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Elina Penttilä

Predictive Factors in Endonasal Endoscopic Lacrimal Surgery

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ELINA PENTTILÄ

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ABSTRACT

Nasolacrimal duct obstruction (NLDO) is the most common and a growing cause of epiphora. Epiphora i.e. tears released from the eye can cause significant social embarrassment and decrease the quality of life. Endoscopic dacryocystorhinostomy (EN-DCR) is an effective surgical technique for treating symptomatic NLDO. The goal of the procedure is to relieve the patient's symptoms by opening an endonasal bypass, a rhinostoma, between the lacrimal sac and the nasal cavity. Although the success rate after primary EN-DCR is high, sometimes the procedure fails due to the occurrence of a fibrotic process at the rhinostomy site. In revision operations, the success rate of EN-DCR is significantly lower, indicating that there could be factors predisposing to failure in some patients. The aim of this prospective study was to investigate the factors predicting to outcomes in EN-DCR.

The study is part of a prospective trial and some earlier results have been published in the dissertation 'Outcome of Endonasal Endoscopic Dacryocystorhinostomy in Adults' by Grigori Smirnov (Smirnov 2010a). The present work includes three independent prospective studies. Study I was a randomized study with two parallel groups to evaluate whether intraoperative therapy with mitomycin C (MMC) could improve the success of EN-DCR (N=30). Study II investigated the inflammatory-related gene expression in the nasal mucosa in patients undergoing EN-DCR. Ten participants were consecutively recruited from patients who underwent primary EN-DCR (5 patients) or septoplasty (5 controls). Study III was conducted first to validate the Nasolacrimal Duct Symptom Score – questionnaire (NLDO-SS), and second to evaluate the long-term success of EN-DCR procedures (N=86).

The success rate after revision EN-DCR with MMC was 93%, and without MMC 60%, (p=0.08). Moreover, the relief of symptoms was significantly better in the MMC-group, mean -23 (SD 17) than in patients treated without MMC -1 (19) (p=0.007). Significant differences in gene expression related to human inflammation between EN-DCR subjects and controls were detected with polymerase chain reaction (PCR) methodology. The most significant increases between EN-DCR and controls were as follows: Selectin E 6.3-fold, Interleukin 6 5.2-fold, Chemokine motif ligand 16 5.0-fold. In the validation the diagnostic accuracy of the NLDO-SS was 84%, sensitivity 82%, specificity 85% and Cronbach's Alpha 0.85. The long-term success rate after EN-DCR was 79% with a mean follow-up time of four years.

The results indicate that the application of intraoperative MMC may improve the outcome in revision EN-DCR, and MMC is now recommended to be included in revision surgery. This study also demonstrates that there is a strong inflammation gene expression response in the nasal mucosa of patients undergoing EN-DCR, which is evidence of the inflammatory etiology of NLDO. The NLDO-SS –questionnaire proved to be a feasible

clinical tool in assessing the success of EN-DCR. The results of the previous study confirm that the success rate of EN-DCR decreases in the long run, and this highlights the importance of long-term follow-up. Based on the NLDO-SS an algorithm was devised to help in the follow-up after EN-DCR. The questionnaire represents a feasible and reliable option for replacing out-patient follow-up visits in NLDO patients, most of whom are elderly.

National Library of Medicine Classification: WO505, WW208

Medical Subject Headings: Dacryocystitis; Dacryocystorhinostomy; Epiphora; Inflammation; Mitomycin C; Validation studies

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TIIVISTELMÄ

Kyynelvuoto on yleistyvä vaiva, joka aiheutuu useimmiten aikuisilla kyynelteiden tukoksesta. Kyynelehtiminen voi aiheuttaa merkittävää sosiaalista haittaa ja elämänladun heikkenemistä. Alakyynelteiden tukoksesta johtuvia oireita voidaan hoitaa tehokkaasti nenänsisäisesti tehdyllä kyynelteleikkauksella. Leikkauksen tarkoituksena on muodostaa avanne kyynelpussista suoraan nenäonteloon. Vaikka leikkaustulokset ovat useimmiten erinomaisia, voi avanne arpeutua umpeen ja kyynelvuoto alkaa uudelleen. Tämän prospektiivisen tutkimuksen tarkoituksena oli selvittää leikkaustulokseen vaikuttavia ennustetekijöitä.

Tutkimus on osa laajempaa kokonaisuutta, ja osa aiemmista tuloksista on julkaistu Grigori Smirnovin väitöskirjatyössä 'Nenänsisäisen kyynelteiden tähystyskirurgian tulokset aikuisilla' (Smirnov 2010a). Tämänkertainen tutkimus koostuu kolmesta prospektiivisesta osatyöstä. Ensimmäisessä työssä tutkittiin, parantaako leikkauksenaikaisen lääkeaineen, mitomysiini C:n, käyttö uusintaleikkauksen onnistumista (30 potilasta). Potilaat oli satunnaistettu kahteen ryhmään sen mukaan, käytettiinkö leikkauksessa lääkeainetta vai ei. Toisen osatyön tarkoituksena oli tutkia leikkauspotilaiden nenän limakalvoilta otetuista näytteistä tulehdusta säätelevien geenien ilmentymistä. Tutkimuksessa oli kymmenen potilasta ja viisi verrokkia, joiden näytteet otettiin nenän väliseinäleikkauksen yhteydessä. Kolmannessa osatyössä validoitiin kyynelteitukospotilaiden oirekysely ja samalla kerättiin myös pitkäaikaistulokset aiemmin leikatuista potilasta (86 potilasta).

Kyynelteiden uusintaleikkaus onnistui mitomysiinillä hoidetuista potilaista 93 %:lla ja ilman mitomysiiniä hoidetuista 60 %:lla (p=0,08). Oireet vähenivät kuitenkin selvästi enemmän niillä potilailla, joiden leikkauksessa oli käytetty mitomysiiniä: keskimäärin -23 (SD17) ja vastaavasti kontrolliryhmässä -1 (19) (p=0,007). Polymeraasiketjureaktio–tekniikan avulla havaittiin merkittävä ero tulehdusta säätelevien geenien ilmentymisessä kyynelteipotilaiden ja verrokkien välillä: merkittävimmät ilmentymisen lisääntymiset todettiin selektiini E:lla (6,3-kertainen), interleukin 6:lla (5,2-kertainen) ja kemokiini motif ligandi 16:lla (5,0-kertainen). Validointityössä oirekyselyn diagnostinen osuvuus oli 84 %, tarkkuus 85 %, herkkyys 85 % ja Cronbachin alfa 0,85. Kyynelteleikkausten onnistumisprosentti oli keskimäärin neljän vuoden seurannassa 79.

Tulokset osoittavat, että leikkauksenaikainen mitomysiinin käyttö saattaa parantaa uusintaleikkausten onnistumista, ja lääkkeen käyttöä suositellaan kaikissa

uusintaleikkauksissa. Tutkimuksessa todettiin myös vahva tulehdusta säätelevien geenien ilmentyminen kyyneltiepotilailta otetuissa nenän limakalvonäytteissä, mikä osoittaa tulehduksen ja kyyneltukoksen kehittymisen välisen yhteyden. Kyyneltiepotilaiden oirekysely osoittautui toimivaksi työkaluksi leikkaustulosten onnistumisen arvioimisessa. Tulokset vahvistavat myös, että kyyneltieleikkausten tulokset heikkenevät ajan myötä, mikä puoltaa pitkäaikaisseurannan tarvetta. Laadimme kyselyn pohjalta seuranta-algoritmin, jolla voidaan korvata pääosin iäkkäiden kyyneltieleikkauspotilaiden seurantakäyntejä.

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Yleinen Suomalainen asiasanasto: Inflammaatio; Kyynelteiden ahtauma; Validointi

To all who gave me strength

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Kuopio, December 2013

Elina Penttilä

List of the original publications

This dissertation is based on the following original publications:

I Penttilä E, Smirnov G, Seppä J, Kaarniranta K, Tuomilehto H. Mitomycin C in revision endoscopic dacryocystorhinostomy: A prospective randomized study. *The American Journal of Rhinology Allergy* 2011;25(6):425-428.

II Penttilä E, Hyttinen J, Kauppinen A, Smirnov G, Tuomilehto H, Seppä J, Nuutinen J, Kaarniranta K. Up-regulation of inflammatory genes in nasal mucosa of patients undergoing endonasal dacryocystorhinostomy. *Journal of Clinical Ophthalmology* in press.

III Penttilä E, Smirnov G, Seppä J, Tuomilehto H, Kokki H. Validation of a symptom score questionnaire and long-term results of endoscopic dacryocystorhinostomy. *Rhinolo*gy in press**.**

Contents

The most commonly used abbreviations

DCR	Dacryocystorhinostomy
EN-DCR	Endonasal endoscopic dacryocystorhinostomy
EXT-DCR	External dacryocystorhinostomy
GBI	Glasgow Benefit Inventory
MMC	Mitomycin C
NLD	Nasolacrimal duct
NLDO	Nasolacrimal duct obstruction
NLDO-SS	Nasolacrimal duct obstruction symptom score
PANDO	Primary acquired nasolacrimal duct obstruction
PCR	Polymerase chain reaction
QoL	Quality of life

1 Introduction

Epiphora is the term commonly used to describe a ”watery eye”. More specifically, lacrimation describes persistent welling of tears in the eye and epiphora is the technical term used when these tears spill over. It is caused either by overproduction of tears or obstruction of the lacrimal pathway.

Epiphora is a common complaint by patients seeking help from otorhinolaryngologists and ophthalmologists. The degree of epihora can vary from a minor inconvenience to a significant discomfort and even social embarrassment. The most common cause of epiphora and discharge of the eye in adults is an obstruction of the nasolacrimal duct (NLD), a condition with an incidence of 20/100 000 (Woog 2007). In the same population –based study by Woog the incidence of NLDO was reported to be increasing.

Dacryocystorhinostomy (DCR) is a surgical technique for treating symptomatic obstructions of the lacrimal sac or the nasolacrimal duct, or dacryocystitis in cases with no response to conservative treatment like stents and antibiotics. The purpose of DCR is to create a bypass, a rhinostoma, between the lacrimal sac and the nasal cavity. The procedure was first described by Caldwell in 1893 (Caldwell 1893). He reported an endonasal approach for the treatment of nasolacrimal duct obstruction (NLDO). However, the technique did not gain popularity due to difficulties in visualization of the rhinostomy site and poor instrumentation. In 1904 Toti reported an external approach for the treatment of NLDO (Toti 1904). This technique, which has a high success rate, has been the gold standard of DCRs for many decades. Nevertheless, this external approach has some disadvantages and it leaves an external scar. Therefore, during the last two decades, less invasive techniques such as endonasal endoscopic dacryocystorhinostomy (EN-DCR) have gained popularity. They became possible with the development of rigid endoscopes and otherwise improved instrumentation. The success of primary EN-DCR has been reported to vary between 74% and 94% and a systematic review of outcomes after DCR in adults indicated that the outcomes after EN-DCR and external DCR were comparable (Leong, Macewen & White 2010). However, revision procedures tend to have a lower success rate (Ben Simon et al. 2005; Muscatello et al. 2005; Tsirbas, Davis & Wormald 2005), indicating that in patients with unsuccessful surgery, there may be some factors predisposing towards failure. The most common reason for the failure is the formation of a scar over the rhinostomy site (Jokinen, Kärjä 1974; Allen, Berlin & Levine 1988). In an attempt to prevent potential excessive scar formation, intraoperative topical application with mitomycin C (MMC) has been used because it exerts antiproliferative effects. The benefit of MMC has however never been scientifically established.

Currently known predictors for success following DCR surgery are e.g. different techniques, adjunctive therapy and sinonasal infections and abnormalities (Davies et al. 2011; Gupta 2011; Mak, Io & Wong 2012). In addition, there may be individual biological factors behind the inappropriate scar formation. It has been reported earlier that intense expression of heat shock protein 47 in metaplastic nasal mucosa could predict a poor outcome after primary EN-DCR (Smirnov et al. 2011). This discovery was the impetus to seek other biological factors, which could lead to NLDO and influence the success after EN-DCR. These factors would then represent potential targets for antiproliferative medication.

To our best knowledge, there is no generally accepted disease-specific questionnaire for adult patients undergoing EN-DCR. Clearly this kind of questionnaire could help in assessing the success after EN-DCR. It could also be a practical tool in preoperative assessment as well as in detecting possible changes in the symptoms during follow-up.

The purpose of this study was to evaluate the predictor factors of outcomes in EN-DCR. First, a prospective randomized study investigated whether the use of MMC would improve the success in revision EN-DCR. In the second study, our aim was to investigate the inflammatory-related gene expression in the rhinostomy site of nasal mucosa in patients with NLDO compared to control patients. Finally, in our prospective study the ultimate goal was to validate the Nasolacrimal Duct Obstruction Symptom Score -questionnaire (NLDO-SS) for use in the follow-up of the patients, and also to evaluate the long-term success of previously operated patients.

2 Review of the literature

2.1. ANATOMY OF THE LACRIMAL PATHWAY

Most tears are secreted by the lacrimal gland, but there are also secretions from mucous accessory lacrimal, meibomian, sebaceous and sweat glands. The lacrimal gland lies in the lacrimal fossa of the frontal bone and the accessory lacrimal glands in turn are found underneath the eyelid where the upper and lower conjuctivae meet. The meibomian (or tarsal) glands are a special kind of sebaceous glands which lie at the rim of the eyelids. The skin of the eyelid contains sweat and sebaceous glands. The lacrimal artery, derived from the ophthalmic artery (a branch of the internal carotid artery), supplies the lacrimal gland. The venous blood circulation returns from the gland via the superior ophthalmic vein.

The lacrimal pathway that drains tears into the nasal cavity can be divided into the upper and lower lacrimal pathways (Figure 1). The upper lacrimal pathway consists of the puncta and lacrimal canaliculi, whereas the lower pathway is made up of the lacrimal sac and nasolacrimal duct (NLD).

The punctal openings to the canaliculi are located at the medial fornix of the eyelids. The inferior opening is slightly larger in diameter than its superior counterpart and most of the tears enter the inferior canaliculus. The superior and inferior canaliculi combine and form the common canaliculus. The canaliculi are surrounded by muscle fibers of the lacrimal portion of Horner's muscle (m. orbicularis oculi). The fold of mucous membrane found at the junction between the common canaliculus and the lacrimal sac is called the valve of Rosenmüller.

The lacrimal sac is located in the lacrimal fossa, which lies in the medial orbital wall behind the orbital rim and it is surrounded by the frontal process of the maxillary bone and the lacrimal bone. The NLD is a continuation of the lacrimal sac and it turns towards the nose under the inferior turbinate. The NLD consists of bony and membranous parts. The bony canal of the NLD is formed by the ethmoid, lacrimal and maxillary bones. At the opening of the distal membranous part is Hassner's valve, which is a mucosal flap preventing lacrimal reflux into the NLD (Gray & Carter 1858).

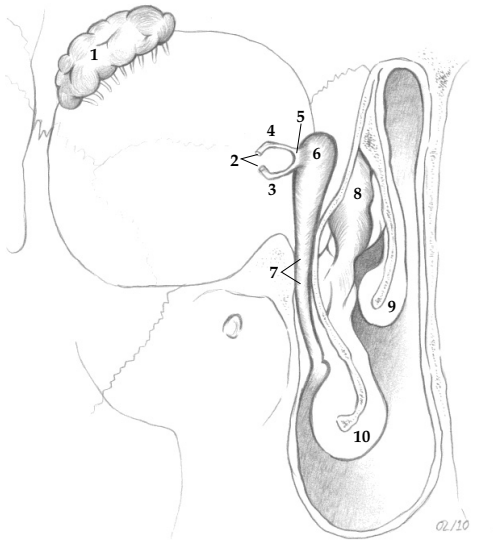

Figure 1. Anatomy of the right lacrimal pathway (Smirnov 2010a)

1. Lacrimal gland
2. Punctal openings
3. Inferior canaliculus
4. Superior canaliculus
5. Common canaliculus
6. Lacrimal sac
7. Nasolacrimal duct
8. Uncinate process
9. Middle turbinate
10. Inferior turbinate

An awareness of the precise endoscopic localization of the lacrimal sac is crucial for the success of EN-DCR. The operating area is located on the lateral nasal wall (Figure 2). Its structures consists of the middle turbinate, middle meatus, uncinate process, agger nasi, and ethmoidal bulla. The anterior connection of the middle turbinate is an important anatomical landmark: the sac is localized on the anterior-superior part of the connection point of the turbinate and the variations are hardly ever encountered. However, the precise location of the sac compared to the middle turbinate is controversial: is the axilla of the middle turbinate the landmark for the roof of the lacrimal sac (McDonogh, Meiring 1989; Sprekelsen & Barberan 1996) or is the major part of the lacrimal sac situated above the axilla of the middle turbinate (Wormald, Kew & Van Hasselt 2000)? When the normal anatomical landmarks on the lateral nasal wall are altered or do not exist, the lacrimal sac can be difficult to locate (McDonogh, Meiring 1989). One way to help in identifying the correct placement of the stoma is to introduce a transillumination probe through the canaliculis (Christensen 1951).

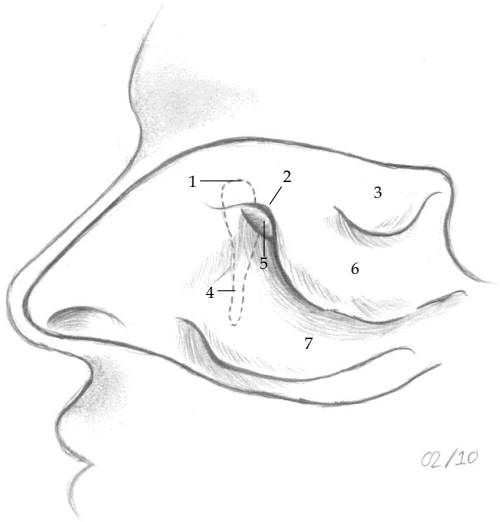

Figure 2. Localization of the lacrimal sac (Smirnov 2010a)

1. Roof of the lacrimal sac
2. Axilla of the middle turbinate
3. Superior turbinate
4. Nasolacrimal duct
5. Uncinate process
6. Middle turbinate
7. Inferior turbinate

The sensory innervation to the lacrimal gland originates either from zygomatic and lacrimal branch of the ophthalmic nerve (uppermost branch of the trigeminal nerve, CN. V). The parasympathetic secretomotor nerve supply of the gland originates from the nervus intermedius (nerve of Wrisberg). Its innervation consists of parasympathetic fibers from the greater superficial petrosal nerve (branch of the facial nerve, CN. VII), which synapses in the sphenopalatine ganglion (Figure 3). In contrast, the sympathetic fibers arise from the superior cervical sympathetic ganglion, located in the parapharyngeal space, and they follow the course of the blood vessels, before they join to the greater petrosal nerve in the pterygoid canal (Vidian nerve). The fibers reach the pterygopalatine ganglion in the pterygopalatine fossa. In contrast to their parasympathetic counterparts, sympathetic fibers do not synapse in

the pterygopalatine ganglion. However, from the ganglion they continue their way to the gland accompanying the parasympathetic fibers. These fibers may be involved in the mechanisms regulating blood flow and secretory functions of lacrimal gland.

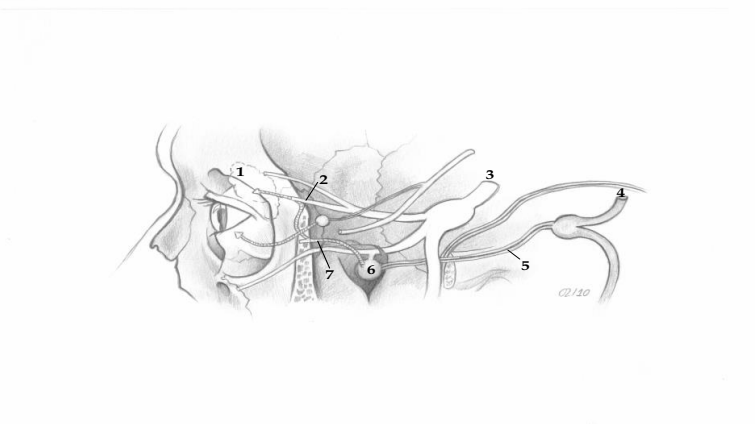

Figure 3. Innervation of the lacrimal gland (Smirnov 2010a)

1. Lacrimal gland
2. Lacrimal nerve
3. Trigeminal nerve
4. Facial nerve
5. Greater petrosal nerve
6. Sphenopalatine ganglion
7. Parasympathetic fibers

The motor innervation to the eyelids originates from the zygomatic and frontal branches of the facial nerve (CN. VII). The orbicularis oculi is a sphincter muscle around the eye and it has important functions in both protecting and moistening the eye. The function of the muscle is crucial in the elimination of tears because this muscle functions as an ocular pumping mechanism: when the eyelids close, they move the tear fluid medially across the eye toward the lacrimal puncta and canaliculi (Gray & Carter 1858).

2.2. PHYSIOLOGY OF THE LACRIMAL SYSTEM

2.2.1 Tear secretion

The tear film is a complex fluid, which protects and moistens the surface of the eye. It consists of three layers: oily, watery and mucin layers. The outer oily layer is a product of meibomian, sebaceous and sweat glands. The primary function of the outer oily layer is to stabilize the tear film. The middle watery layer is produced by the lacrimal gland and the accessory lacrimal glands. Its duty is to ensure that after each blink the cornea remains clean and via smoothing the irregularities of surface epithelium the tear film creates optimal transparency. The inner mucin layer, produced by conjunctival goblet cells, in turn stabilizes the tear film. There are two types of tear secretion: basal tear secretion, which

occurs normally without any stimulation, and more watery reflex tear secretion, which is produced in response to a corneal or conjunctival irritant but which also depends on psychological factors. There are also antimicrobial proteins present in the tear fluid (Ohashi et al. 2006).

The normal amount of tears secreted daily is about 10 mL, but this amount declines with advancing years. Keratoconjunctivitis sicca, also known as dry eye syndrome, is a common disorder. The amount of basal secretion is reduced and this is compensated by a watery reflex secretion causing epiphora (International Dry Eye WorkShop 2007).

The Schirmer's tear test provides objective information about the amount of tear secretion. The test is performed by inserting a strip of paper into the conjunctival sac of the lower eyelid and it poses no risk to the subject. The result is considered normal if after 5 minutes, at least 15 mm of the paper has turned blue, and abnormal if the change is less than 5 mm (Schirmers 1903).

2.2.2 Elimination of tears

A minor fraction of tears is lost either by evaporation or absorption across the conjunctiva, but the majority is eliminated via the nasolacrimal drainage system. The mechanical outflow of tears consists of the lacrimal pump mechanism with blinking (Jones 1957) and distension of the sac. The physical factors influencing the outflow include capillarity, gravity, respiration, evaporation, and absorption of tear fluid through the lining epithelium of the lacrimal pathway (Smirnov 2010a; Paulsen, Schaudig & Thale 2003)

2.3 PATHOPHYSIOLOGY OF THE LOWER LACRIMAL PATHWAY OBSTRUCTION

2.3.1 Dacryostenosis

Primary acquired NLDO (PANDO) accounts for about two thirds of the cases with NLDO (Woog 2007). There can be other reasons for obstruction e.g. secondary acquired NLDO (SANDO) and congenital NLDO. SANDO in adults may result from a wide variety of infections, or inflammatory, neoplastic, traumatic or mechanical causes such as previous surgery (Linberg, McCormick 1986; Bartley 1992b). Congenital NLDO affects about 20% of newborns. There are two forms of this disorder: membranous (77%) and firm (23%), the latter with a poorer prognosis (Hovanar et al. 2000). However, there is a high spontaneous resolution of symptoms during the first years of life (Yound 1996). Probing can treat the cases in which there is no spontaneous resolution but failed probings need to be treated in a facility with a balloon catheter or intubation and with the patient under general anesthesia (Schnall 2013).

The pathogenesis of PANDO is unknown, but the process is characterized by gradual inflammation and fibrosis of the nasolacrimal duct, which leads to NLDO (Linberg, McCormick 1986; Bartley 1993; Mauriello, Palydowycz & DeLuca 1992; Tucker et al. 1997; Lee-Wing, Ashenhurst 1991). In a microbiological analysis of the lacrimal sac, positive cultures were obtained in 45% of cases and these positive cultures were obtained from both patients with and without any history of previous infection. This indicates that an initial

infection may lead to inflammatory response, which in turn can trigger fibrosis and obstruction (DeAngelis et al. 2001). However, in a recent comparison of sinus CT scans, chronic sinusitis alone did not seem to be a causative factor for primary acquired chronic obstructive diseases of the lacrimal drainage system (Borges Dinis, Oliveira Matos & Angelo 2013).

The anatomical abnormalities such as narrow and high infundibulum and septal deviation may play an important role in the pathogenesis of NLDO (Önerci 2002). In addition, the relationships between the nasolacrimal pathway with the lateral nasal wall and paranasal sinuses make it vulnerable to inflammation and obstruction by various pathologies affecting the nose and paranasal sinuses (Wong et al. 1998). Acute and chronic infections in the nasal cavity, paranasal sinuses or conjunctiva can lead to spreading of the infection through the nasolacrimal duct, followed by mucosa inflammation, swelling, scar formation and finally stenosis (Önerci 2002; Ohtomo et al. 2013). The presence of primary open-angle glaucoma and topical timolol therapy has also been suggested to be predisposing factors (Seider, Miller & Beiran 2008).

Primary acquired NLDO seems to occur more often in post-menopausal women (Woog 2007; Linberg, McCormick 1986; Zolli, Shannon 1982; Paulsen et al. 2001; Tarbet & Custer 1995). The narrowness of the bony nasolacrimal canal (Groessl, Sires & Lemke 1997; Janssen et al. 2001) and the increased angle between the bony canal and the nasal floor (Shigeta, Takegoshi & Kikuchi 2007) in elderly females may predispose them to chronic inflammation of the nasolacrimal drainage system. There is no evidence that the use of cosmetics or levels of sexual hormones in women would be predicting factors for NLDO (Kashkouli et al. 2010).

2.3.2 Dacryocystitis

The NLDO causes stasis of tears in the lacrimal sac which subsequently can lead to dacryocystitis, which can be divided in acute and chronic forms. In acute dacryocystitis, the retention of tear fluid predisposes to bacterial infection with symptoms of painful swelling and redness around the lacrimal sac (Huber-Spitzy et al. 1992; Das et al. 2008). In contrast, chronic dacryocystitis is an inflammatory condition of the lacrimal sac which is associated with NLDO (Huber-Spitzy et al. 1992; Russell et al. 1985). The most frequent symptoms encountered in the chronic form are increased lacrimation and chronic conjunctivitis (Das et al. 2008; McEwen 1997) A similar spectrum of bacterial isolates are found both in acute and chronic dacryocystitis. The most common bacteria causing dacryocystitis are *Pseudomonas aeruginosa, Staphylococcus aureus, Enterobacter aerogenes, Citrobacter, Streptococcus pneumoniae, Escherichia coli, and Enterococcus* (Gritz et al. 1997; Martins et al. 2004).

2.3.3 Histology of nasal mucosa

The pathogenesis of NLDO is unknown, but the process is characterized by gradual inflammation and subsequent fibrosis of the nasolacrimal duct, which leads to NLDO. Inflammation accompanied by a combination of varying degrees of fibrosis is the most common histopathological finding in patients with NLDO (Linberg & McCormick 1986). The findings from the specimens taken from nasal mucosa (Mauriello, Palydowycz & DeLuca 1992; Paulsen et al. 2001; Heindl, Junemann & Holbach 2009) and from lacrimal sac

are similar. Descending inflammation from the eye or ascending inflammation from the nose with inflammatory changes in mucosa can lead to NLDO. In addition, repeated dacryocystitis can cause structural epithelial and subepithelial changes, which may eventually lead either to total or at least partial fibrous closure of the NLD (Paulsen et al. 2001). Chronic inflammation related histopathological features of variable degrees may also affect the outcome of EN-DCR (Heindl, Junemann & Holbach 2009; Ozer et al. 2012).

2.3.4 Biomarkers of nasal mucosa

Prolonged tissue inflammation may exaggerate fibrosis that is a central hallmark for the NLDO. Immune response, cell proliferation and transformation and survival mechanisms are tightly regulated by many stress-associated transcription factors such as nuclear factor kappa B (NF-κB), activating protein-1 (AP-1) and heat shock transcription factor 1 (HSF1) (Sasaki et al. 2002; Prasad et al. 2010; Shaulian 2010). Activation of these factors can lead to secondary protective and adaptive responses in all cells including nasal mucosa endothelium. Acute inflammation response is considered as a beneficial repairing process. It can, however, become detrimental in chronic inflammation by secretion of various cytokines and chemokines [e.g. interleukin-1 (IL-1), interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor alpha (TNF-α), chemokine ligands (CCL) proteins], metalloproteinases and other toxins that damage tissue and may finally lead to cell transformation and scar formation (Owen 2008; Toriseva & Kähäri 2009).

Chronic inflammation is not only a detrimental factor in the pathogenesis of NLDO, but it may also decrease the surgical outcome of EN-DCR (Smirnov et al. 2011). After any surgery healing process is usually divided into three phases: the initial inflammatory phase is followed by the proliferation and migration of keratinocytes or fibroblasts with re-epithelialization of the wound (Toriseva & Kähäri 2009). The remodeling phase with angiogenesis finally results in wound closure. In certain cases where the inflammatory phase is prolonged, a larger fibrotic scar is induced. Various pro-inflammatory cytokines that already may be upregulated due to the pathogenesis of NLDO are secreted upon surgical injury (Owen 2008; Toriseva & Kähäri 2009). Healing process represents a delicate balance between early pro-inflammatory signals and negative feedback pathways to suppress inflammation at later stages of wound healing. Thus, in the early healing process cellular differentiation and survival are regulated to inhibit proliferation and hypertrophic scar formation in later healing stages.

It has been suggested that these insights into the coordination of wound healing might contribute to the development of optimized and individualized treatment strategies. This is important, since at the moment no effective anti-fibrotic drugs targeting fibrogenic factors or blocking their receptors exist (Taguchi & Razzaque 2007).

2.4 EVALUATION OF THE LOWER LACRIMAL PATHWAY

2.4.1 Clinical history

It is crucial to carefully review the clinical history of the patient, since interviewing of NLDO patient is one of the most difficult ophtalmological skills to master, especially because NLDO may result from a wide variety of infectious, inflammatory, neoplastic, traumatic or mechanical causes (Linberg, McCormick 1986; Bartley 1992a). Obstruction may also be due to previous nasolacrimal duct intubation, lacrimal and orbital operations, sinonasal surgery (Osguthorpe & Calcaterra 1979), or radiotherapy. Other diseases, medications and general condition are also relevant anamnestic information.

In general, during interview the clinician should gather information claryfying all the possible manifestations of NLDO such as epiphora, discharge from the eye, swelling and pain around the eye and change in visual acuity. Nasal symptoms like nose blockage and nasal cavity discharge are also significant information, because NLDO is often related to paranasal sinus infections (Önerci 2002; Ohtomo et al. 2013). At last but not et least, it is also important to describe the quality of the sensation: what is the impact of the symptoms on the patient's quality of life: is it only a minor inconvenience or is it a significant social embarrassment?

2.4.2 Clinical examination

In the inspection of the puncta lacerations, incorrect position, narrowing or stenoses may be observed. Palpation and inspection of the lacrimal sac region may reveal dacryocystitis, mucocele, abscess formation and tumors. In the nasal endoscopy, normal anatomical landmarks and possible variables need to be identified. The pathological findings, like septal deviation and sinonasal infections, which may have led to NLDO or may interfere with the operation, have to be detected. Postoperatively the patent stoma can be visualized.

The patency of the lacrimal pathway can also be evaluated in several ways: by irrigation, Jones tests, functional endoscopic dye test and by lacrimal duct endoscopy (Guzek et al 1997).

Probing and syringing of the lacrimal pathway are easily performed and sufficient for evaluating the patency of the lacrimal drainage system and for determining the location of obstructions in patients with epiphora. After the application of a topical anesthetic, a conical probe is used to dilate the punctum. Then, the lacrimal system can be irrigated with physiological saline solution through a blunt cannula. If the pathway is open, the saline solution can freely reach the nose. In cases of canalicular stenosis, the cannula cannot contact the bony wall of the lacrimal sac. Canalicular stenosis results in reflux through the irrigated punctum. If the stenosis is in the common canaliculis or in the lower lacrimal pathway, reflux will occur via the opposite punctum (Figure 4).

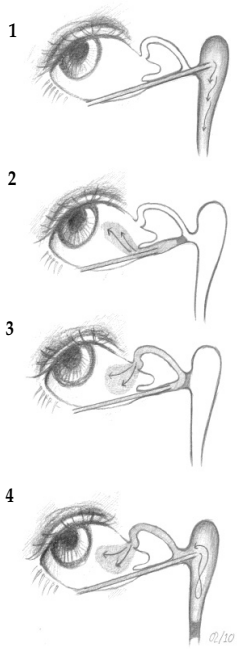

Figure 4. Location of obstruction by irrigating of the lower lacrimal system. (Smirnov 2010a)

1. No obstruction

2. Pre-saccal obstruction (stenosis of the inferior canaliculus)

3. Pre-saccal obstruction (stenosis of the common canaliculus)

4. Saccal or post-saccal obstruction (stenosis within the lacrimal sac or nasolacrimal duct)

The fluorescein dye disappearance test (FDDT), first described by Jacobs (Jakobs 1959) and subsequently documented by Zappia and Milder (Zappia & Milder 1972), measures the disappearance of fluorescein from the tear film (Kashkouli et al. 2013).

In a functional endoscopic dye test (FEDT), a single fluorescein eye drop is instilled into the conjunctiva. The patient is asked to blink normally. The stoma is then inspected at one-minute intervals and the time noted until fluorescein appears in the stoma. The interval is recorded as < 2 minutes, 2 - 5 minutes, or not at all (i.e. inspection reveals no dye even after 10 minutes) (Mistry et al. 2011).

The Jones Primary Dye test is performed using a 20mg/mL fluorescein sodium solution instilled into the conjunctival fornix. If dye-stained tears can be detected after 5 minutes in the nasal cavity, the test is positive and is evidence that the nasolacrimal passage is open. In a case of obstruction, the fluorescein does not reach the nose and the test is negative (Jones 1977).

The secondary Jones test is performed by inserting the fluorescein into the conjunctival fornix and after that by conducting a syringing. The test is positive if fluorescein is detected, showing that it had entered the sac after syringing. The test is negative if no dye is detected after syringing (Jones 1977). The disadvantage of these tests is that there is a high false negative rate and the tests cannot identify those patients with only partial obstruction (Hurwitz & Welham 1975).

Lacrimal duct endoscopy with a fine endoscope can provide direct visualization of the mucous surface of the lower nasolacrimal system. This method was firstly described by Cohen (Cohen et al. 1979) as a supplement of other diagnostic tests. However, ductal endoscopy has not gained popularity as a part of the routine clinical examination.

2.4.3 Imaging

There are several methods available for imaging the lacrimal pathway (Ansari, Pak & Shields 2005; Sagili, Selva & Malhotra 2012). However, most of them are not recommended to be used in routine examinations. In addion, many of the radiological interventions suffer from disadvantages like high costs, poor availability and exposure of the patient to radiation. However, in some cases imaging could be useful as a reliable diagnostic or even interventional technique prior to surgery (Ilgit et al. 2005). In clinical practice, computed tomography (CT) is sufficient for imaging the anatomy and the level of obstruction can be detected by irrigation.

Dacryocystography

Conventional dacryocystography is the standard technique to visualize the shape, position and size of lacrimal pathway and to identify the site of the obstruction. Radiographic contrast material is passed through the canaliculus (either passively or by direct intubation), and the nasolacrimal system is imaged using computed tomography. It has been reported that installation of the contrast material with high pressure may even open a partial obstruction (Wearne et al. 1999).

Radionuclide dacryoscintigraphy

Radionuclide dacryoscintigraphy using 99mTc is considered a physiological way to study of the lacrimal drainage system. Since it provides information about lacrimal pathway function via the tear drainage transit time (Rossomondo et al. 1972; Sagili, Selva & Malhotra 2012). The limitation of this method is the relatively poor morphological resolution.

Computed tomography

Computed tomography with high morphologic resolution does provide information about the structures related to the nasolacrimal system, paranasal sinuses and the surrounding soft tissues. It achieves an excellent contrast between the bony structures and the surrounding soft tissues. High-resolution CT (HRCT) is a more effective imaging modality

than convention CT with which to evaluate the lacrimal system and the surrounding structures (Russell et al. 1985, Groell et al. 1997). However, the disadvantage of HRCT is a higher dose of radiation. Most often, the cone beam computed tomography (CBCT), with lower resolution but also with markedly lower dose of radiation, is sufficient in the preoperative evaluation.

Computed tomography dacryocystography

In computed tomography dacryocystography (CTDCG), the contrast medium instillation dacryocystography is combined with conventional CT to improve visualization (Freitag et al. 2002). With this combination it is possible to characterize both the membranous lacrimal passage and the bony structures. And moreover, it provides information about the function of the lacrimal pathway (Ashenhurst et al. 1991).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a method which can be used to identify the anatomical soft tissue structures such as diverticula and septa (Smirnov 2010a). However, conventional MRI has low sensitivity in distinguishing between lacrimal sac diverticulum and a neoplasm (Önerci 2002). MRI is also relatively expensive and time consuming, and it does not visualize well bony structures.

Magnetic resonance dacryocystography

Magnetic resonance dacryocystography (MRDCG) is a dynamic technique for assessing lacrimal pathway drainage and the site of obstruction and it provides additional information concerning the surrounding soft tissue structures (Goldberg, Heinz & Chiu 1993; Kirchhof et al. 2000). In contrast to other imaging techniques, dynamic (dMD-DCG) does not involve ionizing radiation, or require the use of chemical contrast media, while still offering high resolution images.

2.5 SURGICAL TREATMENT OF THE LOWER LACRIMAL PATHWAY OBSTRUCTION

2.5.1 External dacryocystorhinostomy

An Italian ophtalmologist, Toti, was the first to propose a method for external dacryocystorhinostomy (EXT-DCR) in 1904 (Toti 1904). His technique was to expose the lacrimal sac via cutaneus skin incision. The EXT-DCR technique was later modified by Dupuy-Dutemps and Bourguet with the addition of suturing of the mucosal flaps, thus forming an epithelium-lined stoma (Dupuy-Dutemps & Bourguet 1921). This technique was regarded as the gold standard for the treatment for NLDO for many decades. The benefits of this procedure are its predictability of success and the direct visualization of the anatomy compared with a nasoendoscope. However, the procedure leaves a cutaneous scar. Potential complications include injury to medial canthal structures, cerebrospinal fluid

rhinorrhea, and functional interference with the physiological action of the lacrimal pump (Karim et al. 2011). The overall postoperative complication rate of the technique is about 12% (Leong, Macewen & White 2010).

2.5.2 Endonasal dacryocystorhinostomy (EN-DCR)

The first intranasal operations were conducted by Caldwell at the turn of 19th century (Caldwell 1893). In 1910, West introduced the idea of a window osteotomy by removal of the lacrimal bone and the superior maxilla to access the nasolacrimal duct (West 1910). This technique was modified in 1914 by Halle, who introduced the concept of mucosal-periost flaps to ensure a permanent stoma (Halle 1948). However, these techniques did not gain popularity due to difficulties in the visualization of the rhinostomy site and due to poor instrumentation available to these surgeons and after Toti´s report of an external approach to the treatment of NLDO (Toti 1904); his technique became the gold standard of surgical treatment until only a few decades ago.

Nevertheless, the external approach has its disadvantages and therefore during the last two decades, partly as a consequence of the development of rigid endoscopes and improved instrumentation, less invasive techniques like EN-DCR have gained popularity. The first modern clinical endoscopically assisted endonasal approaches were reported in the late eighties (Rice 1988; McDonogh & Meiring 1989).

Endonasal endoscopic DCR is a minimally invasive procedure and it offers many advantages over EXT-DCR such as the absence of cutaneous scar, the maintenance of pumping mechanism of the orbicularis oculi muscle, less disruption of medial canthal anatomy, decrement of surgical time, decreased postoperative discomfort and the ability to concurrently address any possible etiopathologenic factors such as paranasal sinusitis and septal deviation. In cases of acute dacryocystitis even with abscess formation, EXT-DCR is contraindicated due to the risk of spreading the infection. In those instances, EN-DCR has been reported to be safe and successful method of treatment (Lee & Woog 2001).

Potential disadvantages of EN-DCR include the need for extensive equipment (Tarbet, Custer 1995; Hii, McNab & Friebel 2012) and a deep learning curve (Önerci et al. 2000). However, increased surgical experience is strongly associated with greater procedural success and decreased operative duration (Hii, McNab & Friebel 2012). There is now a substantial body of literature detailing the success rates of the endoscopic approach to DCR and it is known to be at least equivalent to the traditional external techniques (Hartikainen et al. 1998; Leong, Macewen & White 2010; Ben Simon et al. 2005; Karim et al. 2011; Cokkeser, Evereklioglu & Er 2000). However, the failure rate for laser-assisted DCR (LA-DCR) is higher, especially if evaluated with a long-term follow-up (Umapathy et al. 2006; Leong et al. 2010).

Developments in fiberoptic technology and the increasing interest in minimally invasive surgery have fueled advances in transcanalicular surgery. Today, there are different endocanalicular probes, microendoscopes, microdrills, trephines, and antegrade lacrimal balloon catheters available. Transcanalicular surgery represents even more minimally invasive approach than EN-DCR to adult lacrimal drainage obstruction that may also address the pathology causing the obstruction. Long-term success rates of transcanalicular DCR appear to be improving, but so far the cost and the paucity of data on long-term results continue to limit the use of transcanalicular surgery (Athanasiov et al. 2009).

2.5.3 Revision surgery

However, even if the success rate of primary EN-DCR is high, revision operations tend to have a lower success rates, varying between 75 to 94% (Ben Simon et al. 2005; Tsirbas, Davis & Wormald 2005; Zilelioglu et al. 1998; El-Guindy, Dorgham & Ghoraba 2000; Demarco et al. 2007; Choussy et al. 2010; Korkut et al. 2010; Kominek et al. 2011; Paik, Cho & Yang 2013). According to a review of success rates after DCR revision, EN-DCR seems to achieve better outcomes than other techniques, and thus would appear to be favoured in revision cases (Leong, Macewen & White 2010). The poorest results in revision surgery have been reported after LA-DCR (Mickelson, Kim & Stein 1997; Tripathi et al. 2002; Patel et al. 1997; Woo, Moon & Kim 1998), achieving only 43% success in a long-term follow-up (Mickelson, Kim & Stein 1997).

In addition to its many advantages in primary surgery, the endonasal approach offers several benefits in revision surgery as compared to EXT-DCR, including direct visualization of anatomical structures like the residual lacrimal sac (Mickelson, Kim & Stein 1997; Metson 1990) and a complete exposure for anatomical anomalies and the possibility of the checking for inflammatory changes in the normal structures. These advantages of precise and targeted surgery explain why many investigators prefer rather EN-DCR in revision surgery than EXT-DCR (El-Guindy, Dorgham & Ghoraba 2000; Puxeddu et al. 2000; Korkut et al. 2011; Hull, Lalchan & Olver 2013).

Since these anatomical anomalies and inflammatory changes are crucial predisposing factors which can lead to failure, additional surgery, when needed, is an important part of revision surgery for prevention of the recurrence of pathology. Korkut coworkers noted that the need for additional nasal surgery was significantly higher in the revision cases (52%) than in the primary cases (29%; p=0.048), although the success in both groups was similar. They believed that the repair of nasal pathologic findings in the second surgery was approaching the high success of revision cases (Korkut et al. 2011). Secondly, they stated that the success of revision surgery appeared to depend on maintaining a larger osteotomy size. Increasing the size of osteotomy toward the distal portion of the lacrimal sac as far as possible was important if one wished to avoid a sink effect originating from the surgery. In another report the need for adjunctive procedures during revision surgery was similarly emphasized. The investigators conducted partial middle turbinectomy in 53% and anterior ethmoidectomy in 21% of revision cases (Hull, Lalchan & Olver 2013).

Some investigators have hypothesized that the intraoperative topical application of MMC may enhance the success rate, especially in revision EN-DCR (Camara, Bengzon & Henson 2000; Selig, Biesman & Rebeiz 2000). However, the benefit of MMC is still somewhat controversial (Zilelioglu et al. 1998; Penttilä et al. 2011; Ozkiris, Ozkiris & Goktas 2012; Ragab et al. 2012) as is the use of stents in revision cases. Although stents are thought to increase the risk of granulation tissue formation and scarring (Unlu et al. 2002; Smirnov et al. 2008), some clinicians recommend the use of tubes, particularly in revision cases (Orcutt, Hillel & Weymuller 1990; Önerci 2002).

2.5.4 Complications of surgery

The overall intraoperative complication rate in external and endoscopic DCRs is 1% and none of the adverse effects have resulted in long-term disability such as vision impairment (Leong, Macewen & White 2010). The most common intraoperative reported complications of EN-DCRs are: orbital fat exposure, epistaxis, laceration of the puncta and conjunctival fistula.

The overall complication rate after DCRs is reported to be about 6% (Leong, Macewen & White 2010). Although it appears that EN-DCR is associated with a higher risk for postoperative complications, this may be attributed to the fact that nasoendoscopy is routinely conducted to the patients who have undergone endonasal surgery. Thus, some minor complications such as granulation tissue formation and synechiae may be detected. The most common postoperative complications encountered after EN-DCR are the formation of granulation tissue and a scar over the rhinostomy site (Jokinen, Kärjä 1974; Allen & Berlin 1989; Önerci et al. 2000; Konuk et al. 2010). Other postoperative complications of EN-DCR are: periorbital hematoma, synechiae, periorbital emphysema canaliculitis, periorbital edema, dacryocele, maxillary sinusitis and frontal sinusitis.

2.6 OUTCOME EVALUATION AFTER EN-DCR

2.6.1 Criteria for success

The terms success and failure may be difficult to determine definitively in lacrimal surgery. In most studies, the criteria of the success are anatomical patency (objective assessment) of the lacrimal pathway accompanied by the relief of the symptoms (subjective assessment). However, there are no generally agreed, consistent outcome criteria; a problem was emphasized by Olver in 2003 (Olver 2003). He suggested that there are three criteria on which all surgeons should be able to agree: firstly, the success should be assessed at a minimum of 6 months postoperatively; secondly, subjective success should be based on patient's symptoms and thirdly objective success should be assessed based on (i) patency in syringing and (ii) presence of a functioning rhinostomy evaluated using the functional endoscopic dye test.

Certainly an important aspect in assessing the outcome is that there has to be adequate follow-up time. The majority of the ostium shrinkage occurs in 4 weeks after the procedure (Chan & Selva 2013) with the average time of failure varying between 2 and 4 months (Kong, Kim & Kong 1994; Boush, Lemke & Dortzbach 1994). However, obstruction of the rhinostoma can appear even years after the primary operation (Dietrich et al. 2003). To date, based on the lack of generally accepted criteria of adequate follow-up time, only a few studies have investigated the long-term success rates of EN-DCR. In the publications, the success of surgery has variedbetween 58-94% with follow-up times of 3 to 5 years (Önerci et al. 2000; Dietrich et al. 2003; Zenk et al. 2009). In most studies, the follow-up time has not been long enough to allow a reliable conclusion of definitive success, and it is likely that there is a decrease in the success rate of EN-DCR with long-term follow-up.

Subjective success in turn can be assessed from the patients' symptoms. Complete relief or significant improvement of complaints can be considered a subjective success. On the other hand, when symptoms are only slightly improved or even unchanged, the operation has

most often been considered as a failure. However, objective surgical patency does not necessarily correlate with symptom improvement (Sahlin & Rose 2001; Cheung et al. 2007). One possible physiological explanation for this phenomenon may be that the surgery temporarily alters the tear absorption in the sac (Mistry et al. 2011). On the other hand, in some patients with stomal failure, an improvement may be noted in their symptom scores (Mistry et al. 2011). This was explained by psychological factors such as cognitive dissonance or the placebo effect.

Anatomical patency can readily be judged in objective tests: functional endoscopic dye test or inspection of the ostium, irrigation or fluorescein retention test. Nevertheless, patency by syringing indicates anatomic but not always functional success. Functional (sometimes called partial) NLDO was first described by Demorest and Miller in 1955 to encompass lacrimal drainage dysfunction in the presence of anatomical patency (Demorest & Milder 1955). In those cases, there is a need to exclude other conditions causing epiphora, such as hyper-secretion, lacrimal pump failure, discontinuous drainage apparatus (e.g. punctual ectropion) and partial lacrimal duct obstruction (Zaidi, Symanski & Olver 2011; Chan et al. 2012). Rose has proposed an explanation for this lacrimal paradox in terms "lacrimal drainage hydraulics in a 3-compartment model" (Rose 2004). It is unclear whether the patients with initial anatomical success but functional failure may become asymptomatic over time. However, if the symptoms persist in the long-term follow-up, these patients may benefit from revision surgery because even if the stoma seems to be open in clinical examination, there may still sometimes be scarring or dacryoliths in the operated field that interfere with drainage.

The anatomical success rate i.e. the patency is reported to be higher than the functional success, which highlights the importance of measuring the physiological success and the relief of the patient's symptoms. DCR is usually performed to improve quality of life and therefore patient satisfaction is paramount; lacrimal system patency is secondary (Fayers et al. 2009).

2.6.2 Quality of life (QoL)

The patient's satisfaction because of relief of symptoms and improved QoL are the predominant considerations determining the success of surgical interventions. Glasgow Benefit Inventory (GBI) is a validated and generally accepted measure developed for otorhinolaryngological interventions (Appendix) (Robinson, Gatehouse & Browning 1996). The GBI is a quality of life tool, which measures changes in health status. There are also other disease-specific, widely-used, validated instruments like the Otitis Media 6-Item Quality-of-Life Survey (OM-6), the Nasal Obstruction Symptom Evaluation, and the 20-Item Sino-Nasal Outcomes Test (SNOT-20) in otolaryngology literature (Rosenfeld et al. 1997**;** Piccirillo, Merritt & Richards 2002**;** Stewart et al. 2004). The limitation of GBI is that it is intended for post-procedural use and is therefore not appropriate for assessing severity of symptoms before surgery. In the assessment of the outcome of EN-DCR, an other weakness of the GBI is that it is not disease-specific and ocular symptoms are not included. Consequently, there is a clinical need for a generally accepted and validated disease-specific instrument that could be used for the assessment of symptoms and subjective outcome.

In the literature examining patient satisfaction with EN-DCR for primary or revision DCR, surgery has been shown to be comparable to that achieved with EXT-DCR (Mathew et al. 2004). It is also claimed that patients undergoing LA-DCR and EXT-DCR enjoy a

significant benefit in their healthcare status as detected both by the GBI and the ocular symptom scores (Bakri et al. 1999). A similar significant quality of life improvement estimated with GBI was found with EN-DCR and correspondingly in EXT-DCR versus EN-DCR (Ho et al. 2006; Spielmann et al. 2009; Hii, McNab & Friebel 2012; Jutley et al. 2013). Smirnov et al. found that the Nasolacrimal Duct Symptom Score (NLDO-SS) (Appendix) correlated with GBI but it provided more information about the benefits after EN-DCR than GBI alone (Smirnov et al. 2010b). When asked, 86% of patients were found to be willing to recommend the LA-DCR procedure (Tripathi et al. 2002) and 100% after EXT-DCR (Tarbet & Custer 1995).

It widely accepted that patient satisfaction is related to preoperative expectations, which are set by the surgeon. Thus, by taking a realistic approach and modifying these expectations may improve patient satisfaction postoperatively (Cheung et al. 2007).

2.6.3 Symptom questionnaires

Questionnaires are helpful tools on monitoring the subjective success, and also in preoperative evaluation and as ways to measure any changes in signs and symptoms during the follow-up. The availability of a generally accepted and used measure would be also helpful in the comparison between different studies. However, there are only a few questionnaires available, which have been developed for adult lacrimal surgery and they are not universally accepted (Mistry et al. 2011; Cheung et al. 2007). These questionnaires measure not purely the symptoms related to the lacrimal pathway obstruction, but there are also additional items on their social impacts.

The lack of generally accepted symptom-based scoring system for recording outcomes of lacrimal surgery was discussed by Mistry et al in 2011. They stated that the reason for this deficit is the difficulty in assessing the symptoms related to NLDO. Firstly, NLDO can give rise to a variety of pathologies apart from simple epiphora: for example dacryocoele, mucocoele, dacryocystitis, calculus or fistula formation are reported. Patients may therefore present symptoms, of varying severities. Secondly, the obstruction may cause no symptoms at all in some patients; especially those who are elderly and who have reduced tear production. In addition, the sac itself can absorb a certain volume of tears and this can balance the reduced tear production. Alternatively, symptoms may be present, but not sufficiently severe to be perceived as a health problem, and therefore the patient may not seek medical attention. Thirdly, there is no pre-operative clinical test, which can predict severity of symptoms, so there is no objective 'gold standard' against which symptoms can be judged (Mistry et al. 2011).

2.6.4 Predisposing factors for the success of EN-DCR

2.6.4.1 Key points in the success of EN-DCR

In order to improve the success rate of EN-DCR, a number of different methods have been developed earlier where either the stomal size and precise location, mucosal flaps were different or additional surgery has been applied.

Osteotomy size

A small bony ostium is proposed as one of the most important causes of the failure in DCR surgery (Wormald, Kew & Van Hasselt 2000; Önerci 2002; Korkut et al. 2010; Ragab et al. 2012; Rose 2004; Welham & Wulc 1987) This is supported by the experience with LA-DCR: the LA-DCR usually creates a smaller ostium than the external and endonasal approaches, and this is correlated with its lower success rates (Linberg et al. 1982; Rosen, Barak & Rosner 1997; Basmak et al. 2011). EN-DCR is also much more successful with normal or enlarged lacrimal sacs in whom a large ostium can be created in comparison with cicatrized or small lacrimal sacs (Welham & Wulc 1987; Mannor & Millman 1992).

However, there is still considerable debate in the literature about whether the ostium size created during primary or revision DCR plays a crucial role on the surgical success. There are also reports that the success rate has been similar irrespective of whether the osteotomy was larger or smaller than 10 mm in diameter (Beigi et al. 1998) and some clinicians consider the ostium size to be non-significant (Chan & Selva 2013; Linberg et al. 1982), and have recommended the creation of a small ostium involving the inferior portion of the lacrimal bone (Massaro, Gonnering & Harris 1990; Tutton & O'Donnell 1995).

There is no statistically valid correlation between the primary size of the bony opening and the final size of the healed intranasal ostium. While osteotomy may heal with only granulation tissue formation, in some case, it may also heal with new bone formation, which can lead to re-obstruction of the stoma. Previously some investigators have stated that bone regrowth was responsible for failure of the primary operation (Iliff 1971; McLachlan, Shannon & Flanagan 1980). While others have maintained that new bone formation was minimal and that fibrous tissue is primarily responsible for obstructions at the site of the bony rhinostoma (Rose 2004; McLean, Cree & Rose 1999). In revision surgery, an obstruction of the ostium with bone tissue was noted in 30% of the cases (Korkut et al. 2011) and in another study conducted by Tsirbas, there was a need for bone removal in all of their 30 revision cases (Tsirbas, Davis & Wormald 2005). This possible new bone formation, particularly in revision surgery, highlights the importance of creating a sufficiently large bony ostium.

Stoma location

An important factor that affects the surgical success of EN-DCR is the correct localization of the rhinostoma (Korkut et al. 2010) and the precise endoscopic localization of the sac is crucial if one is to avoid failure. The anterior connection of the middle turbinate is an important anatomical landmark: the sac is localized on the anterior-superior part of the axilla of the turbinate with variations hardly ever being encountered (Wormald, Kew & Van Hasselt 2000). The authors recommended the extension of the bony ostium superiorly until the common canaliculus could be directly visualized (Wormald, Kew & Van Hasselt 2000). Placement of the ostium too close to the middle turbinate resulted in subsequent adhesion and occlusions. On the other hand, opening the ostium too high or too low could predispose to incomplete draining of tears, which can lead to the development of Sump syndrome (Welham & Wulc 1987; Jin, Yeon & Choi 2006). Consequently, the stoma should be performed exactly over the sac and the saccal wall should be opened from its middle part. It is widely accepted that not only a small but also a misplaced bony window is a common cause for the failure (Allen, Berlin & Levine 1988; Önerci et al. 2000; Orcutt, Hillel & Weymuller 1990; Welham & Wulc 1987). Ragab et al detected small, misplaced bony window in 43% of their failed patients (Ragab et al. 2012).

Mucosal incision and flaps

During EN-DCR it is recommended to conduct the mucosal incision by making a cut in the mucosa superiorly above the insertion of the middle turbinate on the lateral nasal wall and anterior to the axilla and vertically down the frontal process of the maxilla (Tsirbas, & Wormald 2003). Unnecessary trauma to neighboring tissue should be avoided (Wong et al. 1998; Tsirbas &, Wormald 2003) and it is best that the nasal mucosal flap should include the periosteum (Önerci 2002).

The main task of EN-DCR in addition of creating the largest possible bony ostium is to achieve contact between saccal and nasal mucosa. In the earliest studies, this was achieved by suturing, or stapling with titanium clips, the mucosal flaps (Welham & Wulc 1987; Eloy et al. 1995). Later, Wormald (Wormald 2002) and Tsirbas (Tsirbas & Wormald 2003) described an approach where the lacrimal sac would be fully exposed and marsupialized with nasal and lacrimal mucosa apposition. Greater flap mobility and greater lacrimal sac marsupialization in EN-DCR were associated with better success of early (10 weeks postoperatively) anatomical patency (Davies et al. 2011).

Additional surgery

The additional surgery, like septoplasty, partial resection of anterior middle turbinate, uncinectomy or FESS, when needed, may favour success, because intranasal abnormalities are common causes of DCR failure (Allen, Berlin & Levine 1988; Basmak et al. 2011; Fayet, Racy & Assouline 2002; Lee 2008; Yang & Oh 2012). The incidence of additional procedures was investigated in 256 patients undergoing EN-DCR: 22% of the patients required additional endonasal procedures to improve access to the operation area (Nussbaumer, Schreiber & Yung 2004). In another study it was found that in 13/44 operations (30%) a septoplasty was required, and in 10/44 operations (23%) FESS was performed in conjunction with the DCR (Tsirbas & Wormald 2003).

The need for additional nasal surgery has been reported to be significantly higher in the revision cases than the primary procedures (Korkut et al. 2011; Hull, Lalchan & Olver 2013). The investigators stated that the repair of nasal pathologic findings in the second surgery, and thereby prevention of the recurrence of pathology could have accounted for the good success of the revision cases.

On the other hand, despite the indisputable benefits of the additional surgery in a well-selected patient population, unnecessary trauma to neighboring tissue should be avoided. For example, there are reports that more extensive surgery may induce more scarring and this could lead to reobstruction of the stoma (Allen, Berlin & Levine 1988; Wong et al. 1998; Tsirbas & Wormald 2003; Nussbaumer, Schreiber & Yung 2004).

2.6.4.2 Adjunctive therapy

Mitomycin C

Previous studies have described different methods to modulate wound healing and scar formation with corticosteroids, 5-fluorouracil and mitomycin C (MMC), but the advantages of these options are still debatable (Mora et al. 1997; You & Fang 2001; Zeldovich & Ghabrial 2009).

Mitomycin C is an aminoglycoside antibiotic, isolated from the *Streptomyces caespitosus*. It has also been used as a chemotherapeutic agent, because of its antiproliferative effects (Rubinfeld et al. 1992). MMC prevents replication of fibroblasts and epithelial cells, but it is actually active against all cells, regardless of the cell cycle phase. At lower concentrations, it selectively interrupts deoxyribonucleic acid (DNA) replication causing inhibition of mitosis and protein synthesis, thus affecting the healing process (Bradner 2001; Apuhan et al. 2011).

Animal studies in rabbits indicated that MMC could slow the postoperative healing of the nasal mucosa and reduce stenosis without affecting the re-epithelization process (Rahal, Peloquin & Ahmarani 2001; Ingrams et al. 1998). An experimental study evaluated the effect of brief exposure of MMC on cultured human nasal mucosa fibroblasts (Hu et al. 2000). The investigators claimed that MMC exposure would exert a variable cytotoxic effect and inhibit proliferation of cultured nasal mucosa fibroblasts. It has been shown that MMC can induce cellular apoptosis with a 5-minute exposure time. At higher concentrations, MMC can suppress cellular ribonucleic acid (RNA) and protein synthesis. Ugulbas and co-workers investigated specimens from four patients who had undergone DCR with the application of MMC (Ugurbas et al. 1997). The specimens were collected during surgery and at 15 days, 1 month, 3 months, and 6 months after surgery. The samples were examined under light and electron transmission microscopy and were compared with control specimens. Light microscopy showed attenuated epithelium with intracytoplasmic vacuoles. The subepithelial connective tissue was looser and hypocellular. Electron microscopy confirmed these findings and demonstrated the presence of swollen mitochondria, dilatation of endoplasmic reticulum, and chromatin-dense granules in the nuclei of fibroblasts. The investigators concluded that MMC caused a decrease in density and cellularity of mucosa and so when topically applied it could be predicted to enhance the success of surgery.

Since it can prevent excessive scar formation, intraoperative topical MMC has been widely used in ophthalmologic surgery with favorable results when treating patients with glaucoma, pterygium and strabismus (Singh, Wilson & Foster 1988; Cruz 1996; Palmer 1991; Ollikainen et al. 2010). For the same reason, MMC has also been topically used in some otorhinolaryngological procedures such as myringotomy, choanal atresia, esophageal and tracheal stenosis, endoscopic sinus and lacrimal surgery (Zilelioglu et al. 1998; Ingrams et al. 1998; Ward & April 1998; Rahbar et al. 2002; McLeod, Brooks & Mair 2003; Bast et al. 2009; Senders 2004; Uhlen et al. 2006; Olutoye, Shulman & Cotton 2006).

In the literature, the doses of MMC in lacrimal surgery have ranged between 0.1 and 0.5 mg/mL and the duration of application from 2 up to 30 minutes. The success rates differ widely, from 57 to 91%. However, direct comparison between studies is complicated because of differences in study design, definition of successful surgery, size of study populations, surgical techniques used and the duration of follow-up time. The studies investigating the effect of MMC in DCRs are seen in Table 1.

In the reports investigating the effect of MMC on the ostium size, the medication seems to achieve a final larger stoma (You & Fang 2001; Kao et al. 1997; Tirakunwichcha, Aeumjaturapat & Sinprajakphon 2011). All of the results are consistent, and clearly support the antifibrotic property of the MMC in maintaining the ostium size in the postoperative period (Cheng et al. 2013). However, it is unclear whether the ostium size created during DCR plays any role on the surgical success.

Based on the experience from the ophalmological surgery, topical application of MMC for a short time appears to be very safe. Some complications, such as corneal ulcus, scleral calcification, corneal perforations, secondary cataract, wound infection, endophthalmitis, wound leak, scleral ulceration, punctuate keratopathy and hypotony-related maculopathy, have been reported in pterygium and glaucoma filtration surgeries (Rubinfeld et al. 1992; Shields et al. 1993; Cheung et al. 1997). No systemic adverse effects such as bone marrow suppression, renal toxicity or carcinogenesis are reported. Moreover, there are no reported complications related to the application of MMC in EN-DCRs.

There are some obstacles encountered with the use of MMC: the cost, short shelf life of reconstituted solution (2 weeks) and a relatively small number of the patients who need EN-DCR. Multiple applications in opthalmological and otorhinological procedures could solve some of these difficulties (Selig, Biesman & Rebeiz 2000).

A recent review and meta-analysis indicated that the intraoperative MMC application seems to be a safe adjuvant that could reduce the closure rate of the osteotomy and enhance the success rate after primary and revision EN-DCR (Cheng et al. 2013). However, although there appears to be a favorable short-term effect of MMC, there is no robust evidence regarding its ability for long-term prevention of restenosis. Therefore MMC application has not been adopted in DCRs as a routine procedure.

Table 1. The studies investigating the effect of MMC in DCRs.

	MMC concentration (mg/mL) and application time (min)	Primary (P)/revision (R) RCT randomized-controlled trials	Number of patients	Mean follow-up (months)	Stents (+/-)	Success rate with MMC (%)	Favorable effect (+/-)
Apuhan 2011	0.5 and 2.5	P+R	50	18	+	91	+
Görgulu 2012	0.2 and 5	R	20	17	+	90	+
Tirakunwichcha 2011	0.5 and 3	P+RCT	50	12	+	85	+/-*
Özkiriz 2012	0.5 and 5	R+ RCT	36	12	+	89	+
Ragab 2012	0.5 and 10	R+ RCT	76	12	+	83	-
Zilelioglu 1998	0.5 and 2,5	P	14	18	+	79	-
Zilelioglu 1998	0.5 and 2,5	R	40	18	+	75	-
Selig 2000	0.4 and 3-5	P	8	14	+	88	+
Zilelioglu 2002	0.5 and 2,5	P	64	11	+	80	-
Yuen 2004	0.4 and 5	P	99	18	+	80	-
Tabatabaie 2007	0.2 and 2	P	44	7	+	57	-
Prasannaraj 2012	0.2 and 10	P+ RCT	38	6	-	82	-

* No statistically significant difference between the groups, but in the MMC-group the mean ostium size was predominantly larger than in the control group.

5-Fluorouracil

Like MMC, 5-fluorouracil (5-FU) is an antimetabolic agent. 5-FU is a synthetic pyrimidine that inhibits the formation of thymidine and thus it impairs the synthesis of DNA. 5-FU also affects cell protein synthesis by binding to RNA as a secondary mode of action (Bakri et al. 2003). It has also shown to inhibit Tenon´s capsule fibroblast proliferation (Mallick, Hajek & Parrish 1985; Khaw et al. 1992). The intraoperative application of 5-FU has prolonged the survival in ophthalmological surgery by inhibiting scarring (Lanigan et al. 1994).

There are only a few studies that have used 5-FU intraoperatively during DCR (Yalaz et al. 1999; Bakri et al. 2003; Watts et al. 2001). The doses of 5-FU used varied between 0.5 and

25 mg/mL and durations of application between 4 and 5 min. Yalaz and coworkers concluded in a small study population of 20 patients that intraoperative 5-FU could improve the success rate of EXT-DCR (Yalaz et al 1999). However, in the prospective, randomized, controlled study conducted by Bakri and coworkers there was no significant improvement in success rates in LA-DCR with the application of 5-FU as compared to control group (Bakri et al. 2003). Watts and coworkers reported that EXT-DCR provided better results than 5-FU augmented LA-DCR (Watts et al. 2001). The result may however be explained by the fact the LA-DCR tends to have a lower success rate than EX-DCR. There were no reported complications in these studies.

Corticosteroids

Corticosteroids are known to exert anti-inflammatory, immunosuppressive and anti-mitogenic properties, which have proved useful in ophthalmology. They are thought to delay healing process of the stoma after DCR, preventing overgrowth and they may also result in less scarring and less tissue contraction (Zeldovich & Ghabrial 2009). Zeldovich and Ghabrial reported 89% success of revision EN-DCR following an intraoperative injection of betamethsone to the ostium site (Zeldovich & Ghabrial 2009). However, there was no control group in this rather small case series of 19 eyes and thus it is impossible to draw any definitive conclusions about the advantages of intraoperative corticosteroids in DCR surgery.

2.6.4.3 Postoperative care

It is clear that postoperative care influences the healing process. Postoperative endonasal evaluation for the removal of scars and granulation tissue from the surgical site is of fundamental importance if one wishes surgical success (Demarco et al. 2007; Weidenbecher, Hosemann & Buhr 1994; Metson 1991). In addition to debridement, other postoperative care options include the administration of systemic antibiotics, combination of antibiotic-steroid eye drops, intranasal steroids, frequent nasal cleaning with saline solution (Choussy et al. 2010), and irrigation. Jin et al demonstrated that inappropriate postoperative care was one of the main causes of a lower success rate (Jin, Yeon & Choi 2006). In a prospective randomized trial it was found that a significantly lower number of debridement settings were needed to clean the granulations and crustations in patients treated with MMC(Ragab et al. 2012). The investigators stated that MMC could be beneficial in revision procedures in those patients who are not capable of undergoing close follow-up with repeated debridement sessions.

2.6.5 Risk factors for the failure after EN-DCR

2.6.5.1 Age and gender

There is one single study observing a negative correlation between age and surgical outcome, with younger age at time of surgery being associated with a higher rate of failure (Mak, Io & Wong 2012). The investigators postulated that this association was related to the higher degree of fibrosis in the younger patients. However, in two other studies, age did

not affect the final outcome of EN-DCR (Zenk et al. 2009; Dolmetsch 2010). It has been reported that gender does not influence the outcome (Mak, Io & Wong 2012).

2.6.5.2 Previous trauma

Previous trauma is also associated with a greater rate of failure in DCR surgery (Ben Simon et al. 2005; Zenk et al. 2009; Walland & Rose 1994). Walland found that this association was possibly attributable to the frequent canalicular problems in these patients (Walland & Rose 1994a). Their results suggested that trauma might predispose independently to both failure and soft tissue infection.

2.6.5.3 Preoperative inflammation or infection

Sinonasal inflammatory and infectious conditions may be etiological factors in NLDO (Linberg & McCormick 1986; DeAngelis et al. 2001; Bartley 1993). On the other hand, according to a recent report, the presence of chronic sinusitis alone would not lead to NLDO (Borges Dinis, Oliveira Matos & Angelo 2012). Nevertheless, chronic inflammation related histopathological changes have been postulated to have a role in the outcome of EN-DCR (Heindl, Junemann & Holbach 2009; Ozer et al. 2012) and a history of sinusitis has been shown to increase the risk for failure (Allen, Berlin & Levine 1988; Nussbaumer, Schreiber & Yung 2004). Even though the inflammatory and infectious conditions could well influence the outcome of EN-DCR, the large population based study conducted by Woog revealed that there was higher success rate in patients with a history of dacryocystitis than in those without this kind of history (Woog 2007). These results indicate suggest that the saccal infection would not be a risk factor for the surgical outcome but sinonasal infections would increase the risk of failure.

2.6.5.4 Learning curve in EN-DCR

Since EN-DCR is a relatively infrequently performed operation, with a clear learning curve, the experience of the surgeon plays an important role in the success rate (Hii, McNab & Friebel 2012). In a mean follow-up time of 4 years, the surgical success was 94% in experienced hands but only 58% in inexperienced hands (Önerci et al. 2000). If the physician is experienced in endoscopic surgery, it should be possible to address other nasal pathologies in the same session (Önerci 2002).

2.6.5.5 Stents

It has been proposed that stents might prevent common canalicular stenosis and maintain patency during the healing process, and therefore most investigators still routinely use silicone intubation even although there is no convincing evidence about their benefits (Pakdel 2012). In fact, a recent meta-analysis including 5 randomized controlled trials and 4 cohort studies, found no benefit for silicone tube intubation in primary DCR (Feng et al. 2011).

2.6.5.6 Postoperative infection

The infection rates after EN-DCR have been poorly investigated. In a recent retrospective case series, acute rhinosinusitis was detected in 1.5% of patients after EN-DCR. In those with prior history of chronic rhinosinusitis, the rate was ten times higher (P=0.009). The infection developed within the first post-operative week in patients with a history of chronic rhinosinusitis (Shams & Selva 2013).

In external procedures, the development of a postoperative infection may impair the normal healing process of the stoma and is associated with an increased risk of failure (Allen, Berlin 1989; Walland & Rose 1994a). Thus, appropriately timed follow-up visits are crucial for detecting any possible infection. After open lacrimal surgery, soft tissue infection occurs in about 8% of cases, but the infection rate is only between 1.2 and 2% of cases where prophylactic antibiotics have been prescribed (Walland & Rose 1994b; Dulku 2010). However, antibiotic therapy for established postoperative infection is less effective than prophylactic antibiotic use (Walland & Rose 1994b). In the study of Dulku et al. the number needed to treat to prevent one postoperative infection was 104 and this result suggest that the routine use of systemic antibiotic prophylaxis in EXT-DCR may not be justified (Dulku 2010).

3 Aims of the present study

The present study aimed to investigate whether the postoperative scarring and adhesion formation could be prevented with intraoperative adjunctive therapy in revision surgery. An equally important aim was to validate a questionnaire for postoperative evaluation in patients after EN-DRC. The final objective of this academic dissertation was to investigate the inflammatory gene expression in patients with NLDO i.e. to identify possible fibrogenic factors to be targeted with novel medications.

The specific aims of the individual studies were:

1. During this prospective, randomized consecutive case series of EN-DCR, the ultimate goal was to access whether the intraoperative use of mitomycin C could improve the success rate in endonasal revision DCR procedure (Study I).

2. In the second study, the major aim was to characterize the gene expression profile by quantitative real-time polymerase chain reaction (qPCR) of inflammatory biomarkers in the nasal mucosa over the rhinostomy site in patients undergoing EN-DCR (Study II).

3. To validate the Nasolacrimal Duct Obstruction Symptom Score questionnaire (NLDO-SS) and secondly to evaluate the long-term success rate of EN-DCR procedures (Study III).

4 Patients, material and methods

4.1 PATIENTS

A total of 116 patients participated in the three studies. The characteristics of the study subjects are presented in Table 2.

Table 2. The characteristics of the study subjects.

		Study I	Study II	Study III
Sex				
	Male	3	5	16
	Female	27	5	60
Age (yr), mean (SD)		67 (10)	54 (24)	62 (12)
Diagnosis				
	Dacryostenosis	19	1	57
	Dacryocystitis*	11	4	29

4.1.1 Study I

The recruitment for this prospective study started in 2004 and ended in 2010. The subjects were consecutively recruited from the adult patients referred to the outpatient clinic of the Department of Otorhinolaryngology in Kuopio University Hospital because of re-obstructed NLD. The patients were eligible if they were adults (age 18 years or older), their American Society of Anesthesiologist physical status classification was I-III, and they were scheduled for revision lacrimal pathway surgery because of tearing or recurrent infection of the lacrimal sac. The patients were not recruited if there was pre-saccal obstruction, malignancy in the paranasal sinuses, nasal cavity, or lacrimal pathway, mental disability, pregnancy or breast-feeding.

A total of 32 consecutive revision EN-DCR procedures were conducted. However, there were two dropouts before the 6-month follow-up visit, leaving 30 procedures for analysis.

4.1.2 Study II

The five study patients were consecutively recruited from the adult patients who underwent primary EN-DCR due to tearing or recurrent infection of the lacrimal sac between May and August 2012. The five control patients were individuals who underwent septoplasty during the same time period. The patients who underwent septoplasty were chosen as controls because they were operated for a septal deformity without any

inflammatory or infectious processes or NLDO. There were no dropouts during the 6-month follow-up.

4.1.3 Study III

The study population consisted of patients who had been operated because of NLDO at least one year earlier at the Department of Otorhinolaryngology, Kuopio University Hospital. Altogether, 116 adult patients had undergone primary or revision EN-DCR between 2004 and September 2010. Eleven were excluded due to death or severe illness. A total of 105 consecutive patients were asked to participate, and 76 (72%) agreed. In all, 64 (84%) of these patients had undergone primary operation and 22 (16%) revision. Ten participants had had bilateral surgery; therefore, the outcomes of 86 procedures were could be assessed.

4.2 METHODS

4.2.1 Study design

Study I was a randomized, prospective, clinical trial to evaluate if the use of MMC could improve success rate in revision EN-DCR. There were two parallel groups of patients, which were randomized into MMC-group and control group. The technique of EN-DCR procedure in both groups was similar, except that in the MMC-group at the end of the procedure a piece of tampon soaked in MMC (0.4 mg/mL) was placed into the rhinostoma for 5 minutes. The MMC used (Mitostat 20mg, Orion Oyj, Turku) in the study was delivered by the hospital pharmacy. The allocation was computer-generated and a sealed opaque envelope method was used to ensure blinding until the randomization.

In Study II, the aim was to investigate the biology of nasal mucosa in patients with NLDO undergoing EN-DCR and to compare the findings with the control patients.

The two aims of study III were first to validate the NLDO-SS and second to evaluate the long-term success rate of surgery in this prospective study population. Seventy-six patients (86 eyes) were evaluated at a long-term follow-up visit 1-8 years (mean 4, SD 2) postoperatively between May 2011 and October 2011. The patients filled in the NLDO-SS questionnaire (Appendix) twice, first at home and then again after receiving information at the visit in the outpatient clinic.

4.2.2 Preoperative assessment

In Studies I and II, all patients were examined preoperatively by an otorhinolaryngologist in the outpatient clinic in the Department of Otorhinolaryngology at Kuopio University Hospital. At the visit, the patients filled in the NLDO-SS questionnaire after receiving information from a specialist. Irrigation of the lacrimal sac was conducted to check the patency of the nasolacrimal pathway and to rule out presaccal obstructions. Endoscopic examination of the nasal cavity was performed and the findings were assessed and scored

using the Lund-MacKay staging system (Appendix) (Lund, Mackay 1993). The patients were given oral and written information about the trial protocol and they provided written consent. CT scans were conducted in all patients to clarify the detailed anatomy of nasal cavity, paranasal sinuses and lacrimal pathway and to rule out tumors.

4.2.3 Surgery

All the operations were conducted endonasally with a standardized endoscopic technique with powered instrumentation (Smirnov et al. 2006; Smirnov 2010a). The endotracheal general anesthesia technique was used.

To provide sufficient topical decongestion and hemostasis, all the patients received 40mg/mL cocaine hydrochloride or lidocaine hydrochloride with 1mcg/mL epinephrine solution cotton wads 30 minutes before being taken to the operating theatre. In the operating theatre the patients had an injection of 5mg/mL lidocaine with 10mcg/mL epinephrine into the nasal mucosa over the proposed rhinostomy site after endotracheal intubation.

Each operation was performed jointly by two otorhinolaryngologists: the assisting otorhinolaryngologist introduced a 20-gauge endoilluminator probe (Alcon; Alcon Laboratories, Fort Worth, TX, USA) through the inferior canaliculus into the lacrimal sac. The chief surgeon used 0 and 30° 4-mm rigid endoscopes (Karl Storz, Tuttlingen, Germany) with a video display monitor. After visualizing the lacrimal sac by transillumination, the scar over the rhinostomy site was partially removed and the rest was lifted with a dissector and tucked medially under the middle turbinate. The bony ostium was opened and enlarged with a burr attached to a microdebrider (Xomed; Medtronic Xomed Surgical Products, Inc., Jacksonville, FL, USA using a diamond).

Additional surgery, such as septoplasty, polypectomy, infundibulotomy, was performed when necessary. The surgical procedure was similar in all of the procedures, except that in the mitomycin group in study I a piece of tampon (Merocel®, Medtronic Xomed Surgical Products, Jacksonville, USA) soaked in MMC (Mitostat 20mg, Orion Oyj, Turku) at 0.4 mg/mL was placed at the rhinostomy site for 5 minutes. A bicanalicular lacrimal silicone tube (Bernard, Unomedical Ltd., Redditch, UK) was inserted if the patient had been randomized for tubing group in a previous randomized study. The use of the silicone tubes was rejected after 2008. Hemostasis was achieved with electrocoagulation and nasal packing (Merocel®, Medtronic Xomed Surgical Products, Jacksonville, USA), when needed.

4.2.4 Postoperative care and follow up

Nasal packing was removed at the first postoperative day. The patients were treated with topical dexamethasone-chloramphenicol eye drops for two weeks and intranasal saline spray for one month. During the first postoperative visit, one week after surgery, before irrigation of the lacrimal sac, debridement with nasal suctioning was performed. There were at least three postoperative visits, scheduled at one week, and 2 and 6 months after the surgery. The objective assessment was performed by an otorhinolaryngologist using a rigid endoscope and by lacrimal sac irrigation. The extent of mucosal edema, polyposis, crusting, secretions and scarring was assessed and scored with the Lund-MacKay staging system (Lund & Mackay 1993). The subjective outcome was estimated by using the NLDO-

SS questionnaire. The surgical outcome was considered successful if the saline solution reached the nose freely during the lacrimal sac irrigation and if the patient's symptoms were relieved based on the questionnaire.

4.2.5 NLDO-SS questionnaire

The item areas for the NLDO-SS (Appendix) were developed by an expert panel of individuals with extensive experience in the treatment of NLDO, and questions were based on the literature. In the NLDO-SS, the symptoms are graded based on a Likert scaling model using an 11-point numeric rating scale (0 = no symptoms, 10 = worst imaginable symptom). The total score for the NLDO-SS is in a range from 0 to 70 points.

The NLDO-SS questionnaire comprises five items that focus on the common ocular symptoms (tearing, discharge from the eye, swelling around the eye, pain around the eye and change in visual acuity) and two items relating to the conditions in the nasal cavity (blockage and discharge). Since nasal pathology may underlie some of the NLDO (Önerci 2002) and because it also plays an important role in the failure of the surgery (Allen, Berlin & Levine 1988; Orcutt, Hillel & Weymuller 1990), nasal symptoms were included in the survey. In the initial questionnaire, an additional question concerning the general condition of the patient was included (Smirnov et al. 2010). However, due to the low specificity of this additional question, it was excluded from the final version. In the present study, the patients filled in the NLDO-SS twice: first independently at home and subsequently after receiving information from the otorhinolaryngologist during the visit. If answers to the same question differed by only 1 point, they were categorized as equivalent.

4.2.6 Validation of the NLDO-SS

The validity of the NLDO-SS was evaluated in several different ways. When testing the quality and usefulness of the NLDO-SS, the main outcome measure was the diagnostic accuracy i.e. the percentage of correctly diagnosed patients. Below all of the variables used in the validation are listed and determined.

diagnostic accuracy i.e. correctly diagnosed patients: a+d/a+b+c+d

sensitivity i.e the test's ability to identify obstructed patients: a/a+c

specificity i.e the test's ability to identify cured patients: d/b+d

positive predictive value i.e the patients with obstruction who were correctly diagnosed: a/a+b

negative predictive value i.e the cured patients who were correctly diagnosed: d/c+d

odds ratio (OR): (a/d)/(c/b)

risk ratio (RR): [a/(a+b)]/ [c/(c+d)]

usefulness index (UI): sensitivity×[sensitivity-(1-specificity)]

a= true positive

b= false positive

c= false negative

d= true negative

In addition, to evaluate reliability of the test, Cronbach's Alpha was calculated. To further assess the internal consistency, correlation between single variables and the total scores was calculated for each patient. Test-retest reliability and the stability of the answers were evaluated by comparing the two sets of scores (first filled-in independently at home and then again at the follow-up visit).

4.2.7 PCR array for inflammatory response gene expressions

DNA microarrays enable insights into global gene expression by capturing a snapshot of cellular expression levels at the time of sample collection (Madabusi, Latham & Andruss 2006). In this study ribonucleic acid (RNA) was extracted from tissue samples excised from five patients undergoing EN-DCR surgery and five control patients, first immersed in liquid nitrogen and thereafter stored at -70°C. The manufacturer's instructions (RNeasy® Mini kit, Qiagen, Hilden, Germany), were followed. Initially, the tissue pieces were mechanically ground with a glass pestle homogenizer, including the kit buffer, and chilling the homogenizer on ice. The procedure included also a separate RNase-free DNase I treatment (Qiagen) in the extraction column. The quantity and quality control of the extracted RNAs were conducted with spectrophotometric analysis.

Subsequently, cDNA was prepared using RT2 PreAMP cDNA Synthesis Kit (Qiagen), following the manufacturer's instructions. Both the septoplasty control and EN-DCR surgery samples contained five individually extracted RNAs, which were mixed in equal amounts (1 μg total, 200 ng of each) which acted as templates for the separate cDNA syntheses. Subsequently, in the inflammation gene expression analysis, a 96-well PCR array RT2 ProfilerTM PCR Array for Human Inflammatory Response and Autoimmunity (SABiosciences, Qiagen, Hilden, Germany) was used. The SYBR Green fluorescence detection methodology was employed. Two one-plate runs were performed: one for combined septoplasty controls and the other for EN-DCR samples, which were then amplified in an array PCR (ABI7500 Applied Biosystems, Foster City, California, USA). All the quality control requirements demanded by the manufacturer of the array were fulfilled in both PCR runs (including genomic DNA control, cDNA synthesis control, and positive PCR controls).

The results were calculated by subtracting the GAPDH (glyceraldehyde phosphate dehydrogenase) housekeeping control Ct (threshold cycle) value from each individual gene Ct value within each run. The Ct values were obtained using the same constant amplification threshold level (in the middle of the exponential amplification phase) in both

amplification reactions. Thus gained ΔCt (delta Ct) values from the septoplasty control plate were subtracted from those of the EN-DCR surgery sample plate for each gene across the arrays, subsequently yielding ΔΔCt values. The linear difference of expression, or fold change from EN-DCR sample compared to septoplasty control sample was calculated using the formula 2- ΔΔCt.

4.3 STATISTICS

In all studies, patient characteristics and variables were analyzed with the Statistical Package for Social Sciences (SPSS software version 17 and 18 for Windows, SPSS Inc., Chicago, USA). Correlations between nonparametric variables were tested with Spearman's rho. The differences between groups in categorical variables were assessed with Pearson's Chi-Squared test and Fisher's exact test. The distributions of ordinal variable data that were not normally distributed were compared using nonparametric tests. The Mann-Whitney U test was used for comparing two independent samples, and McNemar's test was used for related samples. The differences were regarded statistically significant if a two-sided P-value was less than 0.05. Data are expressed as the number of cases, the mean ± the standard deviation (SD) or median [minimum – maximum] as appropriate. In addition the reliability of all variables was measured by Cronbach's alpha. Internal consistency was assessed by calculating the correlation between single variables and the total scores for each patient. Test-retest reliability and the stability of the answers were evaluated by comparing the two sets of scores (first independently at home and then the scores provided at the visit).

4.4 ETHICAL ASPECTS

The studies were approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (decision number 59/2004) and they were conducted according to these guidelines and in accordance with the Declaration of Helsinki (The World Medical Association /WMA/ 1998). The trials were registered in a public trial registry (clinicaltrials.gov ID: NCT00571129). Permission was granted and the use of MMC was allowed by the National Agency for Medicines. Oral and written information about the trial protocol were given to the patients and they provided written consent.

5 Results

5.1 STUDY I

Thirty revision EN-DCR procedures were performed between 2004 and 2010. The patients were randomized into two study groups, according to whether intraoperative MMC was applied or not. There were no differences in the baseline characteristics between these groups. The technique of EN-DCR procedure in both groups was similar, except that in the medication-group MMC (0.4 mg/mL) was placed into the rhinostoma for 5 minutes. The surgical outcome at the 6-month follow-up visit was considered successful if the lacrimal sac irrigation had succeeded, and if the patient's symptoms were relieved.

The success rate of revision EN-DCR procedures with intraoperative application of MMC was 93% (14/15), whereas without MMC it was 60% (9/15). Furthermore, the symptoms were substantially better relieved in the MMC-group (Table 3). No intra-operative or immediate postoperative complications were encountered during the study.

Table 3. The ocular symptom scores and NLDO-SS (baseline versus 6 months after surgery) in study groups. The data represent mean scores with standard deviation (SD).

	MMC-group		**Controls**		**P-value**
	Baseline	**Postoperative**	**Baseline**	**Postoperative**	
Ocular symptom score*	14 (3)	3 (5)	13 (6)	9 (8)	0.02
NLDO-SS**	31 (11)	8 (12)	31 (20)	28 (21)	0.007

* Tearing and discharge in the eye (0-20)

** Nasolacrimal Duct Obstruction Symptom Score (0-70)

5.2 STUDY II

There were notable differences in gene expression in nasal mucosa related to human inflammation in EN-DCR patients compared with the control patients. The most significant increases between EN-DCR and controls were as follows: Selectin E (SELE), 6.3-fold, Interleukin 6 (IL6) 5.2-fold, Chemokine (C-C) motif ligand 16 (CCL16) 5.0-fold, Tumor necrosis factor (TNF) 4.5-fold, Chemokine (C-C motif) ligand 2 (CCL2) 3.7-fold, and Chemokine (C-X-C motif) ligand 3 (CXCL3) 3.0-fold. The most notable decreases between EN-DCR samples and controls were: Nitric oxide synthase 2 (NOS2) 0.2-fold, IL8 0.3-fold,

Chemokine (C-X-C) ligand 1 (CXCL1) 0.3 fold, IL1 receptor antagonist (IL1RN) 0.3-fold, Chemokine (C-C motif) receptor 3 (CCR3) 0.3-fold, and Fas ligand, TNF superfamily, member 6 (FASLG) 0.4-fold decrease of expression.

The overall success rate after primary EN-DCR was 60% (3/5 patients) at the 6-month follow-up. In the nasal endoscopy, the two unsuccessful patients displayed a tight fibrous scar over the rhinostomy site, and one of them had also severe synecchiae. Otherwise there were no abnormal endoscopic findings. No other intra- or post-operative complications occurred during the study period.

5.3 STUDY III

A total of 76 previously operated patients underwent clinical examination at the outpatient clinic at 1-8 years (mean 4, SD 2) after surgery. Ten of these patients had undergone bilateral operation, and so there were altogether 86 procedures to analyze. The patients filled in the NLDO-SS questionnaire twice, first at home and then again at the visit to the clinic. The surgical outcome at this long-term follow-up visit was considered successful if the lacrimal sac irrigation succeeded, and if the patient's symptoms were relieved.

In this prospective study, the success of the primary surgery was 83% (53/64 procedures) and that of revisions 68% (15/22). The total success rate of EN-DCR was 79% (68/86 procedures). There was statistically significantly more scarring in the failures ($p<0.001$), but otherwise their endoscopic appearances was similar that encountered in the successful procedures. The interpretability of the NLDO-SS was assessed by comparing the scores: total score as well all the eye symptoms was able to differentiate well between the successes and failures (for all variables $p\leq0.001$). However, there was no difference in nasal symptoms between the successful and failed patients. In a comparison of the questionnaires filled in at home and at the visit, the test-retest reliability provided good evidence that there was a correlation between every variable, and the internal consistency of the questions was also good: the Cronbach's Alpha of the test was 0.85 (Table 4).

Table 4. Scores of the NLDO-SS filled in at home and at the visit, on an 11-point Numeric Rating Scale (0=no symptom, 10=worst imaginable symptom) and the correlations of two times given answers. Data are mean (SD) and median [minimum–maximum]

Variable	**Independently reported N=83**	**Reported at the visit N=86**	**Test-retest reliability**	**Internal consistency**
			Spearman's rho	
Tearing	3 (3) 2 [0-10]	3 (3) 2 [0-10]	0.884	0.818
Discharge in the eye	2 (3) 1 [0-10]	2 (3) 1 [0-10]	0.940	0.786
Swelling around the eye	2 (2) 0 [0-10]	1 (2) 0 [0-10]	0.924	0.641
Pain around the eye	1 (2) 0 [0-9]	1 (2) 0 [0-10]	0.777	0.647
Change in visual acuity	2 (3) 1 [0-10]	2 (2) 0 [0-10]	0.758	0.756
Nose blockage	2 (2) 1 [0-8]	2 (2) 1 [0-8]	0.853	0.495
Nasal cavity discharge	3 (3) 2 [0-10]	2 (2) [0-10]	0.825	0.701
Total score (0-70)	14 (13) 10 [0-56]	13 (12) 9 [0-56]	0.867	

For single variables with the cut-off points of ≤3/10 for successes and ≥4/10 for failures the most significant predictors of outcome were tearing (OR=46, RR=24, UI=0.64) and discharge (OR=92, RR=24, UI=0.70). The diagnostic accuracy of the NLDO-SS was 84%, sensitivity 82%, specificity 85%, positive predictive value 58% and negative predictive value 95% with a cut-off point ≥21/70 for failed and ≤10/70 for succeeded. The total score with these cut-off points provided an OR of 26, RR of 11.5 and UI of 0.55. Based on the NLDO-SS an algorithm for follow-up after EN-DCR was created.

6 Discussion

This study showed that the postoperative scarring and adhesion formation after revision DCR surgery could be in most cases prevented by application of adjunctive MMC; the routine use of MMC in revision surgery is recommended because of its beneficial effects on the healing process. Inflammatory gene expression in patients with NLDO showed to be up-regulated. The characterization of the inflammatory mechanisms via the identification of new disease-related genes may help provide a better understanding of the biology of NLDO and promising new targeted therapies. Finally, the NLDO-SS proved to be a valid instrument for assessment of the outcome after EN-DCR. Based on the reliability of NLDO-SS and on the finding that the long-term success seems to decrease in long-term follow-up, an algorithm was created for the follow-up.

6.1 EFFICACY OF INTRAOPERATIVE MMC IN REVISION EN-DCR

The results of present study indicate that the application of intraoperative mitomycin C may improve the outcome in revision EN-DCR and as a consequence of these results, MMC has been routinely used in our clinic since 2010 in all revision EN-DCRs because of its putative favourable effect on the healing process.

According to our best knowledge, this is the first published randomized, controlled trial study concerning the use of intraoperative MMC in revision DCRs. Recently another randomized study investigating the efficacy of MMC in revision DCR was published with no benefit to the application of MMC (Ragab et al. 2012). Ragab et al. used MMC at a concentration of 0.5 mg/mL for 10 minutes. In the study population of 76 patients, the success rates at the 12-month follow up were 83% (with MMC) and 81% (without MMC). However, the MMC group showed a significant better healing profile with a lower number of debridement procedures to clean granulations and crustations. At the same time Ozkiriş et al reported 36 non-randomized revision DCR procedures with the mean follow-up of 12 months (Ozkiris, Ozkiris & Goktas 2012). The patients were divided into MMC and control groups: in MMC group MMC at 0.5 mg/mL was placed at the osteotomy site for 5 minutes. The control group underwent a similar surgical procedure but no application of MMC. The EN-DCR procedure with adjunctive MMC was successful in 89% of cases but without MMC it was less, 56% ($p < 0.05$). The most important difference between these studies is that in the two other works, postoperative silicone stents were used. The overall results of these two studies are comparable.

However, the calculated study power of 0.57 in present study was too low to reveal any statistical difference between the study groups. Moreover, the study would have been even stronger, if its design had been double-blinded, larger, randomized and placebo controlled.

Based on these published results the definitive efficacy of MMC in revision surgery still needs to be confirmed. In particular, further experimental work is needed to carry on investigating the use of MMC in revision cases in larger population. Although the number of DCRs is increasing, the number of revision cases is low, and in a single-centre it is difficult to achieve a larger study population within a reasonable time. Multicenter randomized trials with long-term follow-up may be a suitable approach to evaluate the role of MMC in DCR surgery, as well determining the appropriate treatment protocol to be adopted (Leong, Macewen & White 2010; Karkos et al. 2011).

6.2 UP-REGULATION OF INFLAMMATION GENES IN NASAL MUCOSA

Here we report for the first time notable differences in gene expression related to human inflammation in EN-DCR patients compared with the control patients. There was a strongly increased expression of mRNA for E-selectin, which is evidence of genes in endothelial cell (EC) responding in the samples isolated from patients undergoing EN-DCR. E-selectin induces relatively weak carbohydrate interactions to blood leukocytes to slow down and roll along the endothelium before their transmigration through the endothelium into the tissue (Sawa & Tsuruga 2008; Collins et al. 1995). Leukocytes become attracted to the target tissue along a gradient of chemokines. The endothelial cells can become activated by bacterial lipopolysaccharide but in the case of NLDO, the activation is more probably mediated by pro-inflammatory cytokines, such as IL-1 and TNF-α. IL-1ß and TNF-α together with the third acute phase protein IL-6 are pleiotropic cytokines playing a variety of roles in cellular functions. In addition to the contributions of acute and chronic inflammation, these genes all have also been associated with the process of fibrosis (Barnes, Anderson & Moots 2011; Oikonomou et al. 2006)). Gradual inflammation and subsequent fibrosis, in turn, are seen as the ultimate reason for the NLDO (Linberg, McCormick 1986; Bartley 1993a)

In acute inflammation, neutrophils are the primary leukocytes, which are attracted to the inflammatory site (Harada et al. 1994). In response to chemokines, such as IL-8 (CXCL8), neutrophils express their IL-6 receptors promoting endothelial cells to decrease IL-8 production and to favor the CCL-2 production, which attracts especially monocytes (Barnes, Anderson & Moots 2011). The decreased expression of IL-8 mRNA and the increased expression of CCL-2 in the present NLDO samples indicate that the inflammation has passed its initiation phase. The increased gene expression of CCL16, CXCL3, CCL13, and CCL3 in NLDO samples compared to those of controls also supports the deviation towards a mononuclear cell type-dominated response (Howard et al. 2000; Smith et al. 2005; Garcia-Zepeda et al. 1996; Maurer & von Stebut 2004). The present results are in line with the previous findings that inflammation is involved in the pathogenesis of NLDO (Linberg, McCormick 1986b; Bartley 1993a).

Nuclear factor kappa B (NF-κB) is a major transcription factor regulating the expression of many inflammation-related genes (Newton & Dixit 2012). In addition to the induction of E-selectin (Collins et al. 1995), NF-κB plays an important role in the expression of other genes, such as CCL2, CCL3, IL-6, IL-1β and TNF-α, the expression levels of which were also strongly increased in the present samples of NLDO patients as compared to the controls. In order to avoid an overwhelming level of inflammation, NF-κB is placed under strict autoregulation (Collins et al. 1995). The dynamic regulation probably explains why there may be no visible increase in the expression of mRNA for NF-κB in DCR patients.

The lack of studies examining the inflammation in nasal mucosa limits our knowledge of the underlying pathogenesis of NLDO. Therefore, the present study does provide new important information. The profile of the investigated markers indicates that the inflammation has passed its initiation state, which is in accordance with the previous findings that long-lasting inflammation is present in NLDO. Since the main reason for the failure after EN-DCR is the scarring over the rhinostomy site (Jokinen, Kärjä 1974; Allen, Berlin & Levine 1988), an anti-fibrotic drug that would target the fibrogenic factors or would block their receptors, could improve the success. Therefore, a potential target for therapy to control the progression of fibrosis is currently being sought (Smirnov et al. 2011). These investigated inflammatory factors are promising because they may represent the potential targets in the development of anti-fibrotic therapy for the prevention of excessive scar formation.

The low overall success rate after primary EN-DCR was 60% (3/5 patients) at the 6-month follow-up could be explained by the small cohort.

In future studies, these up-regulated inflammation genes in nasal mucosa and the correlation between the gene expression and the success of surgery will need to be investigated with a larger study population.

6.3 THE RELIABILITY AND USEFULNESS OF NLDO-SS

NLDO-SS is a valid disease-specific instrument for assessing the outcomes of EN-DCR. It is evident that it is also clinically useful for preoperative assessment and for evaluating the changes in signs and symptoms during the follow-up. The questionnaire may also be feasible for general practitioners to identify patients who should be referred for specialist consultation.

Recently, another DCRs symptom questionnaire, Lac-Q score, was presented (Mistry et al. 2011). Lac-Q appears to be a promising tool for use in patient-reported outcome measures. Similarly to the NLDO-SS, Lac-Q also takes into account the severity of the measured items. The most important difference between these two questionnaires is that the NLDO-SS measures only the symptoms related to the lacrimal pathway obstruction, whereas the Lac-Q includes an additional score for social impact. Moreover, there are no questions concerning nasal symptoms in the Lac-Q; thus, the NLDO-SS could provide useful benefits for patients undergoing surgery via an endonasal approach.

One of the most important issues in validating a questionnaire is an appropriate sample of patients. In this series, there were 76 patients, whereas in the validation process of the Lac-Q, there were only 29 patients in. It would be interesting to test the concurrent validity of NLDO-SS and Lac-Q in a future trial.

There are some limitations that should be taken in account. Firstly: questionnaires have their limitations. EN-DCR is most often performed on elderly patients although they are in good general health. However, elderly individuals may have declining cognitive functions or even dementia, which complicates the use of any questionnaire. This caveat should be kept in mind, and the method (visit or postal questionnaire) for post-operative follow-up needs always to be assessed on an individual basis. However, this current survey appeared to be straightforward, and quick to complete. Secondly, the most important limitation is that the outcome evaluation of patency to syringing is evidence of an anatomic but not necessarily functional patency, i.e., the natural flow of the tears. In further studies, functional fluorescein dye-tests should be used as one of the outcome criteria. Thirdly, the sample size was relatively small and confirmatory studies will be required. Furthermore NLDO-SS should also be tested in subjects with no history of lacrimal surgery.

Based on the NLDO-SS, an algorithm for follow-up after EN-DCR to replace the scheduled one-year follow-up was created for all patients who are capable of reliably completing the questionnaire. When symptom scores are ≤10/70, it is unlikely that there is an obstruction (in this study, only 1 patient out of 18 was misdiagnosed); therefore, there is no need for clinical examination. When scores are 11-20/70, a phone call is made to check the answers, and the original answers are confirmed. For these patients, a new questionnaire is sent after 3 months, and if the symptoms remain, then a clinical

examination should be conducted. If the scores are ≥21/70, the patients are invited for an additional visit as it is likely that the patient has an anatomical or functional obstruction. By using this algorithm, the requirement for follow-up visits would be reduced markedly.

Because of the high negative predictive value (95%) of the NLDO-SS, there are very few false negatives. Since those patients are symptom-free, there is no need for revision surgery. Moreover, even false positives must be suffering some postoperative problems that need to be addressed, and therefore, an additional visit is beneficial.

6.4 THE LONG-TERM RESULTS OF EN-DCR

In this study, the overall success rate of EN-DCR at a mean follow-up of four years was 79%, which is consistent with other reports of long-term follow-ups (Dietrich et al. 2003; Zenk et al. 2009; Önerci et al. 2000; Cokkeser et al. 2003; Muscatello et al. 2005; Yuen et al. 2004). The success rate of 79% shows a notable decline compared with the success of primary operation (93%) with the 6 month follow-up (Smirnov et al. 2010b). This finding highlights the importance of long-term follow-up in determining outcomes of EN-DCR.

However, for most patients, long-term follow-up visits beyond one-year after EN-DCR may be considered unnecessary and inconvenient, particularly as the vast majority of the patients are elderly. A practical and cost-effective solution for both patients and the health care system could be the use of a simple questionnaire. After completing the symptom questionnaire at home, only symptomatic patients would need to be invited for an additional visit. Thus far, there have been no disease-specific, generally accepted measures for assessing outcomes after EN-DCR in adults.

The strengths of this study are its prospective study design and the long follow-up period. However, it has a potential limitation. The long-term success rate was from a cohort of patients who agreed to participate in the trial. This may introduce a potential bias, as the patients without symptoms of nasolacrimal duct obstruction may not have adequate incentive to participate in this kind of study. Conversely, patients with persistent symptoms may be dissatisfied with their previous care and not want to participate in additional studies. However, when the patients were contacted, the most common reasons for not wishing to participate were poor general health condition or the long commuting distances from home to the outpatient clinic.

7 Conclusions

The specific findings of the individual studies were:

1. The intraoperative MMC is an effective adjuvant in the treatment of nasolacrimal duct obstruction. MMC improves the success rate of revision EN-DCR. Based on our results, MMC was introduced into the clinical routine (Study I).

2. We have shown for the first time that in the nasal mucosa of patients undergoing EN-DCR, the expression level of various inflammatory response-related genes is up-regulated. This *de novo* finding is a promising starting point for future studies because these inflammatory biomarkers represent potential targets in the development of anti-fibrotic therapies (Study II).

3. The NLDO-SS is a valid clinical tool for assessing outcomes after EN-DCR. There was a notable decrease in the success rate of EN-DCR at long-term follow-up. Based on these findings a long-term follow-up algorithm with NLDO-SS was created (Study III).

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Appendices

1. Nasolacrimal Duct Obstruction Symptom Score Questionnaire (NLDO-SS)
2. NLDO-SS in Finnish
3. Lund-MacKay staging system for endoscopic appearances
4. Glasgow Benefit Inventory Questionnaire

Nasolacrimal Duct Obstruction Symptom Score Questionnaire (NLDO-SS)

Symptom	**Scores (0-10)**
Tearing	
Discharge in the eye	
Swelling around the eye	
Pain around the eye	
Change in visual acuity	
Nose blockage	
Nasal cavity discharge	
Total scores	

Numeric Rating Scale: 0= no symptom, 10= worst imaginable symptom

NLDO-SS in Finnish

Oirekysely

Oire	**Pisteet (0-10)**
Silmän vetistys	
Silmän rähmiminen	
Silmän alueen turvotus	
Silmän alueen kipu	
Näköhäiriöt	
Nenän tukkoisuus	
Nenän eritteet	
Pisteet yhteensä	

Pisteytys: 0=ei oiretta, 10=pahin kuviteltavissa oleva oire

Lund-MacKay staging system for endoscopic appearances

Clinical findings at the visits	**Scores**
Polyps l.dx.	
Polyps l.sin.	
Edema l.dx.	
Edema l.sin.	
Secretions l.dx.	
Secretions l.sin.	
Synecchiae l.dx.	
Synecchiae l.sin.	
Crusting l.dx.	
Crusting l.sin.	
Total scores	

Scoring: For polyps: 0=none, 1=in the middle meatus, 2=extending outside the middle meatus. For the edema, synecchiae and crusting: 0=none, 1=mild, 2=severe. For secretions: 0=none, 1=light, non-purulent discharge, 2=thick, purulent discharge.

Glasgow Benefit Inventory Questionnaire

1. Has the result of the *nasolacrimal operation* affected the things you do?

Much worse worse	A little or somewhat	No change better	A little or somewhat	Much better
1	2	3	4	5

2. Have the results of the *nasolacrimal operation* made your overall life better or worse?

Much better	A little or somewhat better	No change	A little or somewhat worse	Much worse
5	4	3	2	1

3. Since your *nasolacrimal operation*, have you felt more or less optimistic about the future?

Much more optimistic	More optimistic	No change	Less optimistic	Much less optimistic
5	4	3	2	1

4. Since your *nasolacrimal operation,* do you feel more or less embarrassed when with a group of people?

Much more embarrassed	More embarrassed	No change	Less embarrassed	Much less embarrassed
1	2	3	4	5

5. Since your *nasolacrimal operation*, do you have more or less self-confidence?

Much more self-confidence	More self-confidence	No change	Less self-confidence confidence	Much less self-
5	4	3	2	1

6. Since your *nasolacrimal operation*, have you found it easier or harder to deal with company?

Much easier	Easier	No change	Harder	Much harder
5	4	3	2	1

7. Since your *nasolacrimal operation*, do you feel that you have more or less support from your friends?

Much more support	More support	No change	Less support	Much less support
5	4	3	2	1

8. Have you been to your family doctor, for any reason, more or less often, since your *nasolacrimal operation*?

Much more often	More often	No change	Less often	Much less often
1	2	3	4	5

9. Since your *nasolacrimal operation*, do you feel more or less confident about job opportunities?

Much more confident	More confident	No change	Less confident	Much less confident
5	4	3	2	1

10. Since your *nasolacrimal operation*, do you feel more or less self-conscious?

Much more self-conscious	More self-conscious	No change	Less self-conscious	Much less self-conscious
1	2	3	4	5

11. Since your *nasolacrimal operation*, are there more or fewer people who really care about you?

Many more people	More people	No change	Fewer people	Many fewer people
5	4	3	2	1

12. Since you had the *nasolacrimal operation*, do you catch colds or infections more or less often?

Much more often	More often	No change	Less often	Much less often
1	2	3	4	5

13. Have you had to take more or less medicine for any reason, since your *nasolacrimal operation*?

Much more medicine	More medicine	No change	Less medicine	Much less medicine
1	2	3	4	5

14. Since your *nasolacrimal operation*, do you feel better or worse about yourself?

Much better	Better	No change	Worse	Much worse
5	4	3	2	1

15. Since your *nasolacrimal operation*, do you feel that you have had more or less support from your family?

Much more support	More support	No change	Less support	Much less support
5	4	3	2	1

16. Since your *nasolacrimal operation*, are you more or less inconvenienced by your health problem?

Much more inconvenienced	More inconvenienced	No change	Less inconvenienced	Much less inconvenienced
1	2	3	4	5

17. Since your *nasolacrimal operation*, have you been able to participate in more or fewer social activities?

Many more activities	More activities	No change	Fewer activities	Many fewer activities
5	4	3	2	1

18. Since your *nasolacrimal operation*, have you been more or less inclined to withdraw from social situations?

Much more inclined	More inclined	No change	Less inclined	Much less inclined
1	2	3	4	5

Elina Penttilä

Predictive Factors in Endonasal Endoscopic Lacrimal Surgery

Endoscopic dacryocystorhinostomy (EN-DCR) is an effective surgical technique for treating symptomatic lower lacrimal pathway obstruction. This prospective study investigated the factors predicting to outcomes in EN-DCR. In addition, based on the validated questionnaire, an algorithm was devised to help in the follow-up after EN-DCR.

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