On Nerve Function after Orthognathic Surgery

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Cover illustration: Normal nerve structure under light microscopy

To My parents and family

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ABSTRACT

Background

Orthognathic surgery is a surgical intervention to correct dentofacial anomalies. It is a complicated treatment that involves cooperation of different specialties. The success of orthognathic surgery is multifactorial with many elements to be taken into consideration. It is estimated that about 11 patients among every 100.000 Swedish citizens are in need of orthognathic surgeries (Bergström, Filipsson, Jensen, & Westermark, 1995). The most common surgical procedures for correction of mandibular deformities are the sagittal split osteotomy (SSO) and vertical ramus osteotomy (VRO), which is done either with an intraoral approach (IVRO) or an Extraoral approach (EVRO). Genioplasty is also often done, sometimes combined with other orthognathic surgeries. Despite the various modifications added to these operations to enhance their performance and results, nerve injury afterwards, especially after the SSO can occur. Neurosensory disturbance (NSD) following such trauma is still the main and most common drawback after these operations (Panula, Finne, & Oikarinen, 2001).

Objectives

This thesis is based on five studies. The aims of the first study were to investigate the incidence of sensory changes after SSO and whether it was different between osteotomy alone and osteotomy with genioplasty and to assess the impact of sensory disturbances on patients' satisfaction. The second study aims were to evaluate NSD after SSO and IVRO, asses the difference between questionnaire and patient's record in evaluating the NSD

and to evaluate the discomfort caused by NSD. The aim of the third study was to assess the patients' satisfaction after EVRO and discomfort regarding sensory and motor nerve disturbances. The fourth and fifth study aimed to investigate in an experimental animal model the difference in degenerative and regenerative patterns between a sensory and a motor nerve (the Mental Nerve (MN) and the Buccal branch of Facial Nerve (BF) respectively) using an unbiased stereological technique and further to study the effect of Steroids on nerve de- and regeneration.

Material and Method

For the first 3 retrospective studies, questionnaires were sent to the patients. In addition, answers in the second study were checked against patients' records. Paper 4 and 5 were animal studies; MN and the BF were injured in 48 Wister rats, half of which were treated with steroids perioperatively. The injured nerves were then studied using an unbiased technique called 2D Stereology.

Results

No significant differences in NSD incidence were found between the patients who had osteotomy alone and those who also had genioplasty. Sensory disturbances are not a main determinant of patients' satisfaction. There was disagreement between patients' records and questionnaire in which symptoms of long lasting NSD were underestimated by the surgeon. Only 1% had permanent NSD following EVRO although resultant scar tissue was of concern to 30% of patients involved. The regenerative process is faster and/or more complete in the facial nerve (motor function) than it is in the mental nerve (sensory function). There were an increased number of regenerating axons after perioperative treatment with Betamethasone in both facial and mental nerves indicating that Betamethasone enhanced nerve regeneration in both motor and sensory nerves.

SAMMANFATTNING

Känselstörningar (NSD) är en inte alldeles ovanlig komplikation till kirurgisk korrektion av käkställningsfel. De bakomliggande orsakerna till NSD kan vara direkt mekanisk trauma eller indirekt påverkan på nerven pga olika faktorer.

Syftet med denna avhandling var att svara på en rad frågor om frekvensen av sensibilitetnedsättning i samband med ortognatkirurgi samt effekten av korticosteroider på utfallet av nervläkning. Detta görs med hjälp av 3 retrospektiva studier och 2 djur studier. De 3 retrospektiva studierna är från de käkkirurgiska avdelningarna i Malmö, Lund och Göteborg. Tre olika typer av ortognat kirurgiska ingrepp har studerats. I djurstudierna har vi jämfört nervläkning mellan sensorisk och motorisk nerv, både med och utan korticosterioder.

Resultaten från första studien visar att kombinationen av SSO med hakplastik ökar inte förekomsten av NSD. Sensoriska förändringar efter osteotomier är inte den viktigaste faktorn för patientens totala tillfredsställelse med behandlingen.

Resultaten från andra studien visar att NSD registrerat i frågeformulär och journalen skilde sig och indikerar en oenighet mellan kirurgens och patientens bedömning. Långvarig NSD underskattades av kirurgen jämfört med patientens subjektiva symptom.

Tredje studien visar att trots patientens oro över ärrbildning, finner vi Extraoral Sneda Ramus Osteotomier vara en säker och väl beprövad metod med nästan försumbar nervstörningar i underläppen och hög patienttillfredsställelse.

De fjärde och femte studierna visade ingen skillnad i det degenerativa mönstret mellan sensorisk (Mental) och motorisk (Buccal gren av Facial) nerv; dock BF hade regenereras till det normala antalet axoner, medan MN hade endast återvunnit 50% av det normala antalet axoner. Vi drar slutsatsen att den regenerativ processen är snabbare och / eller mer komplett i ansiktsnerven (motor funktion) än den är i MN (sensorisk funktion). Betamethasone accelererade regenerering för

både nerverna men i olika grader efter att ha följt progression av nervdegeneration och regenerering.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Br J Oral Maxillofac Surg. 2004 Apr; 42(2):105-11. Incidence of neurosensory disturbance after sagittal split osteotomy alone or combined with genioplasty. Al-Bishri A, Dahlberg G, Barghash Z, Rosenquist J, Sunzel B.

II. Int J Oral Maxillofac Surg. 2005 May; 34(3):247-51. Neurosensory disturbance after sagittal split and intraoral vertical ramus osteotomy: as reported in questionnaires and patients' records. Al-Bishri A, Barghash Z, Rosenquist J, Sunzel B.

III. Extraoral Vertical Ramus Osteotomy; a retrospective study on patient satisfaction. Barghash Z, Kahnberg KE,(to be submitted)

IV. Int J Oral Maxillofac Surg. 2013 Dec; 42 (12):1566-74. Degeneration and regeneration of motor and sensory nerves: a stereological study of crush lesions in rat facial and mental nerves. Barghash Z, Larsen JO, Al-Bishri A, Kahnberg KE.

V. Betamethasone effect on regeneration in the rat mental and facial nerves after crush lesion. Barghash Z; Larsen JO; Al-Bishri A; Kahnberg KE. (To be submitted to International Journal of Oral and Maxillofacial Surgery)

CONTENT

ABBREVIATIONS

BF   Buccal branch of Facial nerve

CNS   Central Nervous System

EVRO   Extraoral Vertical Ramus Osteotomy

GCC   Glucocorticoids

IMF   Intermaxillary Fixation

IVRO   Intraoral Vertical Ramus Osteotomy

MN   Mental nerve

NSD   Neurosensory Disturbance

PNS   Peripheral Nervous System

SC   Schwann Cell

SSO   Sagittal Split Osteotomy

VAS   Visual Analogue Scale

VRO   Vertical Ramus Osteotomy

DEFINITIONS IN SHORT

2D Stereology	Computerized microscopic program for unbiased counting
Anaesthesia	Lack of sensation to stimuli that otherwise can cause pain
Axon	Nerve cell projection connecting it to other cells
Corticosteroid	Hormones produced by the adrenal cortex or their derivatives
Genioplasty	Plastic surgery of the chin with an implant or so called sliding osteotomy
Inferior alveolar nerve	Nerve that runs inside the lower jaw
Mandible	Lower Jaw
Maxilla	Upper Jaw
Neuron	Nerve cell, the building block of the nervous system
Neurosensory disturbances	Disruption to normal sensation
Vertical ramus osteotomy	Surgery of the lower jaw for setback
Paraesthesia	abnormal sensation with no apparent cause
Sagittal split osteotomy	Surgery to the lower jaw along the nerve canal
Trigeminal nerve	Fifth cranial nerve responsible for facial and oral sensation

1 INTRODUCTION

1.1 Orthognathic surgery

 Orthognathic surgery is the science and methods for intervention in the facial and oral bones to restore function and esthetics. It is a multidisciplinary process with an outcome that is influenced by many factors. In Sweden it is estimated that about 11 patients among every 100.000 Swedish citizens are in need for such operations (Bergström et al., 1995). Patients needing orthognathic surgery can suffer from unsatisfactory mastication with symptomatic masticatory organs (muscles and joints) combined with dissatisfaction with facial esthetics.

Orthognathic surgeries vary in their technique depending on the type of defect presented and the required correction. Orthognathic operations can be done with an intra- or extraoral approach and each operation has evolved through scientific research and surgical experience to have different modalities for each operation. The major orthognathic operations dealt with here are the sagittal split osteotomy, the vertical ramus osteotomy which can be done with an extraoral or intraoral approach and genioplasty. The majority of the present theses will deal with operations to the lower jaw only. No mention will be done to orthognathic operations in the upper jaw.

Different adjustments and enhancements have been added to orthognathic surgeries throughout the years to enhance the outcome and to eliminate or decrease postoperative discomfort and side effects along with the use of medications for that purpose. One of such medications commonly used is cortisone.

1.1.1 Sagittal Split Osteotomy

 SSO was described by Schuchardt in 1942 (Schuchardt, 1942), and later modified and published by Trauner and Obwegeser in 1957 to be then accepted globally (Trauner & Obwegeser, 1957). Since then various modifications (Bell & Schendel, 1977; Dal Pont, 1961; Hunsuck, 1968;

Spiessl, 1976) have been added to assure good bone healing, increase stability, avoid unfavorable fracture, to eliminate the need for postoperative intermaxillary fixation (IMF) and decrease the incidence of NSD. After the introduction of internal rigid fixation, the need for postoperative IMF was eliminated which allowed direct mouth opening, better bone healing and decreased relapse. NSD after SSO remains the main drawback of this operation. SSO is suitable for mandibular setback as well as mandibular advancement.

1.1.2   Vertical Ramus Osteotomy

The vertical ramus osteotomy was described first as an extra oral procedure by Limberg (LIMBERG, 1925) in 1925 and later by Caldwell (Caldwell & Letterman, 1954) in 1954. The main disadvantages were visible scars extra orally, condylar drop, necrosis of the distal tip of the proximal segment and the need for postoperative IMF. Moose (Moose, 1964) overcame the drawback of the facial scar by introducing intraoral approach. Hall in 1987 (H. D. Hall & McKenna, 1987) advised that a portion of the medial pterygoid muscle should remain attached to the distal tip of the proximal segment in order to eliminate problems with condylar sag and ischemic necrosis of the distal tip of the proximal segment. VRO is only suitable for mandibular setback. VRO has better effect relieving temporomandibular joint symptoms than OSS (Westermark, Shayeghi, & Thor, 2001). Postoperative IMF is still the main drawback of the VRO.

1.1.3   Genioplasty

Surgical operations of the chin, namely genioplasty, are performed to change the shape and /or horizontal and vertical relationship of the lower face. It could be used to set the chin forward or backward or to increase/ decrease the vertical height of the face. Historically, it was first described by Hofer in 1942 (Hofer, 1942) as horizontal sliding osteotomy. In 1957 Trauner and Obwegesser (Trauner & Obwegeser, 1957) introduced the intraoral approach and in 1965 Reichenbach (Reichenbach, 1965) described the wedge osteotomy and the vertical shortening of the chin. Further modifications were added later to enhance esthetics (Field, 1981).

1.2   Neurosensory Disturbance

Despite the various modifications added to these operations to enhance their performance and results, nerve injury is still considered one of its most annoying drawbacks. Nerve injury is not an uncommon complication after orthognathic surgery. Neurosensory disturbance following such trauma is still the main and most common drawback after these operations (Panula et al., 2001).

The incidence of NSD has been documented mostly retrospectively, but also with prospective studies using a variety of subjective and objective testing methods, which vary significantly in their ability to detect and quantify the neurosensory deficit.

1.2.1   Incidence of NSD

The incidence of sensory changes has been estimated by various subjective and objective measures, which vary considerably in their ability to detect and quantify any deficit. The range after SSO was between 9 and 85% (MacIntosh, 1981; Walter & Gregg, 1979) while after VRO the incidence was from 3 to 35% (Walter & Gregg, 1979; Westermark, Bystedt, & von Konow, 1998a).

SSO is associated with higher incidence of NSD compared to VRO. Some of the causes for the high NSD incidence can be found in the way the SSO is done where the surgical technique is more difficult with a closer proximity to the nerve during the operation than is the case with VRO. Injuries to the inferior alveolar nerve during the sagittal split operation may result from stretching of the nerve during medial retraction, adherence of the nerve to the proximal segment after splitting, direct manipulation of the nerve, bony roughness on the medial side of the proximal segment, or mobilization of the segment. The relation of the mandibular canal to the lateral cortex of the mandibular ramus can affect the incidence of nerve damage (Yamamoto, Nakamura, Ohno, & Michi, 2002; Yoshioka et al., 2010). Osteosynthesis may cause injuries by compression of the inferior alveolar nerve during fixation or

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by direct injury to the nerve. The nerve may be interfered with during the osteotomy.

In VRO, if the mandibular foramen comes very near the osteotomy line, nerve injury could occur. This is concerning especially if a long proximal segment is needed. Accidental medial movement of the proximal segment after the osteotomy could also contribute to nerve injury.

1.2.2   General factors influencing NSD

Some of the factors that have major effect on the incidence of NSD after mandibular surgery are

Age of the patient

Patient age has by many authors (Al-Bishri, Dahlberg, Barghash, Rosenquist, & Sunzel, 2004; August, Marchena, Donady, & Kaban, 1998; MacIntosh, 1981; Westermark et al., 1998a; Ylikontiola, Kinnunen, & Oikarinen, 2000) been suggested to be a determinant factor in the outcome of NSD after orthognathic surgery. Patients over the age of 40 have a higher incidence of NSD (Al-Bishri, Dahlberg, et al., 2004). There are many explanations for this effect. While Nishioka et al (Nishioka, Zysset, & Van Sickels, 1987) have the opinion that osteotomy is more easily performed on the young patients, Verdu (Verdu, Ceballos, Vilches, & Navarro, 2000) suggest that it is the process of nerve aging that brings about morphological as well as functional changes to the nerve axon making nerve regeneration slow and more deteriorated. Bearing in mind that in young, healthy individuals a nerve regain only 75% of its normal capacity after regeneration, the capacity is even less in the older population. MacIntosh (MacIntosh, 1981) explained that only reluctantly did he do SSO in patients above the age of 40.

Nature of nerve injury

Seddon (1943) and Sunderland (1951) (Seddon, Medawar, & Smith, 1943; Sunderland & Roche, 1958) have both classified the nature of the nerve trauma with their respective prognosis. Axonotmesis occur in those instances where NSD, paresis or paralysis is delayed or recovery is incomplete as seen in most of the persisting NSD cases we studied ((Al-Bishri, Barghash, Rosenquist, & Sunzel, 2005; Al-Bishri, Dahlberg, et al., 2004). By definition, animal studies have demonstrated that crush injury to a nerve causes an axonotmesis (Cai et al., 1998).

Variation in the ability of the surgeon
As been shown by Westermark, Wolford and Davis and Ylikontiola (D. L. Jones, Wolford, & Hartog, 1990; Westermark, Bystedt, & von Konow, 1998b; Ylikontiola et al., 2000) the skills of the individual surgeon is a determinant factor in the outcome of NSD

Different surgical techniques
The difference between SSO and IVRO in surgical approach and the amount of trauma induced to the operation area differ considerably. Each and every surgeon has his/her own approach to do the operation in the best way as well as the methods used to protect the IAN can differ among different surgeons.it has been found that direct manipulation of the nerve bundle during surgery increased the incidence of NSD postoperatively (Kuhlefelt, Laine, Suominen, Lindqvist, & Thoren, 2014)

Methods of neurological assessment
Many methods have been advised for detecting NSD and these methods differ in their specificity and sensibility to detect NSD (LaBanc, 1992; Ylikontiola et al., 2000). Different tests to detect NSD could give different NSD incidences when done on the same patient group (Nishioka et al., 1987).

Follow up time after surgery
The absence of standardized guidelines in patient follow-up led to the problem of investigating NSD at different postoperative intervals. The difference in NSD measured 3 months respectively 2 years postoperatively can be quite considerable (August et al., 1998; LaBanc, 1992).

Concomitant surgery
Genioplasty done concomitantly with SSO or IVRO might affect the course and nature of NSD (Gianni, D'Orto, Biglioli, Bozzetti, & Brusati, 2002). Although no significant differences in NSD incidence was found in my second paper (Al-Bishri, Dahlberg, et al., 2004), it is still a factor to be mentioned as the same nerve is sometimes subjected to trauma from more than one operation.

Glucocorticoids
The use of premedication as systemic steroids , might decrease the incidence of NSD after SSO (Al-Bishri, Dahlin, Sunzel, & Rosenquist, 2005).

1.3 Peripheral nervous system

All of the nerves affected by orthognathic surgeries belong to the peripheral nervous system and it is therefore essential to discuss its different components in more details

1.3.1 Nerve anatomy

Lingual Nerve

It supplies the mucous membrane of the anterior two-thirds of the tongue. It lies at first beneath the external pterygoid muscle, medial to and in front of the inferior alveolar nerve, and is occasionally joined to this nerve by a branch which may cross the internal maxillary artery. The chorda tympani also join it at an acute angle in this situation. The nerve then passes between the internal pterygoid muscle and the ramus of the mandible, and crosses obliquely to the side of the tongue over the superior pharyngeal constrictor and styloglossus muscles, and then between the hyoglossus muscle and deep part of the submaxillary gland; it finally runs across the duct of the submaxillary gland, and along the tongue to its tip, lying immediately beneath the mucous membrane. Its branches of communication are with the facial (through the chorda tympani), the inferior alveolar and hypoglossal nerves, and the submaxillary ganglion. The branches to the submaxillary ganglion are two or three in number; those connected with the hypoglossal nerve form a plexus at the anterior margin of the hyoglossus muscle.

Inferior Alveolar Nerve

It is the largest branch of the mandibular nerve. It descends with the inferior alveolar artery, at first beneath the pterygoideus externus, and then between the sphenomandibular ligament and the ramus of the mandible to the mandibular foramen. It then passes forward in the mandibular canal, beneath the teeth, as far as the mental foramen, where it divides into two terminal branches, incisive and mental. The branches of the inferior alveolar nerve are the mylohyoid, dental, incisive, and mental. The mylohyoid nerve (n. mylohyoideus) is derived from the inferior alveolar nerve just before it enters the mandibular foramen. It descends in a groove on the deep surface of the ramus of the mandible, and reaching the under surface of the Mylohyoideus

supplies this muscle and the anterior belly of the Digastricus. The dental branches supply the molar and premolar teeth. They correspond in number to the roots of those teeth; each nerve entering the orifice at the point of the root, and supplying the pulp of the tooth; above the alveolar nerve they form an inferior dental plexus. The incisive branch is continued onward within the bone, and supplies the canine and incisor teeth. The mental nerve (n. mentalis) emerges at the mental foramen, and divides beneath the Triangularis muscle into three branches; one descends to the skin of the chin, and two ascend to the skin and mucous membrane of the lower lip; these branches communicate freely with the facial nerve (Clemente, 1985).

Facial nerve

It consists of a motor and a sensory part. The motor part supplies fibers to the muscles of the face, scalp, and auricle, the Buccinator and Platysma, the Stapedius, the Stylohyoideus, and posterior belly of the Digastricus. The sensory part has taste fibers for the anterior two-thirds of the tongue. Nerve branches on the face are Temporal, Zygomatic, Buccal, Mandibular and Cervical.

The Temporal Branches (rami temporales) cross the zygomatic arch to the temporal region, supplying the Auriculares anterior and superior, and joining with the zygomaticotemporal branch of the maxillary, and with the auriculotemporal branch of the mandibular. The more anterior branches supply the Frontalis, the Orbicularis oculi, and the Corrugator.

The Zygomatic Branches (rami zygomatici; malar branches) run across the zygomatic bone to the lateral angle of the orbit, where they supply the Orbicularis oculi.

The Buccal Branches (rami buccales; infraorbital branches) pass horizontally forward to be distributed below the orbit and around the mouth. The superficial branches run beneath the skin and above the superficial muscles of the face, which they supply. The deep branches pass beneath the Zygomaticus and the Quadratus labii superioris, supplying them and forming an infraorbital plexus with the infraorbital branch of the maxillary nerve. These branches also supply the small muscles of the nose. The lower deep branches supply the Buccinator and Orbicularis oris, and join with filaments of the buccinator branch of the mandibular nerve.

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The Mandibular Branch (ramus marginalis mandibulæ) passes forward beneath the Platysma and Triangularis, supplying the muscles of the lower lip and chin, and communicating with the mental branch of the inferior alveolar nerve.

The Cervical Branch (ramus colli) runs forward beneath the Platysma, and forms a series of arches across the side of the neck over the suprahyoid region (Gray, 1918).

1.3.2   The peripheral nerve morphology

The peripheral nerves consist of a number of axons that are surrounded by three layers of connective tissue. The first layer to surround the axons is endoneurium containing fibroblasts, macrophages, capillaries and mast cells. The second layer (perineurium) surrounds multiple axons with their endoneurium forming fascicles, it is a little denser in its structure, and collagen fibres can be seen with a few elastic fibres. The fascicles are then surrounded by the epineurium, which is the outermost layer. It consists of dense connective tissue with irregular collagen and thick elastic fibres. in myelinated nerve fibers, each SC envelopes one axon and providing it with myelin sheath while in the unmyelinated nerve fibers each SC envelopes several axons (Gartner & Hiatt, 2001; Zuniga, 1992).

1.3.3   Nerve degeneration and regeneration

When nerves are subjected to a certain amount of trauma certain type of degradation ensues. This is called Wallerian degeneration. Axonal recovery after Wallerian degeneration can occur in the peripheral nervous system (PNS) but not in the central nervous system (CNS) (Dezawa, 2000; Fenrich & Gordon, 2004). This difference in regeneration capacity between the PNS and CNS is believed to be due to the inhibitory environment of the supporting neuroglial cells of the CNS (astrocytes and oligodendrocytes). However, when the inhibitory glial environment is replaced by a peripheral nerve segment (Brecknell & Fawcett, 1996; Dezawa, 2000) or Schwann cell transplantation (Dezawa, 2000) regeneration occurs indicating that the CNS has the intrinsic capacity to regenerate. Nerve fibres in the PNS can regenerate after a nerve injury. In 12-24 hours after certain injuries the degeneration begins distally to the trauma site and continues in this direction until the axon terminal is destroyed through Wallerian degeneration. Major

histomorphological changes takes place then inside the nerve trunk The axon swells and within 2 days the myelin is degraded by Schwann cells into droplets or small whorls (Stoll & Muller, 1999; Zuniga, 1992). Infiltration of macrophages occurs within 48-72 hours. Two weeks after the injury the macrophages have occupied the basal lamina and together with Schwann cells phagocyte debris. Under this time the Schwann cells proliferate forming cell columns enveloped by the basal lamina known as Schwann cell tubes or band of Bünger (Stoll & Muller, 1999). At the other end of the axon the neuron cell body, called the perikaryon, gets hypertrophied with several other changes. These events peak after 1-2 weeks (Fu & Gordon, 1997) and can persist for several months. Degeneration even occurs proximal to the damage site and ends at the nearest node of Ranvier. Within hours after injury some nerve sprouts begin to form from the proximal portion of the axon (Ide, 1996) and the sprouting increases in the next 2-3 days (Mira, 1984). The sprouts continue to grow distally along Schwann cell tubes at the inside of the basal lamina until they reach the target organ. During the same time SC begin to form myelin around the growing axon or, in case of unmyelinated axons, a Schwann cell sheath. A total regeneration takes 3-6 months (Zuniga, 1992). In-vivo studies show that the regeneration is at a rate of 2.6-3 mm/day. The rate is faster in the unmyelinated axons (Fu & Gordon, 1997; Verdu et al., 2000). Neuromas might form if the growing sprout misses the distal portion of the axon and begin to grow in an uncontrolled manner.

1.3.4   Classification of nerve damage

Many researchers tried over the years to give a good and reliable classification of nerve trauma and subsequent prognosis. Seddon (Seddon et al., 1943) is regarded as a pioneer in this aspect. His classification (later on modified by Sunderland in 1951) is as follows

Neuropraxia

Most of the nerve traumas following orthognathic surgery are of the type neuropraxia and result in paraesthesia. It can be caused by a trauma sufficient to injure the endoneurial capillaries causing intra fascicular oedema, resulting in a conduction block with no degeneration of the axon. It may also result in segmental demyelination or mechanical disruption of the myelin sheaths. Recovery is almost complete after a short period; oedema takes few days to subside and NSD resolve generally within 1 week following nerve injury. In

more severe cases sensory and functional recovery is complete within 1 to 2 months.

Axonotmesis

Axonotmesis is followed by degeneration and regeneration of axons. It can be caused by traction and compression of the nerve and may cause severe ischemia, intra fascicular oedema and demyelination. The axons are damaged, with no disruption of the endoneurial sheath, perineurium, or epineurium. Signs of sensation or function return within 2 to 4 months following injury and continue to improve up to 8 to 10 months, but improvement leading to complete recovery might take as long as 12 months.

Neurotmesis

A neurotmesis is characterized by severe disruption of the connective tissue components of the nerve trunk with compromised sensory and functional recovery. It can be caused by traction, compression, injection injury, leading to a complete disruption of the nerve trunk. The prognosis is poor. Sensory and functional recovery is never complete. There is a high probability of development of neuroma.

Sunderland (Sunderland & Roche, 1958) based his classification more on the degree of tissue injury. In his five-degree classification the first degree, containing 3 sub degrees or types is similar to Seddon's neuropraxia. The second, third and fourth degree are similar to Seddon's classification of axonotmesis while the fifth degree describes nerve transection, similar to Seddon's description of neurotmesis.

A sixth degree was added to Sunderland classification (MacKinnon & Dellon, 1988) describing the coexistence of more than one of Sunderland injury classification within the same nerve trunk.

1.4 Corticosteroids

The adrenal cortex of the adrenal gland is responsible for the production of steroidal hormones. These are divided into 3 different types, mineralocorticoids, glucocorticoids (GCC) and androgens. Cortisol is the main GCC and affects many bodily functions. It has a daily secreted amount of 10-20 mg and this production is increased in certain conditions like stress and trauma (Becker, 2013).

Glucocorticoids affect many organ systems in the body. GCC decrease the number of leukocytes, lymphocytes, eosinophils and basophils associated with the inflammatory response. This occurs 4-6 hours after a single dose and the effect remains for about 24. Glucocorticoids also change the immunological behavior of the lymphocytes (Frydman, 1997) and prevent the production of factors that initiate the inflammatory process. This leads to a decreased secretion of vasoactive substances, lipolytic and proteolytic enzymes, decreasing the infiltration of leukocytes to the injured area. The production of cytokines and plasma leakage is also decreased (Schimmer & Parker, 2007).

There are different forms of synthetic GCC (I.e. Prednisone, Triamcinolone, Betamethasone) that are very similar in their anti-inflammatory effect and differs only in their potency, duration and Sodium-Water retention ability and therefore can be interchanged during treatment if the equipotent dose is given (Becker, 2013). It is widely accepted that a short course of GCC treatment of a week is considered safe in healthy individuals (Salerno & Hermann, 2006)

1.4.1 Steroid effect on neurons

Steroid hormones have a neurotrophic effect (Kawata, 1995). The exact mechanisms of GCC action on nerve trauma are not fully understood (Taoka & Okajima, 1998), but many have tried to explain its neuroprotective action through different mechanisms. GCC have an effect on protein synthesis associated with nerve cell survival, support dendridic and axonal processes, synaptogenesis and neurotransmission (Kawata, 1995). After nerve injury

GCC prolong the period in which mRNA expression is elevated and facilitate projection (Yao & Kiyama, 1995). Damaged neurons respond to exogenous steroid hormones (K. J. Jones, Alexander, Brown, & Tanzer, 2000). One of the mechanisms is its effect on lipid peroxidation. Hall ED (E. D. Hall, 1993) and Galloway (Galloway, Jensen, Dailey, Thompson, & Shelton, 2000) emphasized the importance of steroid as a lipid antioxidant that inhibits the oxygen free-radical-induced lipid peroxidation, which plays important role in pathochemistry of acute CNS injury, supposing that the early administration of compounds with high lipid antioxidants, such as methylprednisolone (Diaz-Ruiz et al., 2000) interrupt posttraumatic degeneration. Many studies have been done regarding the effect of steroid on the CNS. Methylprednisolone is the only medicine used to treat acute spinal cord injuries (Bracken et al., 1997). A significant increase in axonal regeneration compared to controls in an animal spinal cord injury model was noted (Nash, Borke, & Anders, 2002). A study in human (Bracken et al., 1992) showed the same beneficial results of methylprednisolone in significantly promoting both motor and sensory regeneration of the injured spinal cord if the treatment is done not later than 8 hours post operatively.

Al-Bishri (Al-Bishri, Rosenquist, & Sunzel, 2004) found in their study that patients who received moderate doses of GCC (Betamethasone) perioperatively seemed to have less sensory disturbance after sagittal split osteotomy. Animal experiment done by the same authors have shown good effect of GCC, both functionally and, although not significant, morphologically (macrophages and nerve growth factor), after traumatic injury to the sciatic nerve (Al-Bishri, Dahlin, et al., 2005). Seo (Seo, Tanaka, Terumitsu, & Someya, 2004) tried to estimate the efficacy of steroid treatment and determine the appropriate time to give the steroid after NSD related to IVRO and SSO and found favorable effects of steroid in his study. Topical steroid was also shown to be beneficial in significantly reducing NSD after nerve injury (Galloway et al., 2000).

Other authors (Chikawa et al., 2001; Rabchevsky, Fugaccia, Sullivan, Blades, & Scheff, 2002) on the other hand didn't find a beneficial effect for the use of GCC in nerve healing. A study dismissed the hypothesis of the anti-oxidant effect of GCC in nerve trauma providing animal evidence that this effect is transient and do not add to the outcome of the NSD after injury on the CNS questioning the rationale behind using high doses steroids as a treatment of choice after CNS injury. Ohlsson (Ohlsson, Westerlund, Langmoen, & Svensson, 2004) in their animal model of optic nerve injury found the same negative results after treatment with methylprednisolone.

There is no standardized formula to calculate the exact amount of steroid dose that should be given after operation, but it is logical to consider giving a dose of higher efficacy than the daily endogenous production of 15-30 mg which can rise to 300 mg/day of hydrocortisone in time of crisis (Axelrod, 1976). A dose exceeding this limit would suppress the inflammatory process better than the body itself (Gersema & Baker, 1992). Many authors consider a high dose for a short period of time to be better than a dose taking longer time to avoid possible complications such as delayed wound healing and adrenal insufficiency (Gersema & Baker, 1992; Williamson, Lorson, & Osbon, 1980). More recent studies have shown that even within the physiologically produced daily levels, GCC can decrease some inflammatory reactions hindering them from being destructive (Becker, 2013).

2 AIM

2.1 Study 1

1. The aims of this study were to find out the incidence of sensory disturbance after sagittal split osteotomy for mandibular advancement and setback
2. To find out whether the incidence of sensory disturbance was different between SSO alone and SSO with genioplasty, and
3. To assess the effect of the sensory disturbances on patients' satisfaction

2.2 Study 2

1. The aims of this study were to evaluate NSD after SSO and IVRO,
2. Asses the difference between questionnaire and patient's record in evaluating the NSD and the discomfort caused by NSD after SSO and IVRO.

2.3 Study 3

1. To evaluate patient satisfaction after EVRO
2. To evaluate NSD after EVRO
3. To evaluate any other causes of patients discomfort, such as muscle weakness or scar formation after EVRO

2.4 Study 4

1. Compare the normal anatomy between a sensory nerve (MN) and a motor nerve (BF)
2. Compare the quantitative aspects of the degenerative and regenerative patterns between MN and BF after a crush lesion

2.5 **Study 5**

The aim of the study was to investigate the effect of steroids on motor and sensory nerve healing in an animal nerve crush injury model.

3 PATIENTS AND METHODS

The first three retrospective studies were designed to investigate NSD and patient satisfaction postoperatively, through the use of questionnaire sent to the patients. The last two studies were animal studies and Wister rats were used.

3.1 Retrospective studies

3.1.1 Questionnaire

 The questionnaire was developed with the help of specialists in oral and maxillofacial surgery at the Malmö University hospital and was checked for reliability and validity by a pilot study (not published). The questionnaires were prepared to identify the patients' postoperative sensory and motor nerve disturbance as well as patient satisfaction postoperatively.

The patients were asked about any sensory change that they had noticed along the distribution of the inferior alveolar (chin and lower lip) and lingual nerves (tongue) and the duration of these changes. They were also asked about perceived muscle weakness related to facial nerve. A visual analogue scale graded from 0 (no discomfort) to 10 (intolerable discomfort) was included to allow the patients to describe the effect of these changes on their life. The patients were also asked about their satisfaction with the result of the operation. A contact telephone number was provided for any further questions, and a stamped addressed envelope was included. (See the questionnaire form, Appendix 1 and 2.)

Study 1
 All patients had the same preoperative radiographic and clinical examinations, planning of treatment, and preoperative, and postoperative orthodontic treatment. Questionnaires were mailed not earlier than one year after the operation to all patients who underwent sagittal split osteotomy alone (n = 84), (42 men and 42 women) or in combination with genioplasty (n = 37), (19 men and 18 women) in the Department of Oral and Maxillofacial Surgery at Lund University Hospital between 1995 and 2000. Of those patients who had sagittal split osteotomy alone two patients were

excluded because they had additional mandibular osteotomies and transposition of the nerve, and another 16 patients did not respond to the questionnaire. This left 66 patients (131 sides) in this group. Of the 37 patients whose sagittal split osteotomy was combined with genioplasty, one patient was excluded because the patient had an additional mandibular osteotomy and transposition of the nerve, 9 patients did not respond to the questionnaire. This left 27 patients (54 sides) in this group.

Study 2

One hundred and twenty-nine patients who underwent bilateral IVRO (79 patients, 42 females and 37 males) and SSO (50 patients, 31 females and 19 males) between 1995 and 1999 at the department of Maxillofacial Surgery, University Hospital MAS, Malmö, Sweden, were included in this study. The age of the patients ranged between 15 and 58 years with an average of 36.5 years. Questionnaires were mailed to the patients not earlier than one year after the operation. Ninety-six completed questionnaires (74%) were returned, 53 questionnaires from the IVRO patients (30 female and 23 male) and 43 from the SSO patients (27 female and 16 male). The records of all patients who returned the questionnaire were reviewed to identify any reported NSD after the operation. At the maxillofacial department in Malmö all patients are routinely followed up to18 months after the operation. During the 18 months follow up the NSD was always tested subjectively by asking the patients and objectively by using a dental probe to assess the sensory changes along the distribution of the mental nerve (lower lip and chin). All patients went through the same sequence of pre- and postoperative orthodontic treatment, treatment planning, surgical treatment and follow up. Cephalometric radiographs were taken preoperatively, immediately postoperatively, immediately after the release of intermaxillary fixation (6 weeks; IVRO), 6 months and 18 months postoperatively.

Study 3

Extraoral Vertical Ramus Osteotomies for correction of mandibular prognathism performed by Oral and Maxillofacial surgeons at the Sahlgrenska Hospital between the years 1994 and 2006 were assessed. In total, 142 patients were operated. One hundred twenty-five of them have been localized and to whom questionnaires were sent. The questionnaire was mailed to the patients not earlier than 18 months after the operation. Ninety-seven patients (78%) answered the questionnaire, 63 females and 34 males. Patients' age ranged between 15 and 48 years. All of them had bilateral operations except one, summing up a total of 193 operated sides. Eight of the patients (16 sides) had genioplasty simultaneously. The degree of mandibular movement was between 4 and 15 mm.

3.1.2   The surgical procedures

Study 1 and 2

Preparations and medications

In preparation for surgery under general anaesthesia, local anaesthesia Mepivacain with adrenaline (5mg/ml+ 5 □g/ml; Carbocain-adrenalin, Astra-Zeneca, Sweden) was infiltrated in the operated area to control bleeding throughout the operation. Antibiotics and cortisone were routinely administered to all patients during the first 24 hours (benzyl penicillin 3g x 3 or Clindamycin 600 mg x 3 in case of penicillin allergy) and (4 mg betamethasone 4 times) starting immediately before the operation. To avoid postoperative swelling of the lower lip and abrasion of the corner of the mouth a steroid cream was frequently used throughout the operation.

Intraoral Vertical Ramus Osteotomy

The soft tissue incision is made lateral to the anterior border of the ramus starting 1cm above the occlusal plane and running forward along the external oblique ridge ending at area between the first and the second molar. A subperiosteal inferior-lateral dissection was done exposing the antegonial notch. The coronoid process and the lateral surface of the ramus are dissected in order to identify the sigmoid notch. J-stripper is used to free the lower border. The coronoid process clamped and a ramus retractor is inserted to the posterior border of the ramus. A sigmoid notch retractor was then inserted to retract the soft tissue and exposing the lateral surface of the ramus. An oscillating saw is used to cut the ramus starting behind the antelingula, 5-7mm from the posterior border of the ramus, to avoid damage to the neurovascular bundle. The cut is done from the sigmoid notch down to the posterior border of the ramus behind the angle. The proximal segment moved laterally. The fibres of the medial pterygoid muscle are stripped off from the proximal segment. Finally, the wound is packed with saline-moistened gauze. Osteotomy of the contra-lateral side was performed identically. The lower jaw is adjusted to the desire position and fixed to the upper jaw using orthodontic brackets and stainless steel wires (3-0 or 4-0). The wound sutured with 4-0 Vicryl. All patients are kept on intermaxillary fixation for 4-6 weeks postoperatively, then guiding elastic is used for one month to guide into proper occlusion.

Sagittal Split Osteotomy

 The soft tissue incision is made from halfway up the ascending ramus to the region lateral to the first mandibular molar. A subperiosteal dissection is done exposing the lower border of the mandible without stripping off masseter muscle. The dissection continues along the anterior border of the ramus to expose the coronoid process. A clamp on the coronoid and a channel retractor to the lower border are used to aid in retraction. Medial dissection is carried until the lingula and the neurovascular bundle are identified. A mucoperiosteal elevator is used to gently reflect the medial soft tissue. A reciprocating saw is used for a horizontal cut of medial cortex of the ramus above and just posterior to the lingula. The bone cut is continued down the anterior border of the ramus and along the external oblique ridge to the area between the first and second molars using a Lindemann bur. A reciprocating saw is then used to extend the bony cut inferiorly to the lower border. Two osteotomes and a bone spreader are inserted in the osteotomy line to split the mandible. Care is taken to identify the neurovascular bundle during splitting and to keep it attached to the teeth-bearing segment. After completing the splitting, the procedure is repeated on the other side. The teeth bearing segment is moved into the desire position and fixed temporarily with intermaxillary fixation. Final fixation of each side is achieved with two or three bicortical positional screws through a trans-buccal approach. No intermaxillary fixation is used postoperatively except for guiding elastics.

Genioplasty

 Through an incision in the labial vestibule from canine to canine area a mucoperiosteal flap is reflected. A tunnel is then created towards the mental foramina. After adequate exposure and identification of the mental nerves a bow-shaped osteotomy is performed using a reciprocating saw at the lower border of the mandible from the area between the second premolar and the first molar of one side to the same area on the opposite side. The final bone separation is always completed with an osteotome. The osteotomized bony segment is mobilized and placed into to the desired position. Fixation is achieved with an 8- hole or 2 titanium nets.

Study 3

Preparations and medications

All patients were given Glucocorticoids Betamethsone (Betapred¤ Sobi) 4mg the day before the operation, 8mg preoperatively and two 4mg doses on the following 2 days. Antibiotics (mainly penicillin derivatives) were given postoperatively.

Extraoral Vertical Ramus Osteotomy

The operation is performed through a retromandibular incision from the lobule of the ear to the mandibular angle. The angle and the lateral surface of the ramus are exposed after blunt dissection. The periosteum is divided and elevated from the lateral surface. The osteotomy is made with a Lindemann bur in a curved line from the sigmoid notch to a point just above the angle. Sharp bone surface edges are eliminated and the lateral surface beveled when necessary to improve the contact between the fragments. The stylomandibular ligament as well as periosteum and muscular attachments are stripped off from the inferior part of the condylar fragment to make the lateral positioning of the condylar fragment possible. IMF is made before fixation of the condylar fragment and after having checked condylar position in the fossa. Fixation of the condylar fragment have most often been made with 0,4 mm steel wire but if the anatomy allows, plate fixation of the condylar fragment has been made. Depending on type of fragment fixation the IMF can be shortened and even avoided. Healing time normally takes five weeks.

3.2 Animal studies

Forty eight adult female Wistar rats from a commercial breeder (Taconic, Denmark) were used. They were kept in standard cages in a 12:12 h light–dark cycle and had free access to tap water and standard rat food. The animals were kept at the animal facility for 2 weeks prior to the study start to ensure adaptation to the environment. At the study start the rats weighed 250 +- 5 g; 2 weeks later they weighed 290 +- 7 g and a further 2 weeks later they weighed 310 +-6 g. The rats were randomized into 2 groups, a group where

the left mental nerve and the left buccal branch of the facial nerve were subjected to compression and a group where the corresponding right nerves were subjected to compression. All surgical procedures were performed by the same investigator. The first operation was chosen randomly by flipping a coin to be the left side, and thereafter the operations were performed alternately between the right and the left side to cancel out an eventual effect of the investigator becoming more adept at the surgery.

3.2.1 The surgery

Surgery was performed over a period of 25 days. Rats were anaesthetized with an intraperitoneal injection of sodium pentobarbital 30 mg/kg (Pentobarbital Natrium vet. APL, Sweden, 60 mg/ml) and the relevant side of the face was shaved. Using an aseptic technique, the plane superficial to the muscular layer in the buccal area was exposed via a longitudinal incision to identify the buccal branch of the facial nerve (BF), while a submandibular incision was done to allow access to the mental foramen and the mental nerve (MN). The nerves were identified and isolated with blunt dissection using a pair of microsurgical scissors and a dissection microscope (Wild Heerbrugg M651). The actual nerves were compressed by tying them to a glass rod for 30 s. The wound was sutured with an absorbable suture (Vicryl 5-0). Rats were returned to their home cage to recover without antibiotic or analgesic treatment. One rat was excluded from the study for technical reasons. All experimental procedures were conducted in accordance with current national regulations issued by The Swedish Board of agriculture and the regional ethical committee on animal experiments. We chose female rats because they tend to accept the sutures better than male rats. Whether female rats are more prone to nerve damage than males remains to be elucidated.

3.2.2 Perioperative medication

For study five, 23 rats were given Betamethasone (Betapred @ Sweden Oraphan 4mg/ml) subcutaneously (2mg/kg bodyweight/day) divided into three dosages given every 8 hours in the following 24 hours and starting within 20 minutes preoperatively. These animals are referred to as the Betamethasone treated group. The dosage of Betamethasone was determined according to (Cai et al., 1998). Another group of the animals (nr= 25) received in analogy the same volume of saline. The un-operated side for both groups served as the sham operation group.

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3.2.3   Tissue preparation

The animals were sacrificed 3, 7, or 19 days after surgery by perfusion fixation with 5% glutaraldehyde in ¾ Thyrodes buffer. The heads were kept at 5ºC in the same fixative for at least 30 days before dissection. Eight to twelve mm long segments of relevant nerves were dissected.

After 3 rinses in 0.15 M phosphate buffer (pH 7.4) the specimens were post fixed in 2% OsO4 in 0.12 M sodium cacodylate buffer (pH 7.2) for 2 hours. The specimens were subsequently dehydrated in ethanol, transferred to propylene oxide, and embedded in Epon resin according to standard procedures. Semi-thin (1 µm) sections were cut perpendicular to the long axis of the nerve segment 2mm beyond the site of compression with a Reichert Ultracut S microtome (Leica, Herlev, Denmark), stained with toluidine blue, and cover slipped with Pertex mounting medium.

3.2.4   Stereological analysis

The stereological analyses are described in details elsewhere (Larsen, 1998). The total numbers of specified myelinated axons were estimated by the two-dimensional fractionator technique. The myelinated axons were classified into the following four subgroups depending on their morphology: 1) axons with normal morphology, 2) demyelinated axons where the axons had lost its entire myelin sheath but the axonal body could still be identified, 3) degenerating axons where the axons had different degenerative morphology but retained all or part of its myelin sheath, and 4) regenerating axons where the axons were much smaller than normal axons, had a thin myelin sheath and a lightly stained axoplasm and were almost always associated with darkly stained Schwann cells nuclei (see examples in Fig. 2 in Barghash et al, 2013)(Barghash, Larsen, Al-Bishri, & Kahnberg, 2013). The cross-sectional areas and the volume fractions of various tissue components were estimated by the point counting technique (Pakkenberg & Gundersen, 1995). The following tissue components were distinguished: 1) the myelinated axons with their myelin sheath, 2) the endoneurium including unmyelinated axon and the cytoplasm of residing cells and 3) cell nuclei of residing cells. The collected data from the point counting were also used to estimate the volume fractions of the various tissue components. The volume fraction of tissue equals the area fraction of the tissue. The practical procedures were carried out on video images of microscopic fields transmitted to a computer screen onto which the relevant test probe was superimposed using the C.A.S.T.-GRID software (Olympus, Denmark). The entire nerve was delineated at a low magnification (x102 using an x2 PlanApo objective). Both number estimation and area estimation were performed at a final magnification of x5125 using a x100 UPlanApo oil immersion objective (NA=1.35) to which the objective used for delineation was Para centered. At high magnification the computer-controlled stage of the Olympus BX51 microscope was programmed to move the section systematically, random in a raster pattern within the delineated region with step lengths in the x- and y-axes of 25 μm for the number estimation and of 40 μm for the area estimation, respectively. For the number estimation, the image of an unbiased counting frame (of area 30.1 μm2) was superimposed on to the microscope image at each point in the raster pattern and axons were counted using the unbiased counting rules. The sampling fraction was thus 0.04816. In analogy, for the area estimation a single point was superimposed to the image and the area per point was thus 1600 μm2. Nerve cross sections that were of substandard quality mainly due to improper embedding were excluded from the study.

4 RESULTS

4.1 Retrospective studies 1, 2 and 3

The three retrospective studies differ slightly in their objectives but the outcome of the results that are alike can be organized in table 1 below. A description of the results will therefore be supplied for each study.

	Op	sides	NSD%	satisfied%
Study1	SSO	131	37	89
	SSO+GP	54	37	85
Study2	IVRO	106	7,5(3.8)	98
	SSO	86	11,6(8.1)	91
Study3	EVRO	193	1	92

Table 1. *Showing the type of operation, percentage of permanent NSD in lower lip (Percentages between brackets are those registered in patients' records) and patient satisfaction.*

4.1.1 Study 1

Sagittal split osteotomy

Complete questionnaires from 66 patients who had sagittal split osteotomy alone (39 women and 27 men) were returned and analyzed. Patients' ages ranged from 16 to 54 years with a mean of 35. All operations except one were bilateral, so 131 sides were evaluated. Sensory disturbances were reported in 48 (37%). Mandibular advancement was done in 101 sides and mandibular setback in 30 sides. In the advancement group, 36 (36%) had long-lasting sensory disturbances compared with 12 (40%) in the setback group. There was no significant difference between the two groups. There

was no significant difference in the incidence of long-lasting sensory disturbance between men (38%) and women (36%). One patient reported unilateral sensory disturbance of the lingual nerve 1/185 sides (0.5%).

Sagittal split osteotomy with genioplasty

Twenty-seven patients (54 sides) returned the questionnaires. In 20 (37%) of the operated sides long-lasting sensory disturbance was reported but no patient reported disturbance along the distribution of the lingual nerve. See table 2

Degree of discomfort: Out of 47 patients with sensory disturbances, 35 (75%) patients described their discomfort as being mild or mild to moderate.

Patient satisfaction: Fifty-nine of the patients (89%) who had the sagittal split osteotomy alone were satisfied as were 23 (85%) of the patients who had osteotomy combined with genioplasty.
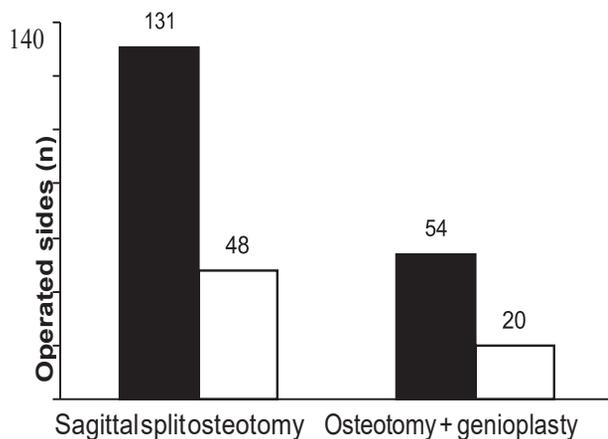

Table 2. *Sensory disturbances after sagittal split with and without genioplasty. (•) Total number operated on; (0) sides with sensory disturbance*

4.1.2   Study 2

Intraoral vertical ramus osteotomy

Questionnaires

Fifty-three completed questionnaires representing 106 operated sides were returned and analyzed. The returned questionnaires reported immediate NSD after IVRO in 11 operated sides (10.4%); three of them regained full sensibility during the first year whereas eight (7.5%) sides had long lasting NSD. In one of the patients, the NSD was bilateral.

Degree of discomfort: Four patients out of seven (57%) with long lasting NSD described the effect of the disturbance as mild.

Patient satisfaction: Ninety-eight percent of the patients operated for IVRO were satisfied with the result of the operation. The only patient, who was dissatisfied, did not have any long lasting NSD after the operation.

Record review

In the files of the 53 patients with 106 operated sides, who returned completed questionnaires, immediate NSD was recorded in eight operated sides (7.5%). Four of them regained full sensibility over a period of one year, leaving four sides (3.8%) with long lasting NSD.

Sagittal split osteotomy

Questionnaires

Questionnaires were returned from 43 patients with 86 operated sides. Immediate NSD was reported in 25 operated sides (29%), 15 sides regained full sensibility after one year while the remaining 10 sides (11.6%) continued to have long lasting NSD.

Degree of discomfort: Fifty percent of the patients with NSD after SSO described the effect of NSD as mild to moderate.

Patient satisfaction: Four out of the 43 patients (9%) were not satisfied with the result of the operation but only one attributed the dissatisfaction to sensory impairment.

Record review

Reviewing the records of the 43 patients, who returned the questionnaires, showed immediate NSD in 33 operated sides (38.4%). Twenty-six of the

affected sides regained full sensibility during the first postoperative year; thus seven operated sides (8.1%) remained with long lasting NSD.

Operation	Total sides	Record review		Questionnaires	
		Immediate	Long lasting	Immediate	Long lasting
IVRO	106	8	4	11	8
SSO	86	33	7	25	10

Table 3. *NSD after IVRO and SSO as reported in returned questionnaires and patients record*

4.1.3 Study 3

NSD
 Sixty-seven patients (134 sides) didn't experience any NSD while 30 patients (49 sides) had variable degrees of sensory disturbance in different areas of the face postoperatively (25%). The onset of the disturbance was immediate in 25 patients and late in 5. While some regained normal sensation later on, 15 patients (22 sides) had permanent NSD in different facial areas (11%).

Lower lip area
 Six patients (8 sides) had NSD postoperatively, 3 cases resolved within 1 year and 3 patients, all females, had permanent NSD in the lower lip, all unilateral (3 sides). All of those 3 patients were satisfied with the outcome of the operation although one of them had moderate discomfort (VAS 7) because of her NSD. The other two had mild discomfort (VAS 0-3). One of these three patients had a genioplasty procedure in association with the EVRO, thus decreasing the number of permanently affected lower lip into 2 sides (2/193=1%) if genioplasty is not to be taken into consideration.

Other actual areas affected by sensory disturbance
 Apart from the lower lip, there were the cheeks, operation site, body of Mandible, the teeth (2 patients, 4 sides) and the tongue (2 patients, 4 sides). Unfortunately the amount of mandibular setback could not be associated with the sensory disturbance as not all the data were available (9 out of 15 patients with permanent disturbance were available).

Degree of discomfort NSD: In all the areas was mostly mild (VAS 0- 3) in 7 of the 11 patients affected by permanent NSD, followed by moderate discomfort in 4 patients (VAS 4-7).

Patient satisfaction: In total there were 8 patients not satisfied with the operation (8%), 4 females and 4 males. One due to muscle weakness, one due to scar tissue, 4 due to occlusion and two patients due to the general facial esthetics.

 The type of sensory disturbance experienced by the patients (With both temporary and permanent loss) was described by, in many times, a combination of different characters, mostly anesthesia in 20 patients followed by different types of paraesthesia (stabbing=6, painful=6, itching=2, burning=1 and another 6 patients with own descriptions). For the patients with permanent loss, the nature of sensory loss experienced was described by anesthesia in 9 patients, painful in 4, stabbing in 3, itching in 2 and burning in 1 occasion. The three patients with permanent NSD in the lower lip all described the nature of the altered sensation as anesthesia.

Fourteen patients (50%) reported having problems with NSD when touching the affected area, 3 more patients reported other activities while 11 didn't report anything.

Four of the patients with permanent sensory disturbance said they chewed on their lip and 3 on their cheeks and one on the tongue because of the sensory disturbance, while 2 patients said that they have burned their lips due to that.

Five of the patients operated had genioplasty operations simultaneously. Only 2 of those had NSD postoperatively, one regained his normal sensation after a year while the other had permanent NSD (1/5).

Muscle weakness
 It was reported by 9 patients (9%), 7 females and 2 males. Patient's age ranged between 15 and 48 with an average of 25 years. 4 patients had mild discomfort (VAS 0-3), 4 patients had moderate discomfort (VAS 4-7) while one patient had severe discomfort (VAS 8-10). This patient was the only one not satisfied with his operation because of the muscle weakness (1/9). See Table 4

Muscle weakness

Mild	Moderate	Severe
4	4	1

Patient discomfort due to muscle weakness
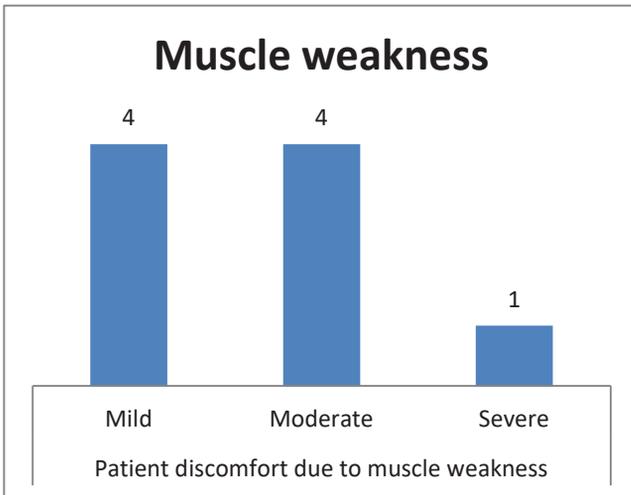
Table 4. *Patient discomfort due to muscle weakness as described by patients in a VAS. Discomfort between 0-3 marked as mild, 4-7 marked as moderate and 8-10 as severe*

Scar tissue

| Mild	Modeerate	Severe
15	11	3

Patient discomfort due to scar tissue
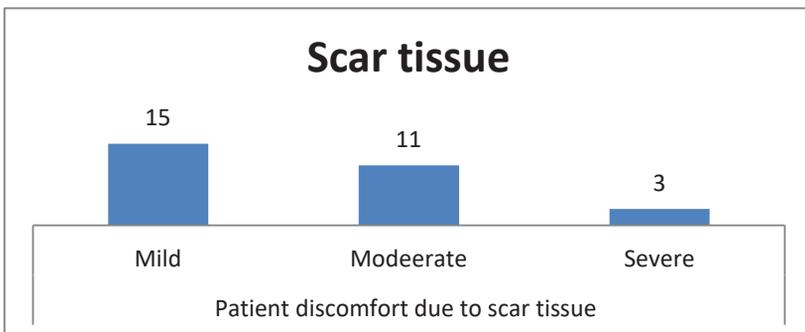
Table 5. *Patient discomfort due to scar tissue as described by patients in a VAS. Discomfort between 0-3 marked as mild, 4-7 marked as moderate and 8-10 as severe*

Scar area

Twenty Nine patients (30%), 17 females and 12 males, were bothered by the scar formation postoperatively. Ages ranged between 15 and 48 with an average of 23.4 years. While 15 had mild discomfort (VAS 0-3), 11 patients had moderate discomfort (VAS 4-7) and 3 had severe discomfort (8-10) due to the scar are. One patient was not satisfied with her operation due to the scar formation. One patient had to have another operation to remove the scar tissue. See table 5.

Gender differences

Sixty three females and thirty four males answered the questionnaire. 30 females and 15 males had no problems. Among female patients 17 had problems with the operation scar vs. 12 males and 7 females had problems with muscle weakness vs. 2 males. Six female patients had temporary NSD and 3 had permanent NSD whilst 1 male patient had temporary and none of them complained of permanent NSD. See table 6
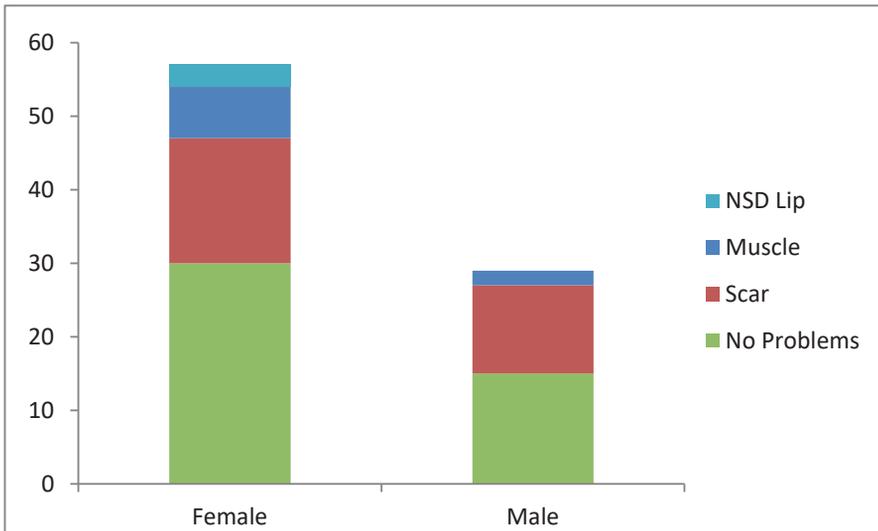

Table 6. *Gender differences: Comparing Temporary NSD in the lower lip, Muscle weakness, Operation Scar disapproval between females and males. Patients from both genders with no problems are also compared at the bottom of the chart staples*

4.2 Results from animal study 4 and 5

4.2.1 Study 4

Differences in normal anatomy

We found significant differences in the normal anatomy of all examined parameters with the exception of the volume fraction of cell nuclei. The total number of myelinated axons was twice as high in the MN as in the BF. The total cross-sectional area of the nerve was approximately 50% higher in the MN than in the BF and all three quantified tissue components were significantly larger in the MN than in the BF. The volume fraction of cell nuclei (excluding Schwann cell nuclei) was small and comparable in the two nerves, but the volume fraction of myelinated axons including their myelin was highest in the MN, whereas the volume fraction of endoneurium was highest in the BF (table 7).

Differences in lesioned nerves

Normal myelinated axons were dominant at day 3 after the crush injury, but degenerating axons were prominent and demyelinated axons were also seen. At day 7 the normal myelinated axons were virtually absent and the dominant axons were the newly formed axons, although some degenerating axons could also be seen. At day 19 we could not distinguish between the regenerating axons which had a more mature morphology and the normal axons, although the regenerating axons were smaller in diameter with a thinner myelin sheath. However, since virtually no normal axons were observed at day 7, the majority of the so-called normal myelinated axons at day 19 must be regenerated myelinated axons. Normal axonal anatomy and a 19 day crush lesion can be seen in fig 1 and 2 respectively. Both figures have the same microscopic magnification. Note the smaller axonal diameter in figure 2.

Mental nerve

In the MN there was a trend towards a loss in the total number of myelinated axons (P = 0.062) and a corresponding significant decrease in the cross-sectional area of myelinated axons at day 3, and both parameters were significantly decreased at day 7. A significant increase in the area of cell nuclei was observed both at days 3 and 7, and a significant increase in the cross-sectional area of intercellular tissue was seen at day 7. The two later changes probably reflect an inflammatory oedema. The increase in the area of the intercellular tissue is cancelled out by the decrease in the area of the

myelinated axons, so that the total area is not increased, i.e. no entrapment was observed in the MN.

Buccal nerve

 In the BF, the axon loss was significant at day 3, although it was smaller than the insignificant loss seen in the MN. The axon number was back to normal at day 7, but the area of myelinated axons was decreased, indicating that the axons are smaller than normal axons. At day 19 the axon number was insignificantly increased, but the axon area was still decreased. The area of cell nuclei was significantly increased at all time points and the endoneurial area was significantly increased at days 3 and 7. In the BF, where the volume fraction of endoneurium is larger than it is in the MN, the increase in the endoneurial tissue entailed a 46% increase in the total area of the BF at day 7. The degenerative and regenerative patterns in the MN and the BF are compared with normalized data in table 9.

Comparing the crushed nerves

 No statistical difference was found between the two nerves at day 3, i.e. the degenerative pattern was comparable between the two nerves. At day 7 the newly formed axons were the most dominant in both nerves, but the total number of axons in the MN was only half of that in the normal reference nerve, whereas it was back to normal in the BF indicating a significantly better regenerative capacity in that nerve after the crush injury. At that time point, some degenerating axons and a few normal axons were still seen and the BF had a significantly higher normalized number of degenerating axons than the MN. At day 19 the BF had regenerated back to a normal number of axons, whereas the MN had only regained 50% of the normal number of axons. The normalized area of cell nuclei was at all time points largest in the BF, but the difference only reached significance at day 19.
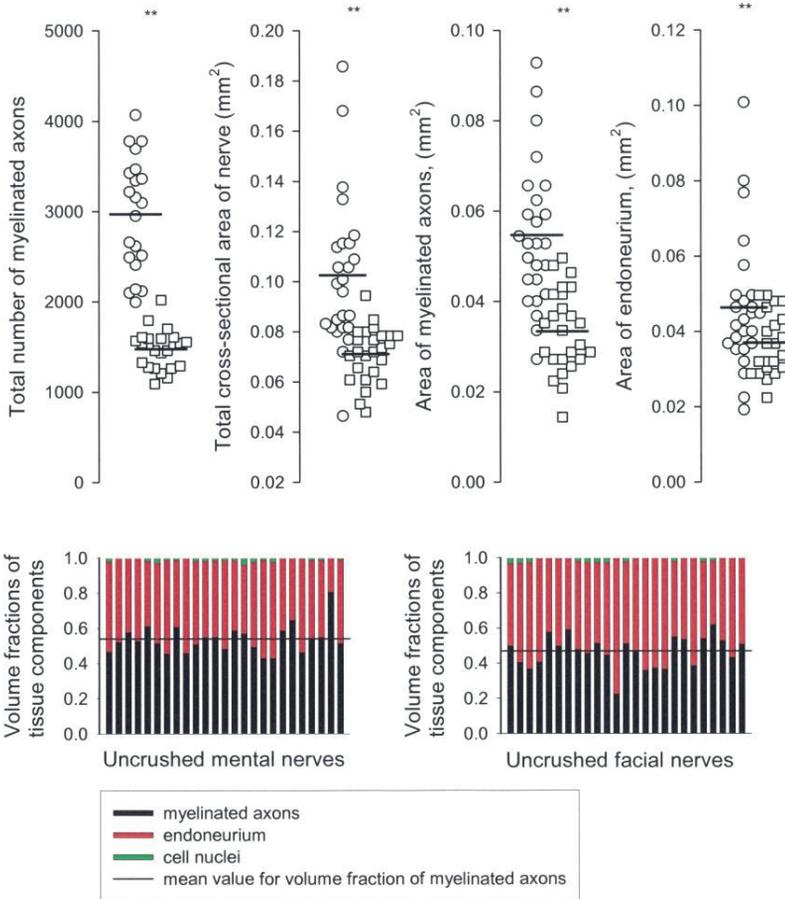
Table 7. *Compares the normal anatomy of MN and BF. The uppermost figure shows from left through right: the total number of myelinated axons, the total cross-sectional area of the nerve, the cross-sectional area of the myelinated axons, and the cross-sectional area of endoneurium axons. MN is shown by open circles and BF by open squares. The horizontal lines show the group mean. The volume fractions (V_V) of tissue components is shown in the lowermost figures where the specified tissue types are color-coded so that black represent the volume fraction of myelinated axons, red represent the volume fraction of endoneurium, and green represent the volume fraction of cell nuclei. ** indicates that a statistical significant difference were found between the two nerves.*
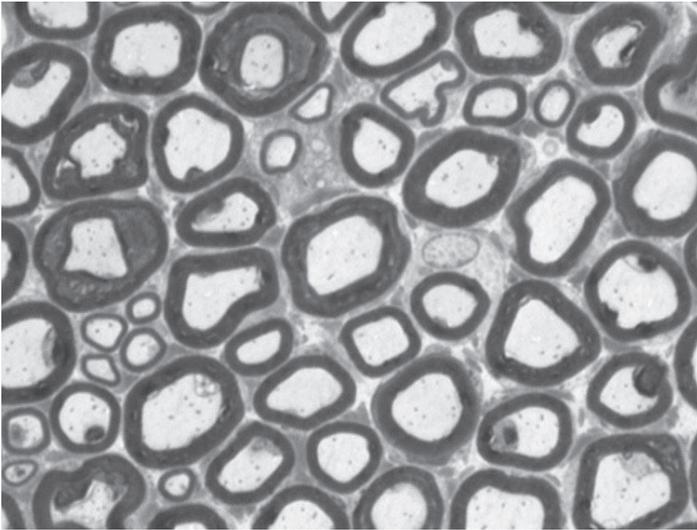
Figure 1. Microscopic picture showing control nerve
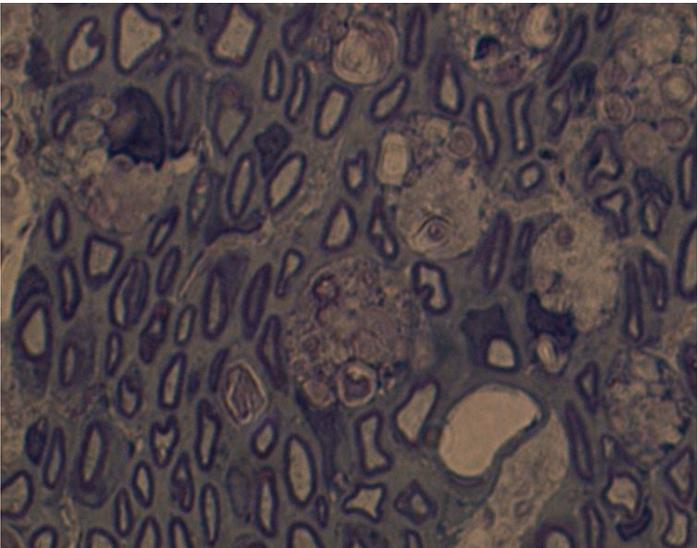
Figure 2. Axons 19 days after crush lesion

Three days **

Seven days **

Nineteen days **

Total number of specified axons in mental nerve

Total number of specified axons in facial nerve

Mental nerve   Facial nerve

○ and □ myelinated axons in uncrushed MN and BF, respectively
● and ■ myelinated and previous myelinated axons in crushed MN and BF
◇   myelinated axons
▲   axons showing axonal degeneration
▽   demyelinated axons
◈   newly formed axons

Table 9. *The numbers of specified axons at day 3 (uppermost figure), 7 (middle figure), and 19 (lowermost figure) after a crush lesion. The mental nerve is shown to the left and the facial nerve to the right. The total number of axon is for MN shown by circles and for BF by squares where the unfilled symbols represent control nerves and the filled symbols represent the crushed nerves. For the crushed nerves where four different axon types were identified the numbers of the specified axon types are shown to the right for the crushed nerves scatter plots, where the open diamond represents the normal myelinated axons, the red triangle the axons that show degeneration, the yellow triangle the axons that show demyelination, and the open diamond with x-hair represent newly formed axons. To facilitate a more direct comparison between the two nerves the mental nerve is plotted against the left axis and the facial nerve against the right axis. The axes have been constructed so that the mean values for the uncrushed control nerves coincide.*

4.2.2   Study 5

Control and sham group

For the sham-operated nerves (both the MN and the BF) no differences were found in any of the estimated parameters between the saline treated and the Betamethasone treated groups (unpaired t-test). Neither were there any significant differences between the three time groups at the sham-operated control side (ANOVA test). The statistical comparisons (unpaired t-tests assuming unequal variance) were performed on normalized data, where the percentage of each axonal subpopulation was calculated as the number of axons in that subpopulation divided by the mean total axonal number of all the sham-operated control nerves multiplied by 100 (all saline-treated and betamethasone treated animals were pooled since no difference were found between the treatment groups nor the time groups in the sham operated groups).

Mental nerve

For the MN we found no significant differences between the two treatment groups regarding the numbers of specified axons at day 3 and 7. At day 19, however, the Betamethasone treated animals had regained 81% of the normal number of myelinated axons whereas the saline treated animals had only regained 48%. At day 3 the Betamethasone treated animals had a significantly larger total cross sectional area comprised by both a larger cross sectional area of myelinated axons (significant difference) and a larger cross sectional area of intercellular tissue (insignificant difference). At day 7 the

Betamethasone treated animals still had a significantly larger cross sectional area of myelinated axons but had now an insignificantly smaller cross sectional area of intercellular tissue.

Facial nerve

For the BF the Betamethasone treated animals had lost significantly fewer myelinated axons at day 3 when compared to the saline treated animals. In addition the Betamethasone treated animals had significantly more newly formed axons at day seven. At day nineteen the saline group was back to normal control levels (104% of sham-operated nerves) whereas there was an (insignificantly) overshooting of myelinated axons in the Betamethasone treated group (141% of sham operated nerves). Apart from a smaller cross sectional area of cell nuclei at day 7 the Betamethasone treated animals did not differ significantly from the saline treated animals as regards the estimated cross sectional areas of specified tissues. Even though it is not significant, the cross sectional areas of the myelinated axons and the intercellular tissue in the BF follow the same pattern as in the mental nerve, i.e. the area of myelinated axons is larger in Betamethasone treated animals at all time points when compared to saline treated animals, whereas the area of intercellular tissue is larger in the Betamethasone treated animals at day 3, but smaller at day 7. See table 10.
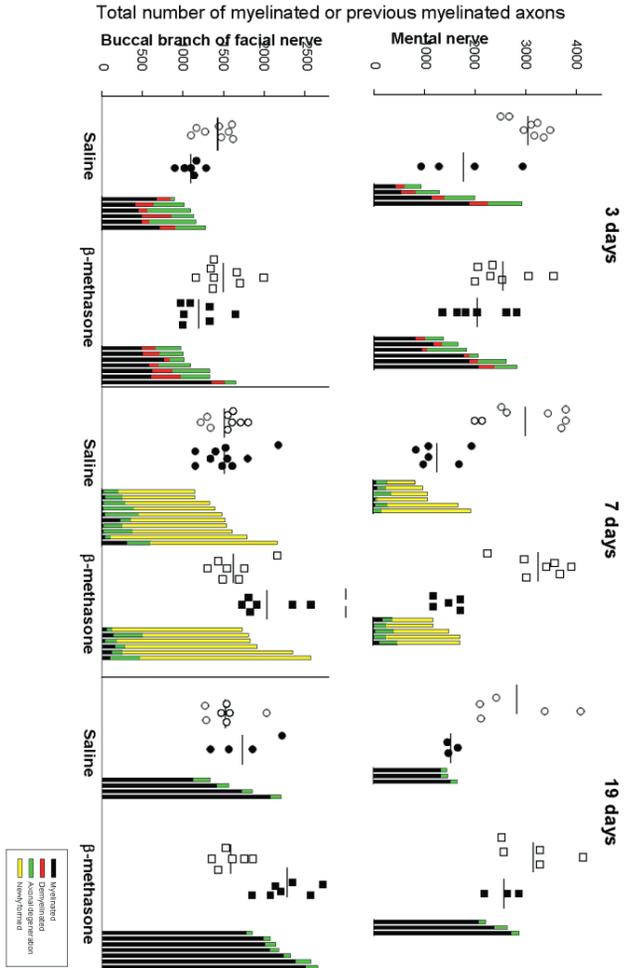
Table 10. *The total numbers of myelinated and previous myelinated axons in mental nerve (upper graphs) and in the buccal branch of the facial nerve (lower graphs). Saline treated animals are shown by circles and Betamethasone treated animals by squares. The crushed nerve is indicated by filled symbols and the contralateral sham-operated nerve by unfilled symbols. The total number of myelinated and previous myelinated axons is for the crushed nerves subdivided into intact myelinated axons, demyelinated axons, axons with degenerative changes, and newly formed axons. This subdivision is given in the stacked bars to the right of each individual plot.*

5 DISCUSSION

What I try to answer in this thesis through the 5 papers included is the patient satisfaction as a whole and specifically in relation to incidence of sensory disturbance following orthognathic surgery through the use of questionnaire, to show if there is a difference in NSD when genioplasty is simultaneously done with other orthognathic surgery, to see if there is any difference between NSD registered in patient records and what the patients feel themselves, to see if there is any difference in the pattern of nerve healing between a motor and sensory nerve and see how GCC treatment might affect the outcome of nerve healing.

Sensory disturbance is still one of the main drawbacks of orthognathic surgeries. In studies 1 and 2 the incidence of NSD varies quite considerably in between them. . This coincide with what was shown earlier through literature reviews. Many causes could account for the incidence variation and one of these causes can be the testing method. There are different methods for measuring NSD and these differ in their reliability and objectivity in detecting conduction problems. Most studies of sensory disturbances after mandibular osteotomies are based either on objective or subjective methods. Purely subjective methods are those relaying solely on the patient expressing changes in sensation through questionnaire. Many purely objective tests that have good reliability to assess nerve function are quite expensive, complicated and not available in everyday practice. An example of these complicated objective tests is the Blink Reflex which was first introduced in 1958 (Kugelberg, 1952). Other tests present are a combination between objective and subjective clinical testing which always relay on the interaction between the examiner and the patient and therefore cannot be called purely objective or purely subjective. These tests could be of mechanoceptive or nociceptive nature. such tests include touch detection threshold, Brush-Stroke Directional Discrimination, Grating Orientation Discrimination, Thermal tests (warm/cold, Cold, Warm and Heat pain detection threshold) and 2-point discrimination on the other hand lacks the pure objectivity as subjective factors of both the patient and examiner disturb the results (Ghali & Epker, 1989). Even with these types of tests, it is only the patients who can decide if his or her sensitivity has changed, and therefore such tests are not properly objective. There have been some discrepancies when comparing these tests with patients own experience. Some authors (L. L. Cunningham et al., 1996; Pratt, Tippett, Barnard, & Birnie, 1996) have shown that patients' subjective

evaluations give a higher incidence of sensory disturbance than objective evaluations, while others have reported the opposite (Coghlan & Irvine, 1986). Blomqvist (Blomqvist, Alberius, & Isaksson, 1998) reported that subjective evaluation one year after the operation showed a good correlation with objective data obtained by static 2-point discrimination, while the pin prick and light touch tests and the vibration threshold test showed a complete recovery of sensation. Chen (N. Chen, Neal, Lingenbrink, Bloomquist, & Kiyak, 1999) reported the same correspondence between the subjective evaluation and the test of 2-point discrimination. No matter which objective test is used to identify sensory defect, assessment of inter-examiner reliability is important, as the ability of the objective test to discriminate between impaired and unimpaired sensation may vary depending on the examiner. It is therefore important to establish a set of testing methods are feasible, repeatable and easily used in everyday practice and not only for research purposes for measuring nerve function postoperatively. These tests should not be examiner-related i.e. multi examiners could get the same results using a specific test.

It is interesting to know that retrospective studies of patient records often assume that the preoperative sensation is normal unless otherwise stated. It was reported that not all subjects responded to stimuli during brush direction tests in the virgin area innervated by the infraorbital nerve (Zaytoun, Phillips, & Terry, 1986). In another study using different testing methods including static light touch , moving touch discrimination , and two-point discrimination (Karas, Boyd, & Sinn, 1990) in 22 patients, reported that in 20 (92%) the lower lip and in 18 (83%) the chin were sensitive to the finest filament (1.65) but the others required two filaments (2.44) indicating that changes to sensation already exist prior to operation.

When reviewing the literature one finds big differences in the armamentarium used in objective evaluation tests of sensory change. This could lead to differences in the definition of sensory changes. Such disadvantages could be solved by standardization of the instrument used for the tests (Agbaje, Salem, Lambrichts, Jacobs, & Politis, 2015).

The use of those different test methods should be done with regard to the type of sensation each test method can examine. The Warm and Cold Detection threshold are used to study the A-delta (small myelinated) and C-fibres (unmyelinated), larger myelinated fibres measured by 2-point discrimination, static light touch and moving touch discrimination (Bailey & Bays, 1984; Nishioka et al., 1987). Fridrich et al (Fridrich, Holton, Pansegrau, & Buckley, 1995) mentioned in their study that the large myelinated fibres recovered

more slowly and to a lesser degree at all time intervals up to 2 years when compared with small myelinated fibres. In other words, receptors that propagate stimuli via small, unmyelinated nerve fibres (C-fibres) and small myelinated nerve fibres (A-delta) regain sensory function sooner than receptors that relay sensations via large myelinated fibres. This can explain some of the differences noticed when testing NSD with test methods for large/alternatively small myelinated and unmyelinated nerve fibres. It is therefore recommended to use more than one method of sensory testing, a combination of both mechanoceptive and nociceptive methods as recommended by Ghali and Epker (Ghali & Epker, 1989), or a combination of clinical and electrophysiological methods as recommended by Teerijoki-Oksa et al (Teerijoki-Oksa, Jaaskelainen, Forssell, Virtanen, & Forssell, 2003), including the Touch-detection test as they found that it is one of the most reliable among the clinical tests using Semmes-Weinstein Aesthesiometer (Monofilaments that exert exact, well calculated and repeatable pressure on the area being tested). More simpler test like tooth sensibility testing was found to be reliable and in accordance with patients own subjective experience and more advanced objectives tests when done 4 days following orthognathic surgery (Ylikontiola, Vesala, & Oikarinen, 2001).

The issue of different degenerative and/or regenerative characteristics in motor and sensory nerves has been discussed thoroughly. Several authors have not distinguished between motor and sensory nerve fibres in their lesion studies (Sunderland & Roche, 1958), while others have emphasized the possible errors that can be introduced by using a mixed nerve population for lesion studies because of the different characteristics of each nerve fibre population (Wendell-Smith & Williams, 1958). In study 4 when comparing the nerve healing between a sensory and a motor nerve, we found histological differences in the healing pattern in favor of motor nerves. If these changes can rise to cause difference in functional healing then examination methods that test both sensory and functional nerve healing should be applied to avoid false positive readings if only motor tests were applied.

Some of the test methods were praised by some authors and disregarded by others. The GO method (Grating Orientation Discrimination) used for examining the spatial resolution (large myelinated fibres) which is said to replace the 2-point discrimination (Johnson & Phillips, 1981; Patel, Essick, & Kelly, 1997) is found to give questionable results and difficult to use in some areas (Teerijoki-Oksa et al., 2003). On the other hand Ylikontiola et al (Ylikontiola, Kinnunen, & Oikarinen, 1998) have found that 2-point discrimination was one of the most accurate clinical tests that gave results

comparable with the subjective tests. The warm/cold test was found by Teerijoki-Oksa et al (Teerijoki-Oksa et al., 2003) to be much less sensitive compared to other objective tests. The explanation for this might be found in the facts mentioned earlier in this assay about the fast healing of the C-fibres that conduct heat/cold sensation compared to large myelinated fibres. The thermal tests might give therefore false positive readings compared to other test methods.

Lastly, in relation to clinical NSD testing is the site of test. Different sites in facial are has different degree of sensitivity. The lip and chin have different somatosensory characteristics (Rath & Essick, 1990). Furthermore, the sensitivity of the chin found to be more than that of the vermilion boarder of the lip (Teerijoki-Oksa et al., 2003). These facts can probably add to the differences in NSD measured by different authors and might also add to the difference between subjective findings and objective clinical tests.

Sagittal split osteotomy for advancement would entail stretching of the nerve whereas osteotomy for setback could cause compression (Takeuchi, Furusawa, & Hirose, 1994). In study 1 we anticipated a higher incidence of sensory disturbance after mandibular setback than after advancement but we found no difference between the two. Sensory changes of the lingual nerve occurred only in one side of one patient 1/185 (0.5%), which compared favorably with previously published result (Takeuchi et al., 1994). We did not find significant gender preponderance in the incidence of sensory change, which agrees with reports by other authors (Westermark et al., 1998a; Ylikontiola et al., 2000). The effect of NSD on the patients' live was mostly mild. Three quarters of the affected patients described NSD effect as mild or mild to moderate in the first study. This corresponds with that published by Cunningham et al (Cunningham, Crean, Hunt, & Harris, 1996), who reported that most patients commented that the symptoms had no effect on their daily life. No significant differences in NSD were found between patients having SSO alone or combined with genioplasty nor were there differences in patients' satisfaction between the patients who had osteotomy alone (89% satisfaction) and those who also had genioplasty (86% satisfaction).

In the present thesis, the record of the patients in study 2 showed immediate postoperative NSD in 33 operated sides (38.4%) while the returned questionnaire showed that 25 operated sides (29%) was affected by NSD in SSO group (Al-Bishri, Barghash, et al., 2005). Of those, 26 of the affected sides according to the patient's record and 15 affected side according to the questionnaire regained full sensibility during the first postoperative year. Thus long lasting NSD was thus present in 8.1% and 11.6% of operated side

according to the patient's record and the questionnaire, respectively. NSD immediately following surgery after IVRO was reported in eight (7.5%) and 11 (10.4%) operated sides in records and questionnaires, respectively. Long lasting NSD after IVRO was 3.8% of the operated sides (four sides) in the records and 7.5% (eight sides) in the questionnaire. These result showed higher incidence of immediate NSD after SSO in the records than in the questionnaires, while the opposite was true in the case of IVRO. This could reflect a higher concern and expectation of surgeons on NSD after SSO than after IVRO. It might also be difficult for the patients to remember a mild, short NSD immediately after the operation when asked a year or more later. The absence of nerve manipulation during IVRO operation could also contribute to the lower incidence of the immediate NSD after the operation although some authors found that postoperative paraesthesia might happen even if the nerve remained intact during surgery (Westermark et al., 1998b). The difference in the incidence of immediate NSD after SSO and IVRO among both questionnaires and the patient's records was significant. Differences were also found comparing long lasting NSD reported in patients' records and questionnaires. Higher incidence of long lasting NSD was reported in returned questionnaires compared to reviewed patients' records for both SSO and IVRO. This higher incidence of the long lasting NSD in the questionnaire comparing to the patients' records is in agreement with the results reported by Pratt et al. (Pratt et al., 1996). The NSD was described as mild in 57% of the affected patients in the IVRO group and no patient described his disturbance as moderate to severe or severe. Fifty percent (four patients) of the affected patients in the SSO describe the effect as moderate to severe and none of them described the effect as a severe effect, all the four patients were above the age of 40 years. This coincided with the result reported by Westermark et al. (Westermark, 1999) where the older patients paid more attention to the NSD than the younger patients did.

In Study 3, returned patient questionnaires following EVRO showed altered sensation in different facial areas, and not necessarily in the lower lip, in 49 operated sides (25%). In the lower lip and chin area the immediate postoperative NSD was found in 8 sides and the permanent NSD in 3 sides (1.5%).

In this study the incidence of permanent NSD in the lower lip was only 1.5% as expected. This coincides with NSD incidence after EVRO mentioned in the literature which varied between 0 and 19% (Astrand, Bergljung, & Nord, 1973; Broadbent & Woolf, 1977; Hogevold, Trumpy, Skjelkbred, & Lyberg, 1991; Westermark et al., 1998a). Other drawback to this surgery found in returned patient questionnaires was muscle weakness eventually due to Facial

nerve injury. The incidence of muscle weakness was 9%. Facial nerve injury, although an uncommon side effect in both Intra- as well as Extra- oral osteotomies, it is still a disadvantage with slightly higher incidence in Extra-oral Osteotomies (J. K. Jones & Van Sickels, 1991). Other area of concern after EVRO is the formation of scar area at the operation site extra orally. Seventy percent of the patients were not bothered by the operation scar while 30% were. There was no question in the questionnaire form regarding if the patient had problems with one side of the operation or both sides regarding scar tissue and muscle weakness and that might explain the higher percentage of patients complaining about those problems, if taking into consideration that the complaint might be single sided as nerve injuries give higher rate if counted by patient rather than those counted by operation side (Westermark et al., 1998a). Out of the 29 patients that were concerned about the scar formation, 3 were severely bothered by it and one of them did do a cosmetic surgery to correct the tissue deformity afterwards. In literature it was found that between 13% and 30% of patients with EVRO had problems with scar formation (Egyedi, Houwing, & Juten, 1981; Hogevold, Mobarak, Espeland, Krogstad, & Skjelbred, 2001; Nagamine, Kobayashi, Hanada, & Nakajima, 1986).It is the younger patients who had significantly more problems with the scar formation (p=0,002) compared to the older patients (Neskoromna-Jedrzejczak, Bogusiak, & Antoszewski, 2015). The scar formation was not found to be an issue affecting the overall patient satisfaction with the operation, which was also found by other studies (Hogevold et al., 1991; Laufer, Glick, Gutman, & Sharon, 1976). One patient (1/97=1%) reported severe discomfort due to muscle weakness and was not satisfied with his operation due to that. The low percentage of facial nerve trauma is in line with findings of other studies (Astrand et al., 1973; Egyedi et al., 1981; Hogevold et al., 2001; Tornes & Gilhuus-Moe, 1987).

Orthognathic surgeries are the method of choice for correction of mandibular deformities despite the drawbacks related. NSD and other functional disabilities might occur due to the nature of these operations. In our studies there were a high satisfaction rate after orthognathic surgeries and the NSD was not a major determinant factor in patient satisfaction. But there still are patients who were quite affected by the NSD and other drawbacks related. Some of the responses obtained from patients questionnaires having neurological and other disturbances post orthognathic surgeries indicate that these changes had an impact on the quality of life of some of the patients suffering them, sometimes causing a lifelong disability to the patient. One of the main ethical and professional responsibilities of the surgeon is to get an informed consent from the patient prior to commencing with surgery. One might discuss the outcome of surgery in relation to postoperative drawbacks

and offer different kind of treatment, if possible, in accordance with patient concerns regarding the different types of postoperative side effects each operation has. The high rate of satisfaction despite the presence of NSD and other side effects could mean that the patients were well informed about the operation and related side effects.

Study 4 and 5 were done closely together. We first wanted to study the effect of GCC on nerve degeneration and regeneration in both a sensory and a motor nerve. This task seemed difficult without first understanding the actual similarities and differences in the regeneration and degeneration pattern in sensory and motor nerve without the effect of GCC to be able then to identify and measure the effect of GCC more correctly. The issue of different degenerative and /or regenerative characteristics in motor and sensory nerves has been discussed thoroughly in the literature before. Several authors have not distinguished between motor and sensory nerve fibres in their nerve lesion studies (Sunderland & Roche, 1958) while others have emphasized the possible errors that can be introduced by using a mixed nerve population for lesion studies because of the different characteristics of each nerve fibre population (Wendell-Smith & Williams, 1958).

In Study 4 we aimed to examine the process of de- and regeneration in both MN (sensory) and BF (motor) nerves after a crush injury model. We, in other words, examined two nerve fibre populations in two different nerves, which necessitated consideration of potential biases when comparing the two populations directly. In this study the MN and BF nerves were subjected to crush injury. Two researchers carried out the whole surgical process but predominantly by the author. The applied pressure was the same in the two nerves, so if one of the nerves was subjected to a larger trauma it should be the smallest nerve, i.e. the BF, which had the smallest total cross-sectional area. Also the relative amount of endoneurium could potentially influence the sensitivity of the nerve fibres to a crush lesion, where a large volume fraction of endoneurium is thought to protect against traumatic nerve lesions. The volume fraction of endoneurium was larger in the BF than it was in the MN, and the BF is therefore from this point of view expected to be better protected against a crush lesion. We found no significant differences between the two nerves as regards the degenerative process (examined at day 3), so these issues must either have been of minor importance in our study or have masked a potential differential degenerative process.

Compartment syndrome is a well document reaction following injury. Due to tissue trauma, pressure inside confined tissues rise above vascular perfusion pressure causing ischemia and neuropathies. The fact that the MN courses

through the mandibular canal before emerging from the mental foramen makes it hypothetically more susceptible to entrapment injury following post-traumatic tissue swelling. In our study, however, the total cross-sectional area of the MN was at none of the examined time points larger than it was in the normal uncrushed nerve so an intraneural oedema leading to additional entrapment trauma in the MN seems unlikely, though it could have been present at time points not examined. We cannot, however, completely exclude the possibility of an extra-neural oedema.

Comparing the degenerative process between the MN and BF nerve fibres, we could not find any significant differences. Large diameter fibres were found to degenerate faster than small diameter fibres (Martinez & Canavarro, 2000; Veronesi & Boyes, 1988). We compared the equivalent axonal diameters (i.e. the axon area was estimated by the two-dimensional nucleator technique and the diameter that a circle of equal area would have was calculated) of the uncrushed MN and BF nerves (unpublished results) and found group means of comparable magnitude (3.236 and 3.343, respectively).

We found at the histological level that the BF regenerated faster and/or more completely than the MN and we believe this difference to be a genuine difference between the motor fibres and the sensory fibres. In support, Williams and Hall (Williams & Hall, 1971) found that motor nerves have a thicker myelin sheath relative to the axon diameter than sensory nerves have. They also found that Schwann cells associated with motor nerves synthesize myelin faster than sensory nerve Schwann cells. The later could account for a faster regeneration in the motor BF when compared to the sensory MN. Martini et al.(Martini, Xin, Schmitz, & Schachner, 1992) reported that guide molecules important for regeneration of the peripheral nerves were found only in motor nerves and not in sensory nerves, whereas Madison et al.(Madison, Archibald, & Brushart, 1996) found analogous molecules in regenerating sensory nerves indicating that different nerve populations use different ways of regeneration. Several studies have yielded results comparable to ours as regards the magnitude of regeneration. After crush lesion of the mental nerve, Savignat et al.(Savignat et al., 2008) found that 65% of the axons had regenerated at 1 month post lesion. Three weeks after a crush lesion of the inferior dental nerve, Berger et al.(Berger & Byers, 1983; Berger, Byers, & Calkins, 1983) found 50–75% regeneration of the normal axon number in the tooth pulp and 25–50% of the normal axon number in dentine. In a compression study of the rabbit facial nerve, Costa et al.(Costa, Silva, Korn, & Lazarini, 2006) found that the total number of axons was 86% of that in the control nerve at 4 weeks post lesion. It has been hypothesized that Wallerian degeneration propagates slower in longer axons found in

higher species (Lubinska, 1982) but in a short review of studies Gilliatt and Hjorth (Gilliatt & Hjorth, 1972) found that degeneration times were comparable in rabbits, guinea pigs, and rats. At the examined time points we found nerve fibres at different degenerative and regenerative stages, supporting other investigators who have found Wallerian degeneration to be asynchronous (Beirowski et al., 2005; Martinez & Canavarro, 2000).

Study 5 in this thesis showed that GCC had a significant impact on increased number of axons in the motor nerve. This view is shared by many other authors. Glucocorticoids are used in the treatment of neuropathies including Bell's palsy and spinal cord injuries (Haghighi, Clapper, Johnson, Stevens, & Prapaisilp, 1998; Lagalla, Logullo, Di Bella, Provinciali, & Ceravolo, 2002). It's well known for its neurotrophic and anti-inflammatory effects (K. J. Jones, 1988; Kawata, 1995; Yao & Kiyama, 1995). Al-Bishri et al (Al-Bishri, Rosenquist, et al., 2004) found in their study that patients who received moderate doses of corticosteroids (Betamethasone) perioperatively seemed to have less sensory disturbance after sagittal split osteotomy. Animal experiments have also shown good effect both functionally and, although not significant, morphologically (macrophages and Nerve Growth Factor), of corticosteroids after traumatic injury to the sciatic nerve (Al-Bishri, Forsgren, Al-Thobaiti, Sunzel, & Rosenquist, 2008). In another animal study utilizing crush lesion to the sciatic nerve of rat, treatment with GCC had a significant improvement for both muscular function and histological findings, in which the muscular function returned to normal levels faster while histological analysis found larger and more abundant axons compared to non-treated rats (Gudemez et al., 2002). Study 5 in this thesis shares the same findings. GCC are found to have an impact on increased number of axons in the motor nerve. Methylprednisolone was also shown to improve functional recovery in rats after sciatic nerve transection by significantly improving motor nerve conduction velocity (Nachemson, Lundborg, Myrhage, & Rank, 1985) GCC was shown to significantly reduce mechanically-induced dysesthesia following lingual nerve injury in animals (Yates, Smith, & Robinson, 2004). GCC were shown to have a direct effect on the myelin thickness after a crush lesion to the rat sciatic nerve. This effect on myelin thickness is believed to be achieved through the direct effect of GCC on the GCC receptors found in Schwann cells (Morisaki et al., 2010). Better nerve regeneration was found after treating transected olfactory nerves in mice with GCC compared to sham group (Kobayashi & Costanzo, 2009). Functional recovery was also significantly improved after treatment with Triamcinolone, a synthetic GCC, in a sciatic nerve transection model in rats (Bansberg & McCaffrey, 1987).

Seo et al (Seo et al., 2004) tried to estimate the efficacy of steroid treatment and determine the appropriate time to give the steroid after NSD related to IVRO and SSO and found favorable effects of steroid in his study. Topical steroid was also shown to significantly reduce NSD after nerve injury (Galloway et al., 2000).

Many studies have been done regarding the effect of steroid on the CNS. Methylprednisolone is the only medicine used to treat acute spinal cord injuries (Bracken et al., 1997). A study on human done by Bracken et al (1992) showed the same effect of methylprednisolone in significantly enhancing both motor and sensory regeneration of the injured spinal cord if the treatment was done no later than 8 hours post operatively. Methylprednisolone was shown to have neuroprotective qualities when in both histopathological and neurophysiological studies if given within 8 hours of an acute injury in rabbits with better recovery of nerve conduction velocity (Gok et al., 2002). In a spinal cord injury model in rats, the combined effect of GCC and Brain derived Neurotrophic Factor had a significantly improved functional recovery compared to Brain derived Neurotrophic factor alone. This was attributed to the enhanced remyelination seen through histochemical investigation (Li et al., 2003). Similar results showing significant improvement in functional recovery and axonal regrowth were presented in another spinal cord injury model on rats where DCC was combined with Ensheathing cells (Glial cells that ensheath the axons of the olfactory receptor neurons) (Nash et al., 2002). It was also shown that GCC significantly improve axonal regeneration into Schwann cells grafted from Sciatic nerve into spinal cord in rats (A. Chen, Xu, Kleitman, & Bunge, 1996).

Other animal studies have shown different results of GCC treatment on neural regeneration. Those studies showing absence of effect were either done in CNS (Chari, Zhao, Kotter, Blakemore, & Franklin, 2006; Ohlsson et al., 2004) or PNS (Lee, Fee, & Terris, 2002; Roh & Park, 2008; Wang et al., 2006). In an animal study of sciatic nerve crush lesion with topical GCC treatment, there was a significant improvement in functional recovery during certain stage of the study solely attributed to GCC treatment but the difference in functional recovery did not statistical difference at the end of the study(Galloway et al., 2000)

There is a marked difference in the way studies on GCC effect are done both in choosing study model, whether it is an animal or human study, the type of animals used, the follow up period, the examination method implemented (histological vs clinical) and type of tests used (different types of histochemical as well as functional tests to study nerve regeneration exist).

All these differences make direct comparison between different types of studies quite difficult. It is also worth considering that not every beneficial effect on histological grounds can be translated into enhancement in functional recovery.

There is no standardized formula to calculate the exact amount of steroid dose that should be given after operation, but it is logical to consider giving a dose higher than the daily endogenous. A dose exceeding this limit would suppress the inflammatory process better than the body itself (Gersema & Baker, 1992). Many authors consider a high dose for a short period of time to be better than a dose taking longer time to avoid possible complications such as delayed wound healing and adrenal insufficiency (Gersema & Baker, 1992; Williamson et al., 1980).

In this thesis, Betamethasone treatment enhanced the posttraumatic outcomes in both the rat mental and facial nerve after crush lesion. In both nerves the total numbers of axons, the total numbers of myelinated axons, and the cross sectional areas of myelinated axons were at all examined time points larger in the Betamethasone treated animals than in the saline treated animals At day three the effect of Betamethasone treatment (as compared to saline treatment) on the total number of myelinated axons was statistical significant in the BF (47% versus 36%) but not in the MN (49% versus 34%). Although comparable in numbers the degree of freedom in the crushed MN nerve was too small to reach statistical significance. These data suggest that Betamethasone decreases the degenerative process. At day 7 the BF has significantly more newly formed axons in the Betamethasone treated animals than in the saline treated animals whereas no effect can be detected in the MN at that time point. When examined at day 19 however, the total numbers of myelinated axons are significantly larger in both BF and MN in the Betamethasone treated animals. These data suggest that Betamethasone enhance the regenerative process. The regenerative process has been shown in a parallel study to be faster and/or more complete in the BF than in the MN (Barghash et al., 2013). We used the axon number, axon area and axon diameter as parameters to determine features of nerve regeneration. Those parameters have been demonstrated to have resolving power to demonstrate the difference when examining peripheral nerve regeneration (Vleggeert-Lankamp, 2007) The fact that the experiment samples were of small size and the follow up time was short might affect the outcome of this study.

6 CONCLUSION

No significant differences were recorded in patients' satisfaction between the patients who had SSO alone (89% satisfaction) and those who also had genioplasty (86% satisfaction). Sensory disturbances are not a main determinant of patient satisfaction, which is probably more dependent on function and aesthetics.

There were disagreement between the judgement of the surgeon and the patient's opinion. Long lasting NSD was underestimated by the surgeon as compared to the patient's subjective symptom.

Considering that only 1% of the operated sites showed a permanent neurosensory disturbance in the lower lip following EVRO, the authors believe that despite having some areas of concern, EVRO is still to be considered a very safe orthognathic surgical method and to be recommended in selected cases.

It was shown in experimental animal model the motor buccal branch of the facial nerve regenerated faster and/or more completely than the sensory mental nerve did. And that there were an increased number of regenerating axons after perioperative treatment with betamethasone in both buccal and mental nerves at 19 days postoperatively indicating that betamethasone enhanced nerve regeneration in both motor and sensory nerves.

7 FUTURE PERSPECTIVES

Further studies are planned to study the interaction between cortisone and nerve trauma in more details, this time with the use of electron microscopy and studying the effect of nerve trauma on the degeneration and regeneration of C-fibres. Hopefully more studies will be planned to study the effect of cortisone and/ other medications on nerve healing in humans.

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APPENDIX

Put appendix material here, either as part of this document or in reprints. If you have a lot of material, for better clarity, consider using a table of contents on this page, use subchapters, and if possible maintain page numbers in the appendix.

7.1 Appendix 1

Questionnaire

1. Have you experienced any sensory disturbance after the operation in:-
   [ ] Upper lip   [ ] Lower lip   [ ] Chin

   [ ] Tongue   [ ] Cheek   [ ] Teeth

   [   ]   No   sensory   changes

2. In which side is you sensation altered?
   [ ] Right   [ ] Left   [ ] both

3. If you have/had any sensory disturbance, when did this begin?
   [   ]   Immediately   after   the   operation
   [ ] Sometime after the operation

   Comments   …………………………………………….

4. Would you describe the sensory disturbance as:
   [ ] Anaesthesia   [ ] Pinching   [ ] Tickling

   [ ] Painful   [   ]   Burning   [   ]   Other
   Comments   …………………………………………….

5. Does the changed sensation cause any problems for you?

[ ] Always   [ ] At touching   [ ] When chewing

[ ] When talking   [ ] When eating   [ ] Other

6. Has the sensory change made you bite yourself by mistake in the
   [ ] Lip   [ ] Cheek   [ ] Tongue

7. Has the sensory change made you burn yourself in the lip or tongue?
   [ ] Yes   [ ] No

   Comments………………………

8. How would you describe the discomfort you experience as a
   consequence of the altered sensation? Indicate with an (x) on the line
   below.
   .0   .   .   .   5.   .   .   .   .   10.
   no discomfort   intolerable discomfort

9. For how long have you had the altered sensation?
   [ ] Less than a month   [ ] Six months

   [ ] One year   [ ] More than one year but
normal now

   [ ] More than one year and still altered

10. In which side your sensation still altered.
    [ ] Right   [ ] Left   [ ] Both

11. Are you satisfied with the result of the operation?
    [ ] Yes   [ ] No

    Comment…………………………….

12. With your experience, would you recommend this kind of treatment?
   [ ] Yes   [ ] No

   Comment…………………………….

7.2 **Appendix 2**

Questionnaire

1. Have you experienced any sensory disturbance after the operation in:-
   [ ] Upper lip   [ ] Lower lip   [ ] Mandible Body

   [ ] Tongue   [ ] Cheek   [ ] Teeth

   [ ] No sensory changes, then go to question nr. 10

2. In which side is your sensation altered?
   [ ] Right   [ ] Left   [ ] both

3. If you have/had any sensory disturbance, when did this begin?
   [   ]   Immediately   after   the   operation
   [ ] Sometime after the operation

   Comments   ………….…………………………….

4. Would you describe the sensory disturbance as:
   [ ] Anaesthesia   [ ] Pinching   [ ] Tickling

   [ ] Painful   [ ] Other   [   ]   Burning
   Comments   ………….……….………………….

5. Does the changed sensation cause any problems for you?
   [ ] Always   [ ] At touching   [ ] When chewing

[ ] When talking   [ ] When eating   [ ] Other
Comments   ……………………………………….

6. Has the sensory change made you bite yourself by mistake in the
    [ ] Lip   [ ] Cheek   [ ] Tongue

7. Has the sensory change made you burn yourself in the lip or tongue?
    [ ] Yes   [ ] No

    Comments…………………………………

8. How would you describe the discomfort you experience as a consequence of the altered sensation? Indicate with an (x) on the line below.
   .0   .   .   .   .   5.   .   .   .   .   10.
discomfort   intolerable discomfort

9. For how long have you had the altered sensation?
    [ ] Less than a month   [ ] Sex months

    [ ] One year   [ ] More than one year but normal now

    [ ] More than one year and still altered

10. Do you have any muscle weakness in or around lower lip?
    [ ] Yes   [ ] No

How would you describe the discomfort you experience as a consequence of the muscle weakness? Indicate with an (x) on the line below.

.0 . . . 5. . . . . 10.
no discomfort   intolerable discomfort

11. Have you had any discomfort with the scar tissue of the operation site?
4. [ ] Yes   [ ] No

How would you describe the discomfort you experience as a consequence of the scar tissue? Indicate with an (x) on the line below.

.0 . . . 5. . . . . 10.
discomfort   intolerable discomfort

5.

12. Are you satisfied with the result of the operation?
      [ ] Yes   [ ] No

      Comment…………………………….