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Grigori Smirnov

Outcome of Endonasal Endoscopic Dacryocystorhinostomy in Adults

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ABSTRACT

Tearing and recurrent or chronic conjunctival discharges are the most frequent symptoms of lacrimal pathway obstruction. The conservative treatments relieve the complaint only temporarily, thus surgery is the treatment of choice. Dacryocystorhinostomy has been accepted as the best treatment for patients with obstructions of the lacrimal system on the level of the sac (saccal obstruction) or below it (post-saccal obstruction). The aim of this operation is to create a bypass between the lacrimal sac and the nasal cavity. For many years, external dacryocystorhinostomy (EXT-DCR) has proven to be an efficient surgical method and thus it represents the gold standard for, less invasive surgical techniques. During the last two decades, endoscopic dacryocystorhinostomy (EN-DCR) has become accepted as a suitable treatment for patients with saccal and post-saccal obstruction of the nasolacrimal system.

The present work includes retrospective (36 patients) and prospective (64 patients) clinical studies. The aims of this trial were to evaluate the overall surgical outcome after EN-DCR, to assess the outcomes after two EN-DCR surgical techniques, with and without the use of lacrimal silicone tubes, to explore the impact of successful primary EN-DCR on the quality of life and symptoms, and to investigate the effect of preoperative changes in nasal mucosa on surgical outcome and the role of heat shock protein 47 (HSP47) expression in scar formation of the nasal mucosa.

This study shows that EN-DCR is an effective and safe procedure for patients with saccal and post-saccal obstruction of the nasolacrimal pathway, with an 89% success rate. EN-DCR had benefical effects on the symptoms and on the quality of life (QoL) of the patients, and silicone stenting after primary EN-DCR proved to be unnecessary. Preoperative histopathological analysis of the nasal mucosa over the lacrimal sac demonstrated that squamous metaplasia and strong expression of HSP47 of the nasal mucosa independently or together predict a poor outcome after EN-DCR. The exact timing for the assessment of surgical outcome is difficult but this study shows that the last follow-up for the final outcome assessment should be one year rather than six months.

National Library of Medicine Classification: WO 505, WW 208

Medical Subject Headings (MeSH): Dacryocystorhinostomy; Endoscopy; HSP47 Heat-Shock Proteins; Lacrimal Duct Obstruction/surgery; Metaplasia; Nasal Mucosa; Nasolacrimal Duct; Silicones; treatmentoutcome; Adult; Humans; Quality of Life,Questionnaires

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TIIVISTELMÄ

Kyynelvuoto ja silmien rähmiminen ovat yleisiä ja kiusallisia ongelmia kyynelteiden tukoksesta kärsiville potilaille. Konservatiivisella hoidolla oireet saadaan pysymään poissa jonkin aikaa, mutta leikkaushoidon teho on todistetusti parempi. Kyynelteleikkauksessa nenän ja kyynelpussin väliin tehdään aukko (avanne), jolloin kyynelteiden alaosan tukos ohitetaan ja kyynelneste pääsee esteettä poistumaan nenäkäytävän puolelle. Perinteisenä leikkausmenetelmänä on käytetty ulkoista kyynelteiekirurgiaa, jossa avanne kyynelpussista nenäonteloon muodostetaan nenän tyveen tehtävän ihoviillon kautta. Viime vuosina tähystystekniikan kehityksen myötä nenän kautta (tähystämällä) suoritettavat, vähemmän traumaattiset leikkaukset ovat yleistyneet.

Väitöstutkimuskokonaisuus muodostuu 36 retrospektiivisen ja 64 prospektiivisen potilaan aineistosta, joille suoritettiin tähystysleikkaus pitkittyneen kyynelteitukoksen vuoksi Kuopion Yliopistollisessa sairaalassa. Väitöstutkimuksessa selvitettiin kyynelteiden tähystysleikkauksen vaikutusta pitkittyneen kyynelteitukoksen hoidossa sekä silikoniputkien käytön tarpeellisuutta leikkauksen yhteydessä. Lisäksi arvioitiin nenän limakalvon stressiproteiinin (HSP47) merkitystä leikkaustulosta ennustavana tekijänä, leikkauksen jälkitarkastusten ajoituksen merkitystä sekä leikkaushoidon vaikutusta potilaiden elämänlaatuun ja oireisiin.

Tutkimustulokset osoittivat, että kyynelteiden tähystysleikkaus on tehokas ja turvallinen toimenpide. Leikkauksen seurauksena kyynelteitukoksesta aiheutuneet oireet hävisivät nopeasti ja lisäksi potilaat kokivat yleistä elämänlaadun paranemista. Silikoniputken käyttö leikkauksessa osoittautui tarpeettomaksi. Lisäksi havaittiin, että nenän limakalvon tulehdusmuutoksilla ja HSP47:n vahvalla ilmentymisellä on yhteys nenänsisäisen kyynelteileikkauksen epäonnistumiseen. Leikkaustulosten arviointi tulisi suorittaa aikaisintaan vuoden kuluttua leikkauksesta.

Luokitus: WO 505, WW 208

Yleinen suomalainen asiasanasto (YSA): kyynelkanavan ahtauma; tähystys; elämänlaatu

To my Family

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Kuopio, June 2010
Grigori Smirnov

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I Smirnov G, Tuomilehto H, Teräsvirta M, Nuutinen J, Seppä J: Silicone tubing after endoscopic dacryocystorhinostomy: is it necessary? American Journal of Rhinology 2006 20(6):600-2.

II Smirnov G, Tuomilehto H, Teräsvirta M, Nuutinen J, Seppä J: Silicone tubing is not necessary after primary endoscopic dacryocystorhinostomy: a prospective randomized study. American Journal of Rhinology 2008 22 (2): 214-7.

III Smirnov G, Pirinen R, Tuomilehto H, Seppä J, Teräsvirta M, Uusitalo H, Nuutinen J, Kaarniranta K: Strong expression of HSP47 in metaplastic nasal mucosa may predict a poor outcome after primary dacryocystorhinostomy: a prospective study. Acta Ophtalmologica 2009 Sep.; (Epub. Sep. 24).

IV Smirnov G, Tuomilehto H, Kokki H, Kemppainen T, Kiviniemi V, Nuutinen J, Kaarniranta K, Seppä J: Symptom score questionnaire for nasolacrimal duct obstructions in adults – a novel tool to assess the outcome after endoscopic dacryocystorhinostomy. Rhinology 2010 (Accepted for publication)

CONTENTS

ABBREVIATIONS

CT-DCG	computed tomography-dacryocystography
DCG	dacryocystography
DCR	dacryocystorhinostomy
EN-DCR	endonasal endoscopic dacryocystorhinostomy
EXT-DCR	external dacryocystorhinostomy
GBI	Glasgow Benefit Inventory
NLD	nasolacrimal duct
NLDO	nasolacrimal duct obstruction
NLDO-SS	nasolacrimal duct obstruction symptom score
PANDO	primary acquired nasolacrimal duct obstruction
QoL	quality of life
SANDO	secondary nasolacrimal duct obstruction

1 INTRODUCTION

Obstruction of the nasolacrimal pathway is a common disorder, especially in elderly patients, clinically manifested by the presence of tearing and/or infection (Woog 2007). The symptoms of nasolacrimal duct obstruction (NLDO) were described in papyrus documents by the ancient Egyptians (Hirschberg 1982), but still relatively little information is available concerning the epidemiology of this problem.

Only two published epidemiological studies concerning lacrimal pathway disorders are found in the literature. In 1967, Dalgleish (Dalgleish 1967) reported that the incidence of nasolacrimal pathway disorder in the population aged over 40 years was 10-14%, but at the age of 90 years it was 40%. Forty years later, Woog (Woog 2007) published a study concerning the epidemiology of acquired symptomatic lacrimal obstruction and showed that the most common form of acquired symptomatic lacrimal obstruction is NLDO, occurring with an annual incidence rate of 0.02%. The same study also confirms that acquired lacrimal pathway obstruction was most common in the middle-aged, with a median age of 67 years. Moreover, 69% of patients with all forms of obstructions and 73% with NLDO were female.

When conservative treatments are ineffective, the definitive treatment for this problem is surgery in which the patency of the nasolacrimal pathway is restored. An endonasal approach to correct the NLDO was first reported by Caldwell (Caldwell 1893). The popularity of an endonasal approach has been limited due to the technical difficulties involved in visualizing the surgical site and removing soft and bony tissues. Therefore, for one hundred years, after the report by Toti (Toti 1904), lacrimal bypass surgery was performed more commonly using an external approach, and the outcomes justify this. However, during the last two decades the advances in rigid endoscopic equipment and other instruments have made it possible to obtain more information about the anatomical landmarks of the nasolacrimal system, leading to less invasive and safer endoscopic techniques.

During the last eight years, an average of 500 lacrimal pathway operations have been performed annually in Finland (KuntaHilmo 2009). However, the suitability of and

outcomes after different techniques of lacrimal surgery have not been established. Moreover, little is known about patient satisfaction after these interventions.

The present trial compared overall results after EN-DCR in a retrospective study. For comparison of outcome after primary EN-DCR with and without silicone tubes, a prospective study was also conducted. In addition, the relationship between the preoperative conditions of nasal mucosa and final outcome of surgery was investigated.

2 REVIEW OF THE LITERATURE

2.1 Anatomy of the lacrimal system

The system that secretes and drains tears into the nasal cavity consists of the lacrimal gland, the upper and the lower lacrimal pathway. The upper lacrimal pathway consists of the puncta and lacrimal canaliculi, whereas the lower lacrimal pathway consists of the lacrimal sac and nasolacrimal duct. The nasolacrimal duct includes a bony part. The anterior part of the bony pathway is formed by the frontal process of the maxilla, and posteriorly by the lacrimal bone (Duke-Elder 1961).

2.1.1 Lacrimal gland

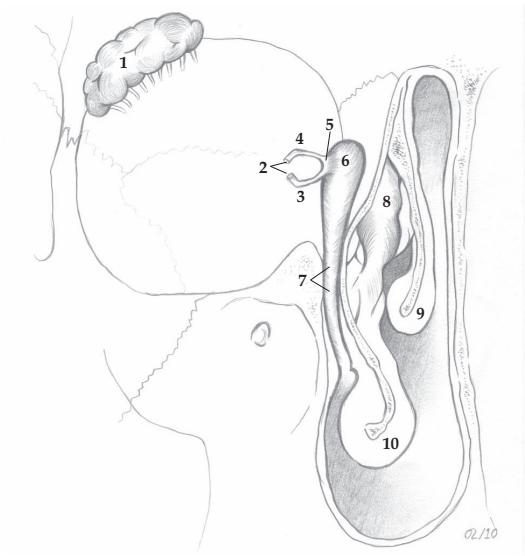
The lacrimal gland lies beneath the superior temporal margin of the orbital bone in the lacrimal fossa of the frontal bone. A palpable lacrimal gland is usually a sign of a pathologic change such as dacryoadenitis. The tendon of the levator palpebrae muscle divides the lacrimal gland into a larger orbital part (two-thirds) and a smaller palpebral part (one-third). Several tiny accessory lacrimal glands (glands of Krause and Wolfring) located in the superior fornix secrete additional serous tear fluid (Duke-Elder 1961).

2.1.2 Puncta and canaliculi

Tears enter the lacrimal system through the punctal openings at the medial ends of the inferior and superior eyelids, then flow along the canaliculus and the common canaliculus into the lacrimal sac and down the nasolacrimal duct into the nose under the inferior turbinate (Figure 1). The inferior canaliculus punctal opening is slightly larger in diameter (0.3mm) than the superior (0.2mm) and about 70% of the tears enter the inferior canaliculus and 30% through the superior. The punctal openings are surrounded by a ring of connective tissue, and normally remain patent. Both the upper and lower puncta are situated on a slight elevation at the groove formed by the plica semilunaris and the eyeball (Allen 1951).

The canaliculi are also surrounded by muscle fibers of the lacrimal portion of Horner's muscle (musculus orbicularis oculi), which form the constrictor muscle of the lacrimal punctum. The length of the horizontal portion of the canaliculi is approximately 8 mm in the upper eyelid and 10 mm in the lower eyelid. At the medial canthal angle after passing behind the medial canthal tendon, the upper and lower canaliculi join to form the common canaliculus, which is 3-5 mm long. The common canaliculus dilates before penetrating the lacrimal sac fascia, termed the sinus of Maier. A fold of mucous membrane is found at the junction between the common canaliculus and the lacrimal sac, termed the Valve Rosenmuller (Aubaret 1908).

Figure 1. Anatomy of the nasolacrimal sysytem



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

2.1.3 Lacrimal sac

The lacrimal sac varies in size from 12 to 14 mm vertically, 4 to 8 mm anteroposteriorly, and 2 to 4 mm in width (Groell et al. 1997, Orhan et al. 2009b). It is lined by double-layered ciliated pseudostratified epithelium. Underneath the epithelium there are a basement membrane and a submucosa layer containing some serous glands (Rivas et al. 1991). The surrounding fibrous tissue contains elastic fibers, supplied by a venous plexus that transforms the layer into erectile tissue continuous with that underlying the nasal mucosa (Duke-Elder 1961). The subepithelial tissue consists also of many nerve endings (Tsuda 1952).

2.1.4 Nasolacrimal duct

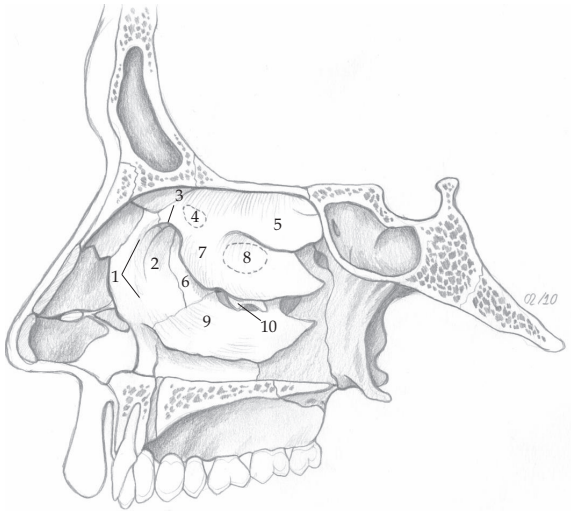
The nasolacrimal duct (NLD) is a continuation of the lacrimal sac. The membranous part of the nasolacrimal duct extends under the inferior turbinate approximately 15 mm from the tip of the inferior turbinate and 30-35 mm from the lower margin of the nostril. The opening of the nasolacrimal canal is oval in cross-section and 3 mm in diameter. The bony canal of the nasolacrimal duct is formed by the ethmoid, lacrimal and maxillary bones, and is 12 mm in length. Hassner's valve, which is a mucosal flap forming the medial wall of the membranous duct, prevents reflux into the lacrimal drainage passage. The nasolacrimal duct is composed of the substantia propria and two epithelial layers that are very similar to those of the lacrimal sac (Schaeffer 1922, Paulsen et al. 2003, Orhan et al. 2009a).

The intranasal orifice of the NLD is located approximately 25 mm from the anterior nasal spine, 14 mm from the nasal floor, and 15 mm from the anterior attachment of the inferior nasal concha. The NLD passes superiorly and anteriorly from the orifice to the anterior attachment of the middle nasal concha (Tatlisumak et al. 2010).

2.1.5 The lateral nasal wall

The lateral nasal wall (Figure 2) is formed by nasal turbinates, which are bony and lined by mucosa. The structures of the lateral wall are the middle turbinate, middle meatus, uncinate process, agger nasi, and ethmoidal bulla. The maxillary line is a ridge of the lateral nasal wall which lies anterior to the insertion of the middle turbinate (axilla) (McDonogh and Meiring 1989). The middle turbinate is a part of the ethmoid bone. The uncinate process is a bony plate located anterior to the middle turbinate with mucosal covering. The agger nasi is a bony protrusion anterior to the insertion of the middle turbinate. The bulla ethmoidalis is a rounded projection of the lateral nasal wall beneath the middle turbinate. The middle meatus is the opening between the middle and inferior turbinate adjacent to the fossa lacrimalis (Rebeiz et al. 1992, Watkins et al. 2003).

Figure 2. Anatomy of the lateral nasal wall



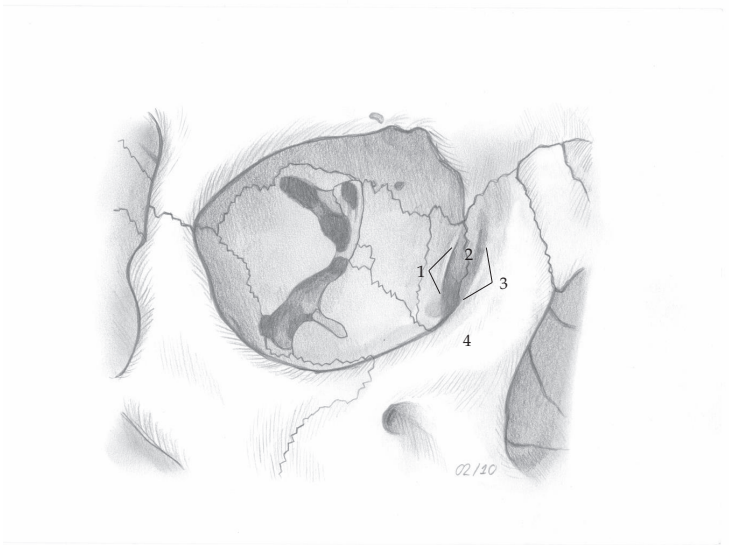
1. Maxillary line
2. Frontal process of maxilla
3. Axilla of the middle turbinate
4. Agger nasi
5. Superior turbinate
6. Lacrimal bone
7. Middle turbinate
8. Ethmoidal bulla
9. Inferior turbinate
10. Uncinate process

2.1.6 The lacrimal fossa

The lacrimal fossa (Figure 3) lies in the medial orbital wall behind the orbital rim which is 10 to 17 mm vertically, 3 to 8 mm in horizontally and 2 to 4 mm antero-posteriorly. The frontal process of the maxillary bone and lacrimal bone forms part of the lacrimal fossa. It is bound in front by the anterior lacrimal crest (part of the maxilla), which is adjacent to the inferior orbital rim and behind the posterior lacrimal crest (part of the lacrimal bone). The floor of the lacrimal bone is very thin with an average thickness of 0.06 mm (McDonogh and Meiring 1989, Woog et al. 1993, Hartikainen et al. 1996).

The position and configuration of the fossa varies substantially. Bisaria examined 240 orbits of 120 skulls and showed that in 20% of the orbits the anterior lacrimal crest was well-defined but the posterior lacrimal crest was ill-defined (Bisaria et al. 1989).

Figure 3. Anatomy of the lacrimal fossa



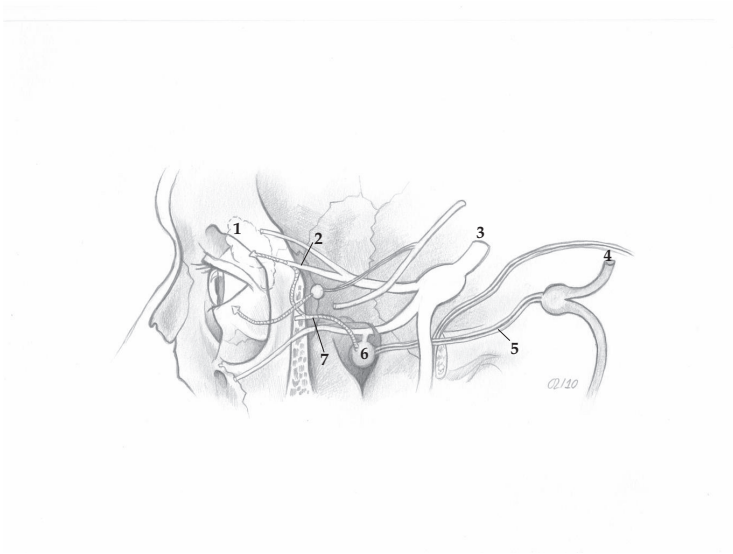
1. Posterior lacrimal crest
2. Lacrimal fossa
3. Anterior lacrimal crest
4. Frontal process

2.2 Physiology of the lacrimal system

2.2.1 Lacrimal gland

The lacrimal gland receives its sensory supply from the lacrimal nerve. Its parasympathetic secretomotor nerve supply comes from the nervus intermedius (nerve of Wrisberg). The lateral and posterior motor roots of the facial nerve containing parasympathetic fibers course to the lacrimal gland via the greater superficial petrosal nerve which synapses in the sphenopalatine ganglion (Figure 4). The sympathetic fibers arise from the superior cervical sympathetic ganglion and follow the course of the blood vessels to the gland (Calkins 1964).

Figure 4. Innervation of the lacrimal gland.



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

2.2.2 Tear secretion

The tear film that moistens the conjunctiva and cornea consists of three layers: an oily layer, which prevents rapid desiccation, a watery layer, which ensures that the cornea remains clean and smooth for optimal transparency and a mucin layer, which like the oily outer layer stabilizes the tear film (Wolff 1946, Wolff 1954). As the eyelids close, they act like a windshield wiper to move the tear fluid medially across the eye toward the puncta and lacrimal canaliculi. With its hydrophobic properties, it prevents rapid evaporation like a layer of wax (Bron et al. 2002).

The outer oily layer (approximately 0.1 µm thick) is a product of the meibomian glands and the sebaceous glands and sweat glands of the margin of the eyelid. The primary function of this layer is to stabilize the tear film (Mishima and Maurice 1961, King-Smith et al. 1999). The middle watery layer (approximately 8-10 µm thick) is produced by the lacrimal gland and the accessory lacrimal glands (glands of Krause and Wolfring), and it cleans the surface of the cornea and ensures mobility of the palpebral conjunctiva over the cornea and a smooth corneal surface for high-quality optical images (Bron et al. 2002). The inner mucin layer (approximately 0.8 µm thick) is secreted by the goblet cells of the conjunctiva and the lacrimal gland. It is hydrophilic with respect to the microvilli of the corneal epithelium, which also helps to stabilize the tear film. This layer prevents the watery layer from forming beads on the cornea and ensures that the watery layer moistens the entire surface of the cornea and conjunctiva (Holly and Lemp 1971, Holly 1973).

Lysozyme, beta-lysin, lactoferrin, and immunoglobulin A are tear-specific proteins that give the tear fluid antimicrobial characteristics. The normal human tear pH ranges from 6.5 to 7.6 (Abelson et al. 1981).

2.2.3 Tear elimination

Tear outflow includes an active lacrimal pump mechanism by contraction of the orbicularis eye muscle with blinking (Jones 1957), and distension of the sac, a mechanism governed by a system of helically arranged fibrillar structures and the action of epithelial secretion products (Thale et al. 1998). The physical factors include

capillarity, gravity, respiration, evaporation, and absorption of tear fluid through the lining epithelium of the efferent tear ducts (Paulsen et al. 2003).

The lumen of the lacrimal sac and the nasolacrimal duct is surrounded by the vascular plexus. This network of large vessels is connected caudally with the cavernous body of the nasal inferior turbinate (Thale et al. 1998, Paulsen et al. 1998). Paulsen and co-workers (Paulsen et al. 2000) hypothesized that the surrounding vascular plexus is comparable to a cavernous body. In addition to regulating the blood flow, it is thought that the specialized blood vessels permit the opening and closing of the lumen of the lacrimal passage, effected by the expanding and subsiding of the cavernous body, and simultaneously control tear outflow. The cavernous body of the efferent tear ducts innervation protects the ocular surface against foreign bodies (Paulsen et al. 2003).

2.3 Obstruction of the nasolacrimal pathway

Patients with symptomatic obstruction of the nasolacrimal pathway are commonly encountered in clinical practice, but the true incidence of this problem is difficult to determine. A recent epidemiological study from Minnesota showed an annual incidence rate up 0.03% and the mean age 61 years for all forms of acquired symptomatic lacrimal obstructions (Woog 2007).

2.3.1 Obstruction of the upper lacrimal system

Obstruction of the puncta lacrimalis

Obstruction of the puncta lacrimalis can be congenital, or acquired, but, there is no uniform grading system in the literature for different degrees and severity of punctual stenosis (Cahill and Burns 1991).

Congenital external punctal occlusion has been defined as either the absence of both punctum and papilla or imperforation of the punctum (Hurwitz 1990).

Acquired external punctual stenosis (AEPS) may result from various infections, lid

malposition, trauma, tumors and toxic effects of topical and system medications (McNab 1998, Lee et al. 1998, Weston and Loveless 2000, Esmaeli et al. 2001). Ageing can be also a risk factor of punctual stenosis (Kristan 1988). Some studies have reported an association between canaliculi and nasolacrimal duct stenosis or obstructions with AEPS (Colla et al. 1994, Weston and Loveless 2000, Esmaeli et al. 2001). In a prospective study, Kashkouli and co-workers (Kashkouli et al. 2003), examined the causes of symptomatic AEPS and assessed the frequency of associated canalicular and nasolacrimal ducts obstruction with AEPS. In this study a significant association between the nasolacrimal duct stenosis and obstruction with AEPS after the age of 70 years was found.

Obstruction of the canaliculus

The causes which lead to obstruction of the canaliculus may be divided into primary (suppurative inflammations) and secondary (non-suppurative inflammations) canaliculitis (Tabbara 1982).

Infections of the canalicular system of the eye are rare and often misdiagnosed. These infections are most common in postmenopausal women and are ascribed to hormonal changes, which probably decrease tear productions predispose to infection (Hussain et al. 1993, Vecsei et al. 1994). The most common cause of this infection is *Actinomyces* species (Hussain et al. 1993). Inflammation leads to the formation of a dacryolith that obstructs the lacrimal duct (Vecsei et al. 1994).

Cases of primary (suppurative) canaliculitis should be distinguished from secondary forms, which may be caused by herpes simplex virus (Harris et al. 1981, Williams et al. 1985), varicella (Sanke and Welham 1982), trachoma (Tabbara and Bobb 1980), erythema multiforme (Williams et al. 1985), or topical (Laibson 1973) or systemic medications (Caravella et al. 1981).

The secondary forms (non-suppurative) of canaliculitis result in punctal and canalicular stenosis, pericanalicular scarring and finally obstructions (Laibson 1973, Caravella et al. 1981, Harris et al. 1981, Sanke and Welham. 1982, Williams et al. 1985).

2.3.2 Obstruction of the lower lacrimal system

2.3.2.1 Primary acquired nasolacrimal duct obstruction

Primary acquired nasolacrimal duct obstruction (PANDO) comprises about two thirds of the cases with stenosis, and the pathogenesis is unknown. The process is characterized by gradual inflammation and subsequent fibrosis of the nasolacrimal duct, which leads to increasing obstruction of the drainage system (Bartley 1993, Önerci 2002).

Predisposing factors: sex and age of the patient

The etiology of PANDO is unknown. Several predisposing factors have been suggested, including cigarette smoking, middle-face trauma, and a history of dacryocystitis. PANDO occurs more frequently in post-menopausal women (Zolli and Shannon 1982, Linberg and McCormick 1986, Tarbet and Custer 1995a). It is possible that the greater prevalence of PANDO in female subjects is caused by the bony nasolacrimal canal's smaller diameter The lower nasolacrimal fossa and the middle bony lacrimal duct are smaller in females than in males, and a narrow bony nasolacrimal canal predisposes to the development of lacrimal duct obstruction (Groessl et al. 1997). Janssen and co-workers (Janssen et al. 2001) reported that female subjects had a significantly smaller minimum diameter (on average 0.35 mm). The smaller diameter in female subjects can cause tear fluid stasis and infections from the nasal cavity, since the bony nasolacrimal canal is flatter in females than in males. Shigeta and co-workers (Shigeta et al. 2007) found that the caliber of the bony lacrimal duct and the angle between the bony lacrimal duct and the nasal floor generally increased with age, primarily before the age of 40 years. Thus, the narrowness of the bony nasolacrimal canal and the acute angle between the bony canal and the nasal floor in females predispose to chronic inflammation of the nasolacrimal drainage system. The individual structural features such as the drain lines from the frontal and ethmoidal sinuses, the anatomically narrow and high

infundibulum and septal deviation may play an important role in the inflammatory processes in NLD (Önerci 2002).

Nasal cavity and paranasal sinus conditions

The relationships of the nasolacrimal pathway with the lateral nasal wall and paranasal sinuses make it vulnerable to inflammation and subsequent obstruction by various pathologies of the nose and paranasal sinuses (Wong et al. 1998). Early reports associated inflammatory sino-nasal diseases with almost 50% of nasolacrimal duct obstructions (Garfin 1942). Acute infections in the nasal cavity and recurrent and chronic infections of the paranasal sinuses have been suggested to lead to spreading the infection through the nasolacrimal duct, followed by mucosa inflammation, swelling, scar formation and finally stenosis (Önerci 2002).

2.3.2.2 Secondary acquired nasolacrimal duct obstruction

Secondary acquired nasolacrimal duct obstruction (SANDO) in adults may result from a wide variety of specific infections, or inflammatory, neoplastic, traumatic or mechanical causes (Linberg and McCormick 1986, Bartley 1992).
Bartley (Bartley 1992) reported that the most common causes of bilateral SANDO are *Actinomyces* infection, sarcoidosis, cicatrical pemphigoid, Steven Johnson syndrome and allergy, whereas *Herpes zoster*, *Adenovirus* and *Aspergillus* may cause unilateral SANDO. Wong and co-authors (Wong et al. 1998) show that bilateral SANDO without facial trauma and sinonasal surgery history may indicate unusual systemic diseases such as sarcoidosis, Wegener granulomatosis and chronic lymphocytic leukemia. Jokinen and Kärjä (Jokinen and Kärjä 1974) showed that nasal allergy, lupus vulgaris and non-specific nasal infections may cause inflammation in the nasolacrimal system. Some investigators have suggested that the inflammation and fibrosis may be secondary to coexisting bacterial infectious colonization within the lumen of the lacrimal sac (Huber-Spitzy et al. 1992, DeAngelis et al. 2001). The progressive atrophy of the nasal mucosa leads to underlying bone inflammation, and

eventually to infection, fibrosis and later mechanical obstruction of the NLD (Singh et al. 2004).

Tumors of the nasolacrimal system usually mimic a unilateral inflammation of the lacrimal sac and may lead to a delay in definitive diagnosis (Ryan and Font 1973). The most common presenting signs and symptoms of lacrimal tumors are tearing, and recurrent inflammation of the sac or lacrimal sac mass (Hornblass et al. 1980, Stefanyszyn et al. 1994). Bloody discharge form the eye may occur in a patient with lacrimal sac melanoma (Yamade and Kitagawa 1978). A review of the literature discloses that 50% of malignant nasolacrimal system tumors relapsed within 5 years (Harry and Ashton 1969, Ryan and Font 1973, Khalil and Lorenzetti 1980, Ni et al. 1982). Malignant epithelial neoplasms often recur locally, and can metastasize and be fatal (Stefanyszyn et al. 1994).

SANDO may occur as a result of nasoethmoidal, nasal, or midfacial fractures, or repair of other midfacial injures (Osguthorpe and Hoang 1991). Sinus and rhinoplastic surgery has a potential risk of damage of the nasolacrimal system (Osguthorpe and Calcaterra 1979, Serdahl et al. 1990). A significant internal mechanical cause of SANDO may be dacryoliths (Baratz et al. 1991), which occur in three times as frequently in females as males (Jones 1965, Herzig and Hurwitz 1979, Berlin et al. 1980). SANDO may also result from external compression of the paranasal sinuses mucoceles, which commonly involves more than one sinus on the same side and commonly occurs in the fronto-ethmoidal and/or maxillary sinuses (Russell et al. 1985, Ormerod et al. 1987, Ajaiyeoba et al. 2006).

2.3.3 Congenital nasolacrimal duct obstruction

Congenital nasolacrimal duct obstruction affects up to 20 % of newborns (MacEwen et al. 2001). Honavar and co-workers (Honavar et al. 2000) observed two types of congenital nasolacrimal obstructions membranous (77%) and firm (23%), and demonstrated than infants with firm obstruction have a poor prognosis. Fortunately, spontaneous resolution of symptoms of nasolacrimal obstruction occurs in approximately 90-96% of cases during the first years of life (MacEwen et al. 2001).

2.3.4 Microbiology of the normal conjunctival flora

Several studies have examined normal ocular flora and found bacteria and fungi. Martins and co-workers (Martins et al. 2004) examined the bacterial conjunctival flora in diabetic and nondiabetic patients, without ocular symptoms In the 60 nondiabetic patients, coagulase negative *Staphylococcus* was identified in 62%, *Cornebacterium* in 39%, *Staphylococcus aureus* in 12%, and *Pseudomonas aeruginosa* in 3% of cases. In another study of normal conjunctival flora coagulase negative *Staphylococcus* was found in 100%, *Diphteroids* in 43% and *Staphylococcus aureus* in 24% of cases (Gritz et al. 1997). In a large study of Indian bacterial and fungal flora of the normal conjunctiva, 86 % were culture positive for bacteria and 12% were culture positive for fungi: the most common bacterial isolates were *Staphylococcus albus* and *Staphylococcus aureus*. The most common fungal isolates were *Aspergillus*, *Mucor*, and *Penicillium* (Tomar et al. 1971).

2.3.5 Clinical manifestations of obstruction of the nasolacrimal pathway

Epiphora is the most prevalent symptom of obstruction of the nasolacrimal system (Önerci 2002). The term *epiphora* comes from the Greek word *epifora*, which in turn is derived from the root words *epi* (upon) and *ferein* (to bring). Epiphora as an isolated symptom may occur in patients with dry eye syndromes, allergical conjunctivits, punctual or canalicular acquired obstruction, lacrimal dysgenesis, abnormalities of lid position or movement, lacrimal pump failure, or obstruction of nasolacrimal pathway (Moss et al. 2000, MacEwen et al. 2001, Butrus and Portela 2005). The obstruction results in stasis of tears in the lacrimal sac and subsequently infection with an accumulation of mucopurulent discharge and inflammation (Huber-Spitzy et al. 1992).

Dacryocystitis is the most frequent disorder of the lower lacrimal system. In most cases it is the result of obstruction of the nasolacrimal duct, and is usually unilateral (Huber-Spitzy et al. 1992). In acute dacryocystitis, stenosis within the lacrimal sac leads to retention of tear fluid and subsequently to bacterial infection**.** Clinical

symptoms include painful swelling and redness in the lacrimal sac region (Huber-Spitzy et al. 1992, Das et al. 2008). The pain may be in the forehead, nose, and teeth. An abscess in the lacrimal sac may develop due to acute dacryocystitis: it can rupture the skin and drain though the fistula (Lee and Woog 2001).

Chronic dacryocystitis is an inflammatory condition of the lacrimal sac which is associated with an obstruction of the nasolacrimal duct due to dilatation of the lacrimal sac, or chronic inflammation of the connective tissue or nasal mucosa (Russell et al. 1985, Huber-Spitzy et al. 1992). The initial characteristic of chronic dacryocystitis is increased lacrimation and in many cases chronic unilateral conjunctivitis (McEwen 1997, Das et al. 2008). No signs of inflammation are usually present, but on applying pressure to the inflamed lacrimal sac, a purulent discharge regurgitates through the punctum (Boruchoff and Boruchoff 1992).

2.3.6 Microbiology of dacryocystitis

The spectrum of bacterial isolates in acute and chronic dacryocystitis is similar. The most common isolates in dacryocystitis are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterobacter aerogenes*, *Citrobacter*, *Streptococcus pneumoniae*, *Escherichia coli*, and *Enterococcus.* (Briscoe et al. 2005, Kubal and Garibaldi 2008).

The spectrum of microorganisms of acute and chronic dacryocystitis varies in different geographical areas and shows a different predominance of the species. Reports from Finland (Hartikainen et al. 1997), North America (DeAngelis et al. 2001), China (Sun et al. 2005), Australia (Sainju et al. 2005) and Saudi Arabia (Chaudhry et al. 2005) show a predominance of either *Staphylococcus aureus* or *Staphylococcus epidermis.* Reports from India show a predominance of *Streptococcus pneumonia, Staphylococcus aureus* and *Staphylococcus epidermis* (Badhu et al. 2006, Bharathi et al. 2008). A study from Israel (Briscoe et al. 2005) showed a predominance of *Pseudomonas aerugenosa*.

To characterize the differences between acute and chronic infection, Mills and co-workers (Mills et al. 2007) conducted a prospective study and showed that Gram-positive organisms were much more common than Gram-negative organisms

overall, and the proportions did not differ significantly between the groups. Moreover, *methicillin-resistant Staphylococcus aureus* was associated with acute dacryocystitis more often than with chronic dacryocystitis.

The high rate of pathogenic fungi in conjunctival flora such as *Fusarium*, *Aspergirum*, *Mucor* and *Actinomyces* species may play a role in the microbiological characteristics of dacryocystitis and overall ocular morbidity (Hussain et al. 1993, Sun et al. 2004, Capriotti et al. 2009).

2.3.7 Histopathology of the nasolacrimal pathway

Inflammation with a combination of varying degrees of fibrosis is the most common histopathological finding in patients with PANDO (Linberg and McCormick 1986). Paulsen (Paulsen 2003) showed that early-stage dacryostenosis is characterized by active inflammation and edema of the epithelial and subepithelial tissue. Goblet cells and subepithelial seromucous glands revealed signs of hypersecretion. The chronic stage of dacryostenosis is characterized by loss of differentiated epithelial cells from thin epithelium to basal cell hyperplasia, which is associated with squamous metaplasia. Descending inflammation from the eye or ascending inflammation from the nose induces swelling of the mucous membrane, rearrangement of connective tissue fibers, malfunctions in the subepithelial cavernous body and temporary occlusion of the lacrimal pathway. Subsequently, epithelial changes can lead to total fibrous obstruction of the lumen (Paulsen 2003). The absence of Goblet cells and the presence of fibrosis and epithelial ulcerations indicate the intensity of the lacrimal sac inflammation (Lee-Wing and Ashenhurst 2001, Bernardini et al. 2002, Anderson et al. 2003, Ciftci et al. 2005).

2.4 Evaluation of obstruction of the nasolacrimal pathway

2.4.1 Clinical history and examination

The clinical history of the patient is essential information. Obstruction of the nasolacrimal pathway may be due to previous nasolacrimal duct intubation, recurrent infections in lacrimal pathway and paranasal sinus, midfacial trauma (Osguthorpe and Hoang 1991), lacrimal and orbital operations, sinonasal surgery (Osguthorpe and Calcaterra 1979), or radiotherapy (Baratz et al. 1991) of head and neck regions, and specific inflammatory diseases may also cause obstruction of the nasolacrimal pathway (Vasquez et al. 1988).

The ophthalmologist is the primary consultant for patients with disorders of the lacrimal duct. There are two main reasons for tearing: epiphora and dry eye. Epiphora is a result of a disorder of tear drainage caused by mechanical obstruction or lacrimal pump failure. The dry eye is due to either tear film watery component production deficiency or increased evoparative loss, which results in irritation of the cornea and reflective excessive tearing by hypersecretion (Mathers and Laine 1998).

The basic examination includes inspection and slit-lamp microscopy of the ocular surface and eyelids. Inspection of the puncta for poor position, narrowing or stenosis may suggest canaliculitis. Palpation and inspection of the lacrimal sac region may reveal dacryocystitis, mucocele, or abscess. If rhinogenic causes of the obstruction are suspected, patients should be referred to an otorhinolaryngologist (Guzek et al. 1997). However, the goal of the basic examination is to differentiate between epiphora and dry eye (Kohn 1988, Moss et al. 2000).

2.4.2 Evaluation of tear formation

The Shirmer tear test provides information about the quantity of the watery component in tear secretion (Foulks 2008). This test is performed by inserting a strip of paper into the conjunctival sac of the temporal third of the lower eyelid. The result is considered normal if after 5 minutes, at least 15 mm of the paper turns blue due to

the alkaline tear fluid, and abnormal if the amount is less than 5 mm (Schirmer 1903). Tear break-up time (TBUT) evaluates the stability of the tear film. This test is performed by the instillation of fluorescein dye (10 µL of a 0.125% fluorescein solution) to the precorneal tear film. The eye is observed using a slit lamp and cobalt blue filter during the blink cycle. Tear film break up under the 10 seconds notes as sign of dry eye. Tear break-up time of at least 10 seconds is considered normal (Cedarstaff and Tomlinson 1983).

2.4.3 Evaluation of tear drainage

Primary and Secondary Jones Dye Tests

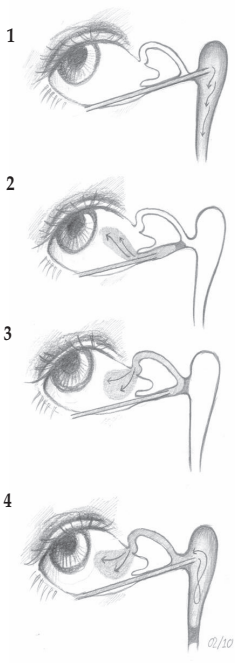
The Primary Jones test is positive if a 20 mg/mL fluorescein sodium solution instilled into the inferior fornix can be detected after five minutes under the inferior turbinate. It indicates that the nasolacrimal passage is unobstructed. The Primary Jones test is negative if no fluorescein is found in the inferior meatus of the nasal cavity (Guzek et al. 1996). The Secondary Jones test is positive if fluorescein is detected, showing that it had entered the sac after syringing. The Secondary Jones test is negative if no dye is detected after syringing (Wobig and Wirta 1998). The disadvantage of these tests is that they cannot differentiate the physiological from the anatomical causes, and cannot localize the level of obstruction. Moreover, there is a high false negative rate (e.g., 22% of normal patients will have no dye in the nose) and the test does not identify patients with a partial obstruction of the nasolacrimal system (Hurwitz and Welham 1975).

Probing and irrigation

Diagnostic probing and syringing of the lacrimal pathway are sufficient for evaluating the function of the lacrimal drainage system or to determine the location and extension of obstructions in patients with epiphora. After the application of a topical anesthetic, a conical probe is used to dilate the punctum. Then the lower lacrimal system is irrigated with physiologic saline solution through a blunt cannula.

If the nasolacrimal pathway is open, the solution flows freely into the nose. Canalicular stenosis results in reflux through the irrigated punctum. If the stenosis is in the common canaliculis or deeper in the post-saccal region, reflux will occur through the opposite punctum (Figure 5) (Calkins 1964).

Figure 5. Location of obstruction by irrigating of the lower lacrimal system.



1. No obstruction
2. Pre-saccal obstruction (stenosis of the inferior canaliculus)
3. Pre-saccal obstruction (stenosis of the commmon canaliculus)
4. Saccal or post-saccal obstruction (stenosis within the lacrimal sac or nasolacrimal duct)

Lacrimal duct endoscopy

Fine endoscopes give direct visualization of the mucous surface of the lower nasolacrimal system. Dacryoscopy was described by Cohen (Cohen et al. 1979) as a supplement of other diagnostic tests. However, up to now, endoscopic examination of the lower lacrimal system has not been a routine procedure (Önerci 2002).

2.4.4 Imaging of the nasolacrimal pathway

Dacryocystography

Radiographic contrast studies have established the shape, position and size of the pathway and the level of obstruction to drainage. Radiographic contrast material is instilled in the same manner as the saline solution through the lacrimal system. Installation of the contrast material can generate high pressure in the nasolacrimal system, which may open a partial obstruction (Wearne et al. 1999).

Radionuclide dacryoscintigraphy

Radionuclide dacryoscintigraphy using ^{99m}Tc may provide information about physiological function involving tear drainage transit time (Rossomondo et al. 1972). The limitation of this procedure is the relatively minimal morphological information and the large variation of normal tear transit times (Robertson et al. 1979).

Computed tomography

Computed tomography (CT) shows excellent contrast between bony structures and soft tissue. Thin-section CT is an effective imaging modality to evaluate the structures related to the nasolacrimal system, paranasal sinuses and the surrounding soft tissue (Russell et al. 1985, Groell et al. 1997).

Computed tomography dacryocystography

Computed tomography can be combined with radiographic contrast medium. This method is useful for characterizing the membranous lacrimal passage and the bony structures. Moreover, it gives information about the anatomical and functional condition of the nasolacrimal pathway (Ashenhurst et al. 1991).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an accessible method to identify anatomic abnormal variations such as divertucula and septa, to differentiate masses, and evaluate postoperative changes in the lacrimal sac. Nonetheless, conventional MRI has a low sensitivity in distinguishing between lacrimal sac diverticulum and neoplasm (Önerci 2002).

Dynamic magnetic resonance dacryocystography

Magnetic resonance dacryocystography (MR-DCG) is suitable for assessing drainage problems of the nasolacrimal duct system and gives additional information concerning the surrounding soft tissue structures, but is not recommended as a routine examination (Goldberg et al. 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. Moreover, it provides information about the level of obstruction in the NLD, and has a sensitivity of 91% and a specificity of 90% in the evaluation of the nasolacrimal system patency (Cubuk et al. 2010).

2.5 Treatment of obstruction in adults

2.5.1 Medical therapy

Ophthalmic infections can cause damage to the structure of the eye and if left untreated can lead to vision loss and even blindness (Snyder and Glasser 1994). Although treatment guidelines of ocular infections recommend laboratory culture for the determination of the causative pathogen, in practice the initial choice of antibiotic therapy is generally made without knowledge of the pathogen (Snyder and Glasser 1994, Callegan et al. 2007). The penicillins, cephalosporins and fluoroquinolones, as bactericidal agents, are generally used to treat ocular infections. Bacteriostatic drugs such as macrolides, chloramfenicol, and sulfonamides are used in cases in which

there in a specific benefit or history of allergy (Mulligan and Cobbs 1989, Bertino 2009).

The most common ocular infection is bacterial conjunctivitis, which is self limiting and presents as an acute infection or as a symptom of chronic dacryocystitis (McCord and Doxanas 1990, Rose 2007). The recommended treatment of dacryocystitis is topical and systemic antibiotics to cover penicillinase-producing staphylococcal bacteria (Bourcier et al. 2003). Some studies suggest parenteral administration in addition to topical antibiotics as a standard therapy for dacryocystitis (Snyder and Glasser 1994).

To avoid the development of antibiotic resistance it is important to modify the antibiotic therapy based on the laboratory culture, sensitivity results and patient's response (Briscoe et al. 2005).

2.5.2 Surgical treatments for saccal and post-saccal obstructions

2.5.2.1 External dacryocystorhinostomy

Dacryocystorhinostomy is an operative treatment to relieve epiphora by creating a free communication between the lacrimal sac and nasal cavity. Toti, in 1904, was the first to propose a method for EXT-DCR (Toti 1904). His technique was to expose the lacrimal sac by an external skin incision, remove the medial wall, punch out a piece of bone using a hammer and chisel, resect a corresponding area of the nasal mucous membrane and sew up the external wound. At that time, like today, the main cause of failure was the formation of granulation tissue. Toti suggested removing part of the middle turbinate bone to enlarge the size of the bony window. In 1914, an improvement of this technique, suturing a flap of nasal mucosa to the periostium, was made by Kuhnt. In 1920, Ohm suggested suturating the margins of the nasal mucosa to the lacrimal sac (Hughes 1986). The modern method was described by Dupuy-Dutemps and Bourguet in 1921 (Hallum 1948). They suggested incising the posterior wall without removing tissue and approximating flaps of lacrimal sac and nasal mucosa. This technique had a high success rate, and for a long time it was the

gold-standard operation performed by ophthalmologists (Hughes 1986, Werb 1986). To prevent closure of the rhinostoma, Gibbs (Gibbs 1967) introduced silicone tubing, which was used by Quickert and Dryden (Quickert and Dryden 1970) to intubate the nasolacrimal sac after EXT-DCR.

2.5.2.2 Evolution of endonasal dacryocystorhinostomy

Caldwell described an endonasal procedure in 1893 (Caldwell 1893). In 1910 an endonasal approach was attempted by West, who introduced the idea of a window osteotomy by removal of the lacrimal bone and the superior maxilla to assess the nasolacrimal duct (West 1914). This technique was modified in 1914 Halle, who also introduced the idea of mucosal-periost flaps to ensure a permanent rhinostoma between the lacrimal sac and nasal cavity (Halle 1914).

Bumsted and colleagues (Bumsted et al. 1982) found that a small healed ostium could provide an excellent functional result and suggested that the size of the surgical anastomosis is not directly related to the success of the procedure. Based on this information, physicians increased the use of endoscopy in lacrimal surgery and Rice (Rice 1988), in a cadaver study, demonstrated that endoscopy is a viable option for DCR. The first modern endonasal approach was described by McDonogh and Meiring (McDonogh and Meiring 1989).

Endonasal DCR can also be performed using an operating microscope. The advantage of this technique is operative precision by allowing for bimanual work (Hausler and Caversaccio 1998, Dietrich et al. 2003). Favorable results using a microscopic endonasal DCR technique have been obtained in children and adults with lacrimal sac distention, acute abscesses in the lacrimal sac, and saccal and post-saccal obstructions (Dietrich et al. 2003).

In 1990, Massaro and co-workers (Massaro et al. 1990), in a cadaver study, introduced endonasal laser-assisted DCR, using argon blue green laser for bone removal. Shortly thereafter carbon dioxide (CO2) and potassium-titanyl phosphate (KTP)/neodyuium-yttrium-garnet (YAG) lasers were approved for lacrimal endonasal surgery (Gonnering et al. 1991). In 1992, Levin and StormoGipson (1992)

introduced endocanalicular laser-assisted DCR in a cadaver study. In 1995, Javate and colleagues (1995) introduced a modified endoscopic laser-assisted technique using a radiofrequency device for incision of the mucosa and bone.
Currently, endonasal approaches can be divided into endonasal laser assisted DCR (Gonnering et al. 1991, Hehar et al. 1997), endocanalicular laser assisted DCR (Pearlman et al. 1997), and powered mechanical endonasal DCR or "cold steel" DCR, with (Sham and van Hasselt 2000) or without (Cokkeser et al. 2000) drills.

2.5.2.3 Endoscopic endonasal dacryocystorhinostomy

EN-DCR is a minimally invasive procedure with improved endoscopic instrumentation. Moreover, EN-DCR has many advantages over EXT-DCR, including the preservation of the pumping mechanism of the orbicularis muscles, avoidance of the external scar and injury of the medial canthus, reduced of operative time, intraoperative hemorrhage, postoperative morbidity, and postoperative recovery time, and the possibility of performing additional sinonasal surgery at the same time when needed (Boush et al. 1994, Weidenbecher et al. 1994, Eloy et al. 1995, Sham and van Hasselt 2000). Also, an acute infection in the lacrimal sac is not a contraindication for endoscopic surgery (Eloy et al. 1995, Lee and Woog 2001). However, some studies have reported that relatively high equipment costs and a significant learning curve are notable disadvantages of EN-DCR (Metson 1990, Kong et al. 1994).

Indications

Primary EN-DCR is indicated in the management of epiphora and infection related to PANDO/SANDO associated with specific inflammatory or infiltrative disorders, when the obstruction site is in the lacrimal sac or the nasolacrimal duct (Unlu et al. 2000, Woog et al. 2001, Önerci 2002). Moreover, EN-DCR is useful in the management of PANDO/SANDO associated with previous surgery in the nasal cavity, paranasal sinuses or trauma of the middle face (Osguthorpe and Calcaterra

1979, Osguthorpe and Hoang 1991, Sham and van Hasselt 2000, Weidenbecher et al. 1994). In addition, EN-DCR may be appropriate in children with congenital dacryostenosis including nasolacrimal duct cyst formation (Cunningham and Woog 1998). EN-DCR is also indicated in revision surgery following previous external or endonasal DCR (Hausler and Caversaccio 1998, Szubin et al. 1999, El-Guindy et al. 2000).

Contraindications

The contraindications of EN-DCR are associated with the suspicion of lacrimal system neoplasia or in patients in whom neoplasia cannot be excluded (Reifler 1993, Bartley 1994, Javate et al. 1995). It has also been reported that lacrimal sac mucocele extending into the eyelid may not be drained using an intranasal approach (Boush et al. 1994, Sprekelsen and Barberan 1996). The obstructions in the upper (pre-saccal) part of the nasolacrimal system such as punctal and canalicular stenosis are also contraindication of using EN-DCR (Eloy et al. 1995, Sham and van Hasselt 2000, Unlu et al. 2000).

Patient selection

EN-DCR is an effective treatment for patients with saccal and post-saccal obstruction of the lacrimal pathway (Sprekelsen and Barbera 1996). Some studies show that EN-DCR provides a good result in patients with functional obstruction of the nasolacrimal system (Mannor and Millman 1992, Wormald and Tsirbas 2004). It has been demonstrated that EN-DCR is an effective procedure for resolving symptoms with a good success rate in patients with acute purulent dacryocystitis with abscess formation (Lee and Woog 2001, Wu et al. 2009a).

Preoperative examination and imaging

Investigation of the lacrimal system should begin with an examination of the upper lacrimal system to exclude agenesis, stenosis or ectropium of the punctum, and palpation of the canthal area to exclude a mucocele, dacryolith or tumor. Lacrimal system irrigation should be performed to confirm anatomical obstruction. Careful evaluation of the nasal cavity using an endoscope is crucial to assess the possible technical problems that can make EN-DCR more difficult (Wormald 2002).

Contaminant infections of the paranasal sinuses and nasal cavity are a potential risk of failure for EN-DCR, so treating these preoperatively is generally recommended whenever possible (Allen et al. 1988).

A considerable proportion of patients with epiphora will have a patent nasolacrimal system on syringing, which raises the question of what is the most appropriate preoperative examination for patients with functional nasolacrimal duct obstruction (Wearne et al. 1999).

Radiological studies suggest CT or CT-DCG to determine the level of nasolacrimal pathway obstruction, the thickness of the bone surrounding the lacrimal sac, and the presence of nasal and paranasal sinuses abnormalities, and to facilitate the planning of possible adjunctive procedures at the time of EN-DCR (Russell et al. 1985, Whittet et al. 1993, Sham and van Hasselt 2000).

2.5.2.4 Key points in the success of endonasal dacryocystorhinostomy

In the last two decades, EN-DCR outcomes have been compared with EXT-DCR outcomes. A review of the literature reveals a success rate of 70-99% for EN-DCR (Allen and Berlin 1989, Ben Simon et al. 2005, Yigit et al. 2007, Leong et al. 2010b).

The following steps of EN-DCR are recognized in the literatures as being important in minimizing failures.

Anesthesia and preparation of the nose

EN-DCR can be performed under general or local anesthesia with intravenous sedation (Howden et al. 2007). Some authors suggest general anesthesia in patients with acute dacryocystitis or difficult nasal anatomy with tight access, and if the patient prefers it, but generally local anesthesia is recommended (McDonogh and Meiring 1989, Smith et al. 2001, Meyer 2000, Durvasula and Gatland 2004).

Ciftici (Ciftci et al. 2005) compared the effectiveness, complications, and patient acceptance of local anesthesia with general anesthesia in young patients for EXT-DCR and showed that postoperative nausea and vomiting (PONV), length of hospital stay, and intraoperative bleeding were reduced in the local anesthesia group. In a study with 66 patients Smith and co-workers (Smith et al. 2001) reported a new lacrimal fossa block, combined with standard intranasal local anesthesia. They showed that this technique can achieve a direct contact with the periosteum of the frontal process of the maxilla within the lacrimal fossa, which provides good intraoperative analgesia.

Regardless of the type of anesthesia, vasoconstriction of the nasal mucosa and anterior ethmoidal and sphenopalatinal nerve block using cocaine or a solution of lidocaine with adrenalin are always carried out preoperatively. The combination of vasoconstriction of the nasal cavity using a long-action decongestant and local anesthetic is effective for outpatient dacryocystorhinostomy, and helps visualization and minimizes intraoperative bleeding (Meyer 2000).

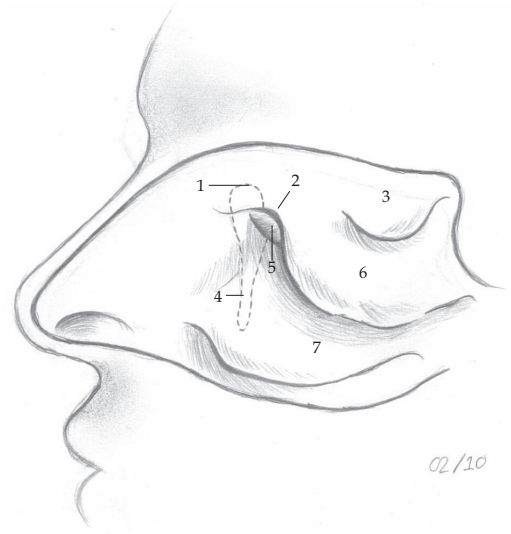
In cases performed under local anesthesia, topical ocular anesthetic is instilled in the operative eye and infiltrated local anesthetic solution in the medial canthal region and medial portion of the eyelid. However, serious ocular complications have resulted from local anesthesia for DCR, including ocular perforation associated with a medial peribulbar block (Kersey et al. 2001), and a moderate retrobulbar hemorrhage resulting from a medial peribulbar local anesthetic infiltration (McNab and Simmie 2002).

Localization of the lacrimal sac

When anatomic landmarks of the lateral nasal wall are altered or do not exist, the lacrimal sac is difficult to find (McDonogh and Meiring 1989). Christensen (1951) introduced the idea of transillumination for visualizing the lacrimal sac localization in dacryocystorhinostomy by using an endoilluminator probe introduced through the canaliculis into the lacrimal sac. Today, endoillumination, as a method for identification for localization of lacrimal sac, is widely use in many endoscopic techniques (Massaro et al. 1990, May et al. 2002, Wormald 2002).

Many authors claim that the axilla of the middle turbinate is a landmark for the roof of the lacrimal sac (McDonogh and Meiring 1989, Sprekelsen and Barberan 1996). However, Wormald and co-authors, in a study with 47 CT-DCG patients, showed that the major part of the lacrimal sac (10 mm) is situated above the axilla of the middle turbinate, extending 1-2 mm below this landmark (Wormald et al. 2000) (Figure 6).

Figure 6. Localization of the lacrimal sac



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

Mucosal incision and flaps

Tsirbas and Wormald (Tsirbas and Wormald 2003) recommend 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.
To avoid trauma of neighboring tissue, the rectangular incisions of nasal mucosa should be made using a scalpel blade (Wong et al. 1998, Tsirbas and Wormald 2003) and the nasal mucosal flap must include the periosteum (Önerci 2002).
The main task in EN-DCR is to create the largest possible bony ostium to completely expose the medial wall of the lacrimal sac, and to achieve contact between the lacrimal sac and the nasal mucosa. In the earliest studies, this was achieved by suturing (Welham and Wulc 1987). Later, Eloy (Eloy et al. 1995) suggested stapling with titanium clips. More recently, Wormald (Wormald 2002) and Tsirbas (Tsirbas and Wormald 2003) describe an approach where the lacrimal sac is fully exposed and marsupialized into the lateral nasal wall of the nose with nasal and lacrimal mucosa apposition. This is a one of the most important keys to the success of EN-DCR.

Location of the osteotomy

Welham and Wulc (Welham and Wulc 1987) suggest the removal of all the bone between the medial wall of the lacrimal sac and axilla to achieve an ideal ostium. On the other hand, some authors advocate leaving approximately 5mm free of bone around the canaliculus, at the junction of the middle turbinate and the lateral nasal wall, as a landmark of the floor of the lacrimal fossa (Whittet et al. 1993). Other authors have recommended developing a larger ostium by removing the frontal process of the maxilla involving the anterior lacrimal crest and superiorly above the attachment of the middle turbinate to remove bone covering the fundus of the lacrimal sac (Boush et al. 1994, Weidenbecher et al. 1994, Sham and van Hasselt 2000, Tsirbas and Wormald 2003). Moreover, it has been claimed that a larger osteotomy with complete sac exposure provides better access to the nasal cavity and reduces the incidence of failure (Mann and Wormald 2006). However, in the literature it seems

that the success rate has been similar whether the osteotomy was larger or smaller than 10 mm in diameter (Beigi et al. 1998).

Rhinostoma size

Some authors consider the ostium size to be non-significant (Linberg et al. 1982), and have suggested creating a small ostium involving the inferior portion of the lacrimal bone (Massaro et al. 1990, Tutton and O'Donnell 1995). In contrast, Önerci (Önerci 2002) suggested removing as much as possible of the medial wall of the lacrimal sac. Metson (Metson 1990) advised the enlargement of the rhinostoma to a diameter of 10 mm, allowing free passage of a lacrimal probe into the nasal cavity through both canaliculi. To prevent the development of sump syndrome, some authors suggest performing "terminal" or "inferior" EN-DCR, in which a relatively small ostium is created by marsupialization of only the inferior portion of the lacrimal sac and the adjacent duct into the nose (Yung and Hardman-Lea 1998, Mortimore et al. 1999). The available data do not show the clear superiority of any option concerning ostium size and location (Woog et al. 2001).

Stenting

To prevent the obliteration of the intranasal lacrimal sac ostium, many surgeons prefer to insert bicanalicular silicone tubes to stent the rhinostoma (Kong et al. 1994, Shun-Shin 1998, Szubin et al. 1999). Some authors believe that silicone intubation after DCR surgery is advisable, while others think it may be a reason for failure (Unlu et al. 2002). Others object that the silicone tubes keep the lacrimal sac flaps separate (Kohn 1988). The tube can be fixated by a knot or clip (Wong et al. 1998). Nonetheless, there is general agreement on using silicone intubation after DCR in cases with canalicular stenosis (Hurwitz et al. 1989, Walland and Rose 1994).
However, silicone tubing has some disadvantages; it may cause granulation tissue formation, infection, or canalicular laceration, and the tubing may become dislocated

from the rhinostomy site (Metson 1990; Walland and Rose 1994), or it may otherwise cause discomfort to the patient (Unlu et al. 2002, Ressiniotis et al. 2005).

Nasal packing

To achieve hemostasis and prevent scar formation, various materials such as dissolvable foam, topical hemostatic sealants, or non-resorbable packs have been tested in the middle meatus after endoscopic nasal surgery (Durrani et al. 2007, Weitzel and Wormald 2008, Leunig et al. 2009, Szczygielski et al. 2010). However, in practice non-resorbable packs are most commonly used to achieve postoperative hemostasis and the effect of these on scar formation remains controversial, and no long term follow-up data are available (Leunig et al. 2009, Szczygielski et al. 2010).

2.5.2.5 Postoperative care

It is indisputable that postoperative care influences the healing process and is important for the success of EN-DCR (Kong et al. 1994, Hong et al. 2005). Postoperative care options include the administration of systemic antibiotics (Hausler et al. 1999), or a combination of antibiotic-steroid eye drops (Wormald 2002), local irrigation of the rhinostomy site with a saline nasal spray (Woog et al. 1993, Szubin et al. 1999, Unlu et al. 2000), intranasal steroids (Kong et al. 1994, Hehar et al. 1997), and debridement of the intranasal wound (Kong et al. 1994, Metson et al. 1994, Hartikainen et al. 1998a).

Silicone stent removal

The optimal time for silicone stent retention is still controversial. In published studies, the recommended time for retaining a stent vary from 4 weeks to 6 months (Boush et al. 1994, Hehar et al. 1997, Wormald 2002). However, in a review article Woog et al. (Woog et al. 2001) recommend that a stent should be retained for at least 11-12 weeks.

Follow-up time

The guidelines of the Royal College of Ophthalmologists suggest that the follow-up time should be at least three months. Some retrospective studies have reported a 5-year average follow-up period, but in this case the success rate fell from 88% after one year to 75% after 5 years (Dietrich et al. 2003). The outcomes of EN-DCR may decline in long-term follow-up (Nussbaumer et al. 2004).

2.5.2.6 Complications

Several early complications have been identified: intraoperative or postoperative hemorrhage (Orcutt et al. 1990, Hartikainen et al. 1998a, El-Guindy et al. 2000), silicone tubing prolapse (Orcutt et al. 1990, Boush et al. 1994), punctal erosion related to silicone tube use, canalicular obstruction (Sadiq and Downes 1998, Hartikainen et al. 1998a, Hartikainen et al. 1998b), orbital fat herniation, orbital and subcutaneous emphysema (Kong et al. 1994, Sprekelsen and Barberan 1996, Sham and van Hasselt 2000), conjunctival fistula formation (Mickelson et al. 1997), retrobulbar hematoma and temporary ophthalmoplegia (Hehar, et al. 1997). There are rare reports of cerebrospinal fluid leaks and meningitis following dacryocystostomy (Neuhaus and Baylis 1983, Beiran et al. 1994, Fayet et al. 2007).

Most of the late complications occur between one and three months after surgery (Moore et al. 2002). The following late complications after EN-DCR have been identified in the literature: scar formation of the rhinostoma (Jokinen and Kärjä 1974, Allen et al. 1988, Boush et al. 1994), synechiae between the rhinostoma and middle turbinate, rhinostoma and the nasal septum, and the septum and the middle turbinate, and granuloma formation within the ostium (Hausler and Caversaccio 1998, Fayet et al. 2002).

2.5.2.7 Wound healing of nasal mucosa

In long-term follow-up, adhesions of the rhinostoma site are the most common findings which explain the failure after EN-DCR, and this is linked to the biology of nasal mucosa wound healing (Goldberg 2004).

The precise mechanisms involved in wound healing in the respiratory mucosa remain unclear. Little information is available regarding the specific wound healing after surgery in the nasal cavity. The repair prossess of tissue injury typically include two well-defined stages: a regenerative stage, in which injured cells are replaced by cells of the same type and the stage of fibrosis, in which connective tissue replaces normal tissue. The new epithelial cells migrating from the undamaged areas gradually switch their major function to protein synthesis and are transformed into myofibroblasts. These play a key role in activating the primary collagen-producting cells and thus they are cellular mediator of fibrosis. It is know that myofibroblasts are activated by a variety of mechanisms, including paracrine signals from lymphocytes and macrophages, and autocrine factors secreted by myofibroblasts. Moreover, many important regulators of fibrosis have been identified, such as cytokines, angiofgenic factors, and acute phase proteins (Wilhelm 1953, Georgopoulos and McFarland 1993, Watelet et al. 2006, Wynn 2008).

If tissue in the vicinity of the wound, has suffered stress stimuli such as heat shock, viral or bacterial infections, autoimmune inflammatory processes, or certain chemical exposures, these evoke the expression of highly conserved heat shock proteins (HSPs). This could affect the migration of epithelial cells, which may delay the transformation of myofibroblasts and resulting in the slowing of wound healing (Georgopoulos and McFarland 1993, Kaarniranta et al. 1998, Kaarniranta et al. 2005, Salminen et al. 2008).

According to their function or molecular size, the HSP are classified into different families (HSP90, HSP70, HSP60, HSP40 and small HSPs) (Georgopoulos and McFarland 1993). HSP47 is closely implicated in fibrotic processes, functioning as a specific chaperone for procollagen molecules as they transit through the endoplasmic reticulum (Nagata 1996).

2.5.2.8 Outcome

The outcome assessments are based on subjective postoperative symptoms and objective signs. However, in clinical practice there is often a discrepancy between objective findings and patient's subjective outcome benefit (Moore et al. 2002, Goldberg 2004, Yigit et al. 2007).

Objective assessment of outcome

The assessments of objective findings include visual (endoscope evaluation) (Minasian and Olver 1999, Önerci et al. 2000), quantitative (postoperative scintigraphy and measurement of lacrimal sac pressure) (Hill et al. 1974, Malbouisson et al. 1997), anatomic (lacrimal sac irrigation) and functional (functional endoscopic dye test (FEDT)) outcomes assessments (Moore et al. 2002, Dietrich et al. 2003).
In a prospective study with 69 patients, Moore and colleagues (Moore et al. 2002) showed that FEDT was useful in assessing rhinostomy patency, but has no advantage over irrigation in the assessment of symptomatic success. Some studies suggest a FEDT as a definitive criterion for functional success (Dietrich et al. 2003). Other studies show that EN-DCR influences the lacrimal pump mechanism and changes tear passage (Kamel et al. 2003). The failure of the lacrimal pump is the most likely cause of continuous epiphora in the presence of a patent rhinostoma and free (positive FEDT) flow of fluorescein into the nose (Wormald and Tsirbas 2004).

Subjective assessment of outcome

Subjective assessment includes evaluation of symptom and Quality of Life questionnaires (Bakri et al. 1999, Holmes et al. 2006). Local symptoms related to NLDO include tearing, irritation, painful swelling, redness in the lacrimal sac region, pain in the forehead and nose, discharge of pus and change in vision (Huber-Spitzy et al. 1992, Bakri et al. 1999, Lee and Woog 2001, Das et al. 2008). However, a

validated symptom questionnaire exists only for NLDO in children (Holmes et al. 2006). In studies with adults, researchers must make up their own questions addressing ocular symptomatology related to NLDO symptoms (Bakri et al. 1999). For measures of symptom severity, one commonly used verbal rating scale consists of four levels: “cure”,”better”,”no change” and “worse” (Ho et al. 2006). For quantitative measures of symptom severity, a visual analogy scale (VAS) or numeric rating scale (NRS), which correlate with each other, must be used (Bijur et al. 2003).

2.5.2.9 Quality of Life

According to the World Health Organization’s definition, “Quality of Life (QoL) includes psychological and social functioning as well as physical functioning and incorporates positive aspects of well-being as well as negative aspects of disease or infirmity” (World Health Organisation 2006). QoL can be measured with generic quality of life instruments, which are suggested for use in patient groups suffering from different diseases, and disease-specific tools designed to evaluate patients suffering from specific diseases.

One generic QoL tool is the Glasgow Benefit Inventory (GBI), which was generated to measure a change in health status resulting from different types of otorhinolaryngological interventions. The GBI is quite commonly used for the measurement of surgical outcomes in rhinological procedures (Chester and Sindwani 2007). The GBI has also been recommended as a feasible tool to compare and evaluate outcome after endoscopic laser-assisted and external DCR techniques (Bakri et al. 1999). Ho and co-workers (Ho et al. 2006) used GBI in a prospective study and found that the non-laser endonasal DCR technique had a positive impact on the quality of life. In a recently published study, patients were grouped according to indication for endonasal DCR, and those with mucocele showed greater improvement in GBI scores than patients with obstruction of the lacrimal system or dacryocystitis (Spielmann et al. 2009).

3 AIMS OF THE STUDY

The aims of the present study were

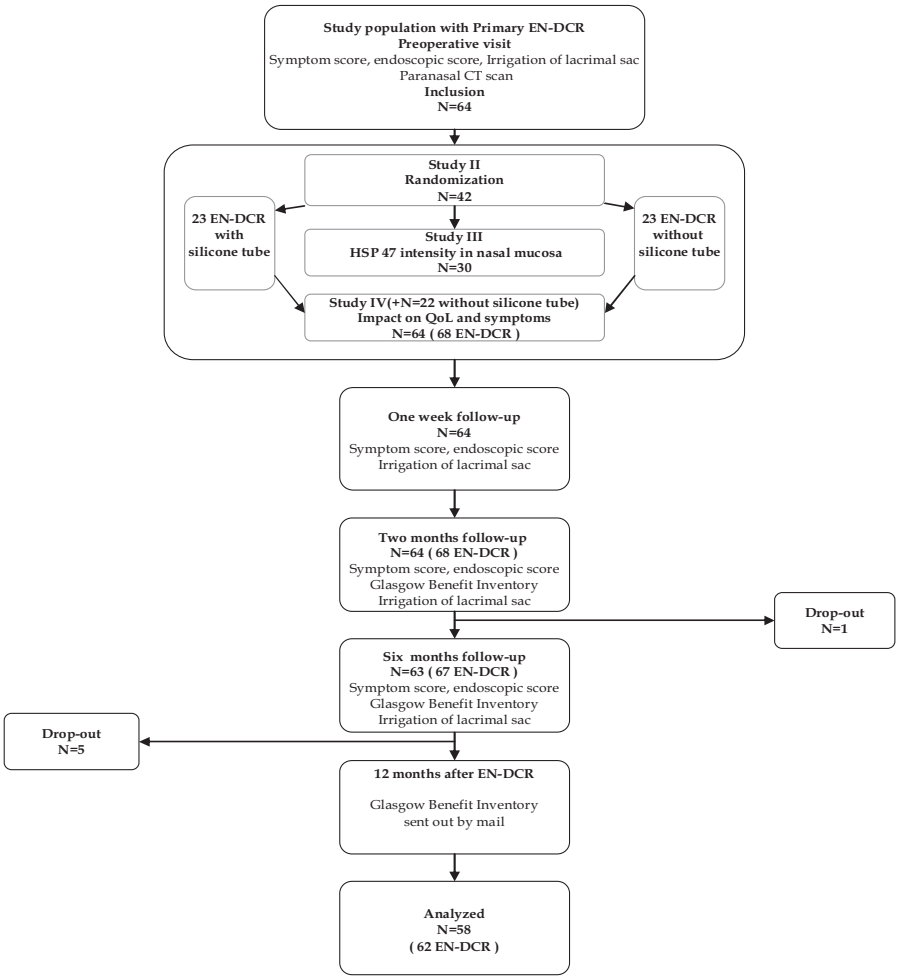
1. To evaluate the overall surgical outcome after EN-DCR (Studies I-II)
2. To evaluate the surgical outcome after primary EN-DCR at the six-month follow-up (Studies II-IV)
3. To evaluate the impact of silicone tubes on the outcome after primary EN-DCR (Study II)
4. To investigate whether there is an association between heat shock protein (HSP) expression and scar formation in the nasal mucosa in patients after primary EN-DCR (Study III)
5. To evaluate the impact of successful primary EN-DCR on the symptoms and the quality of life of the patients (Study IV).

4 MATERIAL AND METHODS

4.1 Patients

The retrospective study involved all 36 adult patients who had underdone 42 EN-DCR between July 2000 and August 2004 in Kuopio University Hospital (Study I).
The recruitment for the prospective study (Studies II-IV) started in September 2004, and ended in May 2008. The participants were consecutively recruited from the adult patients referred to the outpatient clinic of the Department of Otorhinolaryngology at Kuopio University Hospital, in Kuopio, Finland because of nasolacrimal pathway obstruction. The patients were eligible for participation if they were adults (age 18 years or older), were American Society of Anesthesiologist physical status I-III, and were scheduled for primary lacrimal pathway surgery because of tearing or recurrent infection of the lacrimal sac. The exclusion criteria were pre-saccal obstruction, previous nasolacrimal surgery, malignancy in the paranasal sinuses, nasal cavity, or lacrimal pathway, mental disability, pregnancy or breast feeding.
Study II involved 46 consecutive EN-DCR (four bilateral) for 42 patients. Study III involved 30 patients from Study II. Study IV included all the patients in Study II and 22 additional patients who had undergone unilateral primary EN-DCR. The flowchart for Studies II-IV is presented in Figure 7.

Figure 7. Studies II-IV flowchart.



N=number of patients; EN-DCR=endoscopic dacryocystorhinostomy; CT=computer tomography; HSP=heat shock protein; QoL=quality of life.

4.2 Methods

All the patients had a preoperative visit and at least three postoperative visits, at one week, and at 2 and 6 months after the surgery (Studies I-IV). In Studies II-IV, the patients filled out the GBI (Robinson et al. 1996) at two postoperative visits (at 2 and 6 months visits). The same GBI form was mailed twelve months after the surgery to each patient who had participated in the 6-month follow-up.

Study I investigated outcomes after EN-DCR retrospectively and involved 42 (23 primary and 19 revision) consecutive EN-DCR in 36 adults. Bicanalicular silicone stents were inserted in 18 operations and in 24 operations no silicone tubes were used.

Study II was a randomized, prospective, open clinical trial with two parallel groups of patients with primary EN-DCR. The patients were randomized into two study groups, EN-DCR either with or without the insertion of a bicanalicular silicone tube. The allocation was computer-generated and a sealed opaque envelope method was used to ensure blinding.

Studies III and IV were prospective, open clinical trials and investigated the expression of HSP 47 in metaplastic nasal mucosa (Study III), and the impact of primary EN-DCR on the QoL and symptoms (Study IV).

4.3 Preoperative assessment

In Study I, all the patients were examined preoperatively by an ophthalmologist and an otorhinolaryngologist, and their symptoms before the EN-DCR procedure were assessed and recorded in the patients' medical records.

In Studies II-IV, the clinical assessments for all patients were done by an otorhinolaryngologist and included endoscopic examination of the nasal cavity and irrigation of the lacrimal sac, which was performed to check the patency of the nasolacrimal pathway and to rule out presaccal obstructions. Preoperatively all patients underwent CT scans to clarify the detailed anatomy of the paranasal sinuses, the nasal cavity and the lacrimal pathway. Contaminant infections of the paranasal

sinuses and nasal cavity were carefully treated preoperatively. Findings in the nasal cavity were assessed and scored by an otorhinolaryngologist using the Lund-MacKay (Lund and Mackay 1993) staging system (Appendix). The use of anticoagulation medications was checked carefully and ceased ad hoc if possible preoperatively.

During the preoperative visit (Studies II-IV), all the patients filled out a Nasolacrimal Duct Obstruction Symptom Score (NLDO-SS) questionnaire and preoperative data study forms.

4.4 Surgical methods

In Studies I-IV all the operations were performed under standardized endotracheal general anesthesia. To provide sufficient topical decongestion and hemostasis, all the patients received 40 mg/mL cocaine hydrochloride or lidocaine hydrochloride with 1 μg/mL epinephrine solution cotton wads 30 minutes before being taken to the operating theatre, and an injection of 5mg/mL lidocaine with 1 μg/mL epinephrine into the nasal mucosa over the proposed rhinostomy site after endotracheal intubation.

All the operations in Studies II-IV were performed by the same three experienced otorhinolaryngologists. Each operation was performed jointly by two of the surgeons. The assistant surgeon introduced a 20-gauge endoilluminator probe (Alcon®, Alcon Laboratories, Fort Worth, USA) through the inferior canaliculus into the lacrimal sac. The location of the lacrimal sac was visualized endonasally by transillumination. The surgery was done using a 0° 4-mm rigid endoscope (Karl Storz®, Tuttlingen, Germany) with a video display monitor. In Studies II-IV, the mucosa over the rhinostomy site was partially removed for histological analysis at the beginning of the operation and the rest was lifted with a dissector and tucked medially under the middle turbinate. The rhinostomy was accomplished using a diamond burr attached to a microdebrider (Xomed®, Medtronic Xomed Surgical Products, Jacksonville, USA). The lacrimal sac was exposed and opened wide under endoscopic control. A bicanalicular lacrimal silicone tube (Bernard, Unomedical Ltd.,

Redditch, UK) was inserted if the patient had been randomized for tubing (StudyII). Hemostasis was achieved with nasal packing (Merocel®, Medtronic Xomed Surgical Products, Jacksonville, USA) under the middle turbinate, when needed.

4.5 Histology

In Study III, the histological samples from the nasal mucosa were fixed in formalin and further processed according to routine protocols. The adequacy of the samples was confirmed by having the Haematoxylin-Eosin (HE) stained sections analyzed by an experienced histopathologist. The samples were cut into 5 μm thick sections, which were used in immunohistochemical analyses.

4.6 Immunohistochemistry

In Study III, the sections were deparaffinized in xylene and rehydrated in graded ethanols according to standard procedures. Endogenous peroxidase was blocked by 3 mg/mL hydrogen peroxide. A histostain™ Plus Mouse Primary Bulk kit (Zymed Laboratories, San Francisco, USA) was used for immunostaining HSP47 (1:100 dilution, Stress, Ann Arbor, USA). The appropriate dilution and the functionality of the antibody had been tested previously (Razzaque and Taguchi 1997). The negative controls were processed without the primary antibody, and showed no positivity.
All stainings were analyzed by the same observer, unaware of the clinical data of the patients. The staining signal for HSP47 was located in the cell cytoplasm. The staining intensity in the epithelium and stromal tissue was analyzed separately and was graded as follows: 0=negative, 1=weak, 2=moderate, 3=strong. Strong intensity was comparable to that seen in negative controls. Because of the heterogeneous staining intensity found in many slides, a 50% cut-off level was used, i.e. the case was considered moderately or strongly stained if >50% of the epithelial or stromal cells showed that intensity.

4.7 Postoperative treatment and assessments

4.7.1 Postoperative care and objective assessments

In Studies I-IV, during the postoperative period all the patients were treated with topical dexamethasone and chloramphenicol eye-drops for two week, and intranasal saline spray for one month. During the first postoperative visit (Studies II-IV), before irrigation of the lacrimal sac, debridement was performed, i.e. the rhinostoma site and middle meatus were cleaned with suction by using a nasal endoscope in local anesthesia (Studies I-IV).

In Study II, the silicone tubes were removed at the second postoperative visit (at two months after surgery). The objective assessment was done by an otorhinolaryngologist using a rigid endoscope and lacrimal sac irrigation at each visit. In Studies II-IV, the objective findings in the nasal cavity were scored using the Lund-MacKay staging system (Lund and Mackay 1993). The surgical outcome was considered successful (Studies I-IV) if the saline solution freely reached the nose during the lacrimal sac irrigation and if the patients had no tearing or recurrent infection of the lacrimal sac.

4.7.2 Postoperative questionnaires

In Studies II-IV, during each postoperative visit the patients filled in the NLDO-SS questionnaire, which consists of five items focused on the common ocular symptoms of NLDO (Bakri et al. 1999), two items describing the conditions in the nasal cavity, and one item on general condition (Appendix). In the NLDO-SS, the symptoms are graded using an 11-point numeric rating scale (NRS; 0 = no symptoms, 10 = worst imaginable symptom). The questions were carefully explained to the patients each time before they completed the questionnaires, and the answers were checked by the otorhinolaryngologist during the visit.

The Glasgow Benefit Inventory (Robinson et al. 1996) consists of 18 questions, which in Studies II-IV were adapted for use with a nasal operation. In the GBI, the response

to each question is based on a five-point Likert scale (Likert 1932) ranging from a large deterioration in health status through to a large improvement in health status. The GBI is scored into a total score and three subscales, each ranging from -100 (maximal negative benefit) through zero (no changes) to +100 (maximal positive benefit). The subscales consist of a general subscale (12 questions), a social support subscale (three questions), and a physical health subscale (three questions) (Robinson et al. 1996).

4.8 Statistical methods

In Studies I-III, differences between groups were assessed with the Pearson Chi-Square and Fisher's exact test. The correlations between categorical variables were assessed with Pearson's correlation coefficient.

In Study II, twenty-three operations in each group were found to have over 80% power to demonstrate a difference of 35% between the successful and failed procedures in each group when the two-sided level of staistical significance was set to 5%.

In Study IV, repeated measures analysis of variance between groups was used to study the differences between the measurement time points. *Post hoc* tests were based on estimated marginal means and were Bonferroni corrected. Correlations between variables were assessed with Spearman's correlation coefficient.

In Studies I-IV, 95% confidence intervals (CI) were calculated for the main results, and all the analyses were performed on an intent-to-treat basis. Differences were regarded as statistically significant if a two-sided P-value was less than 0.05. Data are expressed as the number of cases or mean with standard deviation (SD). Patient characteristics and variables were analyzed with the Statistical Package for Social Sciences (SPSS software version 11.5-17.0 for Windows, SPSS Inc., Chicago, USA).

4.9 Ethical aspects

The study was approved by the Research Ethics Committee of the Hospital District of Northern Savo, Kuopio, Finland (decision number 59/2004) and it was conducted in accordance with the Declaration of Helsinki (The World Medical Association (WMA) 1998). The patients were given oral and written information about the trial protocol and they provided written consent.

5 RESULTS

In the prospective Studies II-IV, all 64 patients (68 operations) presented at the one-week and two-month follow-up visits. One patient died 4 months after surgery (cerebral palsy, not related to surgery) and thus the 6-month follow-up visit data involved 63 patients and 67 operations. Five patients did not respond to the 12 month questionnaire, and thus the 12 month follow-up data were available for 58 patients (62 operations).

Bilateral surgery was performed in four patients. Additional surgery for abnormalities in the nasal cavity interfering with the operation, such as septal deviation (three patients), hypertrophic middle turbinate resection (two patients) or infundibulotomy (two patients), was performed in seven patients.

5.1 Surgical outcome (Studies I-IV)

In the combined study population (Studies I-IV), the overall success rate after EN-DCR was 89% (98/110 operations), and the overall success rate after primary EN-DCR was 88% (79/90 operations).

The success rate of primary EN-DCR (Studies I-II) with silicone tubing was 80% (28/35 operations), and 91% (30/33 operations) without tubing.

In the observational follow-up study (Study I) of 36 patients with 42 operations, the overall success rate after EN-DCR was 36 out of 42 (81%) operations. The success rate with silicon tubing was 16 out of 18 operations, and without tubing it was 18 out of 24 operations (mean difference 14%, 95% CI of the difference; 10 to 38%, p = NS, Fisher's exact test). Primary surgery was successful in 17/23 (74%) operations, 10/12 (83%) with silicone tubing and 7/11 (64%) without tubing. Revision surgery was successful in 17/19 (89%) operations; 6/6 (100%) with silicone tubing and 11/13 (85%) (p = NS) without tubing.

In the prospective study (Studies II-IV), the overall success rate after primary EN-DCR at the six-month follow-up was 62 out of 67 (93%) operations. At the two-month follow-up visit, each patient's rhinostoma was open (Study II). At the six month

follow-up visit, the rhinostomas of all primary EN-DCR without silicone tubing 23/23 (100%) were open, whereas in the silicone tubing group the rhinostomas were open in only 18/23 (78%) of operations (mean difference 22%, 95% CI of the difference; 4 to 40%, p<0.049).

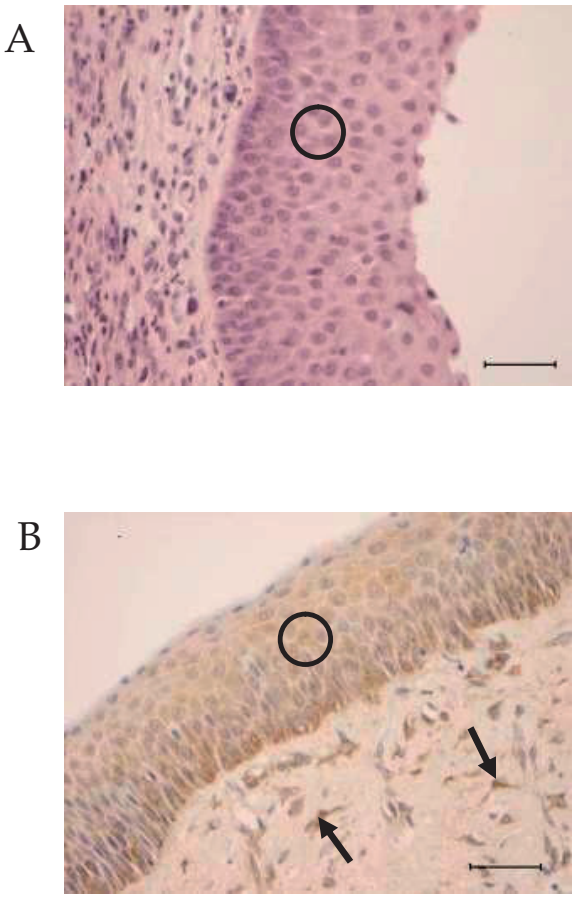
5.2 Expression of HSP 47 in nasal mucosa (Study III)

Histopathological evaluation

In 10 out of 30 patients, squamous metaplasia was noted on the surface epithelium associated with the mild chronic lymphoplasmacytic inflammation in the stroma surrounding the mucus-secreting glands (Figure 8A). Squamous metaplasia in the surface epithelium was associated with unsuccessful EN-DCR (P = 0.031).

A positive expression of HSP47 was noted both in the cells of the surface pseudostratified epithelium and in the columnar epithelium of the stromal glands. A metaplastic change in the surface epithelium was associated more often with moderate or strong expression of HSP47 (Figure 8B). In the samples with metaplasia, moderate or strong stromal expression for HSP47 was found in 8/10 patients (P = 0.02). All cases with failed outcome showed either strong or moderate expression of HSP47 (P = 0.014).

Figure 8 A-B. Histopathology of the nasal mucosa.



A. Hematoxylin-eosin section of the nasal mucosa showing squamos metaplasia in the surface epithelium (circle).

B. Immunohistochemial staining demonstrating strong expression of HSP47 in the metaplastic epithelium (circle). HSP47 expression is also noted in stromal cells (arrows). Bar = 50μm.

5.3 Impact on quality of life and symptom changes (Study IV)

5.3.1 Quality of life

All three questionnaires were fully completed by 58 of 63 (92 %) patients. A significant benefit from the EN-DCR was observed at all three times of assessment. At two months, the GBI scores were higher in all three subsets, and between the two- and six-months assessments a further gain was reported in the general and physical subsets (P = 0.001) (Table I).

Table I. Distribution of GBI scores by subsets at two and six months after EN-DCR.

	Two months	Six months	
	Mean scores (95% Confidence Interval[a])		P - value
Total GBI score	+37.0 *(29.7-44.2)	+52.3 * (45.1-59.5)	0.001
General subset score	+36.4 * (28.8-43.9)	+53.0* (45.7-60.2)	0.001
Physical subset score	+39.6 * (31.5-47.6)	+56.0 * (47.5-64.5)	0.001
Social subset score	+36.8 (27.8-45.9)	+46.1 (37.0-55.2)	0.192

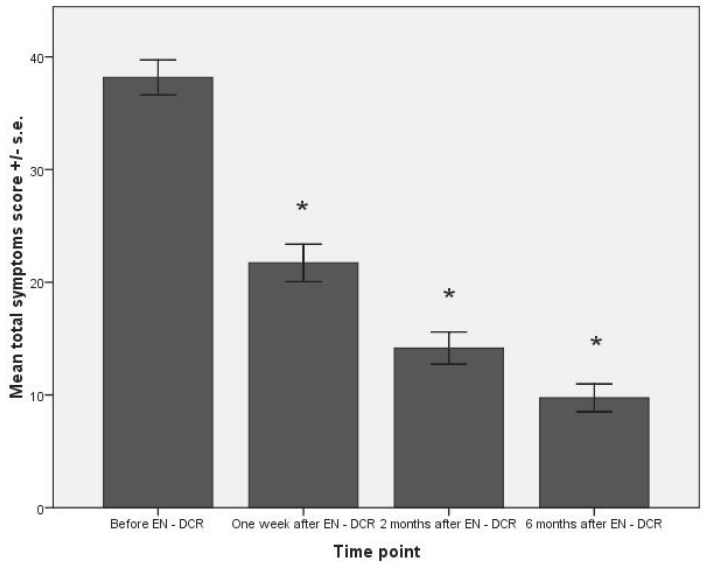
* The mean difference is significant at the P=0.05 level

a. Adjustment for multiple comparisons: Bonferroni.

5.3.2 Nasolacrimal Duct Obstruction Symptom Score (NLDO-SS)

EN-DCR resulted in a significant reduction in all of the eight items: the mean total score fell from 38 points (SD 13) at baseline to 10 (10) points (mean difference 28, 95% CI 23-33, P = 0.001) at six months (Figure 9). The greatest reduction was detected in the five ocular symptoms, in which the mean score decreased from 26 points (9) at baseline to 5 (7) points (P = 0.001) at 6 months (Figure 10).

Figure 9. Total Nasolacrimal Duct Obstruction Symptoms Score (NLDO-SS) at baseline and three assessment times after EN-DCR.

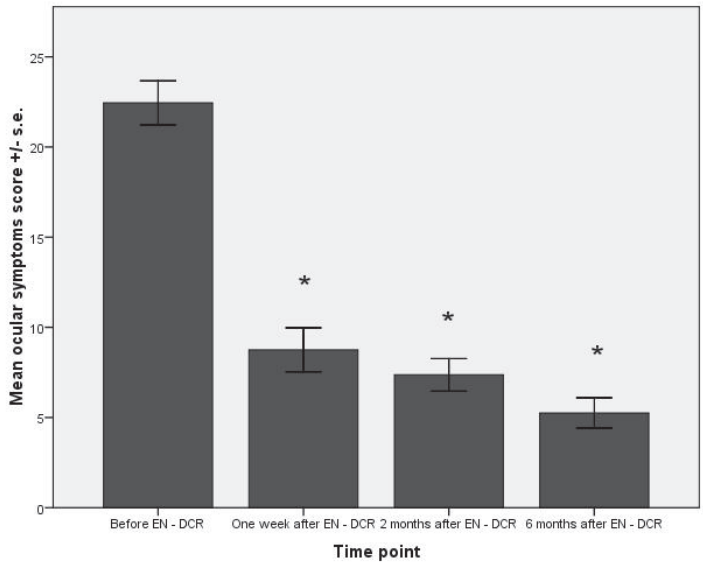


Data are mean with standard error (s.e.)

* Statistically significant difference, P=0.001

EN-DCR= endoscopic dacryocystorhinostomy

Figure 10. The mean scores of five ocular symptoms at baseline and at three assessment times after EN-DCR.



Data are mean with standard error (s.e.)

* Statistically significant difference P=0.001

EN-DCR = endoscopic dacryocystorhinostomy

5.3.3 Correlations

The correlations of GBI, NLDO-SS and Endoscopic Lund-MacKay Score were calculated for the two- and six-month's postoperative visits. There was a negative correlation between total GBI and NLDO-SS (r = -0.314, P = 0.009; r = -0.394, P = 0.001, respectively). A negative correlation was found between total GBI and Endoscopic Lund-MacKay Score at six months after operation (r = -0.258, P = 0.037), and a positive correlation between Endoscopic Lund-MacKay and NLDO-SS at two and six month's postoperative visits (r = 0.289, P = 0.017; r = 0.245, P = 0.046, respectively). There were no correlations between total GBI, Endoscopic Lund-MacKay and NLDO-SS at two months after operation (P = NS) (Table II).

Table II. Correlation between Glasgow Benefit Inventory, Nasolacrimal Duct Obstruction Symptom Score (NLDO-SS) and Endoscopic Lund-MacKay Score at two and six months after EN-DCR.

	At two months after EN-DCR		At six months after EN-DCR	
	r - value	P -value	r -value	P -value
Variable				
Total GBI score <=> NLDO-SS	-0.314**	0.009	-0.394**	0.001
Lund-MacKay score <=> NLDO-SS	0.289*	0.017	0.245	0.046
Total GBI score <=> Lund-MacKay score	0.658	0.055	-0.258*	0.037

r=correlation coefficient

** Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

EN-DCR= endoscopic dacryocystorhinostomy

6 DISCUSSION

Although EXT-DCR is still considered to be the "gold standard" (Tarbet and Custer 1995a), this study shows that EN-DCR is an effective and safe treatment for post-saccal obstruction of the nasolacrimal pathway. The standard procedure for DCR has involved stenting the rhinostoma with a silicone tube at the end of the operation (Gauba et al. 2008). However, the prospective part of this study reveals that silicone tubes do not provide any further benefits. Moreover, in this study successful EN-DCR had a positive impact on the patients' well-being. This study also confirms that adhesions of the rhinostomy site are the main cause of EN-DCR failure and that preoperative histopathological changes in the nasal mucosa may affect the final outcome.

6.1 Overall success of EN-DCR

In the combined study population (Studies I-II), the overall success rate after EN-DCR was 89% (98/110 operations). However, the success rate in the prospective study was higher than in the retrospective study (93% vs. 81%). This may be explained by an effect of the learning curve and the use of the same standard technical approach.

The results in our trial are well in line with those of earlier studies assessing the effect of EN-DCR, where the success rate has varied between 83% (Jokinen and Kärjä 1974) and 96% (Sprekelsen and Barberan 1996).

Outcomes after EN-DCR and EXT-DCR were comparable, with good results maintained over time. A recent retrospective comparison of outcomes between EN-DCR and EXT-DCR showed that the success rate (94%) for EXT-DCR is slightly better than that (86%) for EN-DCR (Leong et al. 2010b). The success rate of microscopic endonasal DCR including laser procedures has varied between 80 and 88% (Hausler and Caversaccio 1998, Dietrich et al 2003). A prospective randomized comparison of EXT-DCR and EN-DCR with the CO2-Nd: YAG laser reported a 91% success rate for the external approach compared with 75% for the endonasal technique (Hartikainen

et al. 1998a). However, Leong and co-workers (2010a), in a systematic review of outcomes after DCR in adults, showed that the failure rate for laser-assisted DCR was higher.

6.2 Use of silicone tubing

The studies evaluating the effect of silicon tubes after EN-DCR have shown considerable inconsistency. There are studies that demonstrate favorable effects of silicone tubing, such as the prevention of the obliteration of the rhinostomy site, leading to more successful EN-DCR (Kong et al. 1994, Shun-Shin 1998, Szubin et al. 1999, Wu et al 2009a). On the other hand, other studies have reported that the omission of silicone tubes does not increase the risk of obliteration (Mortimore et al. 1999, Unlu et al. 2000, Unlu et al. 2002, Ressiniotis et al. 2005). Although the use of silicone tubing after EN-DCR has been widely recommended (Woog et al. 1993, Boush et al. 1994, Weidenbecher et al. 1994) no randomized controlled studies have been carried out on the effects of silicone tubes.

This is the first randomized controlled study on the effect of silicone tubes after primary EN-DCR, and it did not detect any benefit. Furthermore, all failures were found in patients who had undergone silicone intubation after EN-DCR. In the patients suffering a failure, tearing recurred during the four weeks after the removal of the silicone tubes. It was observed that the main reason for failures was the formation of scar tissue obscuring the rhinostomy site. Based on our findings, the insertion of silicone tubes is not recommended after primary EN-DCR.

6.3 Quality of life and symptoms after primary EN-DCR

In the present study, primary EN-DCR was found to result in marked improvements in QoL and in symptoms related to obstruction of the nasolacrimal duct. Moreover, a correlation between the GBI and NLDO-SS questionnaire was found, which together proved to be more effective than the GBI alone for the assessment of outcome after endonasal dacryocystorhinostomy. Our finding supports those of previous studies

reporting a positive impact on QoL related to EN-DCR (Bakri et al. 1999, Ho et al. 2006, Spielmann et al. 2009). Our trial indicates that successful primary EN-DCR has a significant impact on the patients' QoL, and the health benefits improved significantly up to six months after operation. The NLDO-SS questionnaire proved to be reliable, sensitive and simple to use for EN-DCR patients, and together with the GBI gives more information about the outcome after a nasolacrimal intervention than the GBI alone.

6.4 Risk factors for failure in EN-DCR

Several prognostic factors may affect the outcome of primary EN-DCR. Önerci and co-workers demonstrated that EN-DCR is a relatively infrequent operation, with an obvious learning curve. Thus, experience plays an important role in the success of the procedure (Önerci et al. 2000). Therefore, less experienced surgeons performing the procedure infrequently and alone increase the risk of failure. In the present study all operations were performed by three experienced surgeons. Moreover, the teamwork of two surgeons worked well.

A history of chronic or recurrent sinusitis, or additional nasal surgery at the same time with EN-DCR, has been shown to increase the risk of EN-DCR failure (Allen et al. 1988, Nussbaumer et al. 2004). Our results show (Study IV) that patients who had pre- or postoperative infection in the nasal cavity or sinuses, and those who underwent additional surgery at the same time as EN-DCR, were at risk to develop an obstruction between 6 and 12 months after the operation.

A postoperative infection (Osguthorpe and Calcaterra 1979, Osguthorpe and Hoang 1991, Allen and Berlin 1989) also endangers the normal healing process and surgical outcome of EN-DCR, so postoperative care and the timing of the postoperative follow-up visits are considered to be a crucial factor for the success of DCR (Kong et al. 1994, Hong et al. 2005). In the present study, we adhered to the recommendation to clean the rhinostomy site one week after operation (Kong et al. 1994, Metson et al. 1994, Hartikainen et al. 1998a) and performed the local irrigation of the nasal cavity with saline spray (Woog et al. 1993, Szubin et al. 1999, Unlu et al. 2000) and

antibiotic-steroid eye drops for two weeks postoperatively (Wormald 2002).

However, sometimes, regardless of the surgeon's experience, a meticulously executed operation and postoperative care, the outcome may still not be satisfactory. The cause of failure can also be situated at the cell level of the nasal mucosa (Goldberg 2004).

The nasal cavity is normally covered by ciliated columnar pseudostratified epithelium. The epithelium consists of three main cell types: ciliated cells, goblet cells and basal cells. However, alterations in the epithelium occur from pseudostratified portions to ciliated columnar, simple cuboidal and metaplastic change. These cellular changes are considered to be adaptive, controlled by different exposures. The histopathological changes of the nasal mucosa are induced by different toxins, gas, chemical evaporations, smoking, allergy, or recurrent or chronic inflammation of nasal mucosa. All these irritants increase the risk of developing metaplasia in the surface of the nasal mucosa (Skoloudik et al. 2009, Hadar et al. 2009, Lei et al. 2010). However, no data regarding the importance of squamos metaplasia in the surface epithelium in asymptomatic person are available. This is because it is difficult to see the macroscopic difference between squamos metaplasia and normal nasal mucosa. Because squamos metaplasia alone is non-symptomatic, the histopathological changes of the nasal mucosa are observed incidentally when performing a biopsy for some other reasons. On the other hand, squamos metaplasia may be temporary and disappear when the effects of the irritants stop, and the structure of the surface epithelium returns to normal.

In order to evaluate the factors related to wound healing and possibly affecting the final outcome of primary EN-DCR, we analyzed the preoperative histopathological changes of the nasal mucosa. Squamous metaplasia in the surface epithelium was associated with unsuccessful EN-DCR. It was observed in the follow-up that patients with metaplasia in the surface epithelium also had either scar or granulation tissue over the rhinostomy site. Moreover, all cases with failed outcome showed either strong or moderate expression of HSP47, which is implicated in the molecular maturation of various types of collagens.

The present study demonstrates that both preoperative metaplastic changes and strong expression of HSP47 in nasal mucosa predict scar tissue formation after primary EN-DCR. Moreover, if both of these predictors are present, the risk of failure seems to be even higher. These findings open a new perspective for exploring the regulation of inflammation and fibrosis in the nasal mucosa, which might uncover novel predictors of outcomes for operations in the nasal cavity. HSP47 is a promising focus for future studies as a potential target for developing anti-fibrotic therapy in different surgical problems or diseases to prevent scar formation. Further studies are needed to clarify whether these predictors have any implications for operative techniques and preoperative and postoperative treatments in patients with NLDO.

6.5 Limitations of the present study

The number of patients in the present study was not extensive, as has been the case in most other studies concerning EN-DCR. This probably results from the relatively small number of EN-DCR operations performed in single centers. The problem is statistically exaggerated when patients are divided into smaller subgroups within a study.

The objective findings in the nasal cavity were scored using the Lund-MacKay staging system (Lund and Mackay 1993). As was to be expected, a statistically significant difference was found between the preoperative and one-week postoperative Lund-MacKay Endoscopic score, but after mucosa healing we did not find any difference in scores. Moreover, objective assessment and scoring of the postoperative condition in the nasal cavity depends on the individual scorer.

Although the results regarding the necessity of silicone tubing are promising, they need to be replicated in larger studies. Furthermore, a longer follow-up time than six months may give more reliable objective outcome information.

In the present study the completion of the 12 months GBI questionnaire at home turned out to be difficult for the study population, which consisted of elderly patients. Several patients had misunderstood the questions when answering them by themselves without guidance. To prevent misunderstanding of the questionnaire, we

recommend that patients complete the quality of life questionnaire during the follow-up visit.

EN-DCR operations are performed endonasally, whereas the main causes of complaints in patients with NLDO are in the ocular region. NLDO-SS correlates well with the GBI and Lund-MacKay score, but the NLDO-SS questionnaire needs further validation in future prospective randomized studies.

7 CONCLUSIONS

1. EN-DCR is an effective procedure with an overall success rate of 89%.
2. Primary EN-DCR is a highly successful surgical procedure with an overall success rate of 93% at the six-month follow-up.
3. The insertion of silicone tubes after primary EN-DCR operations does not contribute any benefit.
4. Squamous metaplasia in the surface epithelium of the nasal mucosa and strong expression of HSP47 independently or together predict scarring of the rhinostomy site.
5. Successful primary EN-DCR seems to have a significant positive impact on the patients' symptoms and QoL.

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APPENDIX:

Preoperative Data

Nasolacrimal Duct Obstruction Symptom Score Questionnaire (NLDO-SS)

Endoscopic Dacryocystorhinostomy: objective assessements

Surgery Form

Glasgow Benefit Inventory Questionnaire

Original publications I – IV

PREOPERATIVE DATA patient number _____

ENDOSCOPIC DACRYOCYSTORHINOSTOMY

NAME **Tel:**

Gender: _____ **Height/weight:** _____
Smoking 1 Yes 2 No

Predisposing medical condition: _____

_____

Medication during the last two weeks:

_____

Have you taken medicine for nasolacrimal system disorder?
During the last 3 months?
1. Yes, how many times?_____ _____
2. No

During the last 12 months
1. Yes, how many times?_____
2. No

Have you undergone a nasolacrimal procedure?

During the last 12 months
1. Yes, _____times
2. No

During the last 3 years
1. Yes, _____times
2. No

Have you been treated for rhinosinusitits?

1. Yes,_____times
2. No

Have you been on sick-leave because of nasolacrimal problems?

During the last 3 months
1. Yes, _____days
2. No

During the last 12 months _____
1. Yes, _____days
2. No

Do you think that your working capacity has been compromised?
During the last 3 months
1. Yes, _____days
2. No

During the last 12 months _____
1. Yes, _____days
2. No

Patient's name: _____ Patient number_____

NASOLACRIMAL DUCT OBSTRUCTION SYMPTOM SCORE QUESTIONNAIRE (NLDO-SS)

PATIENTS'SYMPTOMS (patients fill in themselves)

SYMPTOM	BEFORE EN-DCR	ONE WEEK AFTER EN-DCR	TWO MONTHS AFTER EN-DCR	SIX MONTHS AFTER EN-DCR
TEARING				
DISCHARGE IN THE EYE/EYES				
SWELLING AROUND THE EYE/EYES				
PAIN AROUND THE EYE/EYES				
CHANGE IN VISUAL ACUITY				
NOSE BLOCKAGE				
NASAL CAVITY DISCHARGE				
GENERAL CONDITION				
TOTAL SCORE _____				

OTHER SYMPTOMS:_____

SCORING:
Grade your symptoms numerically on a scale from 0 to 10
(0 = no symptoms, 10 = worst imaginable symptom)
Thank you!

ENDOSCOPIC DACRYOCYSTORHINOSTOMY: OBJECTIVE ASSESSEMENTS

clinical findings at the preoperative and follow-up visits (filled in by an otorhinolaryngologist)

FINDINGS IN NASOENDOSCOPY

	BASELINE	1 WEEK	2 MONTHS	6 MONTHS
POLYPS, DX				
POLYPS, SIN				
OEDEMA, DX				
OEDEMA, SIN				
SECRETIONS, DX				
SECRETIONS, SIN				
SYNECCHIAE, DX*				
SYNECCHIAE, SIN*				
CRUSTING, DX *				
CRUSTING, SIN				
TOTAL SCORE				

Other findings:_____

SCORING: For polyps: 0=none, 1=in the middle meatus, 2= extending outside the middle meatus.
For the odema, synecchiae and crusting: 0=none, 1=mild, 2= severe.
For secretions: 0=none, 1= light, non-putulent discharge, 2=thick, purulent discharge.
Only for postoperative assessment (Endoscopic Lund-MacKay Score).

EVALUATION OF NASOLACRIMAL DRAINAGE

	BASELINE	1 WEEK	2 MONTHS	6 MONTHS
IRRIGATION, dx				
IRRIGATION,sin				
FLUORECEIN DYE TEST,dx				
FLUORECEINDYE TEST,sin				

SCORING: 0= no obstruction (solution /fluorescein drains freely into the nasal cavity), 1=obstruction (solution reflux through the opposite punctum/no fluorescein in nasal cavity)

Laboratory culture:_____

PREOPERATIVE CT-FINDINGS

SINUS	DEXTER	SINISTER
MAXILLARY SINUS		
ETHMOIDAL SINUSES		
BONY NASOLACRIMAL DUCT		
LACRIMAL SAC		
TOTAL SCORE:		

SCORING: For sinuses: 0=normal aeration, 1=partial opacisication, 2=total opacisication
For bony nasolacrimal duct: 0= unobstructed, 1= partial stenosis, 2= total stenosis
For lacrimal sac: 0= normal size, 1= partially cicatrized, 2= totally cicatrized, 3= dilatated.

SURGERY FORM patient number _____

ENDOSCOPIC DACRYOCYSTORHINOSTOMY

NAME:_____

Date of surgery:_____

ASA class 1 2 3 4 5

Operative diagnosis **1**. Chronic dacryocystitis **2**. Chronic dacryostenosis **3**. Other, specify:_____

_____

Operation

1.DCR without silicone tube **2**.DCR with silicone tube **4**. Revision with MMC **5**.Revision without mitomycin MMC

Additional surgery:

1. Uncinectomy **2**. Middle meatal antrostomy **3**. 1+2 **4**. 1+2 and polypectomy **5**. Other; specify

_____

Surgeon: _____

Beginning of surgery time:_____

End of surgery time:_____

Supplemental anaesthesia during surgery **1**. No **2**. Yes, specify_____

_____

Bleeding:	1. No bleeding
	2. Less than usual
	3. Normal
	4. More than usual
	5. Other, specify?
Amount of bleeding:	Total_____ ml
Hemostasis:	1. None
	2. Packing
	3. Electrocoagulation
	4. Packing and electrocoagulation
	5. Other, specify? _____

Glasgow Benefit Inventory Questionnaire

1. Has the result of the *nasolacrimal operation* affected the things you do?				
Much worse	A little or somewhat worse	No change	A little or somewhat better	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	Much less self-confidence
5	4	3	2	1
6. Since your *operation/intervention, 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/intervention, do you feel that you have more or less support from your friends?**				

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

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

9. Since your *nasolacrimal operation/intervention, 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/intervention, 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/intervention, 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/intervention, do you catch colds or infections more or less often?**

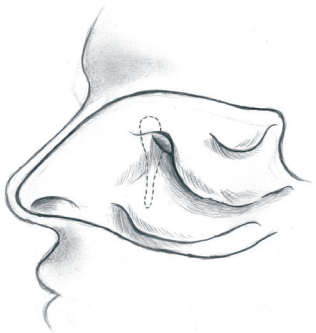
Much more often	More often	No change	Less often	Much less often
1	2	3	4	5

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

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

Grigori Smirnov

Outcome of Endonasal Endoscopic Dacryocystorhinostomy in Adults



Endoscopic dacryocystorhinostomy has become accepted treatment for patients with saccal and post-saccal obstructions of the lacrimal system. In this study the surgical outcome after two endoscopic dacryocystorhinostomy surgical techniques, with and without the use of lacrimal silicone tubes were investigated. In addition, the relationship between the preoperative conditions of nasal mucosa and final outcome of surgery was evaluated. This dissertation also provides new information about effect of preoperative changes in nasal mucosa on surgical outcome and the role of heat shock protein 47 (HSP47) expression in scar formation of the nasal mucosa.

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