nasal and paranasal regions developed as a result of the work of Dr Walter Messerklinger in the 1960s and 1970s. Nowadays, the improvement of ventilation and drainage of the OMC and at the same time the preservation of the mucosal lining of the upper airways has become a goal in surgical technique development. Although external surgical approaches are still mandated in some selected circumstances, endoscopic surgery has become the gold standard for the surgical treatment of CRS and aims to restore the physiological functions of the nasal and paranasal cavities.

In the past decades, three schools of thought have been dominant in the surgical treatment of CRS. Endoscopic sinus surgery (ESS) aims to improve ventilation of the sinuses through the natural ostia. The method is not standardized, but it has been adjusted to meet the individual needs of patients. The minimally invasive sinus technique (MIST) has been suggested as a method whereby each surgical procedure is standardized regardless of disease severity. Balloon catheter dilatation of the sinus ostia without removing any bone or soft tissue.

A review of the literature indicates that surgery improves not only a patient's QoL by decreasing symptoms such as postnasal drip, nasal obstruction, facial congestion and headache but also by improving objective findings of CRS.

2.2.4.1 Endoscopic sinus surgery (ESS)

ESS is the result of the pioneering work of Dr Walter Messerklinger and Dr Heinz Stammberger in Graz, Austria. Other surgeons such as David Kennedy have also made additional contributions (first published in the USA by Dr David Kennedy in 1985). The Messerklinger technique has also been adapted in other fields of medicine.

The aim of ESS is to restore the physiological functions of the nasal and paranasal cavities. Surgery results in an improvement in both subjective and objective findings,
in addition to improvements in QoL. [26, 164-166] Mucosal eosinophilia and nasal polyposis seem to have a negative effect on the effectiveness of ESS. [167]

For the surgical treatment of RS, ESS has become the gold standard. However, some complications associated with ESS have been reported and these complications vary in severity. In most studies, the complications are divided into 'minor' and 'major' categories based on either the researchers' or their patients' perception of severity.

Minor complications may include bleeding, infection, crusting, synchiae formation, ostial stenosis, tooth or lip numbness or recurrence of disease. Major complications may include hyposmia/anosmia, exposure of orbital fat, damage to extraocular muscles, blindness, vascular damage, exposure of dura, cerebrospinal fluid (CSF) leak, intracranial injury or death. [163] Another review study divides the complications into three groups: a) orbital, b) neurological and c) vascular complications. Of these, orbital haemorrhage appears to be the worst nightmare for sinus surgeons. Injury to the anterior ethmoid artery, which is located in the ethmoid sinus adjacent to the superior oblique muscle, is the most usual culprit in about 40% of cases.

Based on the findings of the same study, a thorough knowledge of anatomy and a careful evaluation of radiographic images are essential and serve as cornerstones for the prevention of surgical complications. Imaging discloses possible anatomic variants involving the skull base, the medial orbital wall as well as bony irregularities and dehiscence adjacent to critical structures including the optic nerve and internal carotid artery (ICA).[168]

2.2.4.2 Balloon sinuplasty (BSP)

In the early 2000s, the balloon sinuplasty (BSP) technique was proposed as a therapeutic tool for the dilatation of the ostia of the paranasal sinus system. In principle, BSP aims to remodel the anatomy of the paranasal ostia in an atraumatic way without removing mucosa or bone. Firstly, BSP was used experimentally for the dilatation of the frontal sinus. The results were promising and the use of BSP has subsequently been expanded to the treatment of the maxillary sinus as well.

In the technique, BSP is the cannulation of the sinus ostium with a particular thin, flexible guidewire, which allows atraumatic access to the sinus even through a narrowed ostium. Then, once the location of the guidewire in the sinus has been confirmed, balloon dilatation can be safely performed. The use of a lighted guidewire for transillumination has permitted the identification of the guidewire's
location without using fluoroscopy. As a result, radiation exposure has been eliminated. [169]

In 2006, Brown and Bolger published a preliminary investigation regarding the feasibility and safety of BSP. [170] The use of BSP in patients has so far been proven to be feasible and safe. [170-173] It seems that BSP has a positive effect on CRP symptoms and improves patients' QoL. [174, 175] BSP seems to be also efficient and safe for the treatment of CRS in children. [176] In a few previous studies, ESS was compared with a hybrid sinus surgical technique where the patients underwent a combination of ESS and BSP. [33] An analysis of a case series in immunosuppressive patients showed good results for BSP. [177]

A recent review study analysed 17 studies and it was concluded that current evidence regarding the role of BSP in the treatment of CRS patients remains incomplete. Therefore, more RCTs are needed in order to study ESS and BSP as separate entities. [178]

2.3 Nasal mucosa

2.3.1 Definition- Anatomy

The upper nasal airway has a ciliary epithelium that plays a substantial role in the homeostasis of breathing as it interacts with the environment and regulates the inhaled air. The lower airways are anatomically and functionally a continuity of the upper airways. A pseudostratified respiratory epithelium covers both the upper and lower airway and forms part of an innate and acquired immune defence mechanism.

The nasal conditions that lead to nasal obstruction, stasis of nasal secretions, or infectious disease of the sinonasal mucosa may become a trigger for lower airway pathology in susceptible individuals. [1]

A pseudostratified ciliated columnar epithelium with numerous serous-mucous glands and goblet cells, covers the paranasal and nasal cavities [34] The serous-mucous glands secrete mucous in addition to immunoglobulins, interferons and lysozyme. The anterior portion of the nostrils and the nasal septum differentiates from the rest since it is covered by skin with adnexa. The roof of the nasal cavity is where a specialized olfactory epithelium with bipolar olfactory neurons is located.

The paranasal sinuses comprise four paired sinuses: maxillary, ethmoid, sphenoid and frontal. The fovea ethmoidalis, the roof of the ethmoid sinus, also forms the floor of the anterior cranial cavity and slopes upwards at an angle from the midline.
to extend 2 mm to 3 mm above the cribriform plate. The lamina papyracea, the lateral wall of the ethmoid, is also the medial wall of the orbit. During embryogenesis, the ethmoid sinuses develop initially as outgrowths of the lateral nasal wall and later differentiate to numerous small air cells. The number of ethmoid air cells varies widely with an average number of nine.

The ostiomeatal complex (OMC) is composed of the middle turbinate, the uncinate process, the middle meatus, the hiatus semilunaris and the infundibulum. The drainage pathways for the frontal sinus, the anterior ethmoid sinus and the maxillary sinuses all pass through the OMC. Thus, restriction of this rather narrow path by edematous mucosa, purulent secretions, polyps or other mass lesions will result in post-obstructive RS involving one or more of the referred sinuses. In particular, it has been proposed that it is not just the anatomic bony variations but the contact between the mucosal surfaces of the OMC which predisposes the development of inflammation. [179, 180]

2.3.2 Physiology – Mucociliary clearance (MCC)

The paranasal epithelium comprises a mucociliary system. Secreted mucous warms and humidifies the inhaled air. Both the parasympathetic and sympathetic nerves regulate this mucous blanket, which is renewed every 10 to 15 minutes. The cilia beat 10 to 15 times per second, which moves the mucous blanket toward the natural ostia of the sinuses. [34] Environmental factors interact with the cilia; humidity increases their activity, whereas dehydration and cold temperatures decrease it.

2.3.3 Measurement of MCC

2.3.3.1 Measurement of MCC with 99m-Tc

MCC can be assessed through a clinical test and it has been reported that an isotope technique using 99m-Tc is a reliable method to assess MCC. [183-185] It has been documented that MCC is diminished in CRS. [181] There are some encouraging results from some study groups about improvements in MCC after treatment. [34, 186-188] However, in some other previous studies no significant improvement in MCC was noticed post operatively. [189, 190]
2.3.3.2 Methylene blue dye-saccharine test

While the measurement of MCC using sterile human serum albumin labelled with 
99mTc is the most accurate technique, other techniques using methylene blue or 
saccharine are also used. Methylene blue dye, a water-soluble dye, has been previously 
used for the localization of the sentinel lymph node. [191]

In a murine model, methylene blue dye was instilled transnasally to determine 
the effect of various parameters on the distribution of chemicals to the lower lungs. 
[192] The effect of volatile anaesthetics on bronchial mucus transport velocity was 
previously analysed with methylene blue dye. [193] The assessment of MCC of the 
eustachian tube using methylene blue dye and saccharine showed good results. [194] 
A methylene blue dyed saccharine particle has been previously used for the 
measurement of MCC. [34, 195]

The measurement of MCC using the saccharine method was not correlated with 
the QoL scores of patients. [6] Another study on patients treated with ESS indicated 
that the saccharine test is both simple and accurate and plays a useful role in the 
assessment of MCC in conjunction with nasal endoscopy. [196]

2.3.4 Pathophysiology

2.3.4.1 Impaired MCC in CRS

Dysfunction of the cilia and delayed drainage of mucous increases bacterial and viral 
proliferation. This mechanism is clearly depicted in medical conditions such as 
primary ciliary dyskinesia and cystic fibrosis. In such cases, dysfunctional ciliary 
epithelium pre-exists mucosal inflammation. However, any condition that obstructs 
the drainage of the sinuses (e.g., polyps, inflammation, or edema of the nasal mucosa) 
will lead to RS.

Benign and malignant tumours of the nasal cavity, paranasal sinuses and skull 
base can also lead to an infection in one or more of the paranasal sinuses. [1] Based 
on this theory, correction of the obstructed pathway should treat the inflammation. 
In practice, however, the pathophysiology of CRS seems to be more complicated. It 
has been supported that in CRS there may be pre-existing dysfunctional ciliary 
epithelium before the blockage of the ostium. It has been shown that MCC is 
impaired in patients with CRS. [6, 181, 182] Ciliary beat frequency is affected by 
many biochemical, environmental and mechanical stimuli. Thus, the resultant
inflammatory cytokines secondarily exacerbate the impaired MCC. Also, common microbial pathogens of respiratory mucosa such as Pseudomonas aeruginosa and Haemophilus influenzae have developed toxins that appear to block normal mucociliary function. [1] Additionally, a secondary impairment of MCC is caused by chemical mediators involved in the inflammation process in CRS. Although multiple etiologies contribute to the development of CRS, ineffective sinonasal MCC is the common fundamental pathophysiology. [1]

2.3.4.2 Inflammation and mucosal histopathological changes

Metaplasia of epithelium has been associated with chronic inflammation of nasal mucosa. Before epithelium changes to squamous, it is called cuboidal and ciliogenesis is still present. There is increasing evidence in favour of inflammatory processes over simple obstructive phenomenon as a mechanism in patients with CRS. [60, 63] Obstruction leads to inflammation, but it appears that some kind of inflammation may pre-exist and this is what gradually causes the obstruction leading to a vicious circle. For example, the colonization of mucosa with Staphylococcus aureus has been documented in CRSsNP. [197]

In cases of CRSsNP, neutrophils predominantly and to a lesser degree eosinophils infiltrate the mucosa. Histological changes of CRSsNP include fibrosis, basement membrane thickening, goblet cell hyperplasia, limited subepithelial edema, mononuclear cell infiltration with neutrophils, lymphocytes, mast cells and plasma cells. [64, 197] Mucosal eosinophilia seems to correlate with more severe CRS as it is documented by radiological findings in CT scans and nasal endoscopy. [198] The formation of pseudocysts, an intense edematous stroma with albumin deposition, and subepithelial and perivascular inflammatory cell infiltration characterizes specifically cases of CRSwNP. The extracellular matrix (ECM) is essential for tissue integrity, and MMPs are the major proteolytic enzymes involved in ECM damage or repair. [199, 200] There is increasing evidence supporting the theory that altered homeostasis in the sinonasal epithelium might be important in chronic upper airway inflammation.

2.3.4.3 Epithelial remodelling in CRS

Remodelling is a dynamic process in both health and disease that balances ECM production and degradation, which is regulated by diverse mediators among which
transforming growth factor beta (TGF-b) plays a central role. [201, 202] TGF-b is a multifunctional gene with an immunomodulatory and fibrogenic effect. The immunosuppressive effect of TGF-b seems to be beneficial in many chronic diseases. However, it seems that TGF-b also has an important role in airway remodelling and in fibrosis formation and is suspected of playing a major role in airway remodelling. Activation of the TGF-b pathway initiates a signalling cascade that leads to the activation of many immune cells, the resolving of inflammation and the initiation of the repair process. [197]

MMPs are a subgroup of a larger group of zinc-dependent endopeptidases. More than 20 MMPs have been identified, and they are involved in the breakdown of ECM in normal physiological processes such as embryonic development, reproduction and tissue remodelling in addition to pathological processes such as inflammation, arthritis and metastasis. MMP-9 is one of those proteins and has been found located in the surface nasal epithelium, in the seromucous glands and in polymorphonuclear cells. The active form of MMP-9 is able to cleave type IV and V collagen which are found in the upper airway as well. [199]

Another protein, MMP-10, has been found in the upper airway mucosa and in its active form it is able to degrade proteoglycans and fibronectin. MMP-10 has been shown to be upregulated to airway mucosal epithelial cells following the smoking of a cigarette. It seems that other MMPs are also upregulated in CRS. [203] MMPs have been found to be upregulated in patients with chronic obstructive pulmonary disease (COPD) and they seem to play a crucial role as inflammatory mediators in the pathogenesis of COPD. [204, 205]

Elevated levels of MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) together with high levels of TGF-b1 have been found in cases of CRS without polyps. [203] It has been shown that TGF-b1 induces the release of TIMP-1 and inhibits the proteolytic activity of MMP-9. Thus, it has been proposed that pathologic tissue remodelling in CRS may be a result of an imbalance between MMPs and TIMPs. [199] MMPs appear to be a promising therapeutic target in CRS.

Doxycycline, a tetracycline derivative and a widely used antibiotic, is an MMP inhibitor, which at regular or sub-antimicrobial doses possesses systemic anti-inflammatory characteristics. In a double-blind randomized placebo-controlled trial, the levels of MMP-9 in nasal secretions as well as nasal polyp size were significantly reduced after treatment with doxycycline.

On the other hand, MMP-9 levels in nasal secretions were not affected with methylprednisolone. MMP-9 expression in the ECM is increased during the wound healing process after sinus surgery. As inflammatory cells are the major source of
MMP-9 expression, high secretion levels of MMP-9 after sinus surgery are linked to poor healing quality. MMP-9 expression is increased in the ECM during wound healing and parallels concentrations of MMP-9 in nasal fluids. Inflammatory cells represent the major source of increased MMP-9 expression, which is linked to poor healing quality. [206]
3. AIMS OF THE STUDY

1. To evaluate the impact of BSP as a treatment method on the QoL of patients suffering from CRS or RAR and to compare it with uncinectomy.

2. To evaluate and compare the effects of uncinectomy and BSP on nasal airway resistance and nasal airway patency.

3. To explore whether uncinectomy or BSP have an effect on MCC. Additionally, to compare different methods for the measurement of antral MCC and to assess the possibility of replacing the isotope 99mTc method (gold standard) by a less expensive and easier-to-use technique such as methylene blue dye or saccharine.

4. To study the histopathology of nasal mucosa as well as the expression of MMP-9 and how they are affected by uncinectomy and BSP.
4. MATERIALS AND METHODS

4.1. Study Design

A randomized non-blinded controlled clinical study was designed. Patients were recruited, treated and followed-up at the University Hospital of Tampere over a period of 2 years (2011–2013). All four original publications are based on the study and analysis of data from the same patients.

Diagnosis of CRS or RAR was based on patient history and direct endoscopic nasal examination. Additionally, CBCT scans of the paranasal sinuses were taken and the Lund–MacKay score of the side with the most severe findings was used in patient randomization (see Chapter Sample size and randomization). [61, 62] The inclusion criteria were as follows: (i) recurrent or isolated CRS of the maxillary sinus without severe pathology of other sinuses, (ii) aged between 18 and 65 years and (iii) failure of conservative treatment (i.e. with saline irrigations, antihistamines, prolonged antibiotics and local corticosteroids). The exclusion criteria were the following: (i) previous sinus operations, (ii) asthma, (iii) acetylsalicylic acid (ASA)-intolerance, (iv) diabetes or any other serious comorbidity, (v) visible polyps in nasal direct endoscopy and (vi) pregnancy.

Criteria for surgical treatment was a requirement for the recruitment of patients to this study. Indications for sinus surgery (according to Finnish guidelines for non-emergency surgical treatment criteria for RS, see http://www.terveysportti.fi/xmedia/hoi/hoi38050.pdf) were the following: a) persistent (continuous for more than 2 to 3 months) symptomatic CRS, b) confirmation of more than 3 to 4 episodes of acute rhinosinusitis within one year (RAR) and c) presence of pathological radiological findings as assessed by a sinus CBCT scan. [72, 73]

4.2. Ethical aspects of the study

Informed consent was obtained from all patients in advance. The nasal biopsies are a low-risk, simple procedure that were performed under local anaesthesia in the
outpatient clinic. Patients underwent a CBCT scan twice (once preoperatively and once 12 months after surgery). The dose of radiation that a patient receives from CBCT is 0.09 mSv per scan. This dose is estimated to be 0.03 (3%) of the background radiation dose people are exposed to during a nine-day period. This data indicates that the dose of additional radiation that our patients received was quite low. If there was a possibility of pregnancy at the time of the 12-month follow-up, the second CBCT scan was not taken.

During the study there was regular monitoring of the patients. Usually, CRS patients had one preoperative visit to the outpatient clinic, which was followed by surgery and then one follow-up visit one month postoperatively. The patients that took part in this study had three additional follow-up examinations at three, six and 12 months after surgery. The patients were charged for these three additional examinations. The enrolment of patients in this trial was voluntary, and none of the patients received any financial refund or any other special benefits in exchange for their participation in the study. This study was not sponsored by any pharmaceutical company or any personal or institutional funds. The results of this study were submitted for publication to peer-reviewed international journals.
4.3. Sample size and randomization

The sample size for the paired t-test analysis follows approximately the following formula:

\[
n = \frac{\sigma^2}{\left(\mu_1 - \mu_2\right)^2} \left[ Z(1 - \alpha/2) + Z(1 - \beta) \right]^2
\]

where \( \sigma \) is the estimated standard deviation of the difference, \( \mu_1 - \mu_2 \) is the difference in population means, \( Z(1 - \alpha/2) \) and \( Z(1 - \beta) \) are values from normal distribution tables for selected alpha and power values. The type I error rate or significance level is the probability of rejecting the null hypothesis given that it is true. It is denoted by the Greek letter \( \alpha \) (alpha) and is also called the alpha level. A type II error, also known as an error of the second kind, occurs when the null hypothesis is false but erroneously fails to be rejected, i.e., it fails to assert what is present, a miss. A type II error may be compared with a so-called false negative. The rate of the type II error is denoted by the Greek letter \( \beta \) (beta) and related to the power of a test (which equals \( 1 - \beta \)).

Based on the previously published articles, the highest value for population standard deviation was 1.29; so this value was selected for the calculations to ensure that too few patients were not selected for this study. Also based on previous studies, using SN O T -22 the clinically significant difference was set to 0.8. With alpha of 0.05 and power of 0.8, the calculation gave us approximately 21 study patients. A drop-out rate of approximately 20% to 30% of patients in follow-up had to be taken into account, so an approximately 30-patient cohort was considered to be large enough for our purposes.

Regarding the study of MCC and based on previous measurements, the clinically significant difference was set to 0.3. With alpha of 0.05 and power of 0.8, the calculation suggests 17 study patients for each treatment group. However, the distribution of the change is likely to be skewed and the criteria for using the formula presented above is therefore not accurate. For the purposes of non-parametric analysis, a 16% increase in study population size was used. Also, a drop-out rate of approximately 5% of patients in follow-up had to be taken into account.

Therefore, approximately 21 patients were allocated into each of the two groups in order to be able to detect statistically significant results. Since the distribution of the patients into these two groups may be uneven, the total sample size should be 70 in order to ascertain the required sample size for all groups. For the measurement of MCC only a part of the initial group of patients was selected.
4.4. Surgical methods

Local anaesthesia using 250 mg cocaine (125 mg on each side) diluted in 5 ml of 0.1 mg/ml adrenaline was performed for each patient. Also, four to six ml of 10 mg/ml lidocaine cum adrenaline solution was infiltrated to the mucosa of the uncinate process. Patients were conscious, though lightly sedated by the intravenous administration of 0.5 ml of 0.5 mg/ml alfentanil (Rapifen) and 0.5 ml of 1 mg/ml midazolam.

The uncinate process was removed from all the patients in the uncinectomy group and, where necessary, the pathology in the ostium was removed to ensure the patency, but the ostium was not enlarged.

The principle of balloon sinus dilatation is the catheterization of the sinus ostium with a flexible guide wire that allows an atraumatic entrance to the sinus through even a narrowed ostium. The procedure was made easier by using a lighted guide wire called the Luma Sinus Illumination System (Luma light; Acclarent Inc, Menlo Park, California, USA). A flexible balloon (6 mm × 16 mm) inflated up to 12 atm (Acclarent Inc) was inflated for 1 minute, and the dilatation was repeated one more time in accordance with product instructions for use and the manufacturer's guidelines. The same procedure was performed for both maxillary sinuses. Both the uncinectomy and BSP procedures were performed by specialized, experienced rhinologists.
4.5. Diagnosis

Routine diagnosis of the underlying pathologic condition comprised patient history and direct endoscopic nasal examination. Furthermore, CBCT scans of the paranasal sinuses were performed to evaluate the status of the paranasal sinuses. [72, 73, 207]

Patients were allocated into two groups based on Lund-McKay score: mild (score per side 1 to 2) or severe changes (score per side 3 to 4) at the maxillary sinus and/or the OMC. For classification purposes, the Lund-McKay score of the side with the most severe findings was used. The Lund-McKay score was counted separately for each side and it is a sum of the Lund-McKay score of the maxillary sinus and the OMC. The scale of the Lund-McKay score is from 0 to 2 for each measured area, i.e., 0 to 2 for the maxillary sinus plus 0 to 2 for the OMC. Therefore, there would be a maximum score of 4 if the maxillary sinus and the OMC were completely blocked and a minimum score of 0 if there were no pathology in the maxillary sinus or the OMC. [62]

4.6. Outcomes and variables

4.6.1. Demographics

The following patient demographic information was recorded and evaluated: a) sex, b) age, c) history of allergy, d) usage of nasal or other steroids e) presence of symptoms such as congestion of the nose, runny nose, impaired sense of smell or taste and f) a history of smoking.

4.6.2. Allergy

In addition to recording the allergy history of the patients, blood samples were collected and the serum levels of total immunoglobulin E and radioallergosorbent test (RAST) allergy blood tests were performed on all the patients that participated in this study. More specifically, tests were made for the following allergens common in Finland: a) timothy, b) birch, c) mugwort pollen d) alder, e) dog, f) cat, g) horse, h) mould and i) house-duct mite (D. pteronyssinus).
4.6.3. Sinonasal Outcome Test-22 (SNOT-22) Questionnaire

QoL measurements give the best estimation of the burden of disease for the patient. In rhinology, questionnaires have been widely used in both clinical practice and research to assess health-related quality of life (HRQoL). The HRQoL questionnaire provides information about the severity of other symptoms such as sleep, daily activities or the emotional consequences of the disease. The modified SNOT-16 has mostly been used for ARS and the SNOT-22 [208] or the Rhinosinusitis Outcome Measure-31 (RSOM-31) for CRS. The RSOM-31 contains 31 items divided into seven domains (nasal, eye, ear, sleep, general, functional and emotional problems).

As a modification of the RSOM-31, SNOT-20 comprises 20 nose, sinus and general variables. [6, 209] However, two critical questions: nasal obstruction and loss of smell are not included in the SNOT-20 questionnaire but were re-included in the SNOT-22 questionnaire. [210]

Therefore, SNOT-22 was selected for the present study. [211] The effects of RS as well as its treatment on QoL were assessed before treatment as well as at three, six and 12 months after treatment. In the questionnaire, the presence of 22 symptoms is evaluated. The severity of each symptom is assessed on a scale of 0 to 5 (0 = no symptom, 5 = worst symptoms). Previous validation studies have indicated that the minimally important difference, which is the smallest change in the SNOT-22 score that can be detected in a patient, is 8.9 points.[208, 212]

4.6.4. Acoustic rhinometry and rhinomanometry

Acoustic rhinometry provides a reliable assessment of vasoactive changes in the nasal cavity. [213-217] A nostril is congested if the minimum cross-sectional area (MCA) is smaller than 0.35 cm². Despite the nasal cycle, the total resistance remains relatively constant. A total nasal airway resistance (NAR) of 0.3 Pa/(cm³/s) at 100 Pa, as assessed with rhinomanometry, is the reasonable upper limit of the normal range in unobstructed and untreated healthy noses. [218-222] Both acoustic rhinometry and rhinomanometry measurements were performed before and after treatment. The measurements were initially carried out on a non-decongested nose and then repeated 15 minutes later after decongestion with oxymetazolin 1 mg/mL (2 sprays/nostril). Patients were evaluated at 3 and 6 months postoperatively to determine the effects of the surgical intervention and to detect any possible adverse effects.
4.6.5. Measurement of MCC

Three separate techniques were used simultaneously. Maxillary sinus puncture was performed to both sides of the inferior meatus for 10 minutes after local anaesthesia with 10 mg/ml lidocaine cum adrenaline solution. Irrigation tubes (Sinoject, Atos, Hörby) were introduced through the inferior meatus into the maxillary sinuses at least 30 minutes before the measurement to avoid possible refractory ciliostasis due to puncture. The Sinoject catheter was removed after the measurements had been completed.

4.6.5.1. Using Sterile Human Serum Albumin Labelled with 99mTc

Using a 1 ml syringe, a drop (0.03 ml) of sterile human serum albumin labelled with 99mTc (Venticol, Sorin Biomedica, Saluggia) was infused through the irrigation tube into the bottom of both maxillary sinuses simultaneously. The maximum particle size of the colloid is 200 nm. The syringe contained 0.03 ml 99mTc and the rest was filled in with a methylene blue/saccharine mixture. The patient was then placed in front of a gamma camera (Picker SX-300, MedWOW, Nicosia, Cyprus) with an all-purpose parallel-hole collimator connected to a Gamma-11 system for processing.

The clearance of tracer in both sinuses was monitored from the anterior view for 40 minutes. The areas of initial tracer in the sinuses were marked and the clearance of tracer from the sinuses as well as the possible appearance of activity into the pharynx were measured using dynamic gamma imaging at the following time points of 0, 10, 20, 30 and 40 minutes with residual activity (percentage from the initial) determined in the sinuses. Two cobalt buttons were attached to the forehead and one to the upper part of the sternum to control the errors caused by patient movement.

4.6.5.2. Methylene blue dye and saccharine test

A mixture of methylene blue dye/saccharine and 99mTc were infused simultaneously. A direct nasal endoscopy was performed with a rigid zero degree nasoendoscope in order to detect the dye in the nasal cavity, and with the use of a tongue depressor, the presence of dye in the posterior pharynx was monitored. The time it took for the patient to taste a sweet taste was reported.
4.6.6. Nasal mucosa biopsies from middle turbinate mucosa

Using cutting forceps, four biopsies were taken from the mucosa of the middle turbinate from each participant of the study preoperatively and at 3, 6 and 12 months postoperatively. Before biopsy, local anaesthesia with 4% lidocaine/adrenaline cottons was administered in the nasal mucosa. Tissue samples were fixed by formaldehyde and stored in a refrigerator at 8 oC. Then, the samples were embedded in paraffin and serially sectioned in an axial plane at a thickness of 10 μm. Selected sections were used for haematoxylin and eosin stain (H & E stain).

4.6.7. Histopathology

Selected sections were used for immunohistochemistry. Paraffin sections (5 mm) were stained with H & E stain. All the mucosal samples were studied and interpreted for the presence of chronic inflammation pathological changes. The mucosal samples were impartially reviewed and assessed by a pathologist. Afterwards, the stained sections were observed by a pathologist who was blind to the clinical data. The number of total inflammatory cells and glands in the lamina propria (LP) were studied and classified in different group using a categorical scale. Histological changes of sinonasal mucosa were examined by means of H & E stain for general morphology and inflammatory cell counting in LP.

Furthermore, chronic inflammation causes a remodelling of the airway walls that determines the clinical picture of this disease. The structural alterations include thickening of the LP, mucosal edema, stromal fibrosis, neovascularization, epithelial cell sloughing, cilia cell disruption/shedding, goblet cell hyperplasia and mucus hypersecretion. Chronic inflammation results in epithelial remodelling and desquamation, leading to a denuding of the LP and loss of the epithelial barrier function, which has to be rapidly restored.

The epithelial marker evaluation included the presence of transitional metaplasia, shedding of epithelium (damage of cilia) and epithelium thickening and the presence of inflammatory cells and goblet cells. The epithelial lining was scanned to determine the presence of the metaplasia of respiratory epithelium to transitional epithelium and recorded also as a categorical variable (0=not present, 1=present). The presence of goblet cells was recorded as a categorical variable (0=not present, 1=decreased, 2=normal and 3=hyperplasia). Epithelium was categorized as thin, normal or thick according to its thickness.
Mucosal specimens were assessed for the presence of mucosal inflammation, including cellular (eosinophils, neutrophils, lymphocytes, mast cells, plasma cells, macrophages), epithelial (squamous metaplasia, basement membrane thickening, goblet cells) and stromal markers (subepithelial edema, fibrosis). Mucosal markers such as stromal edema, hyperplasia of blood vessels, presence of mucous/serous glands, presence of inflammatory cells and fibrosis were also assessed in a categorical fashion (0=not present, 1=focal/mild, 2=patchy/moderate and 3=extensive/marked).

4.6.8. Immunohistochemistry (IHC)

Some paraffin sections were selected and used for IHC in order to study the expression of MMP-9 in nasal airway mucosa. IHC was performed in a 1:100 dilution using Santa Cruz MMP-9 antibody sc-21733.

4.6.9. Statistics

Analysis of our data was done with SPSS 9.0 software (SPSS Inc., Chicago, Illinois, USA). Improvement in QoL was analysed with paired t tests (Mann-Whitney and Wilcoxon tests). The measurements used in the comparison of the treatments were the individually calculated differences between the preoperative SNOT-22 values and the postoperative 6-month SNOT-22 values, and P values smaller than 0.05 were considered to be significant. Cohen's d (effect size) was also calculated for the purpose of analysis. Levene's test was used to test the homogeneity of variances. Pearson correlation coefficient was measured to explore any correlation and association between variables and in particular among the techniques for the measurement of MCC.

Based on previous validation of the SNOT-22 questionnaire, a minimally important difference, which is the smallest change in SNOT-22 score that can be detected by a patient, was set to be 8.9 points. [210, 212] The regression to mean was taken into account, and it was acknowledged that the phenomenon of "regression to mean" could affect the results. Therefore, a linear regression analysis was performed in order to evaluate the percentage of the postoperative total SNOT-22 score that can be explained by a linear relationship with the preoperative total SNOT-22.
4.6.10. Follow-up and the Reporting and Assessment of Adverse Effects and Reactions

There was a systematic follow-up of all the patients and any adverse effects. All patients were evaluated at 3, 6, and 12 months postoperatively to determine the effects of the surgical intervention. The report of adverse effects was based on patient symptoms as well as on findings in nasal endoscopy.
5. RESULTS

5.1. Participant flow and baseline data (Study I and II)

For the purposes of this study, 98 patients were evaluated for eligibility to enrol in the study and 74 (75.5%) patients were found to be suitable for the study. Next, the patients were randomized into two treatment groups: the uncinectomy group and the BSP group. Twelve patients dropped out of the trial. The uncinectomy group comprised 32 patients and the BSP group of 30 patients (see Figure 1). The average age of the patients was 39 years (22 males and 40 females). Of these patients, 20 patients (32.2%) were smokers and 42 (67.7%) patients had regularly used intranasal steroids before surgery. The duration of the RS symptoms among patients was on average over 10 years.

The Lund–MacKay classification was used for OMC and the maxillary sinuses and patients were divided to two groups. Group A (worst side’s score 1–2) comprised 39 patients and Group B (worst side’s score 3–4) comprised 21 patients. Although no findings were found in CBCT scan in two patients, their SNOT-22 score was over 50 and, based on nasal endoscopy findings, CRS was confirmed. Overall, regarding the Lund-McKay score, there was no significant difference between the two treatment groups. (Table 1)

A histopathological evaluation of the nasal mucosa was done to a total of 60 patients. (Study IV) One patient from each treatment group experienced biopsy as a quite unpleasant procedure and those patients did not agree to have any further biopsy. MCC was assessed in a total of 29 (46.8%) out of 62 patients (12 males and 17 females), with 16 patients allocated to the uncinectomy group and 13 patients allocated to the BSP treatment group. A test of homogeneity of variance confirmed that the demographic characteristics of the patients were equally distributed between the two treatment groups (no significant difference in variance p > 0.05).
Consort diagram of the study

Assessed for eligibility (n = 98)

Excluded (n = 24)
Not meeting inclusion criteria (n = 19)
Refused to participate (n = 5)

Randomized (n = 74)

Allocated to uncincetomy treatment group (n = 37)
Received allocated intervention (n = 34)

Allocated to balloon sinuplasty group (n = 37)
Received allocated intervention (n = 32)

Lost to follow up (n = 5)

Lost to follow up (n = 7)

Analysis

Analyzed (n = 32)

Analyzed (n = 30)

Figure 1. Consort diagram shows the progress of the study
Table 1. Demographics of patients showed a relative equal distribution of the patients between the two treatment groups (no significant difference in variance p > 0.05)

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy group (N =32 patients)</th>
<th>BSP group (N =30 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients +/- Standard error (years old)</td>
<td>40.25 +/- 2.1</td>
<td>37.17 +/- 1.8</td>
</tr>
<tr>
<td>Sex of patients (number of patients)</td>
<td>22 ♀, 10 ♂</td>
<td>18 ♀, 12 ♂</td>
</tr>
<tr>
<td>Smoking history</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Usage of nasal steroids before surgery</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Mean duration of symptoms (months) +/- SEM</td>
<td>163 +/- 21</td>
<td>102 +/- 19</td>
</tr>
<tr>
<td>Elevated levels of IgE (over 100U/ml) (patients)</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>History of allergies</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Classification based on Lund-McKay score (unilateral score)</td>
<td>0 (no findings): 1</td>
<td>0 (no findings): 1</td>
</tr>
<tr>
<td></td>
<td>1-2 (mild): 16</td>
<td>1-2 (mild): 21 pts</td>
</tr>
<tr>
<td></td>
<td>3-4 (severe): 14</td>
<td>3-4 (severe): 8 pts</td>
</tr>
<tr>
<td>Positive RAST allergy test</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>
5.2. QoL Trends (Study I and II)

QoL, as assessed by total score SN O T-22 score, was statistically improved 3 months after treatment and the positive effect was preserved at 6 months after treatment (p < 0.001; Table 2). Further statistical analysis of the data for the uncinectomy group revealed a Cohen's d (effect size) of 1.25 for the 3-month SN O T-22 score and one of 0.80 for the 6-month SN O T-22 score. For the BSP treatment group, Cohen's d was 1.19 for the 3-month SN O T-22 score and 1.00 for the 6-month SN O T-22 score, respectively.

Thus, based on the high difference in effect size in combination with a p value smaller than 0.05, it was concluded that our sample size was big enough in order to detect any significant change of total SN O T-22 score after treatment. No significant difference was found in the distribution of total SN O T-22 score between the two treatment groups. Cohen's d of the difference between the uncinectomy and the balloon sinuplasty group was calculated, and it was found to be 0.16 preoperatively (total SN O T-22 score = 36.15 to 49.25 with 95% confidence interval), 0.06 at 3-months (total SN O T-22 score = 17.7 to 28.9), and 0.38 at 6-months (total SN O T-22 score = 5.60 to 31.65 with 95% confidence interval).

It was noticed that all the parameters of the SN O T-22 questionnaire were improved. (Figures 2& 3) Thus, the possibility of regression to mean was taken under consideration. Additionally, a linear regression analysis, indicated in the 6-month follow-up, showed only 14.5% (R square = 0.145) of the postoperative total SN O T-22 score can be explained by a linear relationship with the preoperative total SN O T-22 score. This result would suggest that the preoperative total SN O T-22 score itself does not have much of an effect on the postoperative SN O T-22 score (p < 0.01). The Mann-Whitney test indicated no significant differences between the two treatment groups either preoperatively or 6 months postoperatively (all p > 0.05; Table 2).
Table 2. Difference of SNOT 22 score before and after treatment (mean +/- SD)

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy</th>
<th>Balloon sinuplasty</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>45.6 +/- 18.6</td>
<td>42.70 +/- 17.5</td>
<td>p&gt;0.05**</td>
</tr>
<tr>
<td>3 months after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>24.2 +/- 15.2</td>
<td>23.3 +/- 14.6</td>
<td>p&gt;0.05**</td>
</tr>
<tr>
<td>6 months after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>30.5 +/- 17.9</td>
<td>25.8 +/- 20.5</td>
<td>p&gt;0.05**</td>
</tr>
<tr>
<td>12 months after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>30.6 +/- 13.7</td>
<td>27.5 +/- 20.1</td>
<td>p&gt;0.05**</td>
</tr>
<tr>
<td>p&lt;0.05*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Wilcoxon test showed significant improvement of total SNOT 22 score after treatment
** Mann-Whitney test showed no significant difference between the treatment groups (p>0.05)

Table 2. The total SNOT-22 score was decreased after treatment in both groups and it remained decreased during the follow-up.

In both groups, treatment outcome was not influenced by either the sex of the patients or a history of smoking (p > 0.05). When the parameters of the SNOT-22 questionnaire were separately analysed, nasal congestion, postnasal drip, fatigue, running nose and facial pain/pressure were the most common symptoms among the patients suffering from CRS or RAR. (Figures 2& 3) A positive RAST allergy test was correlated with higher levels of total IgE (p=0.01). Treatment outcomes as assessed by SNOT-22 score were not affected by elevated levels of total immunoglobulin E (over 100 mg/dl) and a positive RAST allergy test did not affect the outcome of the treatment (p> 0.05).
Figure 2. All SNOT-22 questionnaire parameters (22 symptoms) in the uncinectomy group were ameliorated after treatment. Symptoms remained improved also 6-months after treatment.
Figure 3. SNOT-22 questionnaire parameters were improved also in the BSP group and changes were still noticeable 6-months after treatment.
5.3. Acoustic rhinometry (Study II)

According to previous studies and reference values, the noses of our patients were not significantly congested [14]. However, in the BSP treatment group, nasal volume was increased (Table 3). This may be explained by a decrease of mucosal edema.

Table 3. Acoustic rhinometry (in non-decongested nose) (mean +/- standard deviation (SD) (%))

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy</th>
<th>BSP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>0.61 +/-0.2</td>
<td>0.53 +/-0.34</td>
<td>p=0.34</td>
</tr>
<tr>
<td>3 months after treatment</td>
<td>0.64 +/-0.13</td>
<td>0.69 +/-0.24</td>
<td>p=0.36</td>
</tr>
<tr>
<td>6 months after treatment</td>
<td>0.65 +/-0.25</td>
<td>0.65 +/-0.2</td>
<td>p = 0.86</td>
</tr>
<tr>
<td>P value</td>
<td>&gt;0.05</td>
<td>&lt;0.05*</td>
<td></td>
</tr>
</tbody>
</table>

Mann-Whitney test showed no significant difference between the treatment groups either before or after treatment (p >0.05)
* Wilcoxon test showed significant difference in nasal volume before and after balloon sinuplasty treatment (p <0.05)

Table 3. Based on acoustic rhinometry in non-decongested nose: in the BSP treatment group, there was some increase in nasal volume but not statistically significant change was observed in uncinectomy group
5.4. Rhinomanometry (Study II)

Both treatments improved nasal airflow. In the uncinectomy group before treatment, the mean NAR in a non-decongested nose was $0.38 \pm 0.75 \text{ Pa/(cm}^3/\text{s})$ and after treatment decreased to $0.18 \pm 0.1 \text{ Pa/(cm}^3/\text{s})$ and $0.19 \pm 0.12 \text{ Pa/(cm}^3/\text{s})$ at 3 and 6 months, respectively. Cohen's $d$ (effect size) of the difference between the pre-treatment and post-treatment nasal airflow was calculated and it was found to be $0.37$ and $0.35$ at 3 months and 6 months, respectively (with 95% confidence interval). The similar effect was documented in the BSP treatment group.

Before treatment, the mean NAR was $0.38 \pm 0.71 \text{ Pa/(cm}^3/\text{s})$, $0.24 \pm 0.22 \text{ Pa/(cm}^3/\text{s})$ 3 months after treatment and $0.25 \pm 0.38 \text{ Pa/(cm}^3/\text{s})$ 6 months after treatment. Cohen's $d$ (effect size) of the difference between the pre-treatment and post-treatment nasal airflow was calculated and it was found to be $0.26$ and $0.22$ at 3 months and 6 months, respectively (with 95% confidence interval). Therefore, nasal airflow was significantly improved in both treatment groups ($p < 0.05$). (Table 4) The moderate difference in effect size in combination with a $p$ value smaller than 0.05 indicates that our sample size was big enough in order to detect any significant change in nasal airflow after treatment.

When comparing the mean NAR, no significant differences between the two treatment groups were found either before or after treatment (all $p \geq 0.05$; Table 4). Cohen's $d$ (effect size) of the difference between the uncinectomy group and the BSP group was calculated and it was found to be 0 preoperatively, $0.35$ at 3 months and $0.21$ at 6 months postoperatively (with 95% confidence interval). Since $p$ was >0.05, it can be concluded that no significant difference was found between the two treatment groups. The low effect size of difference before treatment and 6-month follow-up measurements indicates, however, that a bigger sample size is required in order to be able to detect any possibly existing significant difference between the two treatment groups.
### Table 4. Rhinomanometry (in non-decongested nose)

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy</th>
<th>BSP group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>0.38 +/- 0.75</td>
<td>0.38 +/- 0.71</td>
<td>P=0.997**</td>
</tr>
<tr>
<td>3 months after surgery</td>
<td>0.18 +/- 0.10</td>
<td>0.24 +/- 0.22</td>
<td>P=0.260**</td>
</tr>
<tr>
<td>6 months after surgery</td>
<td>0.19 +/- 0.12</td>
<td>0.25 +/- 0.38</td>
<td>P=0.368**</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.05*</td>
<td>&lt;0.05*</td>
<td></td>
</tr>
</tbody>
</table>

* Wilcoxon test showed significant decrease in air resistance (p < 0.05)
** Mann-Whitney test showed no significant difference between the treatment groups n before treatment (p >0.05) but there was some difference after treatment in favour of the uncinectomy group.

Table 4. Rhinomanometry in non-decongested nose showed that there was a decrease in airway resistance after treatment with changes being more noticeable in the uncinectomy group.

### 5.5. Histopathology of nasal airway (Study IV)

#### 5.5.4. Before treatment

Histopathological analysis was primarily done to all the participants without differentiating between treatment groups. The main findings that stood out were shedding of epithelium (damage of cilia), development of fibrosis in the mucosa, numerous inflammatory cells in epithelium, metaplastic changes in epithelium and hypertrophic serous and mucous glands.

These findings were present in 96.3%, 87%, 96.3%, 85.2% and 81.5% of patients, respectively. Increased thickness of epithelium and edematous mucosa were present in 70.4% and 59.3% of patients, respectively. In about half of the patients, the vascularity of the mucosa was increased. A history of allergy was associated with a loss of cilia (r=0.405, p = 0.01). An increased number of inflammatory cells in epithelium was correlated with a higher number of goblet cells (r=0.391) (Figure 5). A thickening of epithelium was correlated with a higher number of inflammatory...
cells \( (r=0.371) \) and hyperplasia of the blood vessels in the mucosa \( (r=0.287) \) (Figure 4).

5.5.5. Three months after treatment (study IV)

The shedding of epithelium (damage of cilia) and the metaplasia of epithelium from respiratory to transitional epithelium were present in all samples. Treatment showed no effect on the thickness of epithelium in either of the treatment groups. After treatment, there was some decrease in the number of inflammatory cells in epithelium and the mucosa especially among patients with a higher grade of inflammation (see Figure 7).

However, there was no statistically significant difference between the treatment groups. An amelioration of the hyperplasia of the blood vessels and mucous glands was noticed after treatment and it was more obvious in the BSP group. (Study IV)

A history of positive RAST test and an allergy history were associated with a higher number of goblet cells in epithelium after treatment. Also, female sex was associated with a higher number of inflammatory cells in mucosa after treatment \( (r=0.368, p=0.001) \). Shedding of epithelium was associated with a higher SNOT-22 score at three months after treatment \( (r=0.329, p=0.01) \). An increased number of inflammatory cells in epithelium was associated with a higher number of goblet cells \( (r=0.438) \) and thickening of epithelium \( (r=0.270) \) (Figure 5 and 6).
Figure 4. Light microscopy and H&E staining of middle turbinate mucosa: Numerous mucous glands (thin arrows), thickening of epithelium and hyperplasia of blood vessels can be seen. Infiltration of epithelium and mucosa with inflammatory cells (arrowheads), thickening of epithelium as well as thickening of the basal membrane (thick arrow) were noticed (1:20 lens).

Figure 5. (1x20 magnification) (Left) H&E stain of nasal mucosa showed hyperplasia of goblet cells (arrowheads). (Right) Infiltration of epithelium by numerous inflammatory cells (arrowheads).
Figure 6. A thickening of epithelium (asterisk) was observed in the majority of patients.

Figure 7. Number of inflammatory cells (as percentage %) in epithelium and mucosa in the uncinectomy (top row) and the BSP group. (lower row)
5.5.6. Six months after treatment (study IV)

A further decrease in the number of inflammatory cells in the epithelium and mucosa was noticed. Alleviation of inflammation was significantly more noticeable for the uncinectomy group compared with the BSP group (p<0.05) (see Table 1). In the uncinectomy group, the percentage of samples with no inflammatory cells in epithelium (grade 0) was increased from 3.7% before treatment to 66.7% at 6-month control. (see Table 1). Also, the percentage of severe inflammation in the mucosa was decreased from 29.6% to 11.1% after 6 months. This change in the mucosa was not seen in the BSP group.

The epithelium remained thickened and transitional. The presence of fibrotic tissue remained as before. The increased number of inflammatory cells in epithelium was associated with a higher number of goblet cells (r=0.467). The inflammatory cells in epithelium were in association with the inflammatory cells in the mucosa (r=0.467), and an increased number of inflammatory cells in the mucosa was associated with increased edema in the mucosa (r=0.331).

5.5.4. Twelve months after treatment

Hypertrophy of the mucous glands was noticeably decreased in both treatment groups. Hypervascularity (present in half of the samples before treatment) was ameliorated after treatment only in the uncinectomy group showing an advantage of uncinectomy between the treatment groups. The number of inflammatory cells in epithelium was significantly decreased after treatment in 12-month control samples. (Figure 7). All preferred changes were more noticeable for the uncinectomy group.

Damage of cilia, metaplastic epithelium and thickened epithelium as well as the presence of fibrotic tissue in the mucosa were not affected by treatment. The worse QoL scores, as assessed by total SNOT-22, were associated with a higher number of goblet cells (r=0.354) and hypertrophy of the mucosal glands (r=0.369). Increased edema of epithelium was associated with a higher number of goblet cells (r=0.420, p=0.015). Hyperplasia of blood vessels in the mucosa was associated with increased mucosal edema (r=0.314), thickening of epithelium (r=0.362) and an increased number of goblet cells (r=0.407). The presence of fibrosis in the mucosa was negatively associated with edema of the mucosa.
5.6. Histopathology and QoL

Damage of cilia was associated with a higher SN O T -22 at 3 months after treatment (r =0.329, p=0.002). A higher number of mucosal glands (r=0.369) and a higher number of goblet cells (r=0.354) were associated with a greater total SN O T -22 score at twelve months after treatment.

5.7. Expression of matrix metalloproteinase-9 (MMP9) in the nasal airway

In our samples, MMP9 was expressed in epithelium as well as in the mucosal stroma (in ECM) and in blood vessels (Figure 8 & 9). Even though it has been reported in the literature that MMP9 is expressed in the mucosal glands, no significant expression of MMP9 was observed in the nasal mucosal glands. (Figure 10)

Some interesting associations were found between SN O T -22 score, the histopathology of nasal mucosa and the expression of MMP9 protein. The expression of MMP9 in epithelium was positively correlated with inflammatory cells in epithelium and the mucosa (p <0.05). At three months after treatment, there was a strong association between the expression of MMP9 in epithelium and the inflammatory cells in epithelium (r=0.400). At six months after treatment, a strong association was found between the expression of MMP9 in epithelium and the number of inflammatory cells in the mucosa (r=0.639).

5.8. MCC

Pearson correlation was strong (r=0.434) between the taste of sweet saccharine in the mouth and the time it took to see the methylene blue dye in the nasal cavity (p <0.05). Correlation was weak, even though statistically significant (r=0.261, p<0.05), between the 99mTc-labelled tracer technique and the methylene blue technique. A history of smoking was strongly associated with the saccharine test (r=0.618, p<0.05), which means that it took longer for smokers to taste sweet saccharine in the mouth. There was no clear correlation between antral MCC and the improvement of symptoms. Treatment had no significant effect on MCC, and no difference was observed in MCC between the two treatment groups (p>0.05) (Table 5).
Figure 8. Figure 8: The expression of MMP-9 was prominent in inflammatory cells that infiltrated the nasal epithelium.

Figure 9. Immunohistochemistry for MMP-9 protein in nasal epithelium. Expression of MMP-9 in epithelium and in ECM in the mucosa (1:20 lens) (shown in brown).
Figure 10. No expression of MMP-9 was noticed in the mucous glands.
Table 5. Measurement of Mucociliary Clearance with three different techniques

<table>
<thead>
<tr>
<th></th>
<th>Saccharine Test</th>
<th>Methylene Blue</th>
<th>99mTc Labeled Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSP</td>
<td>20.35 ± 11.39</td>
<td>14.52 ± 11.50</td>
<td>71.8 ± 26.57</td>
</tr>
<tr>
<td>Uncinectomy</td>
<td>17.43 ± 9.18</td>
<td>13.71 ± 11.1</td>
<td>60.36 ± 34.78</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSP</td>
<td>18.71 ± 5.64</td>
<td>15.33 ± 9.53</td>
<td>69.65 ± 24.68</td>
</tr>
<tr>
<td>Uncinectomy</td>
<td>20.62 ± 5.92</td>
<td>11.66 ± 7.78</td>
<td>74.76 ± 27.80</td>
</tr>
</tbody>
</table>

*a Wilcoxon and Mann-Whitney tests showed no significant change in mucociliary clearance after treatment and no difference between the 2 treatment groups (p > .05).

*b It shows the percentage of albumin left in maxillary sinus after 40 minutes.

Table 5. Mucociliary clearance in the uncinectomy and BSP groups as assessed by three different methods.

5.9. Adverse Effects (Study I and II)

No one of the 62 patients suffered from a major complication (i.e. major bleeding, CSF-leak, orbital complications). However, minor complications were reported in 11 (17.7%) patients after 3 months and in 25 (40%) patients 6 months after treatment. At 3 months after treatment, the following minor complications were reported: a) for the uncinectomy group: crusting (3 patients/18.7%), infection (4 patients/25%), synechia (6 patients/37.5%), hyposmia (4 patients/25%), bleeding (one patient) and b) for the BSP group: infection (7 patients/53.8%), crusting (2 patients/15.3%), synechia (2 patients/15.3%), hyposmia (1 patient) and bleeding (one patient).

The most remarkable complications reported at 6 months for the uncinectomy group were infection (1 patient), crusting (3 patients/18.7%), synechia (12 patients/75%) and hyposmia (3 patients/18.7%). In the BSP group, the reported
complications were infection (2 patients/15.3%), crusting (2 patients/15.3%) and synechia (3 patients/23%) (Table 6).

Based on the Spearman's correlation test, at six months after treatment there was a positive correlation between the uncinectomy treatment and the development of synechiae ($r = 0.321$). This correlation was weak however statistically significant at the 0.05 level (2-tailed). Moreover, no significant correlation was found regarding the development of synechiae at three months after treatment. (Study I)

### Table 6. Adverse effects

<table>
<thead>
<tr>
<th></th>
<th>3 months after uncinectomy</th>
<th>6 months after uncinectomy</th>
<th>3 months after BSP</th>
<th>6 months after BSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crusting</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>10</td>
<td>15</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Synechia</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dacral duct damage</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 6. *Adverse effects in both treatment groups*
6. DISCUSSION

6.1. Synopsis of the key findings

6.1.4. Improvement of QoL after ESS and BSP (Study I and II)

Both treatment methods show a positive effect on the QoL of RS patients even 6 months after treatment. Analyses of the rhinomanometry results imply an amelioration of inflammation as documented by a decrease in NAR. Regarding QoL and NAR, no difference was found between the two treatment groups either preoperatively or 3 months and 6 months postoperatively. Synechiae were fewer in the BSP group. It is acknowledged that the study group was small and, as the low effect size of difference indicates, a larger sample size is required to detect any difference between the two treatment groups.

6.1.5. Decrease of inflammation in the nasal mucosa after ESS & BSP (Study IV)

Histopathological findings in the nasal mucosa verified the presence of inflammation. Infiltration of the mucosa and epithelium by inflammatory cells, as well as damage of cilia, thickening and metaplasia of epithelium were observed. Additionally, in the mucosa, hyperplasia of blood vessels, hypertrophy of the serous-mucous glands as well as the development of fibrosis were all observed.

Loss of cilia might lead to sensitization of nasal airway epithelium against allergens since cilia plays a protective role against airborne-allergens. However, the association between allergy and shedding of epithelium is more complicated since the presence of allergy is associated with inflammation in the airway, which in turn causes loss of cilia. A thickened epithelium was positively correlated with the number of inflammatory cells and hyperplasia of the blood vessels. This implies the presence of active inflammation in the nasal mucosa.

Neither ESS nor BSP affected MCC in any way. This may be explained, at least to some degree, by the fact that the loss of cilia was not restored after treatment. An increased number of inflammatory cells was positively associated with the number of...
goblet cells before and after treatment, which reflects the affluent secretion of mucous from an inflamed nasal airway.

The correlation between an increased number of inflammatory cells in the mucosa, hyperplasia of blood vessels and increased mucosal edema is also understandable since during the inflammatory process intravascular fluid exudates to the extracellular space. On the other hand, there was a negative association between fibrosis and mucosal edema. Fibrosis is the consequence of chronic inflammation, and the more fibrotic tissue is present the less active is the inflammatory process present in the mucosa.

Shedding of epithelium, hyperplasia of goblet cells and hypertrophy of mucous glands were associated with higher total SN O T -22 score. This reflects the fact that a chronically inflamed abnormal nasal mucosa has a negative effect on patient QoL.

6.1.6. Expression of MMP-9 and inflammation of nasal mucosa (Study IV)

The presence of M M P-9 in the nasal mucosa was analysed and found to be associated with inflammation markers. The expression of M M P-9 in epithelium was strongly and significantly correlated with a higher number of inflammatory cells in the nasal epithelium and the mucosa.

Both ESS and BSP clearly had a positive effect on the inflammation of the nasal mucosa. This is in accordance with the post-treatment improvement of symptoms and QoL. Rhinomanometry revealed a decrease of NAR after treatment. A lower number of inflammatory cells, alleviation of mucosal hypervascularity and a decline in the hypertrophy of the mucous glands may account for a more functional nasal epithelium and lower NAR. A decrease in mucosal edema in the uncinectomy group may also partly explain the lower NAR.

6.1.7. MCC after treatment (Study III)

Even though treatment had a beneficial effect on the QoL of patients, it failed to improve or affect MCC in any way. An improvement in the ventilation of the maxillary sinus did not lead to an improvement in MCC. A remarkable correlation was found between the methylene blue and the saccharine techniques. Based on the saccharine test results, smoking was noticeably associated with worse MCC.

The use of 99mTc-labeled tracer has been the gold standard for the measurement of MCC, and it remains the most accurate technique for the measurement of MCC.
It is, however, expensive, and its use entails a minimal though existing dose of radiation. Furthermore, the procedure is relatively uncomfortable for the patient.

The methylene blue technique is not as accurate, but there was clearly a positive association with the 99mTc-labeled tracer technique. In addition, the fact that the methylene blue technique is more economical, safer and more comfortable for the patient makes this technique more appealing in clinical practice.

Eleven of the 29 patients were smokers, and smoking negatively affects MCC. This might have disguised an improvement in MCC in non-smokers. Smoking was 1 of 4 variables used for the randomization of patients. However, due to our small sample size, smoking was not completely isolated as a confounding variable.

6.2. Strengths of the study

In this study, BSP was not compared with standard ESS (uncinectomy with antrostomy) Instead, uncinectomy and BSP were considered to be separate entities. BSP was performed bilaterally to the maxillary sinus of 30 patients (60 ostia). The selection of patients with isolated RS of the maxillary sinus resulted in a more homogenous study group.

Since there has been a lack of this kind of randomized prospective controlled clinical trial, this study provides valuable information about the histopathological changes in the mucosa in patients with CRS and explores the possible effects of treatment in the nasal airway at a microscopic level.

6.3. Comparisons with other studies

To date, most studies have compared BSP with a hybrid technique comprising a combination of ESS and BSP. [33] Based on a published review, there is an urgent need for more randomized-controlled trials to determine BSP's efficacy over other treatment modalities. Achar et al. [223] have published the results of a controlled randomized study with 24 patients where BSP was found to be as effective as ESS. In a prospective cohort study with 13 patients (24 sinuses of which only 10 were maxillary sinuses) published by Abreu et al. [175], no complications were reported and QoL was improved as assessed by SNOT-20. With the exception of a study by Tomazic et al. [224] where a surprisingly high failure rate was reported, encouraging results have been reported from different study groups. A retrospective controlled study in Finland showed a long-term positive effect and improvement of QoL in
both ESS and BSP groups. [174] It was, however, claimed that ESS may reduce the exacerbations of CRS more efficiently than BSP. [225]

Previous studies have also failed to show an improvement in mucosal function. [190] In only one study were improvements in MCC reported after ESS. It has been previously reported that smokers have a decreased sense of taste, which could explain to some degree why it took longer for smokers to taste saccharine in the mouth. However, previous studies have also shown that smoking has a negative effect on MCC. Therefore, further clinical studies are needed to further investigate the function of nasal mucosal and how treatment may or could affect its function.

6.4. Clinical applicability of the study

This study provides supporting evidence that, in some cases, it may be possible to relieve patient symptoms and improve nasal airflow using less invasive techniques such as BSP. To date, the cost of BSP has been an obstacle for its broader use around the world. However, because fewer synechiae developed in the BSP treatment group and the clinical benefits of the treatment were as good as those of ESS, BSP treatment has a clear advantage.

In this study, patients had sinus disease primarily restricted to the maxillary sinus and OMC with none or minimal changes in other sinuses. In addition, the severity of the findings was relatively mild. It is highly likely therefore that it is difficult to treat certain subgroups of CRS patients (i.e., pansinusitis) exclusively with BSP.

This study has shown that there is some improvement in the inflammatory process after surgical treatment. ESS seems to be more effective in decreasing the inflammatory process in nasal epithelium compared with BSP. However, BSP showed a considerable positive effect on mucosal inflammation, which should not be ignored.
7. CONCLUSIONS

1. Both BSP and ESS improved the QoL of patients with mild CRSsNP, while no significant difference was observed between the two treatment groups.

2. Rhinomanometry revealed a decrease in the NAR, which supports the hypothesis that improvement in QoL may be explained, at least to some degree, by a decrease of inflammation. Fewer synechiae were present in BSP.

3. Neither BSP nor ESS had any effect on MCC. The gold standard 99mTc labelled tracer technique was positively correlated with the methylene blue technique. The saccharine technique, even less accurate, could be useful in clinical practice because it is a quick, easy, inexpensive and safe technique.

4. Histopathological examination of the nasal mucosa in CRS revealed findings consistent with inflammation. The expression of MMP-9 in epithelium was strongly and statistically significantly correlated with a higher number of inflammatory cells in the nasal epithelium and mucosa. A decreased number of inflammatory cells, alleviation of mucosal hypervascularity and a decline in the hypertrophy of mucous glands indicates the positive effect of treatment on the inflammatory process. This may account for the post-treatment improvement of symptoms and QoL that have been previously reported.
ACKNOWLEDGEMENTS

This study was carried out at the University Hospital of Tampere, mainly in the Department of Otorhinolaryngology and Oral Diseases and in collaboration with the departments of Radiology and Pathology during the years 2011-2015. This study received Institutional Review Board approval and financial support was obtained from the Competitive Research Funding of Tampere University Hospital (Grant R10059).

First and foremost, I would like to express my gratitude to my thesis supervisor Professor Markus Rautiainen for his essential contribution to this study as well as for his mentorship. It has been a pleasure and an honour to work with him and to have the opportunity not only to complete my specialization in Otolaryngology but also to carry out this clinical study.

I would also like to thank:

Docent Jura Numminen for his contribution to this study in addition to his mentorship and critical guidance
Rami Taulu for his contribution to this study
Docent Heikki Teppo and Karin Blomgren for reviewing my thesis and for their critical feedback which helped to improve and complete this thesis
research nurse Marja-Leena Oksanen, technician Eini Eskola, statistician Mika Helminen and Peter Heath for their contributions and support throughout the study
my brother George Bizakis for his voluntary contribution in the illustration of this thesis
Tuomas Vallaskangas for letting me love him and proving me that happiness is about sharing.

Last but not least, I would like to thank my parents Maria Bizaki and Ioannis Bizakis for their unconditional support in every step of my life. I am truly blessed to be your daughter.
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Quality of life after endoscopic sinus surgery or balloon sinuplasty: a randomized clinical study*

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Abstract

Objectives: To conduct the first prospective randomized controlled trial that evaluates and compares the clinical outcome and impact of balloon sinuplasty and endoscopic sinus surgery (ESS) on the quality of life of patients suffering from chronic or recurrent rhinosinusitis (CRS) of the maxillary sinus.

Methods: Adult patients with symptomatic chronic or recurrent rhinosinusitis without severe findings in the sinuses, as documented in the sinuses’ Computer Tomography scan and clinical exam, were randomized in 2 groups: ESS and Balloon Sinuplasty. The main variable in our study is the Sinonasal Outcome Test-22 (SNOT 22) and its parameters. These parameters were analysed preoperatively and at 3 months, postoperatively.

Results: There was a subjective improvement in symptoms after surgery. We also noticed an objective improvement in the quality of life of our patients seen as a decrease in the total SNOT 22 score. Both balloon sinuplasty and ESS significantly improved almost all the parameters of SNOT22, with no significant difference being found between these two groups.

Conclusion: Both balloon sinuplasty and endoscopic sinus surgery improved the quality of life of patients with mild chronic or recurrent rhinosinusitis. However, the remarkably higher material cost of balloon sinuplasty compared to ESS sets limits on its broad use. There is an obvious need for further study to find out if, as an office procedure, balloon sinuplasty could deliver cost-savings high enough to cover the higher material cost of balloon sinuplasty. Our study was, however, too small to enable firm conclusions to be drawn.

Key words: balloon sinuplasty, rhino-sinusitis, endoscopic sinus surgery, quality of life, airway inflammation

Introduction
Rhinosinusitis is a common medical problem with significant symptoms that has a substantial impact on the quality of life. The term rhinosinusitis reflects the concurrent inflammatory and infectious processes that affect the nasal passages and the contiguous paranasal sinuses. Infection, mucosal hyperactivity and anatomical variation all contribute to some extent to the pathophysiology of rhinosinusitis.

Recurrent acute rhinosinusitis is diagnosed when four or more episodes of acute bacterial rhinosinusitis occur per year, without signs or symptoms of rhinosinusitis between episodes. If symptoms last for 12 weeks or longer, in addition to clinical evidence of inflammation or oedema of the middle meatus or ethmoid region, and/or radiographical imaging confirms that paranasal sinus inflammation persists for more than 12 weeks, the patient has chronic rhinosinusitis (CRS). It is unclear whether recurrent acute rhinosinusitis is actually a separate
disease category or whether those patients who meet the criteria for recurrent acute rhinosinusitis are simply having frequent exacerbations of chronic rhinosinusitis. For this study, both chronic rhinosinusitis and recurrent acute rhinosinusitis were considered to be one disease.

Chronic rhinosinusitis can be classified as allergic and non-allergic, depending on the presence or not of atopy. In both groups, however, intense eosinophilic infiltration of the mucosa has been noticed. Moreover, the increased levels of immunoglobulin E (IgE) present in allergic CRS has also been reported in CRS even in the absence of a history of allergy and the presence of a negative skin test. However, the basic causative mechanisms responsible for the clinical picture of the disease are not yet clearly defined [2]. The symptoms of CRS and recurrent rhinosinusitis vary in severity and prevalence. Nasal obstruction is the most common symptom, followed by facial congestion-pressure-fullness, discoloured nasal discharge and hyposmia. An improvement in ventilation and the drainage of the ostiomeatal complex and, at the same time, preservation of the mucosal lining of the upper airways is the main aim of surgical technique development [3].

In this study, we carried out a randomized, clinical study of patients with chronic or recurrent rhinosinusitis of the maxillary sinuses without severe pathology of other sinuses. Our goal was to study the clinical outcome and impact on the quality of life of balloon sinuplasty versus endoscopic sinus surgery (ESS) in patients with chronic or recurrent rhinosinusitis (CRS) of the maxillary sinus.

ESS has became the standard for the surgical treatment of rhinosinusitis. The aim of ESS is to restore the physiological functions of the nasal and paranasal cavities. In many studies, it has been shown that surgery results in an improvement in both subjective and objective findings, in addition to improvements in the quality of life of patients [8,9,11].

In 2002, the balloon sinuplasty technique was introduced in the treatment of ostia of the paranasal sinus system. Balloon sinuplasty is a recently introduced minimally invasive tool in rhinology that uses the concept of remodelling the anatomy of the paranasal sinus ostia without removing mucosal tissue or bone [12]. The use of balloon sinuplasty in patients has so far been proven to be feasible and safe [12,13]. In a few previous studies, ESS was compared with a hybrid sinus surgical technique where the patients had a combination of ESS and balloon sinuplasty [14]. It is, however, also very important to study and compare these two techniques as separate entities. This will not only further evaluate the efficacy of balloon sinuplasty for the treatment of patients with chronic or recurrent rhinosinusitis, but it will also facilitate the identification of those patients that will benefit the most from balloon sinuplasty.

Materials and methods

Study design

The randomized and controlled clinical study was carried out at the Department of Otolaryngology, Tampere University, Finland. The study comprised 42 patients that were suffering from chronic or recurrent rhinosinusitis. The patients were collected from the outpatient department. To be accepted into the study, all patients needed to qualify for sinus surgery (according to preferred indications for surgical treatment). Informed consent was obtained from all patients in advance.

Inclusion and exclusion criteria

The following inclusion criteria were used: a) patients had to have been diagnosed with chronic or recurrent rhinosinusitis of the maxillary sinus without severe pathology of other sinuses, b) patients had to be older than 18 years old and younger than 65 years old and c) patients had to fulfil the indications for sinus surgery [15].

In addition to the age limits, the following exclusion criteria were applied during patient recruitment: a) patients with a history of previous sinus operations, b) patients who had been diagnosed with asthma, c) patients with a history of ASA-intolerance, d) patients with a history of diabetes or any other systemic disease, e) patients with visible polyps in nasal direct endoscopy and f) patients that were pregnant at the time of enrolment to the study.

Diagnosis

Routine diagnosis of the underlying pathological condition comprised patient history and direct endoscopic nasal examination. Furthermore, cone beam computed tomography (CBCT) scans of the paranasal sinuses were performed to evaluate their status [16]. An experienced radiologist and an otolaryngologist surgeon subsequently interpreted the images.

Patients were allocated into two groups: mild (score per side 1-2) or severe changes (score per side 3-4) at the maxillary sinus and/or the ostiomeatal complex. For classification purposes, the Lund-McKay score of the side with the most severe findings was used. The Lund-McKay score was counted separately for each side and it is a sum of the Lund-McKay score of the maxillary sinus and the ostiomeatal complex. The scale of the Lund-McKay score is from 0 to 2 for each measured area i.e 0 to 2 for the maxillary sinus plus 0 to 2 for the ostiomeatal complex. Therefore, there would be a maximum score of 4 if the maxillary sinus and the ostiomeatal complex were completely blocked and a minimum score of 0 if there were no pathology in the maxillary sinus or the ostiomeatal complex.
Sino Nasal Outcome Test -22 (SNOT22) Quality of life questionnaire

The SNOT22 questionnaire was used to assess the quality of life of patients. We compared the preoperative SNOT22 score and the SNOT22 score at 3-months, postoperatively. Based on previous validation studies, we considered that the minimally important difference, which is the smallest change in the SNOT22 score that can be detected in a patient, to be 8.9 points \(^{14}\).

Study groups

Using MINIM (MS-DOS program for randomization in clinical trials), the patients were randomized into two treatment groups: the endoscopic sinus surgery group and the balloon sinuplasty group. The patients were randomized based on the following variables: a) smoking history, b) age, c) sex and d) Lund McKay score.

Sample size for paired t-test analysis follows approximately the following formula:

\[
n = \frac{\sigma^2}{\mu_1 - \mu_2} \left[ Z(1 - \alpha/2) + Z(1 - \beta) \right]^2
\]

where \( \sigma \) is estimated standard deviation of the difference, \( \mu_1 - \mu_2 \) is the difference in population means, \( Z(1 - \alpha/2) \) and \( Z(1 - \beta) \) are values from normal distribution tables for selected alpha and power values. Based on the previously published articles, the highest value for standard deviation has been 1.29. This value was, therefore, selected for the calculations to ensure that not too few patients were selected for the study. Also based on previous studies that used SNOT-22, the clinically significant difference was set to 8.9. With an alpha value of 0.05 and a power value of 0.8, the calculation gave us approximately 21 study patients for each study group.

Surgical methods

For both treatment groups, a procedure was performed under regional anesthesia using 250mg cocaine diluted in 5ml of 0.1mg/ml adrenaline. Additionally, we infused the uncinate process with 4-6 ml of 10 mg adrenaline cum lidocaine solution. Conscious sedation was achieved for all patients by the intravenous administration of 0.5 ml of 0.5 mg/ml Rapifen and 0.5 ml of 1 mg/ml Midazolam.

During surgery, patients in the ESS group underwent the removal of the inferior part of the uncinate process and where necessary the pathology in the ostium was removed to ensure the patency, but the ostium was not enlarged. The principal of balloon sinus dilatation is the cannulation of the sinus ostium with a very thin, flexible guidewire that allows an atraumatic entrance to the sinus, even through a narrowed ostium. Following cannulation and prior to balloon dilatation, it is essential to confirm that the guidewire has entered the sinus. To simplify the process, we used a lighted guidewire called the Luma Sinus Illumination System (Luma light) (Acclarent Inc., Menlo Park, CA, USA). The concept is based on transillumination through the sinus walls for the identification of the guidewire’s location. In all the patients, both of the sinuses were treated.

Allergy

In addition to recording the allergy history of the patients, blood samples were collected and the serum levels of total immunoglobulin E and RAST allergy blood tests were performed on all the patients that participated in our study. More specifically, tests were made for the following allergens common in Finland: a) timothy, b) birch, c) leek, d) dog, e) cat, f) horse, g) mould and h) mite (D. pteronyssinus).

Statistical analyses

A workstation with SPSS 9.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical evaluation and graphical representation of the results. Improvement in quality of life was analysed with paired t-tests. The measurements used in the comparison of the treatments were the individually calculated differences between the preoperative SNOT-22 values and the postoperative 3-month SNOT-22 values. P values smaller than 0.05 were considered to be significant.

Follow-up, and the reporting and assessment of adverse effects and reactions

There was a systematic follow-up of all the patients and any adverse effects (Figure 1). All patients were evaluated at 3 months postoperatively to determine the effects of the surgical intervention.

Results

Baseline characteristics / demographics

In total, 46 patients were enrolled on the study. Four female patients dropped out of the treatment programme. Two of them were in the ESS group and two of them in the balloon sinuplasty group. These patients were not included in the statistical analysis because they did not show up for the follow-up control and, therefore, we only have demographics data and the preoperative SNOT22 score for them. They did not give any particular reason for dropping out of the study and there were no complications. They just decided that they did not want to be in the study. The Ethical Committee’s decision about our study included a statement that gave patients the right to drop out of the study at any time without giving any reason for their decision. We analysed our data based on the 42 patients (13 males and 29 females) that remained in the study. Thus, a total of 42 patients participated in our study, with 21 patients allocated to each treatment group.
Quality of Life trends

Statistically significant improvements in quality of life were found between baseline and 3 month follow-up for the total scores of the SNOT22 (p < 0.001; Table 1). Cohen's d (effect size) of the difference between baseline and 3-month postop SNOT22 was calculated for both treatment groups and it was significantly high in both treatment groups: Cohen's d was 1.44 for the ESS treatment group and 1.32 for the balloon sinuplasty group. The high difference in effect size in combination to a p value smaller than 0.05 indicates that our sample size was big enough to detect any significant change of total SNOT22 score after treatment. A linear regression analysis was performed to evaluate the percentage of the preoperative total SNOT22 score that affects and predicts the postoperative SNOT22 score. Based on this analysis, in the ESS treatment group, only 20.8% (R square = 0.208) of the postoperative total SNOT22 can be predicted from the preoperative total SNOT22 score. This result would suggest that the preoperative total SNOT22 score itself does not have much of an effect on the postoperative SNOT22 score. However, this result could not be statistically verified since the p value was higher than 0.05.

When comparing the changes in the total SNOT22 scores of the ESS and balloon sinuplasty groups, we identified no significant differences between the two treatment groups, either preoperatively or 3-months postoperatively (all p ≥ 0.05; Table 2). Cohen's d (effect size) of the difference between the ESS and the balloon sinuplasty group was calculated and it was found to be 0.16 preoperatively and 0.19 at 3-months postoperatively (with 95% confidence interval). Since p was > 0.05, we can say that no significant difference was found between the two treatment groups.

Table 1. Demographics.

<table>
<thead>
<tr>
<th></th>
<th>ESS group (n = 21)</th>
<th>Balloon sinuplasty (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients ± SEM (years old)</td>
<td>40 ± 2.6</td>
<td>39.2 ± 2.3</td>
</tr>
<tr>
<td>Sex</td>
<td>7 M; 14 F</td>
<td>9 M; 12 F</td>
</tr>
<tr>
<td>Smoking history</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Usage of nasal steroids before surgery</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Mean duration of symptoms (months)</td>
<td>136.4 ± 24.9</td>
<td>85.5 ± 21.1</td>
</tr>
<tr>
<td>Elevated levels of IgE (&gt;100 U/ml)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>History of allergies</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Positive RAST allergy test</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

Based on test of homogeneity of variance, the demographic characteristics of patients were equally distributed between the two treatment groups (no significant difference in variance p > 0.05).

The average age of the patients was about 40 years old. Thirteen patients were smokers and 34 patients had regularly used nasal steroids before the surgery. The mean duration of the symptoms of chronic rhinosinusitis before surgery was 112.4 ± 16.8 months. In 13 patients, the levels of total IgE in serum was elevated (over 100U/ml), and in 18 patients the allergy RAST test was positive (Table 1). The Lund-McKay score was calculated based on the findings in the ostiomeatal complex and the maxillary sinuses. Mild disease was found (worst side's score 1-2) in 28 patients and more severe disease (worst side's score 3-4) in 8 patients.

Table 2. Difference in SNOT-22 score before and after treatment (mean ± SEM).

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>After surgery</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS (n = 21)</td>
<td>46.00 ± 3.27</td>
<td>25.05 ± 3.24</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Balloon sinuplasty (n = 21)</td>
<td>43.57 ± 3.64</td>
<td>22.10 ± 3.28</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

* Wilcoxon test showed significant improvement in total SNOT22 score after treatment.
groups. The low effect size of difference indicates, however, that a bigger sample size is required in order to be able to detect any possibly existing significant difference between the two treatment groups.

We cannot be sure whether a difference exist between the two treatment groups and whether or not this is a type II error as our study group was relatively small and the effect size of difference was low. However, based on our current data, we were not able to find any significant difference between the groups. Therefore, more extended studies with a larger number of patients are needed.

The regression to mean has been taken into account. We acknowledged that the phenomenon of “regression to mean” could explain, at least to some degree, the fact that after treatment all the separate variables of SNOT22 were decreased. Neither the sex of patients nor the history of smoking affected the outcome of treatment in any known way (p > 0.05). An analysis of the SNOT22 questionnaire’s parameters preoperatively showed that nasal congestion, postnasal drip, fatigue, runny nose and facial pain/pressure were the most common symptoms among the patients with chronic or recurrent rhinosinusitis (Figure 2).

Allergy
A positive RAST allergy test was associated with higher levels of total immunoglobulin E (p = 0.01). Neither elevated levels of total immunoglobulin E (over 100mg/dl) nor a positive RAST allergy test affected the outcome of the treatment (p > 0.05).

Adverse effects
None of the 42 patients had a major complication. However, minor complications were reported in 21 patients: in 13 patients from the ESS group and in 8 patients from the balloon sinusplasty treatment group. The reported complications in the ESS group were infection (4 patients), crusting (3 patients), synechia (6 patients), anosmia (4 patients) and bleeding (1 patient). In the balloon sinusplasty group, the reported complications were infection (7 patients), crusting (2 patients), synechia (2 patients), anosmia (1 patient) and bleeding (1 patient) (Table 3). Based on Spearman’s correlation test, a weak but not statistically significant positive association was found between ESS treatment and the development of synechia (r = 0.243) and anosmia (r = 0.221) (p > 0.05).

Discussion
Although many studies have examined outcomes after sinus surgery, few have done so in a prospective fashion with randomized groups. There remains a need for prospective trials that compare the methods used in the treatment of chronic sinusitis. In cases of CRS, both balloon sinusplasty and endoscopic sinus treatment seem to improve the quality of life of patients. Three months after treatment, we were not able to find any significant difference between the two methods.

We acknowledge that our study group was small, and that it is likely that there is a difference between these two treatments. However, based on statistical analysis of our present data, we were not able to find any significant difference between these two treatment methods with regard to their effect on the previous studies SNOT22 score. Based on the results of this study, the evidence suggests that chronic rhinosinusitis might be targeted with less invasive treatment methods i.e. balloon sinusplasty in the first instance, with more invasive and radical treatment being reserved for more severe and refractory cases.

Table 3. Adverse effects.

<table>
<thead>
<tr>
<th>Adverse effect / complication</th>
<th>Total of patients</th>
<th>ESS group</th>
<th>Balloon group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Crusting</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Synechia</td>
<td>8</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Anosmia</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

With regard to adverse effects, no significant difference was found between ESS and balloon sinusplasty (p < 0.05).
Balloon sinuplasty is a delicate, minimally invasive tool, and our results demonstrate promising outcomes in terms of safety and effectiveness. The results of this study have important implications for future clinical trials designed to evaluate the comparative effectiveness of treatments for CRS.

In our study, patients had sinus disease primarily restricted to the maxillary sinus and ostiomeatal complex with none or minimal changes in other sinuses. In addition, the severity of the findings was relatively mild. It is highly likely that it is difficult to treat certain subgroups of CRS patients, such as those with pansinusitis, with only balloon sinuplasty. In the present study, we did not include any hybrid operations to avoid any confusion in the results caused by combined operative techniques.

This study does not allow conclusions about quality of life (QOL) changes and the efficiency of treatment methods in the long-term. It is probable that certain subgroups of CRS patients, possibly those with severe findings in CT or severe clinical symptoms, will develop recurrent disease over time and a subsequent worsening of QOL measurements. There is a group of patients that suffers from recurrent rhinosinusitis during the infection seasons in winter in spite of proper conservative treatment without any severe findings in CT scans. Some patients have near-normal disease-specific QOL, but have one or more prominent symptoms that still drive them to elect surgical treatment for their disease. This group of patients has little room for improvement in QOL, even though surgery may have been clinically successful.

Conclusion
Both balloon sinuplasty and endoscopic sinus surgery improved the quality of life of patients with mild, chronic or recurrent rhinosinusitis. However, the remarkably higher material cost of balloon sinuplasty compared to ESS sets limits on its broad use. There is an obvious need for a study to find out if, as an office procedure, balloon sinuplasty could bring cost savings that would cover the higher material cost. To further study balloon sinuplasty’s potentials and limits as a method requires more research and long-term studies.

Acknowledgement
To research nurse Marja-Leena Oksanen for ensuring patients’ smooth coordination and support throughout the study.

Authorship contribution
AB: recruitment of new patients, collection and analysis of data, clinical examination of patients before and after surgery, writing of the manuscript. RT: performed endoscopic sinus surgery and balloon sinuplasty, clinical examination of patients. JN: performed endoscopic sinus surgery and balloon sinuplasty, clinical examination of patients, manuscript review. MR: Principal researcher of the study, recruitment of new patients, performed endoscopic sinus surgery and balloon sinuplasty, manuscript review.

Conflicts of Interest
None of the authors had any conflict of interest with any financial organization.

References
Objective: The aim of this study was to evaluate and compare the clinical outcome of balloon sinuplasty and uncinectomy for patients suffering from isolated chronic rhinosinusitis of the maxillary sinus.

Design: A prospective, randomised, non-blinded, controlled trial was conducted.

Setting: The study was carried out at the Department of Otolaryngology, Tampere University Hospital, Finland.

Participants: Adult patients with symptomatic isolated chronic or recurrent rhinosinusitis without severe findings in the sinuses, as documented in the sinus' Computer Tomography scan and clinical examination, were randomised into two groups: uncinectomy and balloon sinuplasty.

Main outcome measures: The variables in our study are the Sinonasal Outcome Test-22 (SNOT 22), acoustic rhinometry and rhinomanometry. These parameters were analysed preoperatively and postoperatively (after 3 and 6 months).

Results: The preliminary results of our study have been previously published. Both balloon sinuplasty and uncinectomy significantly improved almost all the parameters of SNOT22 (P < 0.05), with no significant difference being found between these two groups (P > 0.05). Based on rhinomanometry results, airway resistance decreased after treatment. Regarding adverse effects, balloon sinuplasty was significantly associated with a lesser risk of synechia.

Conclusions: Both balloon sinuplasty and uncinectomy improved the quality of life and decreased upper airway resistance of patients with mild, isolated chronic or recurrent rhinosinusitis. The smaller risk of postoperative synechiae with balloon sinuplasty combined with its promising efficiency could partially compensate for its high material cost.
Methods

Trial design

With the approval of the hospital’s ethical committee and patients’ informed consent, a randomised, non-blinded, controlled clinical study was carried out. Recruitment, treatment and follow-up were carried out at the University Hospital of Tampere over a period of 2 years (2011–2013). Diagnosis was based on patient history and direct endoscopic nasal examination. Additionally, cone beam computed tomography (CBCT) scans of the paranasal sinuses were taken and the Lund–MacKay score of the side with the most severe findings was used in patient randomisation (see Chapter Sample size and randomisation).

The inclusion criteria were as follows: (i) recurrent or isolated chronic rhinosinusitis of the maxillary sinus without severe pathology of other sinuses, (ii) aged between 18 and 65 years and (iii) failure of conservative treatment (i.e. with saline irrigations, antihistamines, prolonged antibiotics and local corticosteroids). The exclusion criteria were the following: (i) previous sinus operations, (ii) asthma, (iii) acetylsalicylic acid (ASA)-intolerance, (iv) diabetes or any other serious comorbidity, (v) visible polyps in nasal direct endoscopy and (vi) pregnancy.

Surgical methods

Conscious sedation was achieved by the intravenous administration of 0.5 mL of 0.5 mg/mL alfentanil (Rapifen) and 0.5 mL of 1 mg/mL midazolam. Cocaine (125 mg/side) diluted in 5 mL of 0.1 mg/mL adrenaline was used as a local anaesthetic, followed by infusion of the uncinate process with 4–6 mL of 10 mg/mL adrenaline cum lidocaine solution. Both sinuses were treated. In the uncinectomy group, the inferior part of the uncinate process was removed, but the ostium was not, however, enlarged.

Balloon sinuplasty is a technique that involves the cannulation of the sinus ostium with a flexible guide wire that allows an atraumatic entrance to the sinus. A lighted guide wire called the Luma Sinus Illumination System was used for transillumination through the sinus walls and identification of the guide wire’s location. Dilatation was performed with a flexible balloon (6 × 16 mm) inflated up to 12 atm (Acclarent Inc, Menlo Park, CA, USA) for 1 min, and then, the dilatation was repeated one more time in accordance with product instructions for use and the manufacturer’s guidelines.

Outcomes and variables

Quality of life was assessed before treatment, at 3 months after treatment and 6 months after treatment using the Sino Nasal Outcome Test-22 (SNOT-22) questionnaire (includes 22 symptoms). The symptoms are presented on a scale of 0–5.

Acoustic rhinometry provides a reliable assessment of vasoactive changes in the nasal cavity. A nostril is congested if the minimum cross-sectional area (MCA) is smaller than 0.35 cm². Despite of the nasal cycle, the total resistance remains relatively constant. A total nasal airway resistance (NAR) of 0.3 Pa/(cm³/s) at 100 Pa is the reasonable upper limit of the normal range in unobstructed and untreated healthy noses.

Both acoustic rhinometry and rhinomanometry measurements were performed before and after treatment. The measurements were initially carried out in an undecongested nose and then repeated 15 min later after decongestion with oxymetazolin 1 mg/mL (2 sprays/nostril).

Patients were evaluated at 3 and 6 months postoperatively to determine the effects of the surgical intervention and to detect any possible adverse effects.

Sample size and randomisation

A statistician calculated the approximate sample size needed for the paired t-test analysis. Based on previous studies that used SNOT-22, the clinically significant difference was set to 8.9, and the highest value for standard deviation was estimated to be 1.29. With an alpha value of 0.05 and a power value of 0.8, the calculation gave us approximately 21 study patients for each study group. Using MINIM (MS-DOS program for randomisation in clinical trials), the patients were randomised into two treatment groups: the uncinectomy and the balloon sinuplasty group. The patients were randomised based on the following variables: (i) smoking history (smokers, non-smokers), (ii) age (18–33, 34–49 and 50–65 years old), (iii) sex (male, female) and (iv) Lund–MacKay score for maxillary sinus and ostiomeatal complex (Group A = Lund–MacKay score per side 1–2 and Group B = Lund–MacKay score per side 3–4).

Statistics

SPSS 9.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical evaluation and graphical representation of the results. Improvement in quality of life and nasal tests’ results were the individually calculated differences between

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the preoperative SNOT-22 values and the postoperative 3-month and 6-month SNOT-22 values, and \( P \) values smaller than 0.05 were considered to be significant. Cohen’s \( d \) (effect size) was also calculated for the purpose of analysis. Levene’s test was used to test the homogeneity of variances.

**Results**

**Participant flow and baseline data**

In total, 98 patients were assessed for eligibility to enrol in the study. From the 98 patients, 74 patients were found to be suitable for the study and were randomised into two treatment groups. Twelve patients dropped out of the treatment programme. Of these, five were in the uncinectomy group and seven in the balloon sinuplasty group. A total of 62 patients with an average age of 39 years (22 males and 40 females) were analysed, 32 from the uncinectomy group and 30 from the balloon sinuplasty group (Fig. 1). Twenty patients were smokers, and 42 patients had regularly used intranasal steroids before the surgery. The mean duration of the rhinosinusitis symptoms was over 10 years. The Lund–MacKay score was calculated based on the findings in the ostiomeatal complex and the maxillary sinuses. Group A (worst side’s score 1–2) included 39 patients and Group B (worst side’s score 3–4) included 21 patients (Table 1). Two patients had zero findings in CT scan, but their SNOT-22 score was over 50 and, based on nasal endoscopy findings, mucosal oedema was found to be present.

**Quality of life trends**

Improvement in quality of life was observed 3 months after treatment and the positive effects were preserved at 6 months after treatment (\( P < 0.001 \); Table 2). Cohen’s \( d \) (effect size) of the difference between SNOT-22 score before and after treatment was calculated for both treatment groups, and it was significantly high in both groups. In the uncinectomy treatment group, Cohen’s \( d \) was 1.25 for the
3-month score and 0.80 for the 6-month score. In the balloon sinuplasty group, Cohen’s d was 1.19 for the 3-month SNOT-22 and 1.00 for the 6-month SNOT-22. The high difference in effect size in combination with a P value smaller than 0.05 indicates that our sample size was large enough to detect any significant change of total SNOT-22 score after treatment.

A linear regression analysis was performed to evaluate the percentage of the preoperative total SNOT-22 score that affects and predicts the postoperative SNOT-22 score. Based on this analysis, at the 6-month follow-up only 14.5% (R square = 0.145) of the postoperative total SNOT-22 can be predicted from the preoperative total SNOT-22 score. This result would suggest that the preoperative total SNOT-22 score itself does not have much of an effect on the postoperative SNOT-22 score (P < 0.01).

When comparing the changes in the total SNOT-22 scores of the uncinctomy and balloon sinuplasty groups, we identified no significant differences between the two treatment groups either preoperatively or 3 months postoperatively (all P ≥ 0.05; Table 2). Cohen’s d of the difference between the uncinctomy and the balloon sinuplasty group was calculated, and it was found to be 0.16 preoperatively (total-SNOT22 = 36.15–49.25 with 95% confidence interval), 0.06 at 3 months (total SNOT22 = 17.7–28.9) and 0.38 at 6 months (total SNOT22 = 5.60–31.65 with 95% confidence interval).

Neither the sex of the patients nor a history of smoking affected the outcome of treatment in any way (P > 0.05). An analysis of the SNOT-22 questionnaire’s parameters preoperatively showed that nasal congestion, post-nasal drip, fatigue, runny nose and facial pain/pressure were the most common symptoms among the patients with isolated chronic or recurrent rhinosinusitis (Fig. 2).

**Nasal tests**

In the balloon sinuplasty treatment group, a statistically significant improvement of nasal volume was documented (Table 3). There was an improvement in nasal airflow after treatment (see Table 4). In the uncinctomy group before treatment, the mean NAR in an undecongested nose was 0.38 Pa/(cm³/s) ± 0.75 and decreased, respectively, to 0.18 ± 0.1 and 0.19 ± 0.12 Pa/(cm³/s) at 3 and 6 months after treatment. Cohen’s d (effect size) of the difference between the pre-treatment and post-treatment nasal airflow was calculated to be 0.37 and 0.35 at 3 months and 6 months, respectively (with 95% confidence interval). A similar effect was observed in the balloon sinuplasty treatment group. Before treatment, mean NAR was 0.38 ± 0.71, 0.24 ± 0.22 Pa/(cm³/s) 3 months after treatment and 0.25 ± 0.38 Pa/(cm³/s) 6 months after treatment. Cohen’s d of the difference between the pre-treatment and

---

**Table 1. Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy group (32 patients)</th>
<th>Balloon sinuplasty (30 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients ± Standard error (SEM) (years old)</td>
<td>40.25 ± 2.1</td>
<td>37.17 ± 1.8</td>
</tr>
<tr>
<td>Sex of patients</td>
<td>10 males, 22 females</td>
<td>12 males, 18 females</td>
</tr>
<tr>
<td>Smoking history (patients)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Usage of nasal steroids before surgery (patients)</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Mean duration of symptoms (months) ± SEM</td>
<td>163 ± 21</td>
<td>102 ± 19</td>
</tr>
<tr>
<td>Classification based on Lund–Mackay score (unilateral score)</td>
<td>0 (no findings): 1</td>
<td>0 (no findings): 1</td>
</tr>
<tr>
<td></td>
<td>1–2: 16 pts</td>
<td>1–2: 21 pts</td>
</tr>
<tr>
<td></td>
<td>3–4: 14 pts</td>
<td>3–4: 8 pts</td>
</tr>
</tbody>
</table>

*Based on Levene’s test for homogeneity of variance, the demographic characteristics of patients were equally distributed between the two treatment groups (no significant difference in variance P > 0.05).

---

**Table 2. Difference of SNOT22 score before and after treatment (mean ± SE mean)**

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>3-month after treatment</th>
<th>6-month after treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncinectomy (n = 32 for 3 months and n = 30 for 6 months)</td>
<td>45.63 ± 3.29</td>
<td>24.25 ± 2.68</td>
<td>30.54 ± 3.2</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Balloon sinuplasty (n = 30)</td>
<td>42.70 ± 3.2</td>
<td>23.31 ± 2.72</td>
<td>25.31 ± 3.81</td>
<td>&lt;0.05**†</td>
</tr>
</tbody>
</table>

*Wilcoxon test showed significant improvement of total SNOT22 score after treatment.
†Mann–Whitney test showed no significant difference between the treatment groups pre-op and 3 months after surgery (P > 0.05).
post-treatment nasal airflow was calculated to be 0.26 and 0.22 at 3 months and 6 months, respectively (with 95% confidence interval).

No significant differences between the two treatment groups were found either before or after treatment (all \( P \geq 0.05 \); Table 4). Cohen’s \( d \) of the difference between the uncinectomy and the balloon sinuplasty group was calculated to be 0 preoperatively, 0.35 at 3 months, and 0.21 at 6 months, postoperatively (with 95% confidence interval).

Adverse effects

There were no major complications (i.e. major bleeding, CSF-leak orbital complications). Minor complications were reported in 25 patients: in 16 patients from the uncinectomy and in nine patients from the balloon sinuplasty group. In the uncinectomy group was reported infection in one patient, crusting in three patients, hyposmia in three patients and synechia in 12 patients. In the balloon sinuplasty group was reported infection in two patients, crusting in two patients and synechia in three patients (Table 5). A positive statistically significant correlation was found between the uncinectomy treatment and the development of synechias (Spearman’s \( r = 0.321, P < 0.05 \)).

Discussion

Synopsis of key findings

Both treatment methods show a positive effect on the quality of life of rhinosinusitis patients even 6 months after treatment. Analyses of the rhinomanometry results imply an amelioration of inflammation as documented by a decrease in nasal airway resistance. The moderate difference in effect size in combination with a \( P \) value smaller than 0.05 indicates that our sample size was large enough to detect any significant change in nasal airflow after treatment. Regarding quality of life and airway resistance, no significant difference
was found between the two treatment groups either preoperatively or 3 months and 6 months postoperatively ($P \geq 0.05$; see Table 2). Synechia were fewer in the balloon sinuplasty group. We acknowledge that our study group was small and, as the low effect size of difference indicates, a larger sample size is required to detect any difference between the two treatment groups.

**Strengths of the study**

Although balloon sinuplasty was not compared with standard ESS (uncinectomy with antrostomy), this is a randomised, controlled, prospective clinical study that compares uncinectomy and balloon sinuplasty as separate entities. Balloon sinuplasty was performed bilaterally to the maxillary sinus of 30 patients (60 ostia). To have a homogenic study group, only patients with isolated sinusitis on the maxillary sinus were selected.

**Comparisons with other studies**

Based on a published review, there is an urgent need for more randomised-controlled trials to determine balloon sinuplasty’s efficacy over other treatment modalities. Achar et al. have published the results of a controlled randomised study with 24 patients, where functional endoscopic dilatation sinus surgery was found to be as effective as ESS. In a prospective cohort study with 13 patients (24 sinuses of

---

**Table 3. Acoustic rhinometry (undecongested nose)**

<table>
<thead>
<tr>
<th></th>
<th>Mean minimum cross-sectional area (MCA) ± standard deviation (SD) (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>Uncinectomy ($n = 32$ for 3 months and $n = 30$ for 6 months)</td>
<td>$0.61 \pm 0.2$</td>
</tr>
<tr>
<td>Balloon sinuplasty ($n = 30$)</td>
<td>$0.53 \pm 0.34$</td>
</tr>
</tbody>
</table>

*Wilcoxon test showed significant difference in nasal volume before and after Balloon sinuplasty treatment ($P < 0.05$).

†Mann–Whitney test showed no significant difference between the treatment groups neither before nor after treatment ($P > 0.05$).

---

**Table 4. Rhinomanometry (undecongested nose)**

<table>
<thead>
<tr>
<th></th>
<th>Mean ± standard deviation (SD) (Pa/cm³/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
</tr>
<tr>
<td>Uncinectomy ($n = 32$ for 3 months and $n = 30$ for 6 months)</td>
<td>$0.38 \pm 0.75$</td>
</tr>
<tr>
<td>Balloon sinuplasty ($n = 30$)</td>
<td>$0.38 \pm 0.71$</td>
</tr>
</tbody>
</table>

*Wilcoxon test showed significant decrease in air resistance ($P < 0.05$).

†Mann–Whitney test showed no significant difference between the treatment groups neither before nor after treatment ($P > 0.05$).

---

**Table 5. Adverse effects**

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Crusting</th>
<th>Infection</th>
<th>Bleeding</th>
<th>Synechia</th>
<th>Anosmia</th>
<th>Dacrimal duct damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>3 months after uncinectomy</td>
<td>6 months after uncinectomy</td>
<td>3 months after balloon sinuplasty</td>
<td>6 months after balloon sinuplasty</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
which only 10 were maxillary sinuses) published by Abreu et al.,24 no complications were reported and quality of life was improved as assessed by SNOT-20. With the exception of a study by Tomazic et al.,25 where a surprisingly high failure rate was reported, encouraging results have been reported from different study groups.

**Clinical applicability of the study**

This study provides supporting evidence that, in some cases, it may be possible to relieve patient symptoms and improve nasal airflow using less invasive techniques such as balloon sinuplasty. The cost of balloon sinuplasty has been an obstacle for its broader use around the world. However, because fewer synechiae developed in the balloon sinuplasty treatment group, and the clinical benefits of the treatment were as good as those of uncinectomy, balloon sinuplasty treatment has a clear advantage.

In our study, patients had sinus disease primarily restricted to the maxillary sinus and ostiomeatal complex with none or minimal changes in other sinuses. In addition, the severity of the findings was relatively mild. It is highly likely that it is difficult to treat certain subgroups of chronic rhinosinusitis patients (i.e. pansinusitis) exclusively with balloon sinuplasty.

**Conclusion**

Both treatment methods have a positive effect on the quality of life of patients with mild rhinosinusitis without polyps, while no significant difference exists between the two treatment groups. Rhinomanometry revealed a decrease in the nasal airway resistance, which supports the hypothesis that improvement in quality of life may be explained, at least to some degree, by a decrease of inflammation. As a randomised, controlled, prospective, clinical study, it provides valuable knowledge for the limits and strengths of this relatively new technique.

**Keypoints**

- Balloon sinuplasty.
- Nasal airway.
- Sinusitis.

**Acknowledgements**

Authors would like to thank research nurse Marja-Leena Oksanen for smooth patient coordination and support throughout the study.

**Conflict of interest**

The authors have no conflict of interests to disclose.

**Funding**

This study was financially supported by the Competitive Research Funding of the Tampere University Hospital (IRB = Grant R10044).

**References**


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A controlled, randomized clinical study on the impact of treatment on antral mucociliary clearance: uncinectomy versus balloon sinuplasty.

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1 Department of Otorhinolaryngology, Tampere University and Tampere University Hospital, Finland

Abstract

Objectives: To find out the effect of minimal invasive sinus surgery and balloon sinuplasty on mucociliary clearance and to compare different methods of measuring mucociliary clearance

Methods: Twenty-nine patients with chronic rhinosinusitis were randomized in two operative groups (uncinectomy or balloon sinuplasty). Before and 6 months after the treatment, patients filled out a quality of life questionnaire (SNOT-22) and mucociliary clearance was measured with endoscope and gamma camera after 0.03 ml of saccharine, methylene-blue dye and human albumin labelled with Tc99m was introduced to the bottom of maxillary sinuses. Results: In uncinectomy group, SNOT-22 score decreased but treatment had no effect on mucociliary clearance. (Based on saccharine test, smoking was associated with worse mucociliary clearance ($r= 0.618$, $p<0.05$. Methylene blue test results associated with saccharine test ($r= 0.434$) ($p < 0.05$) and Tc99m-labelled tracer technique ($r= 0.261$, $p=0.039$) separately. Conclusion: Treatment positively affects patients’ quality of life, however, it has no effect on mucociliary clearance. There was a statistically significant correlation between the Tc99m-labelled tracer technique and the methylene blue technique. The saccharine technique was even less accurate, but it can be useful in clinical practice because it is a quick, easy and safe technique.

Introduction

Mucociliary clearance is a major element of the respiratory mucous membrane and protects the sinuses against infection. Mucus cleanses the nose and throat by flushing out invading microorganisms and pollutants through its constant movement down the upper respiratory tract. Mucus also moderates the effects of humidity and temperature on the respiratory tract. There are millions of cilia that sweep back and forth pushing the mucus along at an average of 10 - 20 beats per second. Mucociliary clearance clears the sinuses of their secretions in less than 10 minutes. The mucus then drains from the nose to the throat in about 20 - 30 minutes. (1,2)

A decrease in mucociliary clearance can be identified through a clinical test and it has been reported that the measurement of MCC using an isotope technique is a reliable and rapidly obtainable parameter.
for determining nasal mucociliary function. (1-3) Other techniques that have been used to measure mucociliary clearance are the saccharin time test and the India Ink Test. (4) The saccharin time test has been mostly used for screening purposes, because it is easy to perform.

Chronic sinusitis is a medical condition of upper airway with significant effect in quality of life. It is characterized by chronic inflammation of nasal mucosa associated with decreased mucociliary clearance. However no clear association has been found between the severity of the symptoms and the mucociliary clearance. (5,6)

Primary treatment of chronic sinusitis is conservative with antibiotics, local decongestants and corticosteroids. Endoscopic sinus surgery is nowadays the gold standard treatment of chronic sinusitis for cases with poor response to conservative treatment. (7-10) Balloon sinuplasty is a relatively new endoscopic method with quite promising results for the treatment of chronic sinusitis. Both methods aim to improvement of ventilation of paranasal sinuses. (11-13)

Endoscopic sinus surgery and balloon sinuplasty has been shown to improve patients’ symptoms and quality of life (8-13) however; there are controversial studies about the effect of endoscopic surgery to mucociliary clearance (14-16). The purpose of this study was to compare the effect of uncinectomy and sinus balloon sinuplasty in mucociliary clearance.

Methods

Study Design

The randomized and controlled clinical study was carried out at the Department of Otolaryngology, Tampere University, Finland. This study received IRB approval and financial support obtained from the Competitive Research Funding of the Tampere University Hospital (IRB = Grant R10059). Informed consent was obtained from all patients in advance.

Initially, 40 patients collected from the outpatient department were assessed for eligibility to enrol in the study. Out of the initial 40 patients, 36 patients were found to be suitable for the study and they were randomized in two treatment groups. Seven patients, however, dropped out of the study. Of the seven patients, three were in the uncinectomy group and four in the balloon sinuplasty group. No particular reason was given for their dropping out of the study and there were no complications. These patients were not included in the statistical analysis because they did not show up for the follow-up control, and therefore we only had the demographics data and the preoperative SNOT22 scores for
them. To be accepted into the study, all patients needed to qualify for sinus surgery (according to preferred indications for surgical treatment).

**Inclusion and Exclusion Criteria**

The recruitment of patients was performed based on the following criteria: a) presence of acute recurrent rhinosinusitis or isolated chronic rhinosinusitis of the maxillary sinus without severe pathology of other sinuses, b) age between 18-65 years old, and c) patients had to fulfil the indications for sinus surgery (7).

In addition to the age limits, the following exclusion criteria were applied during patient recruitment: a) history of previous sinus operations, b) asthma, c) history of ASA-intolerance, d) history of diabetes or any other comorbidity, e) Patients with chronic rhinosinusitis with polyps visible and f) pregnancy at the time of recruitment.

**Diagnosis**

Patient history and direct endoscopic nasal examination were routinely used for the diagnosis of the underlying clinical condition. Additionally, cone beam computed tomography (CBCT) scans of the paranasal sinuses were performed to evaluate the status of the paranasal sinuses (19). An experienced radiologist reviewed and evaluated the images.

Patients were classified into two groups: Group A (Lund-McKay score per side 1-2) or Group B (score per side 3-4) at the maxillary sinus and/or the ostiomeatal complex. For classification purposes, the Lund-McKay score of the side with the most severe findings was used. The Lund-McKay score was calculated separately for each side and it comprises a sum of the Lund-McKay score of the maxillary sinus and the ostiomeatal complex. The scale of the Lund-McKay score is from 0 to 2 for each measured area, i.e. 0 to 2 for the maxillary sinus plus 0 to 2 for the ostiomeatal complex. Therefore, the maximum score would be 4 if the maxillary sinus and the ostiomeatal complex were completely blocked and the minimum score would be 0 if there were no pathology in the maxillary sinus or the ostiomeatal complex.

**Sino Nasal Outcome Test-22 (SNOT-22) Quality of life questionnaire**

The effects of sinusitis as well as its treatment on the quality of life were estimated before treatment as well as 6-months after treatment by using the SNOT-22 questionnaire. In the questionnaire, the presence of 22 symptoms is evaluated. The severity of each symptom is assessed on a scale of 0 to 5 (with 0 = no symptom, 5 = worst symptoms). Previous validation studies have indicated that the
minimally important difference, which is the smallest change in the SNOT-22 score that can be detected in a patient, is 8.9 points (17).

Surgical Methods

Local anaesthesia using 250 mg cocaine (125 mg on each side) diluted in 5 ml of 0.1 mg/ml adrenaline was performed for each patient. Additionally, the uncinate process was infiltrated with 4-6 ml of 10 mg/ml lidocaine cum adrenaline solution. Conscious sedation was achieved for all patients by the intravenous administration of 0.5 ml of 0.5 mg/ml alfentanil (Rapifen) and 0.5 ml of 1 mg/ml midazolam.

In the uncinectomy group, we performed removal of the uncinate process and where necessary the pathology in the ostium was removed to ensure the patency, but the ostium was not enlarged.

The principle of balloon sinus dilatation is the catheterization of the sinus ostium with a flexible guide wire that allows an atraumatic entrance to the sinus, through even a narrowed ostium. To simplify the process, we used a lighted guide wire called the Luma Sinus Illumination System (Luma light) (Acclarent Inc., Menlo Park, CA) and dilatation was performed with a flexible balloon (6 mm x 16 mm) inflated up to 12 atm (Acclarent Inc, Menlo Park, CA) for 1 minute and the dilatation was repeated one more time. The same procedure was repeated for both maxillary sinuses (11-12).

Statistics

Analysis of our data was done with SPSS 9.0 software (SPSS Inc., Chicago, IL). Improvement in quality of life was analysed with paired t-tests (Mann-Whitney and Wilcoxon tests). The measurements used in the comparison of the treatments were the individually calculated differences between the preoperational SNOT-22 values and the postoperative 6-month SNOT-22 values, and $p$ values smaller than 0.05 were considered to be significant. Pearson correlation coefficient was measured to explore any correlation and association between variables and in particular among the techniques for the measurement of mucociliary clearance.

Follow-up and the Reporting and Assessment of Adverse Effects and Reactions

There was a systematic follow-up of all the patients and the occurrence of any adverse effects.
Measurement of mucociliary clearance

Three separate techniques were used simultaneously. Maxillary sinus puncture was performed to both sides after local anaesthesia of the inferior meatus for 10 minutes with 10 mg/ml lidocaine cum adrenaline solution. Irrigation tubes (Sinoject™, Atos, Hörby) were introduced through the inferior meatus into the maxillary sinuses at least 30 min before the measurement to avoid the possible reflectory ciliostasis due to puncture. The sinoject catheter was removed after the measurements had been completed.

a. Using sterile human serum albumin labelled with $^{99m}$Tc \textsuperscript{(1-3)}

Using a thin cathedra and 1 ml syringe, a drop (0.03 ml) of sterile human serum albumin labelled with $^{99m}$Tc (Ventico, Sorin Biomedica, Saluggia) was applied through irrigation tube into the bottom of both maxillary sinuses at the same time. Maximum particle size of the colloid is 200 nm. The patient was then seated in front of the gamma camera (Picker SX-300) with all-purpose parallel-hole collimator connected to a Gamma-11 system for processing.

The clearance of tracer in both sinuses was monitored at the same time from the anterior view for 40 min. The areas of initial tracer in the sinuses were marked and clearance of tracer from the sinuses as well as the possible appearance of activity into the pharynx was measured with dynamic gamma imaging at the time points of 0, 10, 20, 30 and 40 min from the anterior view, with residual activity (percentage from the initial) determined in the sinuses. Two cobolt buttons were fixed on the forehead and one on the upper part of sternum for controlling the errors caused by movements of patients.

b. Methylene blue dye-saccharine test \textsuperscript{(4)}

A direct nasal endoscopy was performed with a rigid zero degree nasoendoscope in order to detect the dye in the nasal cavity and, with the use of a tongue depressor, we checked for the presence of dye in the posterior pharynx. The time it took for the patient to taste a sweet taste was reported.

Results

Baseline Characteristics / Demographics

A total of 29 patients participated in our study (12 males and 17 females), with 16 patients allocated to the uncinectomy group and 13 patients allocated to the balloon sinuplasty treatment group (Figure 1). The average age of the patients was 38 years old. Eleven of the patients were smokers and eighteen patients had regularly used intranasal steroids before the surgery. The mean duration of the symptoms
of isolated chronic rhinosinusitis before the surgery was 175.93 +/- 22 months (standard error) (Table 1). The Lund-McKay score was calculated based on the findings in the osteomeatal complex and the maxillary sinuses. Group A (worst side’s score 1-2) comprised 13 patients and Group B (worst side’s score 3-4) comprised 16 patients. Based on the test of homogeneity of variance, the demographic characteristics of the patients were equally distributed between the two treatment groups (no significant difference in variance p > 0.05)

**Quality of life trends**

According to total score of the SNOT-22, improvement in quality of life was observed 6-months after treatment in both treatment groups. However, only in the uncinectomy group was the change of total SNOT-22 statistically significant (p < 0.05; Table 2). Cohen's d (effect size) of the difference between SNOT-22 score before and after treatment was calculated for both treatment groups and it was significantly high in both groups. In the uncinectomy treatment group, Cohen's d was 1.18 and in the balloon sinuplasty group it was 0.23.

The high difference in effect size (this applies to the uncinectomy group) in combination with a p value smaller than 0.05 indicates that our sample size was big enough to detect any significant change of total SNOT-22 score after treatment. A linear regression analysis that affects and predicts the postoperative SNOT-22 score was performed in order to evaluate the percentage of the preoperative total SNOT-22 score. Based on this analysis, in the 6-month follow-up, 30.4% (R square = 0.304) of the variation in postoperative total SNOT-22 can be explained by a linear relationship with the preoperative total SNOT-22.

When comparing the changes in the total SNOT-22 scores of the uncinectomy and balloon sinuplasty groups, we identified no significant differences between the two treatment groups either preoperatively or 6-months postoperatively (all p ≥ 0.05; Table 2).

No major complications presented during the treatment and follow-up period. In three patients (one from the balloon sinuplasty group and two from the uncinectomy group), there was noticeable crusting and also some synechiae were observed in four patients from the uncinectomy group. In one patient from the uncinectomy group, there was some dysfunction of the lacrimal duct after treatment. *Patient complained for excessive tearing and in the clinical exam there was epiphora and redness in patient’s eye. Patient received some antibiotic eye drops for a few days. Symptoms improved which improved with time so no further diagnostic exams were done.*
Mucociliary clearance

Pearson correlation was strong (r= 0.434) between the taste of sweet saccharine in the mouth and the time it took to see the methylene blue dye in the nasal cavity (p < 0.05). Correlation was weak, even though statistically significant (r= 0.261, p<0.05), between the 99mTc-labelled tracer technique and the methylene blue technique. A history of smoking was strongly associated with the saccharine test (r= 0.618, p<0.05), which means that it took longer for smokers to taste sweet saccharine in the mouth. We did not find any clear correlation with antral mucociliary clearance and the improvement of symptoms. Treatment had no significant effect on mucociliary clearance, and no difference was observed in mucociliary clearance between the two treatment groups (p>0.05) (see Figure 2).

Discussion

The outcomes of sinus surgery have been widely studied previously. However, there have only been a few prospective randomized clinical trials that compare the different operative methods used in the treatment of isolated chronic rhinosinusitis.

Based on the results of our previous study, both treatment methods seem to have a positive effect on the quality of life of rhinosinusitis patients (13). However, in this study, significant improvement in quality of life was only documented in the uncinectomy group. The low effect size of difference for the balloon sinuplasty group indicates, however, that a larger sample size is required in order to be able to detect any possibly existing significant change in total SNOT-22 after treatment. With regard to quality of life, no significant difference was found between the two treatment groups either preoperatively or 6-months postoperatively (all p ≥ 0.05; see Table 2). Since p was > 0.05, we can say that no significant difference was found between the two treatment groups.

Even though treatment had a beneficial effect in patients’ quality of life, it failed to improve or affect in any way the mucociliary clearance. Improvement in ventilation of the maxillary sinus did not lead to an improvement in mucosal function. Previous studies also failed to show an improvement in mucosal function (14, 15). In one study (16), an improvement in mucociliary clearance was reported after functional endoscopic sinus surgery (FESS). Therefore, further clinical studies are needed to further investigate the function of nasal mucosal and how treatment may or could affect its function.

Our study has produced some interesting results. The use of 99mTc-labelled tracer has been the gold standard for the measurement of mucociliary clearance, and it remains the most accurate technique for
the measurement of mucociliary clearance. It is, however, expensive, and its use entails a minimal though existing dose of radiation and it is relatively uncomfortable for the patient. The methylene blue technique is not as accurate, but there was clearly a positive association with 99mTc-labelled tracer technique. In addition, the fact that the methylene blue technique is more economical, safer and more comfortable for the patient makes this technique more appealing in clinical practice. A remarkable correlation was found between the methylene blue and the saccharine techniques.

Smoking was noticeably correlated with the saccharine test’s results. It has been previously reported that smokers have a decreased sense of taste (19), which could explain in some degree why it took longer for smokers to taste saccharine in the mouth. However, previous studies have shown that smoking has a negative effect in mucociliary clearance (20). Eleven of 29 patients were smokers and smoking negatively affects mucociliary clearance. This might have disguised an improvement of mucociliary clearance in non-smokers. Smoking was one of four variables used for patients’ randomization. However, due to our small sample size, smoking was not completely isolated as a confounding variable.

Conclusion

In this manuscript, we determined that quality of life improves after treatment irrespective of operative technique. In addition, neither balloon sinuplasty nor uncinectomy had any effect on mucociliary clearance. The gold standard 99mTc-labelled tracer technique is statistically significant and positively correlated with the methylene blue technique. The saccharine technique, even less accurate, could be useful in clinical practice because it is a quick, easy and safe technique.
References


### Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy group (16 patients)</th>
<th>Balloon sinusplasty group (13 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age of patients +/– Standard error (SEM) (yrs. old)</strong></td>
<td>37.06 +/- 2.4</td>
<td>38.92 +/- 3.6</td>
</tr>
<tr>
<td><strong>Sex of patients</strong></td>
<td>6 males, 10 females</td>
<td>6 males, 7 females</td>
</tr>
<tr>
<td><strong>Smoking history (patients)</strong></td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>Use of nasal steroids before surgery (patients)</strong></td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td><strong>Mean duration of symptoms (months) +/- SEM</strong></td>
<td>175.63 +/- 31</td>
<td>176.36 +/- 33</td>
</tr>
<tr>
<td><strong>History of allergies (patients)</strong></td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td><strong>Classification based on Lund-McKay score (unilateral score)</strong></td>
<td>1-2: 7 pts</td>
<td>1-2: 6 pts</td>
</tr>
<tr>
<td></td>
<td>3-4: 9 pts</td>
<td>3-4: 7 pts</td>
</tr>
</tbody>
</table>

*Based on the test of homogeneity of variance, the demographic characteristics of patients were equally distributed between the two treatment groups (no significant difference in variance p > 0.05)*

### Table 2. Difference in SNOT22 score before and after treatment (mean +/– SD)

<table>
<thead>
<tr>
<th></th>
<th>Before surgery</th>
<th>6 months after surgery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncinectomy (n=16)</strong></td>
<td>47.68 +/- 14.76</td>
<td>30.43 +/- 14.26</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td><strong>Balloon sinuplasty (n=13)</strong></td>
<td>36.76 +/- 24.94</td>
<td>30.76 +/- 27.73</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

* Mann-Whitney test showed no difference between the two treatment groups (p > 0.05)

* Wilcoxon test showed significant improvement in total SNOT22 score after treatment
### Table 3. Measurement of mucociliary clearance

<table>
<thead>
<tr>
<th></th>
<th>99mTc labelled albumin* (%)</th>
<th>Methylene blue (min)</th>
<th>Saccharine test (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncinectomy</td>
<td>60.36 +/- 34.78</td>
<td>13.71 +/- 11.1</td>
<td>17.43 +/- 9.18</td>
</tr>
<tr>
<td>Balloon sinuplasty</td>
<td>71.8 +/- 26.57</td>
<td>14.52 +/- 11.50</td>
<td>20.35 +/- 11.39</td>
</tr>
<tr>
<td><strong>After treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncinectomy</td>
<td>74.76 +/- 27.80</td>
<td>11.66 +/- 7.78</td>
<td>20.62 +/- 5.92</td>
</tr>
<tr>
<td>Balloon sinuplasty</td>
<td>69.65 +/- 24.68</td>
<td>15.33 +/- 9.53</td>
<td>18.71 +/- 5.64</td>
</tr>
</tbody>
</table>

*It shows the percentage of albumin left in maxillary sinus after 40 min

** Wilcoxon and Mann-Whitney tests showed no significant change in mucociliary clearance after treatment and no difference between the two treatment groups (p > 0.05)
Figure 1: Consort diagram of the study

Figure 2: (Above left) Shows a case with good mucociliary clearance where only around 20% of tracer was still present after 40 min. (Above middle) In this case, the mucociliary clearance was quite slow (60% percentage of active tracer was left after 40 mins). (Above right) In this case, the mucociliary clearance was remarkably slow, since 90% of tracer was still detectable after 40 mins). Blue color represents left sinus and red color represents right sinus.
Treatment of Rhinosinusitis and Histopathology of Nasal Mucosa: A Controlled Randomized Clinical Study

Argyro J. Bizaki, MD; Jura Numminen, MD; Rami Taulu, MD; Ivana Kholova, MD; Markus Rautiainen, MD

Objectives/Hypothesis: To study the pathology of upper airway mucosa, as well as evaluate and compare changes in pathology after the treatment of chronic rhinosinusitis (CRS) patients with balloon sinuplasty versus uncinectomy.

Methods: A prospective randomized controlled trial in patients with CRS of the maxillary sinuses without severe pathology of other sinuses. Patients were randomized into two groups: uncinectomy and balloon sinuplasty. The main variables in our study are histopathology of nasal mucosa and expression of metalloproteinase-9 protein. These parameters were analyzed preoperatively and at 3 months, 6 months, and 12 months postoperatively.

Results: Thickened epithelium, absence of cilia, metaplasia of epithelium, hyperplasia of mucosal glands, angiogenesis, and increased inflammatory cells were observed in the majority of preoperative samples. History of allergy was associated with a higher number of goblet cells, and shedding of epithelium was associated with worse quality of life. A higher number of inflammatory cells were associated with an increased number of goblet cells preoperatively, as well as after treatment. Both treatments resulted in a decrease of inflammation in the mucosa and epithelium. Hypertrophy of the mucosal glands, hyperplasia of blood vessels, and mucosal edema decreased after treatment. These changes were more noticeable in uncinectomy group. Balloon sinuplasty was associated with a higher number of inflammatory cells at 6 months after treatment (P < 0.05).

Key Words: Rhinosinusitis, inflammation, balloon sinuplasty, uncinectomy, nasal mucosa.

Level of Evidence: 1b.

INTRODUCTION
The upper airway epithelium plays an important role in sensing the environment and regulating the inhaled air. The lower airways are anatomically a continuity of the upper airways. Supporting evidence exists that, in susceptible individuals, nasal conditions that cause nasal obstruction, stasis of nasal secretions, or infectious diseases of the sinonasal mucosa may become a trigger for lower airway pathology.1

The respiratory epithelium of the paranasal sinuses comprises a pseudostratified ciliated columnar epithelium with goblet cells, and numerous serous and mucous glands are present. In addition to mucus, serous-mucous glands secrete immunoglobulins, interferons, and lysozyme.2

Rhinosinusitis is a common medical condition with remarkable symptoms and a noticeable impact on quality of life.3,4 The term rhinosinusitis reflects the concurrent inflammatory and infectious processes that affect the nasal passages and the contiguous paranasal sinuses.5–11

The clinical symptoms of chronic rhinosinusitis (CRS) vary in intensity and prevalence. Nasal obstruction is the most common, followed by facial congestion-pressure-fullness, discolored nasal discharge, and hypoosmia.3,4 Documentation of persistent mucosal inflammation is the key to the diagnosis of CRS. In cases of CRS, it has been shown that pathological changes occur in the ciliary epithelium.5–11

Chronic inflammation of the nasal mucosa has been associated with epithelial metaplasia. The transitional phase between respiratory and squamous epithelium is cuboidal epithelium, at which stage ciliogenesis is still present.5–11

Histological studies of nasal epithelium indicate the potential role of several genes and proteins in chronic inflammatory changes and abnormal mucosal remodeling. Matrix metalloproteinases (MMP) are a group of Zn2+-dependent endopeptidases, with more than 20 members, which are involved in the breakdown of the extracellular matrix in normal physiological processes such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes such as inflammation, arthritis, and metastasis. Matrix metalloproteinase-9 has been found in surface nasal epithelium, serous-mucous glands, and polymorphonuclear cells.12–17
Primary treatment is conservative, and surgery is reserved for patients who are refractory to medical treatment. Nowadays, endoscopic sinus surgery has become the gold standard method for the treatment of CRS. The treatment involves widening the natural pathway of the sinuses so that they can drain and not become blocked.

In 2002, the balloon sinuplasty technique made its debut in the field of rhinology. The technique is a minimally invasive tool that uses the concept of remodeling the anatomy of the paranasal sinus ostia without removing mucosal tissue or bone, and facilitating the drainage of the mucus that builds up in patients suffering from chronic or recurrent acute rhinosinusitis. The balloon sinuplasty technique differs from traditional endoscopic sinus surgery (ESS) in that it requires no cutting or removal of bone and tissue.

Improvement of ventilation and drainage of the ostiomeatal complex and the preservation of the mucosal lining of the upper airways have become a fundamental goal in the treatment CRS.

In previous studies, ESS is followed by an improvement in both subjective and objective findings and an improvement in the quality of life of patients. The aims of this clinical study were to study and document the effects of treatment on the histopathology of nasal mucosa in patients, as well as on the expression of metalloproteinase 9 (MMP-9).

MATERIALS AND METHODS

Trial Design

With the approval of the hospital's ethical committee and patients' informed consent, a randomized, nonblinded, controlled clinical study was carried out. Recruitment, treatment, and follow-up were carried out at the University Hospital of Tampere, in Tampere, Finland, over a period of 2 years (2011–2013).

Sample Size and Randomization

A statistician calculated the approximate sample size needed for the paired t test analysis. Based on previous studies that used Sino-Nasal Outcome Test-22 (SNOT-22), the clinically significant difference was set to 8.9, and the highest value for standard deviation was estimated to be 1.29. With an alpha value of 0.05 and a power value of 0.8, the calculation gave us approximately 21 study patients for each study group. Using Minim (MS-DOS program for randomization in clinical trials), the patients were randomized into two treatment groups: the uncinctomy group and the balloon sinuplasty group. The patients were randomized based on the following variables: 1) smoking history (smokers, nonsmokers), 2) age (18–33, 34–49, and 50–65 years old), 3) sex (male, female), and 4) Lund-Mackay score for maxillary sinus and ostiomeatal complex (group A: Lund-Mackay score per side 1–2; group B: Lund-Mackay score per side 3–4).

Demographics

The following demographic patient information was recorded and evaluated: 1) sex, 2) age, 3) history of allergy, 4) use of nasal or other steroids, and 5) history of smoking.

Inclusion and Exclusion Criteria

The following inclusion criteria were used: 1) patients had to have been diagnosed with chronic or recurrent rhinosinusitis of the maxillary sinus without severe pathology of other sinuses; 2) patients had to be older than 18 years old and younger than 65 years old; and 3) patients had to fulfill the indications for sinus surgery.

In addition to the age limits, the following exclusion criteria were applied during patient recruitment: 1) previous sinus operations, 2) asthma, 3) acetylsalicylic acid intolerance, 4) of diabetes or any other severe systemic disease, 5) visible polyps in nasal direct endoscopy, and 6) pregnancy at the time of enrollment to the study.

Diagnosis

Routine diagnosis of the underlying pathologic condition comprised patient history and direct endoscopic nasal examination. Furthermore, cone beam computed tomography scans of the paranasal sinuses were performed to evaluate the status of the paranasal sinuses. Patients were allocated into two groups, mild changes (score per side 1–2) or severe changes (score per side 3–4), based on the Lund-McKay score.

Surgical Procedure

Seventy-four patients suffering from chronic maxillary rhinosinusitis who had not responded adequately to conservative treatment were randomized to an uncinctomy group or a balloon sinuplasty group. Both sinuses were treated in all patients.

Nasal Mucosa Biopsies From the Middle Turbinate Mucosa

Four biopsies in total were performed on the patients (preoperatively; and 3, 6, and 12 months postoperatively). All the biopsies were done under local anesthetic of the nasal mucosal using 1% lidocaine cum adrenaline solution. Tissue samples were fixed by formaldehye and stored in a refrigerator at 8°C.

Histopathology

All the mucosal samples were studied by a pathologist. Samples were embedded in paraffin and sectioned in an axial plane (4 μm of thickness). Selected sections were stained with hematoxylin and eosin dye.

The epithelial evaluation included the presence of transitional metaplasia; shedding of epithelium (damage of cilia); epithelium thickening, including lamina propria thickening, mucosal edema, stromal fibrosis, angiogenesis, epithelial cell sloughing, goblet cell hyperplasia, and mucus hypersecretion; and the presence of goblet cells. The number of total inflammatory cells and glands in the lamina propria, as well as stromal edema, angiogenesis, and fibrosis, were also evaluated in a categorical way (0 = not present, 1 = focal/mild, 2 = patchy/moderate, and 3 = extensive/marked). The epithelial lining was scanned to determine the presence of metaplasia of respiratory epithelium to transitional epithelium and also recorded as a categorical variable (0 = not present, 1 = present). The presence of goblet cells was recorded as a categorical variable (0 = not present, 1 = decreased, 2 = normal, and 3 = hyperplasia). Epithelium was categorized as thin, normal, or thick, according to its thickness.
was associated with loss of cilia (r = 59.3% of patients, respectively. A history of allergy to pollens and edema of the mucosa were present in 70.4% of patients, respectively (Table II). Thickening of epithelium and fibrotic tissue in the mucosa, infiltration of epithelium with inflammatory cells, metaplasia of epithelium, and decreased (Table II). Changes were more noticeable for the uncinectomy group compared to the balloon sinuplasty group (Table III). An amelioration of increase of blood vessels and mucous glands was noticed after treatment, and this was more obvious in the balloon sinuplasty group (Table III). There was no statistically significant difference between the treatment groups. A history of positive radioallergosorbent test (RAST) and allergy history were associated with a higher number of goblet cells in epithelium. An increased number of inflammatory cells in epithelium was associated with a higher number of goblet cells (r = 0.438) and thickening of epithelium (r = 0.270) (Table IV).

Six Months After Treatment. A further decrease of inflammatory cells in epithelium and the mucosa was noticed. Alleviation of inflammation was significantly more noticeable for the uncinectomy group compared with the balloon sinuplasty group (P < 0.05) (Table I). After 6 months, the percentage of severe inflammation in the mucosa had decreased from 29.6% to 11.1% (only for uncinectomy group). The increased number of inflammatory cells was associated with a higher number of goblet cells (r = 0.467) and with increased edema in the mucosa (r = 0.331).

Twelve Months After Treatment. A significant decrease in mucous gland hypertrophy was noticed in both treatment groups (Table III). Additionally, increase of number of blood vessels (presented to half of samples before treatment) decreased after treatment. Infiltration of epithelium with inflammatory cells was noticeably decreased (Table II). Changes were more noticeable for the uncinectomy group. Increased edema of epithelium was associated with a higher number of goblet cells (r = 0.420, P = 0.015) (Table IV). Hyperplasia of blood vessels in the mucosa was associated with increased mucosal edema (r = 0.314), thickening of epithelium (r = 0.362), and an increased number of goblet cells (r = 0.407) (Table IV). The presence of fibrosis in the mucosa was negatively associated with edema of the mucosa (Table IV).

TABLE I. Demographics.

<table>
<thead>
<tr>
<th></th>
<th>Uncinectomy Group (32 patients)</th>
<th>Balloon Sinuplasty (30 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients ± SEM (yrs. old)</td>
<td>40.25 ± 2.1</td>
<td>37.17 ± 1.8</td>
</tr>
<tr>
<td>Sex of patients</td>
<td>10 males, 22 females</td>
<td>12 males, 18 females</td>
</tr>
<tr>
<td>Smoking history (patients)</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Usage of nasal steroids before surgery (patients)</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Mean duration of symptoms (months) ± SEM</td>
<td>163 ± 21</td>
<td>102 ± 19</td>
</tr>
<tr>
<td>Classification based on Lund-McKay score (unilateral score)</td>
<td>0 (no findings): 1</td>
<td>0 (no findings): 1</td>
</tr>
<tr>
<td></td>
<td>1–2: 16 pts</td>
<td>1–2: 21 pts</td>
</tr>
<tr>
<td></td>
<td>3–4: 14 pts</td>
<td>3–4: 8 pts</td>
</tr>
</tbody>
</table>

*Based on Levene’s test for homogeneity of variance, the demographic characteristics of patients were equally distributed between the two treatment groups (no significant difference in variance P > 0.05).

SEM = standard error of the mean.

Immunohistochemistry

Immunohistochemistry for MMP-9 was performed in a 1:100 dilution using Santa Cruz MMP-9 antibody sc-21733 (Santa Cruz Biotechnology, Inc., Dallas, TX).

RESULTS

Demographics

The uncinectomy group consisted of 31 patients, and the balloon sinuplasty group consisted of 29 patients. The Lund-McKay score was quite evenly divided for both treatment groups.

None of our patients had been used oral steroids before the treatment. Also at the time of the recruitment, patients did not use any antibiotics. However, all the patients had tried some different antibiotics in the past. Noncomplicated acute sinusitis is mostly treated in the health centers by family doctors and not in the university hospital. So it is difficult, if not impossible, to track with any detail the kind of antibiotics that our patients had used before being referred to our clinic.

Histopathology of Nasal Airway

Before Treatment. Damage of cilia, presence of fibrotic tissue in the mucosa, infiltration of epithelium with inflammatory cells, metaplasia of epithelium, and hypertrophy of serous and mucous glands were found to be present in 96.3%, 87%, 96.3%, 85.2%, and 81.5% of patients, respectively (Table II). Thickening of epithelium and edema of the mucosa were present in 70.4% and 59.3% of patients, respectively. A history of allergy was associated with loss of cilia (r = 0.405, P = 0.01). An increased number of inflammatory cells in epithelium was associated with a higher number of goblet cells (r = 0.391). In about one out of two patients, there was increased vascularity of the mucosa as well as edema of the mucosa (Table III) (Figs. 1 and 2). Thickening of epithelium was associated with a higher number of inflammatory cells (r = 0.371) and increased of blood vessels in the mucosa (r = 0.287) (Table IV).

Three Months After Treatment. Shedding of epithelium (damage of cilia) and metaplasia of epithelium from respiratory to transitional epithelium was present for all samples. Treatment showed no effect on the thickness of epithelium in either of the treatment groups. There was some decrease after treatment in the number of inflammatory cells in epithelium and the mucosa (Table II). An amelioration of increase of blood vessels and mucous glands was noticed after treatment, and this was more obvious in the balloon sinuplasty group (Table III). There was no statistically significant difference between the treatment groups. A history of positive radioallergosorbent test (RAST) and allergy history were associated with a higher number of goblet cells in epithelium. An increased number of inflammatory cells in epithelium was associated with a higher number of goblet cells (r = 0.438) and thickening of epithelium (r = 0.270) (Table IV).
Histopathology and Quality of Life

As it has been previously published, the Wilcoxon test showed significant improvement of total SNOT-22 score after treatment. The Mann-Whitney test showed no significant difference between the treatment groups preoperatively and after surgery ($P > 0.05$). In the uncinctomy group, the SNOT-22 scores were $45.63 \pm 3.29$ (before treatment), $24.25 \pm 2.68$ (3 months after treatment), $30.54 \pm 3.2$ (6 months after treatment), and $30.59 \pm 2.6$ (12 months after treatment). In the balloon sinuplasty group, the corresponding scores were $42.70 \pm 3.2$ (before treatment), $23.31 \pm 2.72$ (3 months after treatment), $25.31 \pm 3.81$ (6 months after treatment), and $27.47 \pm 4.1$ (12 months after treatment).23,26

The damage of cilia was associated with a higher SNOT-22 at 3 months after treatment ($r = 0.329$, $P = 0.002$). A higher number of mucosal glands ($r = 0.369$) and goblet cells ($r = 0.354$) was associated with a greater total SNOT-22 score at 12 months after treatment.

Expression of MMP9 in Nasal Airway

In our samples, MMP9 was expressed in the epithelium, as well as in the mucosal stroma (extracellular

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**TABLE II.**
Quantitative Analysis of Inflammatory Cells in Mucosa and Epithelium.

<table>
<thead>
<tr>
<th>Grade of Inflammation</th>
<th>Inflammatory Cells %</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESS Group</strong></td>
<td><strong>Mucosa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Tx</td>
<td></td>
<td>0</td>
<td>11,1</td>
<td>59,3</td>
<td>29,6</td>
</tr>
<tr>
<td>3 months after Tx</td>
<td></td>
<td>0</td>
<td>34,5</td>
<td>37,9</td>
<td>27,6</td>
</tr>
<tr>
<td>6 months after Tx</td>
<td></td>
<td>7,4</td>
<td>37</td>
<td>44,4</td>
<td>11,1</td>
</tr>
<tr>
<td>12 months after Tx</td>
<td></td>
<td>0</td>
<td>51,7</td>
<td>44,8</td>
<td>3,4</td>
</tr>
<tr>
<td><strong>Epithelium</strong></td>
<td></td>
<td>3,7</td>
<td>66,7</td>
<td>22,2</td>
<td>7,4</td>
</tr>
<tr>
<td>Before Tx</td>
<td></td>
<td>44,8</td>
<td>44,8</td>
<td>10,3</td>
<td>0</td>
</tr>
<tr>
<td>3 months after Tx</td>
<td></td>
<td>66,7</td>
<td>29,6</td>
<td>3,7</td>
<td>0</td>
</tr>
<tr>
<td>6 months after Tx</td>
<td></td>
<td>72,4</td>
<td>27,6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>BSS Group</strong></td>
<td><strong>Mucosa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before Tx</td>
<td></td>
<td>3,8</td>
<td>15,4</td>
<td>53,8</td>
<td>26,9</td>
</tr>
<tr>
<td>3 months after Tx</td>
<td></td>
<td>7,4</td>
<td>22,2</td>
<td>48,1</td>
<td>22,2</td>
</tr>
<tr>
<td>6 months after Tx</td>
<td></td>
<td>0</td>
<td>39,1</td>
<td>39,1</td>
<td>21,7</td>
</tr>
<tr>
<td>12 months after Tx</td>
<td></td>
<td>3,8</td>
<td>30,8</td>
<td>42,3</td>
<td>23,1</td>
</tr>
<tr>
<td><strong>Epithelium</strong></td>
<td></td>
<td>23,1</td>
<td>42,3</td>
<td>26,9</td>
<td>7,7</td>
</tr>
<tr>
<td>Before Tx</td>
<td></td>
<td>55,6</td>
<td>37</td>
<td>7,4</td>
<td>0</td>
</tr>
<tr>
<td>3 months after Tx</td>
<td></td>
<td>34,8</td>
<td>43,5</td>
<td>17,4</td>
<td>4,3</td>
</tr>
<tr>
<td>6 months after Tx</td>
<td></td>
<td>76,9</td>
<td>15,4</td>
<td>7,7</td>
<td>0</td>
</tr>
</tbody>
</table>

BSP = balloon sinuplasty; ESS = endoscopic sinus surgery; Tx = treatment.

---

**TABLE III.**
Changes in Histopathology of Nasal Mucosa.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Timepoint (months)</th>
<th>Hyperplasia of Blood Vessels in Mucosa %</th>
<th>Hypertrophy of Mucous Glands %</th>
<th>Hypertrophy of Serous Glands %</th>
<th>Edema of Mucosa %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESS group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (pre-Tx)</td>
<td></td>
<td>59,2</td>
<td>74,1</td>
<td>66,6</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>48,2</td>
<td>75,8</td>
<td>82,8</td>
<td>79,3</td>
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<tr>
<td>6</td>
<td></td>
<td>37</td>
<td>44,4</td>
<td>59,3</td>
<td>37</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>17,2</td>
<td>48,2</td>
<td>62</td>
<td>58,6</td>
</tr>
<tr>
<td><strong>BSP group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (pre-Tx)</td>
<td></td>
<td>46,2</td>
<td>76,9</td>
<td>80,7</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>25,9</td>
<td>48,2</td>
<td>77,8</td>
<td>81,5</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>30,4</td>
<td>47,8</td>
<td>82,6</td>
<td>60,9</td>
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<tr>
<td>12</td>
<td></td>
<td>23,1</td>
<td>34,6</td>
<td>50</td>
<td>65,4</td>
</tr>
</tbody>
</table>

BSP = balloon sinuplasty; ESS = endoscopic sinus surgery; Tx = treatment.
matrix) and in blood vessels (Fig. 3). No significant expression of MMP9 was observed in the nasal mucosal glands. Expression of MMP9 in epithelium was positively correlated with inflammatory cells in the epithelium and mucosa ($P < 0.05$). At 3 months after treatment, there was a strong association between expression of MMP9 and inflammatory cells in the epithelium ($r = 0.400$). At 6 months after treatment, a stronger association was found between the expression of MMP9 in epithelium and the number of inflammatory cells in the mucosa ($r = 0.639$).

**DISCUSSION**

**Synopsis of Key Findings**

Analysis of the histopathology of the nasal mucosa revealed findings that are consistent with inflammation. Chronic inflammation results in epithelial remodeling and desquamation. There was a loss of cilia, a thickening of epithelium, and metaplasia of respiratory epithelium to transitional epithelium. There was infiltration of epithelium with inflammatory cells and an increase of inflammatory cells in the mucosa. There was angiogenesis and fibrosis in the mucosa. Hypertrophy of the serous and mucous glands in the mucosa were present. These findings are consistent with active inflammation in the nasal mucosa.

The loss of cilia was associated with positive RAST test and history of allergy. Cilia functions as a protective mechanism against airborne allergens; thus, the shedding of epithelium most likely results in the sensitization of nasal airway epithelium against allergens. On the other hand, the presence of allergy is related to inflammation in the airway, which results in the loss of cilia. A thick epithelium was positively associated with the number of inflammatory cells in the mucosa.

A previous study has shown that there is no change in mucociliary clearance after treatment. This is consistent with the finding that shedding of epithelium was not restored after treatment.$^{25}$ An increased number of inflammatory cells was positively associated with the number of goblet cells before and after treatment, which reflects the affluent secretion of mucous from the inflamed nasal airway.

The number of inflammatory cells in the mucosa and hyperplasia of blood vessels were positively associated with mucosal edema. This finding was expected because intravascular fluid exudates to the extracellular space during the inflammatory process. On the other hand, the degree of fibrosis in the mucosa was negatively associated with the presence of mucosal edema. Fibrosis is the consequence of chronic inflammation; the more fibrotic tissue is present, the less active the inflammatory process is in the mucosa.

The loss of cilia, a higher number of goblet cells, and hypertrophy of mucous glands were associated with a higher total SNOT-22 score. Thus, a pathological chronic inflamed nasal mucosa has a negative effect on the quality of life of patients. Expression of MMP-9 in the epithelium was strongly correlated with a higher number of inflammatory cells in nasal epithelium and

![Fig. 1. Histology of nasal epithelium (H&E staining). (Left) Light microscopy and H&E staining on middle turbinate (1:10 lens). Numerous mucous glands, thickening of epithelium, and hyperplasia of blood vessels are seen. (Right) Infiltration of epithelium and mucosa with inflammatory cells, thickening of epithelium, as well as thickening of basal membrane/lamina propria were noticed (1:20 lens). H&E = hematoxylin and eosin.](image1)

![Fig. 2. Active remodeling is present in epithelium, as well as numerous inflammatory cells (dark small cells) (1:20 lens).](image2)
Inflammatory cells represent the major source of increased MMP-9 expression, which is linked to poor healing quality. MMP-9 plays a major role in tissue destruction and remodeling; it might be responsible for the development of tissue edema in chronic rhinosinusitis.

Examination of the nasal mucosa revealed a positive effect of treatment on the inflammatory process. This is consistent with the posttreatment improvement of symptoms and quality of life that have been previously reported. In a previous study, rhinomanometry revealed a decrease in nasal airway resistance after treatment. The decreased number of inflammatory cells, alleviation of mucosal hypervascularity, and decline in the hypertrophy of mucous glands may account for a more functional nasal epithelium and lower nasal airway resistance. In the uncinectomy group, there was a noticeable decrease in mucosal edema 6 months after treatment, which may in part account for the decreased nasal airway resistance at that timepoint.

**Strengths of the Study**

As a randomized, prospective, controlled clinical trial, this study provides valuable information about the histopathological changes in nasal mucosa in patients suffering from chronic rhinosinusitis and explores the possible effect of treatment on the nasal airway at a microscopic level.

**Clinical Applicability of the Study**

Although uncinectomy seems to be more effective than balloon sinuplasty in decreasing the inflammatory process in nasal epithelium, the latter showed a considerable positive effect in mucosal inflammation that should not be ignored.

**CONCLUSION**

Histopathological examination of nasal mucosa in chronic rhinosinusits reveals findings consistent with inflammation. Expression of MMP-9 in epithelium was strongly and statistically significantly correlated with a higher number of inflammatory cells in nasal epithelium and mucosa.

A decreased number of inflammatory cells, alleviation of mucosal hypervascularity, and decline in hypertrophy of the mucous glands indicate a positive effect of treatment on the inflammatory process, which may account for a more functional nasal epithelium and lower nasal airway resistance. This may also account for the posttreatment improvement of symptoms and in quality of life, which has been previously reported.

**Acknowledgments**

Authors would like to thank research nurse Marja-Leena Oksanen and technician Eini Eskola for their contribution and support throughout the study.

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**TABLE IV.**

<table>
<thead>
<tr>
<th>Pearson Coefficient (r) (P ( \leq ) 0.05)</th>
<th>Timepoint (months)</th>
<th>Goblet Cells</th>
<th>Width of Epithelium</th>
<th>Edema of Mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy</td>
<td>3</td>
<td>r = 0.378</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal inflammatory cells</td>
<td>0</td>
<td>r = 0.371</td>
<td>r = 0.331</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>r = 0.391</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelium inflammatory cells</td>
<td>0</td>
<td>r = 0.438</td>
<td>r = 0.270</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>r = 0.467</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>r = 0.287</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplasia of blood vessels</td>
<td>0</td>
<td>r = 0.407</td>
<td>r = 0.362</td>
<td>r = 0.314</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>12</td>
<td></td>
<td></td>
<td>r = 0.325</td>
</tr>
</tbody>
</table>

Pearson coefficient (r) (P \( \leq \) 0.05). Analysis of histopathological changes in nasal mucosa revealed some statistically significant associations among those changes. Specimens were analyzed before treatment (timepoint of 0 months) and also after treatment (timepoint 3, 6, 12, respectively). Only the statistically significant associations have been included in this table.

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Fig. 3. Immunohistochemistry for MMP-9 protein in nasal epithelium. (Left) Inflammatory cells in epithelium and blood vessels are positive for MMP-9 (1:40 lens). MMP = metalloproteinase 9.
BIBLIOGRAPHY