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DIAGNOSTIC AND THERAPEUTIC MANAGEMENT OF IATROGENIC LESIONS OF LINGUAL AND INFERIOR ALVEOLAR NERVE

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Introduction

Trigeminal nerve branches injuries are more and more frequent because of the wide spread of oral surgery. When the nerve damage involves the lingual nerve (LN) or the inferior alveolar nerve (IAN), the negative impact of the nervous dysfunction on the daily life of patients is relevant.

Patients usually describe their condition as a crippling disease interfering with their common daily activities (talking, eating and drinking) and, consequently, forcing them to give up their social life. This difficult situation is undoubtedly worse when pain is present. It is about a neuropathic pain due to the nerve damage and the wrong regeneration process that make a mixture of nervous fibres and scar tissue. It is a dull pain described by one of our patient as “a monster that never gives up, always present as a new life-mate”. Moreover, all these feelings and patients’ adaptability have always to be correlate to the kind of surgery that caused the symptoms themselves. It’s not easy to understand and accept a complete lingual anaesthesia associated with continuous pain appeared after the removal of an asymptomatic wisdom molar! The same symptoms appeared after the removal of a malign tumour are usually more acceptable.

Unfortunately, even today, there is no worldwide consensus about how to early recognize and eventually treat this kind of lesions. Nowadays, these iatrogenic nerve damages culminate more and more frequent in legal matters.

A standardization of diagnostic and therapeutic management is necessary, to clarify which the correct approach for each patient is.

This project aimed to standardize through the founding of a specific Clinic the management of patients affected by lingual nerve and inferior alveolar nerve lesion, in order to propose a common diagnostic process, followed by both the patient-specific

reconstructive surgery and the regular clinic and neurophysiological follow up. The standardized management allows to understand the actual efficacy of this kind of surgery.

Chapter 1: Classification of peripheral nerve lesions

Numerous classifications were proposed during the last century to categorize peripheral nervous lesions. They depend on the localization / aetiology / kind of damage / histology / symptomatology of the injury itself. The most common classification systems, clinicians are usually used to resort to, are Seddon classification[1] and Sunderland classification[2].

Seddon stratified the peripheral nerve injuries into three different groups, according to the optical microscopic histological features, the residual motor function and the following prognosis:

- Neurapraxia (Class I): it is the mildest peripheral nerve type of injury. It is characterized by a temporary interruption of nerve conduction without loss of axonal continuity. No macroscopic injuries of the nerve are present: the endoneurium, the perineurium and the epineurium are intact and no Wallerian degeneration is reported. The microscopic assessment shows oedema and some morphological deficits of the myelin sheath. Recovery of nerve conduction deficit is spontaneous and complete within few weeks[1].
- Axonotmesis (Class II): it is a more severe injury than the neurapraxia, characterized by a complete interruption of the myelin sheath. No loss of continuity of the three connective sheaths (epineurium, perineurium, endoneurium) is present. No macroscopic deficits are detectable.

  Wallerian degeneration occurs distal to the site of nerve injury, where there is no nerve conduction. This type of injury can be due to nerve compression exercised by some external factors. Axonal regeneration occurs through the neuronal tube that acts like a scaffold to the regeneration process.

Spontaneous recovery is possible within three months, but it depends on the distance between the site of injury and the innervated area (the nerve regeneration occurs at a speed of 1mm/day)[1,3].

- Neurotmesis (Class III): it is a macroscopic partial or complete disruption of the entire nerve fibre. The loss of nervous function is complete and the spontaneous recovery unlikely, since it depends on both the size of the gap and the process of formation of scar tissues between the proximal and distal stumps of the nerve. When the nervous stumps are juxtaposed, a partial spontaneous recovery can occur. In all those cases where a complete section of the nerve is present, a complete recovery can't occur because, during the nervous regeneration process, 30-40% of nerve fibres are not able to bypass the nervous gap. The spontaneous recovery may be better when a nerve laying in a bone canal is involved (i.e. the inferior alveolar nerve), because the bone canal acts as a scaffold guiding the spontaneous nerve regeneration[1].

Symptomatology referred by patients is the same both in case of axonotmesis and neurotmesis, but the prognosis and the type of treatment is different[1].

Both clinicians and surgeons have to know which kind of lesion affects the patient, in order to choose the best treatment. The timing of injury is as important as the kind of lesion and the reconstructive surgeon has always to consider, as well as the referred symptomatology, how long the nerve lesion has occurred: the complete anaesthesia of the lower lip/tongue associated with the lack of any kind of improvement within three months from the nerve injury suggests a complete section of the nerve and the patient should be referred to the surgical treatment, in order to explore and, eventually reconstruct, the IAN/LN. The same treatment should be performed in all those cases where the labial/lingual pain is present. In case of absence of symptomatology improvement within

90 days from the nerve trauma, there is less chance of spontaneously recovering (9.3-62.9%)[4].

Through the surgical exploration of the nerve, the surgeon is able to understand which kind of lesion is present: the nerve will be exposed and assessed under microscopic vision. A complete or partial nervous section and some scar tissue between the nerve stumps can be highlighted: those features are responsible for pain[1].

In 1951, Sunderland proposed a new peripheral nerve classification, depending on the size of epineural, perineural and endoneural damage[2].

Sunderland proposed five degrees of peripheral nerve injuries:

- First Degree: It is a temporary conduction block, due to the presence of some perineural oedema, that can undergo to spontaneous recovery within three months. The microscopic assessment and the histopathological examination usually show either slight damage or absence of nerve injury. Authors usually consider Sunderland's first degree as Seddon's neurapraxia[2].
- Second Degree: No loss of continuity of the three connective sheaths (epineurium, perineurium, endoneurium) is present. The microscopic assessment usually shows slight damage involving the axons corresponding to the site of lesion. Second Degree could correspond to Seddon's axonotmesis.

  Wallerian degeneration occurs distal to the site of nerve injury, where there is no nerve conduction; since the connective sheath system maintains its continuity, this structure will work as a scaffold for the nervous regeneration process (1mm per day).

  The spontaneous recovery is possible within three months[2].
- Third Degree: This kind of injury corresponds to Seddon's axonotmesis and the endoneurium is usually involved, while both the epineurium and the perineurium are still intact. No macroscopic nerve damage is detectable, but there are some scar

tissues inside the endoneurium that could prevent, acting as a mechanical obstacle, the complete nervous regeneration reducing the chance of a complete spontaneous recovery[2].

- Fourth Degree: This kind of injury corresponds to Seddon's axonotmesis and both the endoneurium and the perineurium are usually involved, while the epineurium is still healthy. Compression, stretching and traction of the nerve could cause this type of lesion. The nerve is still macroscopically healthy, since the epineurium is intact. The spontaneous recovery is possible but it could not be complete, because of the scar tissues inside the epineurium. Wallerian degeneration occurs distal to the site of nerve injury, where there is no nerve conduction; the distal stump of the nerve degenerates, leading to a complete peripheral denervation. The spontaneous recovery is not possible, so, in order to get a functional recovery, the surgical exploration and the nerve reconstruction are required[2].
- Fifth Degree: This lesion corresponds to Seddon's neurotmesis and is characterized by a complete section of the peripheral nerve. The spontaneous recovery cannot occur, so, in order to get a functional recovery, the surgical exploration and the nerve reconstruction are required[2].

Clinically, peripheral nerve injuries can be subdivided into two groups: *closed* and *open* lesions.

The former are all those unrecognized nerve damages: the most of trigeminal injuries remain misunderstood till the post-operative period when the patient complains about some pain and loss of nervous function. The latter, both intentional and accidental, on the contrary, are immediately identified during the same surgical procedure. In case of open lesion, the surgeon can fix the nerve damage immediately, during the same procedure, increasing the possibility of complete recovery of the *function lesa*[3].

Chapter 2: Anatomy

2.1 Peripheral Nerves

In order to well understand what happens to the nervous structure when a peripheral nerve injury occurs, surgeons have to know in detail the anatomy of the peripheral nerves.

The axons of the effector neurons and Schwann cells, that function to support neurons, make the fibres of the peripheral nerve system. Depending on the relation between axons and satellite cells, nerve fibres can be myelinating and non-myelinating.

Non-myelinating Schwann cells wrap around axons using only a thin cytoplasmic sheath; they include small axons and their normal nervous impulses travel at 2–2.5 m/s.

Myelinating Schwann cells wrap around axons many time, in order to form the myelin sheath. Between two consecutive Schwann cells, there is a gap called node of Ranvier. The distance between two adjacent nodes is usually the same. The electric potential travels from one node to the following one, increasing the conduction speed (150 m/s), compared with the non-myelinating fibres.

Every peripheral nerve fibre is composed by a connective scaffold, where blood vessels lay, providing trophic, supportive and protective functions to the nerve itself. The role of the connective tissue is essential and its structure very specific:

- The Epineurium is an adventitia layer, wrapping the nerve; it is composed by elastic fibres and collagen. From the inner surface of the epineurium, some lamellar connective tissues dispose themselves concentrically forming the Perineurium that wraps the nerve files.
- The Perineurium is a thin, stretchy, ductile and strong connective layer, working as a barrier that maintains the correct ionic concentration in the endoneurial space. The Perimeurium wraps a variable number of axons: the number of nerve fibres usually changes depending on the position inside the nerve (i.e. the inferior alveolar

nerve has 18-21 nerve fibres in the proximal region corresponding to the mandibular angle that decrease to approximately 12 in the most distal part of the nerve, corresponding to the mental foramen)[5].

- The Endoneurium is composed by some connective *septae* coming from the perineurium and wrapping the single nerve fibres. It is composed by connective tissue full of blood and lymphatic vessels[6,7].

2.2 Oral Cavity – Trigeminal nerve branches

2.2.a Inferior Alveolar Nerve

The IAN is a branch of the mandibular nerve, the third division of the Trigeminal Nerve, the fifth cranial nerve. The Mandibular Nerve is composed by both sensitive (98%) and motor (2%) fibres (the sensitive fibres come from Gasser's ganglion, while the motor fibres come from the trigeminal motor nucleus).

This nerve emerges from the Meckel cave and runs vertically and downward in order to emerge from the cranial base to the infratemporal fossa through the *foramen ovale*. In the upper part of the infratemporal fossa, this nerve divides into two terminal branches, the antero-lateral and the postero-medial division. The first one is predominantly a motor branch for the masticatory muscles (masseteric nerve, deep temporal nerves and pterygoid nerves). The second one has sensitive fibres, runs downward and forward and splits into two terminal branches (inferior alveolar nerve and lingual nerve). The IAN is a sensitive nerve, that arises from the mandibular nerve in a cranial and medial position respect to the mandibular foramen, running downward, forward and laterally to the mandibular foramen on the medial surface of the mandibular ramus. Through the mandibular foramen itself, the IAN comes into the mandibular canal, together with the inferior alveolar artery and vein.

The IAN lays into the mandibular canal, suppling the lower teeth with sensory branches that form the inferior dental plexus and give off small dental nerves to the teeth (Fig. 2.2); it runs medially and forward to the mental foramen, where it divides into two terminal branches, the mental nerve and the incisal nerve. The former comes out from the mandibular canal through the mental foramen and supplies the soft tissues of the symphysis region, while the latter runs inside the bone canal to the interforaminal teeth and the bone of the symphysis region. In the medial region, both the incisal and the mental nerves give off small branches that would anastomose with the contralateral ones. Wide

anatomical variability was described (i.e. multiple mental *foramina*, different ramification of both the mental and incisal nerves)[2,8,9].

The average diameter of this peripheral nerve is about 2.4mm[5].

2.2.b Lingual Nerve

The LN is one of the terminal branches of the postero-medial division of the Mandibular Nerve. It is a sensitive nerve that runs medially, downward and forward from the infratemporal fossa between the medial and lateral pterygoid muscles to the mouth floor. It joins to the *corda tympani*, coming from the facial nerve. In the posterior part of the mouth floor, the LN lays medially to the inferior third molar; in this region, the nerve changes its course and runs on the upper surface of the mylohyoid muscle horizontally, medially and forward, giving off small branches directed to the lingual muscles and mucosa. In the posterior part of the mouth floor, the LN gives off the parasympathetic fibres directed to the submandibular gland.

The average diameter of this peripheral nerve is ranged between 1.5 and 3mm[9,10].

2.3 Peripheral nerves typically used to reconstruct trigeminal nerve lesions

2.3.a Sural Nerve

The sural nerve is a sensitive nerve running in the postero-lateral surface of the leg and suppling the fifth toe and the lateral surface of the foot. This nerve rises from the union of the medial cutaneous collateral branch of the tibial nerve (medial sural cutaneous nerve) and the lateral collateral branch of the common peroneal nerve (lateral sural cutaneous nerve)[6,7].

From the popliteal fossa, the sural nerve runs downward, in the posterior part of the leg, to the lateral malleolus, where it changes its direction, becoming horizontally and going on forward as lateral dorsal cutaneous nerve.

The average diameter of the sural nerve is about 2.1mm[11].

2.3.b Great Auricular Nerve

The Great Auricular Nerve is a sensitive nerve rising from the *Ansa Cervicalis* of the cervical plexus (C2 and C3), running upward and forward on the superficial surface of the sternocleidomastoid muscle to the auricular pavilion and suppling the skin of the mastoid and parotid region, the parotid fascia and part of the auricular pavilion[6,7].

The average diameter of the great auricular nerve is about 1.5mm[5].

Chapter 3: Physiopathology of the peripheral nerve lesions

Literature describes lots of surgical steps that may lead to iatrogenic injury of some branches of the Trigeminal Nerve. When the nervous lesion can be immediately recognized, the surgeon has to proceed, during the same surgical step, with the nerve reconstruction (usually through a direct neurorrhaphy of the proximal and distal stumps of the injured nerve). The immediate neurorrhaphy represents the gold standard in term of functional results, because, during the following weeks, the healing process starts and lots of scar tissues modify the clinical and histopathological features of the injured nerve[12].

The trigeminal iatrogenic lesions can be subdivided into two groups:

- *Mechanical injuries*[12-16]:
    - *Compressive nerve injuries*:
        - Using surgical retractors and elevators, during tooth extraction or implant placement;
        - Foreign bodies located in the mandibular canal (i.e. dental implants, bone fragments, dental roots, endodontic material);

      The spontaneous recovery is usually possible within a period ranged between few weeks and three months; in all that cases where a foreign body is present, this material has to be removed in order to make the healing process starts.
    - *Stretch nerve injuries*: using surgical retractors and elevators, during tooth extraction or implant placement; the spontaneous recovery is possible within a period of 20-90 days from the traumatic event. The stretch lesion can lead to a partial axonal injury (axonotmesis): in those cases, only a partial spontaneous recovery is possible.

- *Partial nerve section*: using medical sharps (surgical elevators, cold scalpels), electrical instruments (bipolar forceps, electrocautery) and rotating burs. The prognosis is worse than that following both a compressive and a stretch lesion, because there is always a section of the nerve structure: the spontaneous healing (within a period of 3-12 months) is possible but the recovery cannot be complete.
- *Complete nerve section*: using medical sharps (surgical elevators, cold scalpels), electrical instruments (bipolar forceps, electrocautery) and rotating burs. The complete section is macroscopically visible. The prognosis depends on the localization of the lesion:
    - Nerve lesion inside the mandibular canal (typical of the IAN): the bone canal works as a regenerative guide for the nervous fibres from the proximal stump to the distal one; the prognosis is the same of the partial section prognosis: the recovery starts within 2-3 months from the traumatic event and continues for 2 years. In order to start the correct spontaneous regenerative process, no foreign body (dental implants, tooth roots, bone fragments, endodontic material) must be displaced into the mandibular canal; otherwise the spontaneous healing process cannot start and the reconstructive surgeon has to surgically remove the obstacle and reconstruct the nerve.
    - Nerve lesion in the soft tissues (typical of the LN): the nervous stumps usually retract and lots of scar tissue form between them, making the spontaneous recovery impossible.

- *Chemical injuries*:
    - Troncular anaesthesia (articaine 4%, mepivacaine 3%, prilocaine 3% and lidocaine 2%) is a rare but described cause of trigeminal nerve injury. The

incidence is variable depending on the literature studies (0.003-3.3%). Patients usually complain about loss of sensibility, dysesthesia, pain, dysgeusia and allodynia. The spontaneous recovery is possible within 8 weeks[17].

- Chemical agents of the endodontic material (Sodium Hypochlorite, root canal filling material): in case of displacement of this material during the root canal treatment. Literature describes temporary or permanent dysesthesia in 30% of cases[18].

Chapter 4: Physiopathology of the peripheral nerve repair

The spontaneous nervous healing is a cell repair process: nervous cells are not able to reproduce themselves, so they cannot increase their total number. The cellular answer to a traumatic event anywhere in the peripheral fibre far from the neuron body is based on some processes aimed at both the injured tissue removal and the nerve repair[19]. The first process involves the myelin sheath that, immediately after the injury, retracts from the nodes of Ranvier, increasing the myelin incisures. During the following hours, the nerve injuries spread to Schwann cell cytoplasm, the distal axons and the non-myelin fibres.

24 hours after the traumatic event, the distal axon degeneration becomes more and more evident: the non-myelin cell degeneration involves the entire nervous fibre, while the myelin cells start the protein biosynthesis, in order to cover the nodes of Ranvier. 48 hours after the lesion, the myelin sheaths are thinner and thinner and there is an evident swelling of the nervous fibres. In the period ranged between 3 and 15 days after the trauma, the macrophages start the process of myelin debris removal and they remain in the injury region for the following three months[19-23].

5 days after the trauma, the repair process starts in the cytoplasm of the proximal stumps[24].

Chapter 5: Etiopathology of the peripheral nerve lesions

Iatrogenic injuries of the trigeminal nerve branches are common, in particular those involving the IAN and the LN; the iatrogenic lesion of the infraorbital nerve are less frequent, because of its favourable position. Otherwise, the IAN has the major risk of injury because of its position inside the mandibular bone canal, near the lower tooth root (reported incidence: 0.26-8.4%)[25-28]. Nowadays, the oral surgery procedures (lower third molar extraction, implantology, endodontic treatments, orthognathic surgery, mandibular lesions removal) are more and more frequent, so that the incidence of iatrogenic nerve lesions is increasing[12,15,16,29]. Moreover, the LN may be involved during oral and maxilla-facial surgery procedures, leading to significant functional impairments (partial or complete loss of lingual sensibility, dysesthesia, pain, hyperaesthesia, dysgeusia). Burning dysesthesia accompanies anaesthesia in almost 40% of patients. In 8% to 15% of patients, pain remains the most debilitating sequela, requiring adequate treatment[30-32]. Lots of procedure may involve these branches of the mandibular nerve, in particular in case of non-optimal pre-operative surgical planning:

- Troncular anaesthesia of the nerve (in particular of the IAN, the mental nerve and the infraorbital nerve): it is a common procedure during implant placement and lower third molar extraction. It is usually a chemical injury, but sometimes the direct needle penetration in the peripheral nerve can lead to a nerve injury. When it is a mechanical trauma, the patient complains about an electric shock in the area supplied by the injured nerve, when the needle penetrated the nerve itself. There is also another mechanical mechanism that can injure the nerve during local anaesthesia: it is a mechanical compressive process due to some bleeding and haematoma occurring after the needle penetration. It is usually a temporary nerve damage[17,33-37].

- Lower molar extraction (in particular the wisdom tooth): both the IAN and the LN can be involved[38-42]. The nerve injury can be either chemical (during troncular anaesthesia) or mechanical (during the use of cold scalpels, surgical retractors and elevators, rotating burs)[43-45].
- Dental implantology (in particular in the posterior part of the mandible): both the IAN and the LN can be injured. The incidence of temporary and permanent deficits is 0-40%[26,29,46-49]. The most part of IAN lesions during implant placements follows the use of rotating burs, but the nerve lesion can be either chemical (during troncular anaesthesia) or mechanical (during the use of cold scalpels, surgical retractors and elevators, rotating burs)[50,51].
- Endodontic treatment: this kind of lesion involves mostly the IAN. This injury may be a chemical lesion (i.e. using the Sodium Hypochlorite) or a mechanical lesion (compression of the IAN inside the bone canal following the extravasation of the endodontic material; sometimes the process called “overinstrumentation” occurs: the surgeon uses the surgical instruments over the canal of the tooth, reaching the mandibular canal and the IAN)[52-56].
- Orthognathic surgery: a mechanical nerve damage can occur during sagittal osteotomy of the mandible and mentoplasty. 100% of patients who undergo sagittal osteotomy of the mandible complain about temporary loss of sensibility of the lower lip during the immediate post-operative period. The incidence of permanent damage is described as 12.8-39% of cases[57,58].
- Traumas: IAN injuries can occur after mandibular fractures involving both the body and the ramus. Mental nerve and LN injuries can occur after soft tissues traumas of the mouth and the lower lips[59,60].
- Removal of benign lesions of the oral cavity.

- Oncologic surgery: in some cases, the surgeon has to sacrifice some branches of the trigeminal nerve in order to get a radical removal of the tumour[61-63].

Chapter 6: Founding of a Clinic specifically aimed at peripheral nerve lesion of the oral cavity

The iatrogenic lesions of the trigeminal nerve branches that occur more and more frequently during oral and maxillo-facial surgery procedures are still a misunderstood chapter of the reconstructive surgery. The aim of this research project was to standardize the management of adult patient affected by iatrogenic injury of both the IAN and the LN following oral surgery, dental implantology, local anaesthesia, endodontic treatment and other maxilla-facial procedures, through the founding of a specific Clinic, called “Nervous Lesion Clinic”. This Clinic was organized once every two weeks at the Maxillo-facial Surgery Department of the San Paolo Hospital (ASST Santi Paolo and Carlo) in Milan. The patients have the possibility to book a visit through the hospital reservation centre or directly using the e-mail address of the Clinic that they can find on the hospital website.

These patients complain about partial or total loss of sensitivity of either the tongue or the lower lip, sometimes associated with dysesthesia, paraesthesia, neuropathic pain, allodynia, dysgeusia of the same areas.

No temporal limits between the traumatic event and patient’s presentation has been considered.

A subjective, clinical and neurological assessment have been performed in order to get the best evaluation of the treatment endpoints.

The subjective assessments include the administration of a pre-operative questionnaire focused on the quality of life, the general oral health of the patient; a personalized questionnaire was obtained through the combination of specific aspects taken from specific tests described in literature and their translation into Italian language:

- Satisfaction with Life Scale (SWLS)[64];

- Center for Epidemiological Studies Depression scale (CESD-20)[65];
- Short Form-36 Health Survey (SF-36)[66];
- Short-Form Oral Health Impact Profile (OHIP-14)[66].

The clinical assessment includes:

- *Patient's history:* Some data are essential to choose the best treatment for each patient (type and timing of the traumatic event; symptoms; symptoms progression);
- *Physical examination;*
- Evaluation of *Orthopantomography* and *Cone Beam CT scan* for patients affected by IAN lesion;
- *Sensorineural tests.*

The neurophysiological evaluation has been based on the assessment of the presence of the Masseter Inhibitory Reflex (MIR), the tactile and pain thresholds and the tactile and pain Sensory Deficit Ratio (SDR).

Patients have been classified in different groups depending on:

- Patients' history;
- Localization of the nervous lesion (LN or IAN);
- Aetiology;
- Symptoms (Partial or total loss of sensitivity of the lower lip or tongue; pain/dysesthesia/paraesthesia/allodynia/ageusia);
- Time between the traumatic event and the first evaluation of the patient.

According to all the above-mentioned data and the clinical and neurophysiological results, the best treatment (surgical versus medical therapy) has been chosen for each patient.

In the same Clinic, a standard follow up has been carried out, every three months after surgery and a neurophysiological test was performed 12 months after surgery.

Chapter 7: Preliminary patient evaluation

7.1 Clinical assessment

Asking the patient to tell his/her history is the first step to frame the clinical picture:

- Which symptoms does the patient report?
- When did the patient start to complain about the above-mentioned symptomatology?
- Is there a temporal relation between the appearance of that symptomatology and a traumatic event?
- How much time has elapsed since the symptomatology started?
- How was the progression of symptoms?
- Are there some trigger factors that worsen the symptomatology?
- Did the patient try some medical/surgical therapy to treat the symptoms?
- The reconstructive surgeon should know if, during the traumatic event, the nerve was cut, because, in that case, the nerve reconstruction should be performed immediately, with a higher possibility of recovery. In all those cases where the reconstructive surgeon could not know what happened to the nerve during the traumatic event, the reconstructive surgery has to be delayed waiting for a spontaneous recovery of the nervous function. When pain is present, the reconstruction has always to be performed immediately to prevent the chronicity of pain.

Patients affected by a trigeminal nerve lesion usually complain about lots of different symptoms, according with the International Association for the Study of Pain[67,68]:

- Partial (Hypoesthesia) or complete (Anaesthesia) loss of sensitivity of either the homolateral tongue (in case of LN lesion) or the homolateral lower lip and lower alveolar arch (in case of IAN lesion);
- Pain of either the tongue or the lower lip and lower alveolar arch. The Visual Analogic Scale (VAS) should be used to quantify the reported pain;
- Paraesthesia and Dysesthesia: “an abnormal sensation, whether spontaneous or evoked”[68];
- Hyperesthesia: “increased sensitivity to stimulation, excluding the special senses”[68];
- Allodynia: “pain due to a stimulus that does not normally provoke pain”[68];
- Hyperalgesia: “increased pain from a stimulus that normally provokes pain”[68];
- Distortion (Dysgeusia) or complete lack (Ageusia) of the sense of taste: this symptom is typically present in case of LN lesion;
- Accidental bite of the tongue (LN lesion), labial incontinence (IAN lesion), swallowing/speaking/eating difficulties (both)[69].

The clinical examination helps to define the area involved in the sensitive damage.

Speaking about an IAN injury, the patient complains about a partial or complete loss of sensitivity of the homolateral lower lip that would reduce during the months following the traumatic event.

The tongue and lip palpation is mandatory to know where the dysfunction is localized and to find some points that could trigger the pain (i.e. when touching the posterior mouth floor, just medially to the lower wisdom tooth, the patient with a LN lesion complains about pain, usually described as an electric shock involving the homolateral tongue, and the traumatic neuroma can be appreciated)[40].

Several sensorineural tests, reproducible by different health workers, are nowadays used to objectify the reported symptoms. It deals with non-invasive, easy to achieve tests, that the reconstructive surgeon should perform during the pre-operative evaluation. Each test

has to be performed both on the healthy side and on the injured side of the tongue/lip. In this way, the patient can compare the different sensation and asymmetry[70].

Among the most common tests, there are:

- Pain and light touch sensation: with the patient's eyes closed, the surgeon has to touch in a single point the tongue/lip with a gauze and then with a 27-gauge needle to investigate respectively the light touch sensation and the pain.
- The pressure test involves sensation produced by touch to a localized area (tongue/lip) using an instrument that indicates the pressure needed to produce sensation.
- The two-point discrimination test assesses the ability to perceive the difference between one or two points of touch.

If symptoms involving the lower lip were present, the assessment of the Orthopantomography and the Cone Beam CT scan was performed in order to study the mandibular canal and the eventual presence of some foreign bodies inside it.

The patient's history, the clinical examination and the sensorineural tests have to be documented through photographic and video material.

7.2 Neurophysiological examination

In order to define the objective degree of loss of sensitivity and the nerve injury and to choose the best treatment for each patient, neurophysiological tests are used[71,72]. During the pre-operative evaluations, patients should undergo a neurological assessment. LN and IAN function was evaluated bilaterally in each patient before surgery by assessing the lingual and labial tactile and pain sensory thresholds and masseteric inhibitory reflex (MIR) by electrical stimulation performer on both the healthy and affected sides. The diagnostic method involved electrical stimulation of the tongue and the lip by a suitably designed Teflon-coated monopolar needle and electrodes (SPES Medica, Italy) to identify the

perceptual tactile and pain thresholds expressed in milliamps (mA). Electromyographic recording of the suppression of the masseter muscle activity was simultaneously performed as recorded with surface electrodes and acquired with a 2-channel electromyographic unit (Neuro-MEP-Micro; Neurosoft, Russia)[29,73-77].

Figure 7.1: Neurophysiological examination

7.3 Pre-operative imaging

Pre-operatively, all the patients affected by an IAN lesion have to perform both a Orthopantomography and a Cone Beam CT scan: these radiographic images allow to identify both the presence in the mandibular canal of foreign bodies (dental implants, endodontic material, dental roots, bone fragments) and bone gaps in the mandibular canal walls due to the use of rotating burs[40,76].

The radiographic imaging is not enough to make diagnosis of trigeminal nerve injury: the presence of some foreign bodies in the mandibular canal in an asymptomatic patient is never enough to recommend surgery!

Nowadays, there are some preliminary works about the use of MRI to study the course of the LN and IAN nerve and identify the injured part of the nervous structure[78-83].

Chapter 8: Diagnostic & Therapeutic pathways

8.1 Timing of surgery

Once the nerve lesion is ascertained, the most important item to consider is *time*.

"How much time has elapsed since the symptomatology started?" is the question the reconstructive surgeon has to ask to the patient, in order to make a therapeutic decision:

- Is a spontaneous recovery of the nervous functions possible?
- Is a nerve reconstruction necessary?
- When has the nerve reconstruction to be performed?

The therapeutic management is different depending on both the symptomatology and the knowledge of the ascertained nerve section[10,12-16,29,56,84]. (See Table 8.1)

1. If possible, *immediately* after injury, during the same surgical time
2. *As soon as possible*, in case of ascertained nerve injury
3. *As soon as possible*, if pain is present
4. *After 3 months*, in case of persistent complete anaesthesia
5. *After 8 months*, if insufficient spontaneous recovery (persistent severe hypoesthesia)
6. *Personalized assessment* of the patient in case of severe dysesthesia

Table 8.1: Suitable timing of surgery in case of nerve lesion of the oral cavity

1. <u>If possible, *immediately* after injury, during the same surgical time</u>

   In case of nerve section, the gold standard of treatment is the immediate neurorrhaphy of the proximal and distal nervous stumps, in order to get the best results in term of functional recovery.

In order to perform the nerve reconstruction during the same surgical time, the oral/maxillo-facial surgeon must become aware about the nerve lesion. Since this kind of awareness is not always possible, most of the time the reconstructive surgeon has to wait and test the residual nerve function in order to ascertain the nerve injury and the immediate reconstruction cannot be performed.

2. *As soon as possible*, in case of ascertained nerve injury

   In case of ascertained nerve injury, the sooner the nerve reconstruction is performed, the better results can be obtained.

3. *As soon as possible*, if pain is present

   If the patient complains about pain of the lower lip or tongue (even if the nerve lesion is uncertain), the reconstructive surgery has to be performed as soon as possible, in order to stop the chronicity process.

4. *After 3 months*, in case of persistent complete anaesthesia

   In case of uncertain lesion, the patient has to be assess again after three months, in order to understand if a spontaneous recovery of the nerve function is possible. In all those patients who still complain about a complete labial or lingual anaesthesia after three months from the traumatic event, the reconstructive surgery of the nerve is proposed.

5. *After 8 months*, if insufficient spontaneous recovery (persistent severe hypoesthesia)

   In all those cases where, after three months from the supposed nerve damage, a mild spontaneous recovery has occurred, an 8-month assessment of the patient is necessary to make the best decision for each patient. In case of IAN lesion there are excellent chances of spontaneous recovery because of its position inside the mandibular canal that acts as a scaffold, driving the nerve regeneration (with a reported functional recovery of 75-85%). In case of LN damage, if a severe hypoesthesia is still present after three months, there are low chances of acceptable spontaneous

functional recovery, because of the LN position inside the soft tissue of the mouth floor that helps the formation of a gap between the proximal and distal stumps, preventing the spontaneous regeneration process.

6. *Personalized assessment* of the patient in case of severe dysesthesia

   There are lots of borderline cases, where the patient complains about dysesthesia or paraesthesia described as electrical shock or mild to severe pain of the lower lip or tongue. It is mandatory to investigate about the influence of these symptoms on the daily life of the patient, in order to undertake the best therapeutic program for each patient.

After 18-24 months, results vary so much that repair of the nerve is usually not recommended, one reason being the apparently reduced ability of neuronal bodies to produce axoplasmic fluid through axons of the proximal stumps. In 2015, Biglioli and his équipe proposed the cross-tongue procedure in order to rehabilitate an old LN lesion using the stimulus coming from the healthy side of the tongue[85].

8.2 Surgical technique

8.2.a Lingual Nerve Injury

Microsurgical reconstruction of the LN must be performed under general anaesthesia to ensure absolute immobility of the patient for the duration of the surgery; the average duration of surgery is about 1 hour. Moreover, during surgery it may be necessary to extend cranially the surgical field toward the masticatory spaces in order to find the proximal stump of the LN: this procedure is not manageable if the patient is awake.

After infiltrating with adrenaline (1:200,000) to minimize bleeding and maintain a clear, open surgical field, the LN is localized easily into the posterior part of the floor of the mouth just underneath the mucosa. The incision is performed using a cold scalpel and, then, a scissors is inserted to a depth of a few millimetres to dissect the soft tissues along the axis

of the nerve. Then, the incision is extended cranially and laterally, in order to find the proximal stump of the nerve. Strong internal scarring is always present; the scar incorporates the nerve making difficult to trace it here. So, in order to spare time, surgery proceeds cranially to the scar. The lower fibres of the internal pterygoid muscle are dissected to identify the LN stumps. In most cases, the nerve is characterized by a complete loss of continuity and the proximal stump is retracted by a couple of centimetres because of its elasticity. The proximal stump is generally larger than the distal one and it exhibits a bulging end, the traumatic neuroma. This portion of the LN is excised and pathologically examined for a definitive diagnosis. Neuroma excision may also be performed if the nerve is not completely sectioned, thus creating two nerve stumps. Finally, after the removal of the distal stump extremity, a direct epineural neurorrhaphy between the proximal and distal stumps is performed. After a sufficient dissection of the nerve stumps inside the soft tissue and the cut of the nerve branches containing the parasympathetic fibres directed to the submandibular gland, providing 1.5 to 2.5 cm of extra excursion of the distal stump toward the proximal one, an interposition graft is not necessary to approximate the LN stumps without any excessive tension. The neurorrhaphy of the LN stumps is performed under microscope magnification. A coloured rubber background is placed under the nerve stumps to better distinguish the nerve from the surrounding tissues during the microsurgical neurorrhaphy. In case involving little tension on the neurorrhaphy (either because of removal of part of the damaged nerve tissue or because of the drawer action of the floor of the mouth), two 8/0 polypropylene sutures are first placed 180º to each other. This arrangement provides greater stability to the neurorrhaphy, which is completed with other non-absorbable, inert 10/0 stitches in order to reduce the interference with the process of axonal regeneration. Fibrin glue is applied around the neurorrhaphy for stabilization. Haemostasis is carefully performed. Finally, simple one-layer mucosal closure is performed to end the procedure[29].

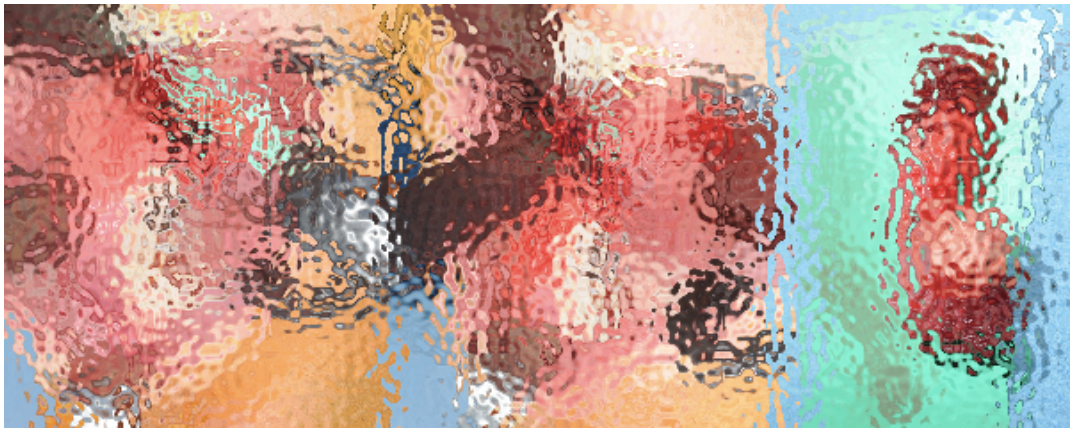

Figure 8.1: Damaged LN (on the left); Repaired LN (in the middle); Traumatic Neuroma (on the right)

8.2.b Inferior Alveolar Nerve Injury

Microsurgical reconstruction of the IAN must be performed under general anaesthesia to ensure absolute immobility of the patient for the duration of the surgery; the average duration of surgery is about 2 hours. Moreover, during surgery it may often be necessary to perform an ostectomy of the mandible to get the mandibular canal: this procedure is not manageable if the patient is awake. Depending on the position of the nerve injury, either a sagittal osteotomy of the mandible (in case of posterior lesions, for example after wisdom tooth removal) or a temporary removal of a vestibular cortical bone segment to get access to the mandibular canal (in case of more anterior nerve lesions), has to be performed. In both cases, piezoelectric instruments are used and a pre-plating through titanium plates and screws is performed. The cortical bone fragment is displaced using chisels and retractors, and stored in sterile saline. The IAN is exposed and isolated from the surrounding residual trabecular bone and mandibular canal walls using a piezoelectric scalpel. The site and type of injury is identified using an operating microscope. The appropriate surgical procedure is determined intraoperatively based on the surgical findings.

If the nerve is intact, IAN neurolysis (if the patient complains about pain) and removal of the foreign bodies (if presents) have to be performed.

If the continuity of the nerve is partially or completely disrupted, after the resection of the damaged nerve segment and the removal of foreign bodies from the canal, the nerve reconstruction has to be performed with an interpositional graft. The position of the IAN, inside a bone canal, reduces the elasticity of the nerve, so that a direct neurorrhaphy cannot be performed because of the gap. The nerve gap can be filled using an autologous nerve graft (the sural nerve and the great auricular nerve are usually used to achieve this goal), an allogenic cryopreserved nerve graft or a collagenous synthetic conduit. The last two techniques are still under study and only few patients underwent this kind of reconstruction. The sural nerves used in interpositional grafting is 2–5 cm long and harvested through 2-cm longitudinal incisions posterior to the lateral malleolus. The IAN is repaired using interrupted 10-0 nylon epineurial sutures on the proximal and distal sides. Suturing is guided by an operating microscope, with the sutures placed around the proximal and distal nerve stumps and stabilized by a few 10-0 stitches. After completion of the IAN repair, the vestibular cortical bone is replaced and fixed with titanium microplates and screws, followed by primary soft-tissue closure with absorbable sutures[12,56]. (Fig. 8.2)

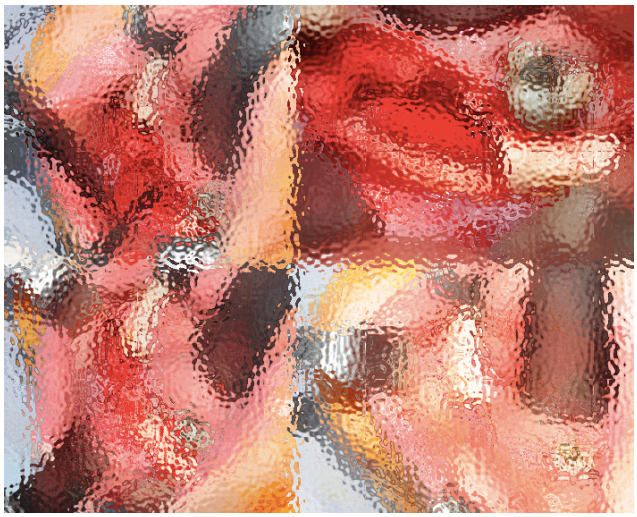

Figure 8.2: Damaged IAN (on the left upper corner); Repaired IAN with a collagenous conduit (in the right upper corner); Repositioning of the bone window (on the lower left corner); Suture of the mucosal incision (on the lower right corner)

Chapter 9: Post-Operative recommendations and follow up

Pre-operative antibiotic prophylaxis with an intra-venous cephalosporin is recommended (Cephazolin 2g i.v., one hour before the beginning of surgical procedure).

The post-operative antibiotic therapy is performed using Amoxicillin 875mg combined with Clavulanic Acid 125mg 3 times/day, administered orally during the following 7 days.

During the first post-operative 24 hours, both an intra-venous pain-relief therapy (Ketoprofen 160mg 3 times/day) and an anti-oedema therapy (Dexamethasone 12mg twice/day) are administered.

During the first post-operative day, the patients affected by an IAN lesions undergo X-Ray evaluation through an Orthopantomography to check the correct position of both the bone fragments and titanium plates and screws. Moreover, the Orthopantomography allows the surgeon to check the patency of the canal.

Patients are usually discharged after 48-72 hours with some significant home recommendations they have to respect for the following 2 weeks:

- Accurate oral hygiene using manual teeth brushing after every meal and chlorhexidine solution twice/day;
- Soft and cold diet;
- Patients affected by LN lesions are instructed to avoid forcing against trismus for the first 2 weeks after surgery to avoid possible stretching of the LN neurorrhaphy.

The first post-operative assessment is usually performed after 10-12 days to check the oral wound healing and to remove the sutures.

In the above-mentioned Clinic, a standard follow up has been carried out, every three months after surgery. The final clinical and neurophysiological evaluation is usually performed 12 months after surgery.

Chapter 10: Material & Methods

In October 2016, at the Maxillo-Facial Surgery Department of San Paolo Hospital (ASST Santi Paolo and Carlo) in Milan, a new project started with the founding of the “Nervous Lesion Clinic”. This project is aimed to standardize the diagnostic and therapeutic program for all those patients affected by a supposed or ascertained injury of trigeminal nerve branches, in particular involving the IAN and the LN.

We included in the study all patients who had their first evaluation in this specific Clinic, complaining about symptoms amenable to a LN or IAN injury, in the period ranged between October 2016 and September 2018.

All these patients had a history of a previous oral surgery after that the symptoms started.

Since 10 patients complained about symptoms involving the lower lip, an homolateral IAN lesion was suspected; the other 28 patients had a suspected LN injury: they complained about lingual symptomatology.

Among these 38 patients, 3 patients (2 affected by lower lip anaesthesia and 1 affected by lingual hypoesthesia) were not included in the present study because, 8 months after the traumatic event, they got a spontaneous, even if partial, recovery of their symptomatology and they refused surgery.

Therefore, the present study includes 35 patients who underwent surgical microscopic reconstruction of either the LN or the IAN, in the period between October 2016 and September 2018, at the Maxillo-Facial Surgery Department of San Paolo Hospital.

27 patients (22 females and 5 males) came to our attention because of the presence of lingual symptomatology (on the right part of the tongue in 21 cases, in the left part of the tongue in the remaining 6 patients), appeared after an oral surgery procedure (in 25 cases the traumatic event was the extraction of a lower third molar, while in the last 2 cases the troncular anaesthesia was the responsible of the LN injury). 8 patients (7 females and 1

male) came to our attention complaining about symptoms involving the lower lip (on the right part in 5 cases and in the left one in the remaining 3 patients) appeared after the extraction of the lower third molar in 2 cases, the extraction of the lower second molar in 1 case and an implant placement posteriorly to the mental *foramen* in the last 5 cases.

The mean age of patients affected by a LN lesion was 32.41 ± 9.46 (ranged between 17 and 54 years); the mean age of patients affected by an IAN lesion was 52.25 ± 12.12 (ranged between 35 and 70 years). (See Table 10.1)

		LN	IAN
Mean age (years)		32.14 ± 9.46	52.25 ± 12.12
Sex (n° of patients)	*Female*	22	7
	Male	5	1
Side (n° of patients)	*Right*	21	5
	Left	6	3
Aetiology (n° of patients)	*Extraction of lower third molar*	25	2
	Extraction of lower second molar	0	1
	Implant placement	0	5
	Troncular anaesthesia	2	0

Table 10.1: Epidemiologic data of patients included in the study

The symptoms referred by patients affected by an IAN lesion included: severe hypoesthesia (5 patients; 62.5%) or anaesthesia (3 patients; 37.5%) of the homolateral lower lip, pain of the homolateral lower lip (all patients; 100%) and allodynia (3 patients; 37.5%).

The symptoms referred by patients affected by a LN lesion included: severe hypoesthesia (10 patients; 37.04%) or anaesthesia (17 patients; 62.96%) of the homolateral tongue, pain of the homolateral tongue (22 patients; 81.48%) and dysesthesia of the tongue, described as unpleasant electrical shocks (7 patients; 25.93%). Among patients complaining about dysesthesia, in five cases they did not complain about continuous pain:

pain could be evoked both by applying pressure medially to the trigone (LN damage pathognomonic manoeuver) and by exercising (most probably due to neuroma compression by contraction of the internal pterygoid muscle). Among the entire group of patients, only in 7 cases (25.93%), the pain was not triggered by intense exercise. 26 patients (96.30%) reported partial or complete homolateral loss of taste sensitivity, tested by placing alternatively chocolate, salt, and sugar on the affected side of the tongue and asking patients to chew the food and to report the taste sensation. (See Table 10.2)

	LN (%)	IAN (%)
Anaesthesia	62.96	37.5
Severe Hypoesthesia	37.04	62.5
Pain	81.48	100
Dysesthesia	25.93	0
Allodynia	0	37.5
Ageusia	96.30	0

Table 10.2: Pre-operative symptomatology

Among patients affected by an IAN lesion, surgery was performed after a mean time of 13.63 months (ranged between 2 and 27 months) from the traumatic event. In particular, one patients, complaining about anaesthesia, excruciating pain and allodynia of the lower lip after implantology underwent surgery 2 months after the implant placement (immediately after our first assessment) in order to remove the implant from the mandibular canal and try to stop the disabling pain. In all patients affected by an IAN injury, the intraoperative findings showed a damaged nerve that required a reconstruction through an interpositional graft: in one patient, the nerve damage involved the extra-osseous part of the IAN, just distally to the mental foramen, and a direct neurorrhaphy was enough to reconstruct the nerve; in 2 patients, an autologous nerve graft was used to reconstruct the IAN, while in 5 patients, a collagenous conduit was used as a scaffold to guide the nerve regeneration.

Among patients affected by a LN lesion, microsurgery was accomplished after at least 3 months from LN injury to allow spontaneous recover of LN, unless LN injury was already ascertained (1 patient). In this patient, surgery was performed 1 month after LN injury. Upon partial LN function recovery by 3 months after LN injury, an 8-month re-evaluation was carried out: in case of persistent reduced nerve function, surgery was recommended. Patients reporting pain after LN injury were referred to immediate intervention. Microsurgery was performed after a mean time of 11.19 months (ranged between 1 and 36 months) from the traumatic event. All these patients underwent a reconstruction of the LN through a direct neurorrhaphy between the proximal and distal stumps of the nerve. The intraoperative findings showed a section of the nerve in 25 patients, while in 2 patients (the patients reported a LN injury following the troncular anaesthesia) the macroscopic continuity of the nerve was maintained.

All patients underwent preoperative clinical examinations and they answered to a pre-operative questionnaire focused on their quality of life. (See Table 10.3a and Table 10.3b)

Valutazione pre-operatoria della salute generale				
1. In generale direbbe che la sua salute è				
Eccellente	Molto Buona	Buona	Passabile	Scadente
0	1	2	3	4
2. Rispetto al periodo precedente l'evento traumatico, come giudicherebbe, ora, la Sua salute in generale?				
Decisamente migliore	Lievemente migliore	Uguale	Lievemente peggiore	Decisamente peggiore
0	1	2	3	4
3. Nelle ultime quattro settimane, in che misura la Sua salute fisica o il suo stato emotivo hanno interferito con le normali attività sociali con la famiglia, gli amici, i vicini di casa, i gruppi di cui fa parte?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
4. Le sue condizioni di salute le hanno impedito di dormire in maniera adeguata?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
5. Le sue condizioni di salute l'hanno ostacolata nel lavoro che svolge abitualmente, sia in casa sia fuori?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
6. Le sue condizioni di salute le hanno impedito di alimentarsi in maniera adeguata?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo

0	1	2	3	4
7. La sua salute è come quella degli altri?				
Certamente vero	In gran parte vero	Non so	In gran parte falso	Certamente falso
0	1	2	3	4

Table 10.3a: Pre-operative questionnaire – Part A: focused on the general health of the patient

Valutazione pre-operatoria della salute orale				
1. Ha avuto difficoltà nel pronunciare parole a causa di problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
2. Ha avvertito un peggioramento nel senso del gusto a causa di problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
3. Ha avvertito sensazione di dolore a lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
4. Ha trovato difficoltà a mangiare determinati cibi a causa di problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
5. Ha consapevolezza dei propri problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
6. Ha avvertito una sensazione di disagio a causa dei propri problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
7. Ha avuto problemi nella deglutizione dopo l'evento traumatico?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
8. Ha trovato difficoltà a rilassarsi a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
9. Si è sentito imbarazzato a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
10. Si è sentito maggiormente irritabile con gli altri a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
11. Ha trovato difficoltà nello svolgere le attività quotidiane a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
12. Ha avvertito che la sua vita in generale è meno soddisfacente a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
13. È mai stato completamente incapace di svolgere una attività a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
14. Ha dolore a lingua/labbro inferiore/denti/bocca in seguito a sforzi intensi?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4

Table 10.3b: Pre-operative questionnaire – Part B: focused on the oral health of the patient

A pre-operative neurophysiological test was performed in order to objective the referred symptoms and the degree of loss of sensitivity. Among patients affected by an IAN injury, in one case, the neurophysiological test was not performed because the patient complained about severe pain and anaesthesia of the lower lip appeared after the placement of a mandibular implant, whose apex was, according to the pre-operative imaging, inside the mandibular canal, compressing the IAN. The pre-operative findings were enough to treat the patient immediately.

Through the neurophysiological tests, LN and IAN function was evaluated in each patient before surgery and at the end of the follow-up period (12 months after surgery) by assessing the lingual/labial tactile and pain sensory thresholds, the Sensory Deficit Ratio (SDR) and the Masseteric Inhibitory Reflex (MIR) by electrical stimulation performer on both the healthy and affected side.

The hospitalization lasted 2 days for all patients. During this period an intravenous antibiotic, analgesic and anti-oedema therapy was administered (See Chapter 9 for posology), and the patients affected by an IAN lesion underwent a post-operative radiologic control through an Orthopantomography to check the correct position of titanium screws and plates and of the access bony windows and the patency of the mandibular canal.

Upon hospital discharge, the patients were instructed to call when experiencing the first symptoms of either LN or IAN recovery. They revisited the hospital at that time and again at 3, 6 and 12 months postoperatively. During all visits, the patients underwent clinical examinations and sensory testing. A final clinical and neurophysiological evaluation was performed 12 months postoperatively; at that time the patients answered to a post-operative questionnaire. (See Table 10.4a and Table 10.4b)

Valutazione post-operatoria della salute generale				
1. In generale direbbe che la sua salute è				
Eccellente	Molto Buona	Buona	Passabile	Scadente
0	1	2	3	4

2. Rispetto a prima dell'intervento, come giudicherebbe, ora, la Sua salute in generale?				
Decisamente migliore	Lievemente migliore	Uguale	Lievemente peggiore	Decisamente peggiore
0	1	2	3	4
3. Dopo l'intervento, in che misura la Sua salute fisica o il suo stato emotivo hanno interferito con le normali attività sociali con la famiglia, gli amici, i vicini di casa, i gruppi di cui fa parte?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
4. Le sue condizioni di salute le hanno impedito di dormire in maniera adeguata?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
5. Le sue condizioni di salute l'hanno ostacolata nel lavoro che svolge abitualmente, sia in casa sia fuori?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
6. Le sue condizioni di salute le hanno impedito di alimentarsi in maniera adeguata?				
Per nulla	Molto poco	Un po'	Molto	Moltissimo
0	1	2	3	4
7. La sua salute è come quella degli altri?				
Certamente vero	In gran parte vero	Non so	In gran parte falso	Certamente falso
0	1	2	3	4

Table 10.4a: Post-operative questionnaire – Part A: focused on the general health of the patient

Valutazione post-operatoria della salute orale				
1. Ha avuto difficoltà nel pronunciare parole a causa di problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
2. Ha avvertito un peggioramento nel senso del gusto a causa di problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
3. Ha avvertito sensazione di dolore a lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
4. Ha trovato difficoltà a mangiare determinati cibi a causa di problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
5. Ha consapevolezza dei propri problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
6. Ha avvertito una sensazione di disagio a causa dei propri problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
7. Ha avuto problemi nella deglutizione dopo l'intervento?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
8. Ha trovato difficoltà a rilassarsi a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
9. Si è sentito imbarazzato a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
10. Si è sentito maggiormente irritabile con gli altri a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
11. Ha trovato difficoltà nello svolgere le attività quotidiane a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				

Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
12. Ha avvertito che la sua vita in generale è meno soddisfacente a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
13. È mai stato completamente incapace di svolgere una attività a causa dei problemi a livello di lingua/labbro inferiore/denti/bocca?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4
14. Ha dolore a lingua/labbro inferiore/denti/bocca in seguito a sforzi intensi?				
Mai	Quasi mai	Occasionalmente	Abbastanza spesso	Molto spesso
0	1	2	3	4

Table 10.4b: Pre-operative questionnaire – Part B: focused on the oral health of the patient

Statistical analyses were performed using the v. 25.0 SPSS software (SPSS Inc, Chicago, IL). Values of $P < 0.05$ were considered statistically significant. All tests chosen were two tailed. Wilcoxon signed rank test for paired samples was used to assess the statistical significance of differences between preoperative and postoperative values of objective test and questionnaires. Spearman's Rho test was used to assess the correlation between preoperative and/or postoperative objective test results; the correlation between preoperative and/or postoperative answers to selected questionnaires questions (more specifically questions concerning pain, impairment during daily activities and impairment during specific activities); and, last, the correlation between the time passed from injury to surgery and all objective test results and questionnaires questions answers. Specific test used for each evaluation are detailed along with their results in the results section. All statistical analyses were separately performed for LN patients and IAN patients. Whenever the statistical analysis required evaluating the objective test results, the sample was restricted to patients without missing data for unperformed tests, i.e. 22 patients in the LN group and 7 patients in the IAN group.

Chapter 11: Results

The LN was completely sectioned in 25 patients (92.59%), while in the remaining 2 patients (7.41%; those affected by an injury due to troncular anaesthesia), the nerve was macroscopically safe, but thin and with a microscopic bulging because of the presence of the traumatic neuroma. The IAN was completely sectioned in all patients (100%).

The surgeon removed the traumatized part of the nerve that was microscopically analysed: the histopathological examination confirmed the diagnosis of traumatic neuroma in all cases, both for LN and IAN injuries.

No major post-operative complications were observed. Partial mucosal dehiscence of the oral floor wound was observed in two patients who underwent LN reconstruction: healing occurred spontaneously but the patients complained about severe post-operative pain that required a new 3-day hospitalization in order to administer intravenous painkillers. The pain was described as a local pain of the mouth floor, not involving the lingual mucosa, and different from the pre-operative neuropathic algic symptomatology.

All patients affected by a LN injury underwent a pre-operative neurophysiological test to objective the LN damage. Among these patients, only 22 patients (81.48%) underwent a post-operative neurophysiological test 12 months after reconstructive surgery. The remaining 5 patients (18.52%) refused to repeat the test because of a subjective excellent recovery of pre-operative symptomatology. 7 patients (87.5%) affected by an IAN injury underwent a pre-operative neurophysiological test, while in the remaining case (12.5%), the neurophysiological test was not performed because the patient complained about severe pain and anaesthesia of the lower lip appeared after the placement of a mandibular implant, whose apex was, according to the pre-operative imaging, inside the mandibular canal, compressing the IAN. The pre-operative findings were enough to treat the patient immediately.

According to the neurophysiological tests and the statistical assessment that we performed (See Table 11.1), all patients affected by both a LN and IAN damage partially recovered their lingual/labial sensitivity; no patients completely recovered the lingual/labial function; no patients had a worsening of the LN/IAN function. Pre-operative neurophysiological test results showed a difference between the heathy and the affected side in term of tactile and pain thresholds (in the LN group: the mean tactile threshold was 1.01 mA ± 0.21 in the healthy side and 7.39 mA ± 4.25 in the affected side; the mean pain threshold was 2.91 mA ± 0.57 in the healthy side and 22.44 mA ± 12.15 in the affected side. In the IAN group: the mean tactile threshold was 1.03 mA ± 0.05 in the healthy side and 4.33 mA ± 2.14 in the affected side; the mean pain threshold was 3 mA ± 0 in the healthy side and 16.79 mA ± 11.05 in the affected side).

The Sensory Deficit Ratio (SDR) was calculated as: 100 – (tactile or pain threshold healthy side/ tactile or pain threshold affected side x 100).

The SDR ranged from:

- 30% and 93.33% for the tactile threshold in the LN injured patients;
- 40% and 94% for the pain threshold in the LN injured patients;
- 54.55% and 87.50% for the tactile threshold in the IAN injured patients;
- 55.88% and 90% the pain threshold in the IAN injured patients.

In normal controls, side-to-side SDR doesn't exceed 30%.

In all assessed patients (both for LN and IAN evaluation), pre-operative MIR was altered with poor to absent suppressor answered to the electrical stimulation in the affected part of the tongue/lower lip. Recovery of the excitability of MIR suppression components SP1 and SP2 was observed, often with increased latencies but consistent with a functional recovery.

Wilcoxon signed rank test we performed to assess the statistical relevance on pre- and post-operative tactile and pain thresholds, the pre- and post-operative SDR and the pre- and post-operative MIR (for both LN and IAN injuries groups) showed a statistically significant improvement of all those parameters, except for the pre- and post-operative tactile and pain thresholds on the healthy side. (See Table 11.1)

LN								
	Pre-op (n=27)							
		Tactile threshold healthy side (mA)	*Tactile threshold affected side (mA)*	*Pain threshold healthy side (mA)*	*Pain threshold affected side (mA)*	*Tactile SDR (%)*	*Pain SDR (%)*	*MIR*
	Mean	1.01	7.39	2.91	22.44	79.94	81.13	18 absent
	SD	0.21	4.25	0.57	12.15	14.63	14.03	9 reduced
	Post-op (n=22)							
		Tactile threshold healthy side (mA)	*Tactile threshold affected side (mA)*	*Pain threshold healthy side (mA)*	*Pain threshold affected side (mA)*	*Tactile SDR (%)*	*Pain SDR (%)*	*MIR*
	Mean	1.04	3.14	3.03	9.66	59.10	58.76	22
	SD	0.11	1.69	0.23	6.13	17.53	18.58	increased
	Significance	0.78500	<0.001	1.00000	<0.001	<0.001	<0.001	<0.001
IAN								
	Pre-op (n=7)							
		Tactile threshold healthy side (mA)	*Tactile threshold affected side (mA)*	*Pain threshold healthy side (mA)*	*Pain threshold affected side (mA)*	*Tactile SDR (%)*	*Pain SDR (%)*	*MIR*
	Mean	1.03	4.33	3.00	16.79	70.89	73.32	3 absent
	SD	0.05	2.14	0.00	11.05	13.18	16.14	4 reduced
	Post-op (n=8)							
		Tactile threshold healthy side (mA)	*Tactile threshold affected side (mA)*	*Pain threshold healthy side (mA)*	*Pain threshold affected side (mA)*	*Tactile SDR (%)*	*Pain SDR (%)*	*MIR*
	Mean	0.98	1.84	2.80	5.21	43.93	41.29	8
	SD	0.14	0.54	0.40	1.94	12.13	16.40	increased
	Significance	0.56400	0.01800	0.41400	0.01800	0.01800	0.01800	0.01500

Table 11.1: Neurophysiological test results

The use of Spearman's Rho Test allows us to find some statistically significant correlations between our results. In particular, it seems interesting to highlight the following relations:

- For the LN injuries:
    - Spearman's Rho test shows correlation between pre-operative tactile SDR and:
        - Pre-operative pain SDR (Correlation coefficient 0.858; $p<0.001$);
        - Pre-operative MIR (Correlation coefficient -0.709; $p<0.001$);
        - Post-operative tactile SDR (Correlation coefficient 0.567; $p=0.006$);
        - Post-operative pain SDR (Correlation coefficient 0.513; $p=0.015$).
    - Spearman's Rho test shows correlation between pre-operative pain SDR and:
        - Pre-operative MIR (Correlation coefficient -0.699; $p<0.001$);
        - Post-operative tactile SDR (Correlation coefficient 0.806; $p<0.001$);
        - Post-operative pain SDR (Correlation coefficient 0.811; $p<0.001$).
    - Spearman's Rho test shows correlation between pre-operative MIR and:
        - Post-operative tactile SDR (Correlation coefficient -0.547; $p=0.008$);
        - Post-operative pain SDR (Correlation coefficient -0.540; $p=0.01$).
    - Spearman's Rho test shows correlation between post-operative tactile SDR and post-operative pain SDR (Correlation coefficient 0.914; $p<0.001$).
- For the IAN injuries:
    - Spearman's Rho test shows correlation between pre-operative tactile SDR and:
        - Pre-operative pain SDR (Correlation coefficient 0.955; $p=0.001$);
        - Pre-operative MIR (Correlation coefficient -0.866; $p=0.012$).
    - Spearman's Rho test shows correlation between post-operative tactile SDR and pre-operative MIR (Correlation coefficient -0.874; $p=0.01$).

All patients, both in the group of LN injuries and in that one of alveolar damage, answered to a pre- and post-operative (12 months after reconstructive surgery) questionnaires about their general and oral health (See Chapter 10).

Analysing the questionnaires' answers, we can appreciate a subjective improvement of the quality of life in all patients, with a reported reduction of the pain and an easier carrying out of daily activities. (See Table 11.2)

In particular, we used the Wilcoxon Signed Rank Test for paired samples, applied to all the pre- and post-operative questionnaires' variables:

- In patients affected by a LN injury, this assessment shows a statistically significant improvement of all the variables, except that one investigating the role of the LN injury during swallowing (comparing pre- and post-operative answers, we can appreciate a non-statistically significant improvement, although an improvement is reported); (See Table 11.2)
- In patients affected by an IAN lesion, this assessment shows a statistically significant improvement of all the variables, except the answers to following questions:
    - Perception of their own general health compared to the general population's health;
    - Pronunciation difficulties;
    - Taste perception deficits;
    - Awareness of the disease;
    - Swallowing difficulties;
    - Pain after intense physical exercise.

  Questions about perception of their own health, pronunciation difficulties, taste perception and pain after exercises show a non-statistically significant improvement, while questions about awareness of disease and swallowing

difficulties show no improvement comparing pre-and post-operative answers to the questionnaires. (See Table 11.2)

Evaluation of patients' general health

Question		*1*					*2*					*3*					*4*					*5*					*6*					*7*				
Answer score		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
LN	*Preop*	0	0	17	8	2	0	0	0	24	3	0	4	18	5	0	3	11	11	2	0	1	11	11	3	1	0	6	14	6	1	0	1	17	7	2
	Postop	0	2	24	1	0	5	13	14	5	0	15	9	3	0	0	23	3	1	0	0	17	5	3	2	0	11	9	5	2	0	0	8	16	3	0
	Significance	0.004					<0,001					<0,001					<0,001					<0,001					<0,001					0.002				
IAN	*Preop*	0	0	3	4	1	0	0	0	4	4	0	0	3	5	0	1	0	4	3	0	0	0	5	3	0	1	0	2	5	0	0	0	2	3	3
	Postop	0	0	7	1	0	2	4	2	0	0	1	4	2	1	0	2	4	1	1	0	0	5	2	1	0	3	3	1	1	0	0	2	2	3	1
	Significance	0.025					0.011					0.014					0.046					0.02					0.026					0.059				

Evaluation of patients' oral health

Question		*1*					*2*					*3*					*4*					*5*					*6*					*7*				
Answer score		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
LN	*Preop*	6	7	9	3	2	1	1	8	10	7	4	1	4	12	6	1	1	11	12	2	0	0	0	4	23	0	1	9	13	4	21	0	1	2	3
	Postop	13	9	3	2	0	8	9	7	1	2	11	10	5	1	0	12	6	9	0	0	0	0	2	14	11	9	12	2	3	1	20	4	1	2	0
	Significance	0.005					<0,001					<0,001					<0,001					0.003					<0,001					0.123				
IAN	*Preop*	2	1	1	2	2	7	1	0	0	0	0	0	0	2	6	1	0	0	3	4	0	0	0	1	7	0	0	1	2	5	8	0	0	0	0
	Postop	3	2	2	0	1	8	0	0	0	0	1	3	2	1	1	1	3	3	0	1	0	0	0	1	7	0	3	3	1	1	8	0	0	0	0
	Significance	0.066					0.317					0.017					0.024					1					0.026					1				

Question		*8*					*9*					*10*					*11*					*12*					*13*					*14*				
Answer score		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
LN	*Preop*	0	0	10	8	9	0	1	13	11	2	0	0	14	10	3	0	4	14	7	2	0	1	20	4	2	3	11	7	5	1	7	1	6	7	6
	Postop	10	9	4	2	2	13	11	1	2	0	11	11	3	1	1	9	15	3	0	0	7	15	5	0	0	16	7	4	0	0	15	8	3	1	0
	Significance	<0,001					<0,001					<0,001					<0,001					<0,001					<0,001					<0,001				
IAN	*Preop*	0	0	0	2	6	0	0	0	3	5	0	0	0	2	6	0	0	1	2	5	0	0	1	3	4	0	2	2	3	1	2	1	1	1	3
	Postop	0	3	2	1	2	0	4	1	2	1	0	3	2	2	1	1	4	2	0	1	0	1	6	0	1	2	3	2	1	0	3	3	1	1	0
	Significance	0.024					0.026					0.016					0.016					0.026					0.037					0.168				

Table 11.2: Questionnaire results

The use of Spearman's Rho Test allows us to find some statistically significant correlations between our results. In particular, it seems interesting to highlight the following relations:

- For the LN injuries:
    - The timing between the traumatic event and the reconstructive surgery has a weak statistically significant correlation with the post-operative perception of patients' own health (Correlation coefficient 0.403; p=0.037);
    - The pre-operative algic symptoms has a correlation with the pre-operative inability to perform daily life activities (Correlation coefficient 0.611; p=0.001);
    - The pre-operative presence of difficulties in the daily life has a correlation with the inability to perform daily life activities both pre-operatively (Correlation coefficient 0.560; p=0.002) and post-operatively (Correlation coefficient 0.411; p=0.033);
    - The pre-operative inability to perform daily life activities has a correlation with the post-operative inability to perform daily life activities (Correlation coefficient 0.667; p<0.001);
    - The post-operative presence of difficulties in the daily life has a correlation with the inability to perform daily life activities (Correlation coefficient 0.706; p<0.001).
- For the IAN injuries:
    - Lots of correlations are identified between timing of surgery and some questions (The results of this test, obtained with our data, can be misrepresented because of the small number of patients; we are aware of the necessity of a more representative sample of patients in order to draw more significant conclusions in the IAN group):
        - Question number 2 of the pre-operative general health questionnaire (Correlation coefficient 0.853; p=0.007);

- Question number 7 of the pre-operative general health questionnaire (Correlation coefficient 0.729; p=0.040);
- Question number 1 of the pre-operative oral health questionnaire (Correlation coefficient 0.766; p=0.027);
- Question number 6 of the pre-operative oral health questionnaire (Correlation coefficient 0.746; p=0.033);
- Question number 9 of the pre-operative oral health questionnaire (Correlation coefficient 0.833; p=0.010);
- Question number 11 of the pre-operative oral health questionnaire (Correlation coefficient 0.746; p=0.010);
- Question number 12 of the pre-operative oral health questionnaire (Correlation coefficient 0.792; p=0.019);
- Question number 20 of the pre-operative oral health questionnaire (Correlation coefficient 0.716; p=0.046);
- Question number 3 of the post-operative general health questionnaire (Correlation coefficient 0.728; p=0.041;
- Question number 5 of the post-operative general health questionnaire (Correlation coefficient 0.726; p=0.041);
- Question number 4 of the post-operative oral health questionnaire (Correlation coefficient 0.831; p=0.011);
- Question number 8 of the post-operative oral health questionnaire (Correlation coefficient 0.709; p=0.049);
- Question number 11 of the post-operative oral health questionnaire (Correlation coefficient 0.731; p=0.039);
- Question number 13 of the post-operative oral health questionnaire (Correlation coefficient 0.818; p=0.013.

- The pre-operative algic symptoms has a correlation with the pre-operative inability to perform daily life activities (Correlation coefficient 0.816; p=0.013);
- The post-operative algic symptoms has a correlation with the post-operative inability to perform daily life activities (Correlation coefficient 0.839; p=0.009) and the post-operative presence of difficulties in the daily life (Correlation coefficient 0.808; p=0.015);
- The post-operative presence of difficulties in the daily life has a correlation with the post-operative inability to perform daily life activities (Correlation coefficient 0.924; p<0.001).

Chapter 12: Discussion

Although both LN and IAN injuries are extremely common in maxillofacial and oral surgery practice, a worldwide common consensus about diagnostic and therapeutic management of these patients is not present. In Italy, only few specific centres handle this kind of iatrogenic and widespread issue.

Therefore, this project aims to standardize the diagnostic path in order to choose, if suitable, the best treatment for each patient, with a strong focus on the timeliness of the surgical intervention. One of the primary purposes of this project is to take into account both the subjective perspective of the patients about their symptoms and their influence on patients' daily life (through the patients' history and the general and oral health questionnaires) and the objective data collected through the pre- and post-operative neurophysiological tests. This kind of evaluations allows to compare the subjective point of view with the objective assessment of the nerve function and to make an adequate evaluation of the efficacy of the proposed treatments.

Literature reports the lower third molar extraction as the most common cause of LN (0.6-2%) and IAN iatrogenic lesions (0.4-25%)[15,16,29,31,40,77,84].

Other reported causes include implant placement, Wharton duct stone removal, mandibular lesions removal, orthognathic surgery, oncologic surgery and traumas[35]. Moreover, troncular anaesthesia causes temporary LN damage in about 0.15% to 0.54% of patients, while permanent injuries are noted in 0.01%, a non-negligible morbidity given the large number of local anaesthetic procedures performed every year[16,29,86].

The importance of the clinical patient's history about how and when the symptoms started is unquestionable as so as the clinical assessment using sensorineural tests. Many clinical tests utilized to ascertain LN and IAN lesions (i.e. stimulation of the tongue surface/lower lip with a sharp tip or a swab; rubbing the swab on the lingual/labial surface and asking the

patient to recognize the direction of rubbing) may sometimes be influenced by emotions, psychological states, pain threshold and legal issues[29,58]. According to these considerations, we tried to standardize a new protocol of diagnostic and therapeutic management of the patients affected by LN and IAN injuries, adding to these classic evaluations two other assessment systems in order to better understand the subjective aspect (through the individual questionnaires) and to objective the reported symptoms (through the neurophysiological tests and the evaluation of the tactile and pain threshold, the MIR and the SDR). The subjective and objective data have always to be compared in order to choose the best treatment for each patient. Neurophysiological tests help to evaluate the situation more objectively and avoid unnecessary surgery[29,74,76].

Unfortunately, we did not have pre- and post-operative neurophysiological tests for all patients included in the present study. Our objective results are complete with pre- and post-operative evaluation in 7 patients affected by an IAN lesion and in 22 patients affected by a LN damage:

- 1 patients affected by an IAN lesion did not underwent the pre-operative neurophysiological evaluation because the severe pain and the presence of the apex of a dental implant inside the mandibular canal compressing the IAN made the surgery to be performed immediately after our first evaluation;
- 5 patients affected by a LN damage refused to perform the post-operative neurophysiological test 12 months after surgery, because they referred an excellent surgical result in term of nerve function restoration associated with a complete resolution of the algic symptoms.

In the present study, both the MIR and the SDR results documented an objective and statistically significant improvement in LN and IAN function with surgery, although no patient fully recovered nerve function. This must be kept in mind and explained to the patient prior to surgery to avoid creating unrealistic expectations. The results show a

statistically significant improvement of tactile and pain thresholds in all patients in affected side, while, obviously, no improvement was reported in the healthy side (See Table 11.1).

The statistical analyses performed on the pre- and post-operative SDR and MIR data, using Spearman's Rho Test, show some interesting statistically significant correlations. In the group of patients affected by a LN injury, pre-operative tactile and pain SDR have a direct correlation with each other and with post-operative tactile and pain SDR; also post-operative tactile and pain SDR have a direct correlation with each other, while an inverse correlation is present with the pre-operative MIR results; an inverse correlation is also present between pre-operative MIR and post-operative tactile and pain SDR: all patients show a statistically significant improvement in their objective results (tactile and pain thresholds, SDR and MIR), but patients with a worse pre-operative nerve function were able to get a worse post-operative result (higher post-operative tactile and pain thresholds and higher percentage of post-operative SDR than patients with a better pre-operative nerve function).

In the group of patients affected by an IAN injury, the pre-operative tactile SDR has a direct correlation with the pre-operative pain SDR, while the pre-operative MIR has an inverse correlation with both the pre-operative and the post-operative tactile SDR. We can draw the same conclusion we described for the patients with a LN lesion, but we have always to consider the small group of patients (and the following lower statistical significance) affected by an IAN lesion that implies the necessity to extend the sample and perform further analyses.

All patients answered to pre- and post-operative questionnaire about their general and oral health. The statistical evaluations managed on the pre- and post-operative questionnaire results show a satisfactory post-operative improvement on both the symptomatology and the patients' quality of life. When dealing with patients affected by neuropathic pain, the subjective assessment of symptoms and the eventual impact of them on the patients' daily

life is fundamental. In particular, for patients affected by LN lesions, we found a statistically significance for all the tested questions, except that investigating swallowing difficulties connected to the LN injury (most of patients did not complain about swallowing problems either pre-operatively or post-operatively). In the second group (patients affected by an IAN lesion), the statistical significance is lower in term of both “p” values and number of statistically significant answers (See Chapter 11): in particular, there is only a mild improvement of the perception of patients’ own general health; pronunciation and swallowing difficulties and loss of taste are not significant in patients affected by an IAN lesion (we can explain this report thinking about the physiology of speech, swallowing and taste). No statistical significance is showed for the reported improvement of the algic symptoms after intense exercise: this is an important symptom in patients affected by LN injuries because of the common position of the traumatic neuroma that can be compressed by the contraction of pterygoid muscles during physical exercises; we suppose that the severe pain reported by patients affected by an IAN lesion after intense physical exercise cannot be triggered by the same cause. Only for two questions that does not show statistical significance, we found no subjective improvement: no improvement was reported about swallowing difficulties, that are not typical in case of IAN injury and no improvement was reported about the awareness of the own health condition (even after reconstructive surgery, patients are always conscious of their oral condition).

Although the immediate reconstruction is the gold standard in term of functional results, the LN and the IAN are often difficult to visualize during some surgical intervention and the first signs of LN or IAN injury often occur the day after surgery, when hemitongue/hemilip anaesthesia is still present. For this reason, the reconstructive surgeon has to wait some time to avoid unnecessary surgical intervention, because a spontaneous recovery is possible, in particular in case of IAN damage. The surgical reconstruction is usually recommended in case of persistent anaesthesia 3 months after surgery or in case of

persistent severe hypoesthesia 8 months after injury. An exhaustive examination of pros and cons with the patient is always recommended, in particular in case of persistent hypoesthesia of the lower lip because of the presence of some compensatory mechanisms of adaptation that make the IAN damage more tolerable than the LN injury[38].

The Spearman's Rho Test allowed us to test some correlations between our data: we found particularly interesting the correlation between timing of reconstructive surgery of both the LN and the IAN and the subjective perception of the own general health, both pre-operatively and post-operatively.

Pain is the most disabling symptom. Our statistical evaluation showed a direct correlation between the presence of pain and the difficulties to perform everyday activities. Early pain is caused by exposure of axons to inflammatory tissue, and later pain is caused by the scar. Both situations may damage axons, leading to various types of paraesthesia and pain. When these symptoms are present, surgery has to be performed as soon as possible to stop the chronicity process[15,16,29,87].

Another situation that makes the immediate surgery necessary is the association between symptoms involving the lower lip and the presence of foreign bodies in the mandibular canal: implant's apex, bone fragments, dental root, endodontic material compress the IAN inside the bone canal preventing the regeneration process. The removal of the foreign bodies has to be performed as soon as possible, eventually associated with the nerve reconstruction[12,38,39,41,56].

Nerve reconstruction managed after 12-18 months from the occurrence of the damage are not unanimously recommended because of the reduced chance of functional recovery, except in case of pain. Recently, some authors showed some promising results after late LN reconstruction[85,88].

In order to reconstruct the LN, the removal of the damaged nerve is recommended and a direct neurorrhaphy is usually feasible because of the sufficient elasticity of the proximal

and distal stumps of the nerve due to their position in the soft tissues of the mouth floor. In all those cases where a tension between stumps is present, the surgeon can cut the parasympathetic fibres directed to the submandibular gland in order to increase the elasticity of the stumps and perform a tensionless suture. When the LN is not completely sectioned, the removal of the damaged part of the nerve is recommended to get the best possible functional result[29].

The reconstruction of the extra-osseous IAN nerve can be performed through a direct neurorrhaphy because its course in the soft tissues of the mental and labial region can make the nerve stumps more elastic. The reconstruction of the intraosseous IAN nerve, instead, requires nearly always an interpositional graft to fill the gap between the proximal and distal stumps (their course inside the bone canal prevents the possibility of nerve stumps sliding)[12].

Nowadays, the interpositional material can be autologous (nerve or vein), allogenic (cryopreserved nerve) or synthetic (collagenous scaffold conduit). According to the literature, the best functional results have been obtained using autologous nerve graft, while the use of the autologous vein graft showed worse results with post-operative uncontrolled pain, probably due to the scar formation process and the following contraction of the venous tissue[12,89-94]. According to the results proposed by a wide study conducted by our team, in this study, the venous interpositional graft was no longer used[12].

The research of some alternative materials to fill the gap between the IAN stumps is guided in order to prevent the donor-site complications associated with the harvest of autologous nerve grafts. The most common nerves used to this goal are the sural nerve and the great auricular nerve, harvested by a second surgical team during the same surgical time. Unavoidably, the harvest of both the sural nerve and the great auricular nerve compromises the sensibility of the heel and the earlobe, respectively; moreover, the patient would have some cutaneous scars on the posterior part of the leg or on the neck.

Recent studies show promising results using bio-absorbable collagenous conduits to fill the gap between stumps, in particular in presence of subcentimeter nervous gap[95,96]. The preliminary results proposed by this work seem to validate the efficacy of the use of these devices. Obviously, 5 patients aren't still enough to make some statistically significant observations: this is the reason why we decided not to propose a comparison of our results using different surgical technique.

Recently, some authors proposed the use of processed nerve allograft. The use of this type of grafts started from the recovery of the brachial plexus damages[97], but, in 2016, Salomon and colleagues published some promising preliminary results about the use of cryopreserved nerve graft for the reconstruction of the IAN nerve in 7 patients[98]. These nerves are homologous graft cryopreserved from cadaver donor: the cryopreservation process and the reduced size of the graft allow to prevent the immunogenicity, so that no immunosuppressive therapy is needed[99-105].

Pharmacological therapy, through antiepileptic drugs, is usually recommended in case of pain present for longer than 12 months or when pain recur after reconstructive surgery[106].

Chapter 13: Conclusions

LN and IAN injuries are serious complications that can occur more frequently than people think during oral and maxillo-facial surgery.

A standardization of the diagnostic management of these patients was needed to better understand when and how reconstructive surgery is necessary to restore functional recovery of the nerve and to stop the algic pain, improving the quality of daily life of the patients.

The subjective experience reported by patients has always to be compared with the objective data that we can collect through neurophysiological tests assessing the MIR, the SDR and the tactile and pain threshold both on the healthy and the injured side.

The standardized diagnostic process allows the reconstructive surgeon to choose the best possible treatment for each patient.

The standardized follow up allows the reconstructive surgeon to objectively assess the functional outcome of the nerve reconstruction.

Early microsurgical reconstruction of both the LN and the IAN allows to achieve an unequivocal, although incomplete, functional recovery associated with an excellent pain control.

Patients' satisfaction was well correlated with the objective post-operative data.

Further diagnostic and surgical achievements are possible in the future, thanks to the current preliminary studies about both new diagnostic imaging (MRI and Fibre Tractography) and new surgical technique (collagenous conduits and cryopreserved nerve graft).

References

1. Seddon HJ. Three types of nerve injury. Brain. Vol. 66, pp. 237-288, 1943
2. Sunderland S. A classification of peripheral nerve injury producing loss of function. Brain. Vol. 74, pp. 491-516, 1951
3. Payton OD, Jackson O, Di Fabio RP. Manual of physical therapy. New York: Churchill Livingstone, 1989
4. Susarla SM, Blaeser BF, Magalnick D. Third molar surgery and associated complication. Oral Maxillofac Surg Clin North Am. Vol. 15, p. 177, 2003
5. Svane TJ. The fascicular characteristics of the human inferior alveolar nerve. J Oral Maxillofac Surg. Vol. 44, pp. 431-434, 1986
6. Balboni GC. Anatomia umana. Milano: Edi-Ermes, 2000
7. Standring S. Gray's anatomy 41st Edition. s.l.: Elsevier, 2015
8. Chiapasco M. Manuale Illustrato di Chirurgia Orale. Milano: Edra Masson, 2013
9. Lloyd Dubrul E. Anatomia Orale di Sicher. Milano: Edi.Ermes, 1988
10. Biglioli F, Allevi F, Lozza A**.** Diagnosi, trattamento e follow-up delle lesioni trigeminali del cavo orale. Dental Cadmos, pp. 31-48, 2014
11. Brammer JP, Epker BN. Anatomic-histologic survey of the sural nerve: implications for inferior alveolar nerve grafting. J Oral Maxillofac Surg. Vol. 46, pp. 111-117, 1988
12. Biglioli F, Allevi F, Lozza A. Surgical treatment of painful lesions of the inferior alveolar nerve. J Craniomaxillofac Surg. Vol. 43, pp. 1541-1545, 2015
13. Biglioli F. Diagnosi e terapia delle lesioni nervose del cavo orale. Dentista moderno. Vol. 4, pp. 39-59, 2010
14. Biglioli F, Colombo V. Le lesioni del nervo linguale in chirurgia orale. Dent Clin. Vol. 4, pp. 9-20, 2010

15. Biglioli F, Allevi F, Lozza A. Inquadramento, follow up e terapia delle lesioni del nervo alveolare inferiore. Dentista Moderno. Vol. 4, pp. 46-60, 2014
16. Biglioli F, Allevi F, Lozza A. Diagnosi, trattamento e follow up delle lesioni trigeminali del cavo orale. Dental Cadmos. Vol. 82, pp. 89-106, 2014
17. Hillerup S, Jensen RH, Ersboll BK. Trigeminal nerve injury associated with injection of local anesthetics: needle lesion or neurotoxicity? J Am Dent Assoc. Vol. 142, pp. 531-539, 2011
18. Pogrel MA. Damage to the inferior alveolar nerve as the result of root canal therapy. J Am Dent Assoc. Vol. 138, pp. 65-69, 2007
19. Fu SY, Gordon T. The cellular and molecular basis of peripheral nerve regeneration. Mol Neurobiol. Vol. 14, pp. 67-116, 1997
20. Chaudhry V, Cornblath DR. Wallerian degeneration in human nerves: serial electrophysiological studies. Muscle nerve. Vol. 15, pp. 687-693, 1992
21. Gaudet AD, Popovich PG, Ramer MS. Wallerian degeneration: gaining perspective in inflammatory events after peripheral nerve injury. J Neuroinflam. Vol. 8, pp. 110-123, 2011
22. Geuna S, Raimondo S, Ronchi G et al. Histology of the peripheral nerve and changes occurring during nerve regeneration. In International review of neurobiology-essays on peripheral nerve repair and regeneration. New York: Elsevier, 2009
23. Gilliat RW, Hjorth RJ. Nerve conduction during Wallerian degeneration in the baboon. J Neurol Neurosurg Psychiatry. Vol. 35, pp. 335-341, 1972
24. Coleman MP, Freeman MR. Wallerian degeneration, wld(s), and nmnat. Annu Rev Neurosci. Vol. 33, pp. 245-267, 2010

25. Gulicher D, Gerlach KL. Sensory impairment of the lingual and inferior alveolar nerves following removal of impacted mandibular third molars. Int J Oral Maxillofac Surg. Vol. 30, pp. 306-312, 2001
26. Juodzbalys G, Wang HL, Sabalys G. Injury of the inferior alveolar nerve during implant placement: a literature review. J OralMaxillofac Res. Vol. 2, p. e1, 2011
27. Leung YY, Cheung LK. Risk factors of neurosensory deficits in lower third molar surgery: a literature review of prospective studies. Int J Maxillofac Surg. Vol. 40, pp. 1-10, 2011
28. Tay AB, Zuniga JR. Clinical characteristics of trigeminal nerve injury referrals to a university centre. Int J Oral Maxillofac Surg. Vol. 36, pp. 922-927, 2007
29. Biglioli F, Lozza A, Colletti G, Allevi F. Objective assessment of lingual nerve microsurgical reconstruction. J Craniofac Surg, Vol. 29, pp. 740-744, 2018
30. Devine M, Yilmaz Z, Hirani M, Renton T. A case series of trigeminal nerve injuries caused by periapical lesions of mandibular teeth. Br Dent J, Vol. 222, pp. 447-455, 2017
31. Pippi R, Spota A, Santoro M. Prevention of lingual nerve injury in third molar surgery: literature review. J Oral Maxillofac Surg, Vol. 75, pp. 890-900, 2017
32. Posnick JC, Choi E, Singh N. Lingual nerve injury in association with sagittal ramus osteotomy and bicortical screw fixation: a review of 523 procedures in 262 subjects. Int J Oral Maxillofac Surg, Vol. 45, pp. 1445-1451, 2016
33. Haas DA, Lennon D. A 21 year retrospective study of reports of paresthesia following local anaesthetic administration. J Can Dent Assoc. Vol. 61, pp. 319-330, 1995
34. Kingon A, Sambrook P, Goss A. Higher concentration local anaesthetics causing prolonged anaesthesia. Do they? A literature review and case reports. Aust Dent. Vol. 56, pp. 348-351, 2011

35. Pogrel MA. Summary of: trigeminal nerve injuries in relation to the local anaesthesia in mandibular injections. Br Dent J. Vol. 209, pp. 452-452, 2010
36. Pogrel MA. Permanent nerve damage from inferior alveolar nerve blocks: a current update. J Calif Dent Assoc. Vol. 40, pp. 795-797, 2012
37. Renton T, Janjua H, Gallagher JE, Dalgleish M, Yilmaz Z. UK dentists' experience of iatrogenic trigeminal nerve injuries in relation to routine dental procedures: why, when and how often? Br Dent J. Vol. 214, pp. 633-642, 2013
38. Alling CC III. Dysesthesia of the lingual and inferior alveolar nerves following third molar surgery. J Oral Maxillofac surg. Vol. 44, pp. 454-457, 1986
39. Goldberg MH, Nemarich AN, Marco WP II. Complications after mandibular third molar surgery: a statistical analysis of 500 consecutive procedures in private practice. J Am Dent Assoc. Vol. 111, pp. 277-279, 1985
40. Hillerup S. Iatrogenic injury to the inferior alveolar nerve: etiology, signs and symptoms and observation on recovery. Int J Oral Maxillofac Surg. Vol. 17, pp. 704-9, 2008
41. Kipp DP, Goldstein BH, Weiss WW Jr. Dysesthesia after third molar surgery: a retrospective study and analysis of 1377 surgical procedures. J Am Dent Assoc. Vol. 100, pp. 185-92, 1980
42. Robert RC, Bacchetti P, Pogrel MA. Frequency of trigeminal nerve injuries following third molar removal. J Oral Maxillofac Surg. Vol. 63, pp. 732-735, 2005
43. Jerjes W, Swinson B, Moles DR. Permanent sensory nerve impairment following third molar surgery: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. Vol. 102, pp. e1-7, 2006
44. Queral-Godoy E, Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Incidence and evolution of inferior alveolar nerve lesions following lower third molar extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. Vol. 99, pp. 259-264, 2005

45. Valmaseda-Castellon E, Berini-Aytes L, Gay-Escoda C. Inferior alveolar nerve damage after lower third molar surgical extraction: a prospective study of 1117 surgical extractions. Oral Surg ORal Med Oral Pathol Oral Radiol Endod. Vol. 92, pp. 377-83, 2001
46. Bartling R, Freeman K, Kraut RA. The incidence of altered sensation of the mental nerve after mandibular implant placement. J Oral Maxillofac Surg. Vol. 57, pp. 1408-1412, 1999
47. Ellies LG, Hawker PB. The prevalence of altered sensation associated with implant surgery. Int J Oral Maxillofac Implants. Vol. 8, pp. 674-679, 1993
48. Lin CS, Wu SY, Huang HY, Lai YI. Systematic review and meta-analysis on incidence of altered sensation of mandibular implant surgery. PLoS One. Vol. 11, p. e0154082, 2016
49. Shavit I, Juodzbalys G. Inferior alveolar nerve injuries following implant placement - importance of early diagnosis and treatment: a systematic review. J Oral Maxillofac Res. Vol. 5, p. e2, 2014
50. Dao TT, Mellor A. Sensory disturbances associated with implant surgery. Int J Prosthodont. Vol. 11, pp. 462-469, 1998
51. Juodzbalys G, Kubilius M. Clinical and radiological classification of the jawbone anatomy in andosseous dental implant treatment. J Oral Maxillofac Res. Vol. 4, p. e2, 2013
52. Chong BS, Gohil K, Pawar R, Makdissi J. Anatomical relationship between mental foramen, mandibular teeth and risk of nerve injury with endodontic treatment. Clin Oral Investig. Vol. 21, pp. 381-387, 2016
53. Kockapan, C. Overfilling into the mandibular canal as an endodontic complication. A review. Schweiz Monatsschr Zahnmed. Vol. 103, pp. 20-28, 1993

54. Lorenzini G, Viviano M, Di Vece L, Parrini S, Autelitano L, Biglioli F. Surgical treatment of bifid mental nerve damaged by root canal therapy. A case report. Minerva Stomatologica. Vol. 57, pp. 369-376, 2008
55. Olsen JJ, Thorm JJ, Korsgaard N, Pinholt EM. Nerve lesions following apical extrusion of non-setting calcium hydroxide: a systematic case review and report of two cases. J Craniomaxillofac Surg. Vol. 42, pp. 757-762, 2014
56. Biglioli F, Kutanovaite O, Autelitano L, Lozza A, Moneghini L, Bulfamante G, Allevi F. Surgical treatment of painful inferior alveolar nerve injuries following endodontic treatment: a consecutive case series of seven patients. Oral Maxillofac Surg. Vol. 21, pp. 461-466, 2017
57. Agbaje JO, Salem AS, Lambrichts I, Jacobs R, Politis C. Systematic review of the incidence of inferior alveolar nerve injury in bilateral sagittal split osteotomy and assessment of neurosensory disturbances. Int J Oral Maxillofac Surg. Vol. 44, pp. 447-451, 2015
58. Gianni' AB, D'Orto O, Biglioli F, Bozzetti A, Brusati R. Neurosensory alterations of the inferior alveolar and mental nerve after genioplasty alone or associated with sagittal osteotomy of the mandibular ramus. J Craniomaxillofac Surg. Vol. 30, 5, pp. 295-303, 2002
59. Bagheri SC, Meyer RA, Khan HA, Steed MD. Microsurgical repair of peripheral trigeminal nerve injuries from maxillofacial trauma. J Oral Maxillofac Surg. Vol. 67, pp. 1791-1799, 2009
60. Schenkel JS, Jacobsen C, Rostetter C, Grätz KW, Rücker M, Gander T. Inferior alveolar nerve function after open reduction and internal fixation of mandibular fractures. J Craniomaxillofac Surg. Vol. 44, pp. 743-748, 2016

61. Biglioli F, Frigerio A, Rezzonico A, Autelitano L, Rabbiosi D, Carota F. Microsurgical reconstruction of oropharynx, lingual and inferior alveolar nerves. Minerva Stomatologica. Vol. 16, pp. 43-50, 2005
62. Biglioli F, Liviero F, Frigerio A, Rezzonico A, Brusati R. Function of the sensate free forearm flap after partial glossectomy. J Craniomaxillofac Surg. Vol. 34, pp. 332-339, 2006
63. Gennaro P, Gabriele G, Della Monaca M, Facchini A, Mitro V. Mandibular nerve fascicular cross-face for sensitive recovery after mandibulectomy: a new technique. J Plast Surg Hand Surg. Vol. 47, pp. 228-231, 2013
64. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction with Life Scale. J Pers Assess, Vol. 49, pp. 71-75, 1985
65. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas, pp. 385–401, 1977
66. Leung YY, McGrath C, Cheung LK. Trigeminal neurosensory deficit and patient reported outcome measures: the effect on quality of life. PLoS One, Vol. 8, pp. 1-5, 2013
67. Walter JM Jr, Gregg JM. Analysis of postsurgical neurologic alteration in the trigeminal nerve. J Oral Surg. Vol. 37, pp. 410-414, 1979
68. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Redefinition and a grading system for clinical and research purposes. Neurology. Vol. 70, pp. 1630-1635, 2007
69. Castro Ar, Siqueira SR, Perissinotti DM, Teixeira MJ, Siqueira JT. Emotional aspects of chronic orofacial pain and surgical treatment. Int J Surg. Vol. 7, pp. 196-199, 2009

70. Kim YK, Yun PY, Kim JH, Lee JY, Lee W. The quantitative sensory testing is an efficient objective method for assessment of nerve injury. Maxillofac Plast Reconstr Surg. Vol. 37, p. 13, 2015
71. Hartmann A, Welte-Jzyk C, Seiler M, Daubländer M. Neurophysiological changes associated with implant placement. Clin Oral Implants Res. Vol. 19, pp. 725-732, 2016
72. Zuniga JR, Meyer RA, Gregg JM, Miloro M, Davis LF. The accuracy of clinical neurosensory testing for nerve injury diagnosis. J Oral Maxillofac Surg. Vol. 56, pp. 2-8, 1998
73. Jones DL, Thrash WJ. Electrophysical assessment of human inferior alveolar nerve function. J Oral Maxillofac Surg. Vol. 50, pp. 581-585, 1992
74. Biasotta A, Cascone P, Cecchi R, Cruccu G, Iannetti G, Mariani A, Spota A, Truini A. Iatrogenic damage to the mandibular nerve as assessed by the masseter inhibitory reflex. J Headache Pain. Vol. 12, pp. 485-488, 2011
75. Cabib C, Biglioli F, Valls-Solé J. Traumatic lingual nerve injury assessed by sensory threshold and masseter inhibitory reflex. J Neurol. p. 260, 2013
76. Cruccu G, Inghilleri M, Fraioli B, Guidetti B, Manfredi M. Neurophysiologic assessment of trigeminal function after surgery for trigeminal neuralgia. Neurology. Vol. 37, pp. 631-638, 1987
77. Renton T, Thexton A, McGurk M. New method for the objective evaluation of injury to the lingual nerve after operation on third molars. Br J Oral Maxillofac Surg. Vol. 43, pp. 238-245, 2005
78. Voskuilen L, Mazzoli V, Oudeman J, Balm AJM, van der Heijden F, Froeling M, de Win MML, Strijkers GJ, Smeele LE, Nederveen AJ. Crossing muscle fibers of the human tongue resolved in vivo using constrained spherical deconvolution. J Magn Reson Imaging. Vol. 50, pp. 96-105, 2019

79. Terumitsu M, Matsuzawa H, Seo K, Watanabe M, Kurata S, Suda A, Nakada T. High-contrast high-resolution imaging of posttraumatic mandibular nerve by 3DAC-PROPELLER magnetic resonance imaging: correlation with the severity of sensory disturbance. Oral Surg Oral Med Oral Pathol Oral Radiol. Vol.124, pp. 85-94, 2017
80. Manoliu A, Ho M, Piccirelli M, Nanz D, Filli L, Dappa E, Liu W, Ettlin DA, Boss A, Andreisek G, Kuhn FP. Simultaneous Multislice Readout- Segmented Echo Planar Imaging for Accelerated Diffusion Tensor Imaging of the Mandibular Nerve: A Feasibility Study. J Magn Reson Imaging. Vol. 46, pp. 663-677, 2017
81. Kotaki S, Sakamoto J, Kretapirom K, Supak N, Sumi Y, Kurabayashi T. Diffusion tensor imaging of the inferior alveolar nerve using 3T MRI: a study for quantitative evaluation and fibre tracking. Dentomaxillofac Radiol. Vol. 45, pp. 1-7, 2016
82. Cassetta M, Pranno N, Pompa V, Barchetti F, Pompa G. High resolution 3-T MR imaging in the evaluation of the trigeminal nerve course. Eur Rev Med Pharmacol Sci. Vol.18, pp. 257-264, 2014
83. Assaf AT, Zrnc TA, Remus CC, Schönfeld M, Habermann CR, Riecke B, Friedrich RE, Fiehler J, Heiland M, Sedlacik J. Evaluation of four different optimized magnetic-resonance-imaging sequences for visualization of dental and maxillo-mandibular structures at 3 T. J Craniomaxillofac Surg. Vol. 42, pp. 1356-1363, 2014
84. Biglioli F, Colletti G. Protocollo diagnostico e terapeutico dei danni neurologici a carico del nervo alveolare inferiore nella chirurgia dell'ottavo. Il dentista moderno. pp. 128-137, 2006
85. Biglioli F, Allevi F, Colletti G, Lozza A. Cross-tongue procedure: a new treatment for long-standing numbness of the tongue. Br J Oral Maxillofac Surg. Vol. 53, pp. 880-882, 2015
86. Kumar MPS. Paresthesia following local anesthetic administration in dentistry. Int J Pharma Bio Sci. Vol. 6, pp. 112–116, 2015

87. Zuniga JR, Yates DM. Factors determining outcome after trigeminal nerve surgery for neuropathic pain. J Oral Maxillofac Surg. Vol. 74, pp. 1323–1329, 2016
88. Robinson PP, Smith KG. A study on the efficacy of late lingual nerve repair. Br J Oral Maxillofac Surg. Vol. 34, pp. 96-103, 1996
89. Bagheri SC, Meyer RA, Cho SH, Thoppay J, Khan HA, Steed MB. Microsurgical repair of the inferior alveolar nerve: success rate and factors which adversely affect outcome. J Oral Maxillofac Surg. Vol. 70, pp. 1978-1990, 2012
90. Jones RH. The use of vein grafts in the repair of the inferior alveolar nerve following surgery. Aust Dent J. Vol. 55, pp. 207-213, 2010
91. Pogrel MA, Maghen A. The use of autogenous vein graft for inferior alveolar and lingual nerve reconstruction. J Oral Maxillofac Surg. Vol. 59, pp. 985-988, 2001
92. Pogrel MA. The results of microneurosurgery of the inferior alveolar and lingual nerve. J Oral Maxillofac Surg. Vol. 60, pp. 485-489, 2002
93. Coulthard P, Kushnerev E, Yates JM, Walsh T, Patel N, Bailey E, Renton TF. Interventions for iatrogenic inferior alveolar and lingual nerve injury. Cochrane Database Syst Rev. Vol. 16, CD005293, 2014
94. Kushnerev E, Yates JM. Evidence-based outcomes following inferior alveolar and lingual nerve injury and repair: a systematic review. J Oral Rehabil. Vol. 42, pp. 786-802, 2015
95. Ducic I, Yoon J. Reconstructive Options for Inferior Alveolar and Lingual Nerve Injuries After Dental and Oral Surgery: An Evidence-Based Review. Ann Plast Surg. Vol. 82, pp. 653-660, 2019
96. Meyer RA, Bagheri SC. A bioabsorbable collagen nerve cuff (NeuraGen) for repair of lingual and inferior alveolar nerve injuries: a case series. J Oral Maxillofac Surg. Vol. 67, pp. 2550-2551, 2009

97. Squintani G, Bonetti B, Paolin A, Vici D, Cogliati E, Murer B, Stevanato G. Nerve regeneration across cryopreserved allografts from cadaveric donors: a novel approach for peripheral nerve reconstruction. J Neurosurg. Vol. 119, pp. 907-913, 2013
98. Salomon D, Miloro M, Kolokythas A. Outcomes of Immediate Allograft Reconstruction of Long-Span Defects of the Inferior Alveolar Nerve. J Oral Maxillofac Surg. Vol. 74, pp. 2507-2514, 2016
99. Cho MS, Rinker BD, Weber RV, Chao JD, Ingari JV, Brooks D, Buncke GM. Functional outcome following nerve repair in the upper extremity using processed nerve allograft. J Hand Surg Am. Vol. 37, pp. 2340-2349, 2012
100. Griffin JW, Hogan MV, Chhabra AB, Deal DN. Peripheral nerve repair and reconstruction. J Bone Joint Surg Am. Vol. 95, pp. 2144-2151, 2013
101. Lin MY, Manzano G, Gupta R. Nerve allografts and conduits in peripheral nerve repair. Hand Clin. Vol. 29, pp. 331-348, 2013
102. Pabari A, Lloyd-Hughes H, Seifalian AM, Mosahebi A. Nerve conduits for peripheral nerve surgery. Plast Reconstr Surg. Vol. 133, pp. 1420-1430, 2014
103. Szynkaruk M, Kemp SW, Wood MD, Gordon T, Borschel GH. Experimental and clinical evidence for use of decellularized nerve allografts in peripheral nerve gap reconstruction. Tissue Eng Part B Rev. Vol. 19, pp. 83-96, 2013
104. Houschyar KS, Momeni A, Pyles MN, Cha JY, Maan ZN, Duscher D, Jew OS, Siemers F, van Schoonhoven J. The Role of Current Techniques and Concepts in Peripheral Nerve Repair. Plast Surg Int. 2016
105. Safa B, Buncke G. Autograft Substitutes: Conduits and Processed Nerve Allografts. Hand Clin. Vol. 32, pp. 127-140, 2016
106. Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. Neurology. Vol. 59, pp. S14-S17, 2002