



UMEÅ UNIVERSITY

Percutaneous Balloon Compression for the Treatment of Trigeminal Neuralgia

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When the fit came, there was, to use My Lady's own expression of it, as it were a flash of fire all of a suddaine shot into all those parts, and at every one of those twitches which made her shreeke out, her mouth was constantly drawn on the right side towards the right eare by repeated convulsive motions, which were constantly accompanied by her cries.

John Locke, 1677

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Abstract

Background. Trigeminal neuralgia (TN) is a paroxysmal unilateral facial pain condition. That it is rather rare is of little comfort to those who are affected, as TN is often described as one of the worst pains known to mankind. Advanced age and multiple sclerosis (MS) are risk factors for developing TN. The first line of treatment is medical, primarily with carbamazepine. When medical treatment fails, as it does in many patients, there are several surgical options. One of the minimally invasive options, suitable for patients with comorbidity, is percutaneous balloon compression (PBC). Despite its introduction in the early 1980s, PBC is arguably the least well studied of the minimally invasive procedures for the treatment of TN.

Aims. The aim of this thesis was to evaluate the efficacy of PBC, both overall and in MS-TN patients specifically. Further, it intended to identify and evaluate pre- and intraoperative parameters associated with the efficacy of PBC. It also investigated changes in sensory function after PBC, and identified side effects and complications associated with PBC. Finally, it sought to evaluate how efficacy, side effects and complications differed between PBC and another minimally invasive technique; percutaneous retrogasserian glycerol rhizotomy (PRGR).

Methods. Cohorts of patients treated with PBC in Umeå and Stockholm, and with PRGR in Umeå, were followed retrospectively. Data from an existing database was combined with data from medical records, radiographs and telephone interviews.

Results. After PBC, 90 % of the patients were completely pain free without medication for TN. The median time to recurrence of pain was 28 months. In patients with concurrent MS, the initial success rate was 67 % and the median time to recurrence was 8 months. In patients without MS, who had not previously been treated surgically, the initial success rate was 91 % and the median time to recurrence was 48 months. The procedure could, however, be repeated with good results. A good compression, indicated by a pear-shaped balloon as seen on intraoperative lateral radiograph, was crucial to achieve good pain relief. Postoperative hypoesthesia was present in the majority of patients, but after 3-6 months, sensibility was partly or fully normalized in most patients. Severe complications were rare, but included transient cardiac arrest, meningitis and dysesthesia. The side effects profile was favorable to that of percutaneous retrogasserian glycerol rhizotomy, in that the latter produced more cases of dysesthesia and decreased corneal sensibility. The efficacy of the two treatments were, however, not significantly different.

Conclusions. PBC is an effective and relatively safe treatment option for patients with TN refractory to medical treatment. It deserves its place among the standard treatments for TN, and could be considered for those patients eligible for surgery for which open surgery is a less suitable option.

Abbreviations

BNI	Barrow Neurological Institute
CT	computed tomography
E-MVD	endoscopic microvascular decompression
ICHD-3	International Classification of Headache Disorders, 3 rd edition
MRI	magnetic resonance imaging
MS	multiple sclerosis
MS-TN	trigeminal neuralgia in patients with multiple sclerosis
MVD	microvascular decompression
PBC	percutaneous balloon compression
PRGR	percutaneous retrogasserian glycerol rhizotomy
PSR	partial sensory rhizotomy
RCT	randomized controlled trial
RFT	radiofrequency thermocoagulation
SRS	stereotactic radiosurgery
TN	trigeminal neuralgia
TN-1	trigeminal neuralgia type 1
TN-2	trigeminal neuralgia type 2
UmU	Umeå University
V1	ophthalmic nerve
V2	maxillary nerve
V3	mandibular nerve

List of Original Publications

I. Bergenheim AT, Asplund P, Linderöth B. Percutaneous retrogasserian balloon compression for trigeminal neuralgia: review of critical technical details and outcomes. *World neurosurgery*. 2013;79(2):359-68.

II. Asplund P, Linderöth B, Bergenheim AT. The predictive power of balloon shape and change of sensory functions on outcome of percutaneous balloon compression for trigeminal neuralgia. *Journal of neurosurgery*. 2010;113(3):498-507.

III. Asplund P, Blomstedt P, Bergenheim AT. Percutaneous Balloon Compression vs Percutaneous Retrogasserian Glycerol Rhizotomy for the Primary Treatment of Trigeminal Neuralgia. *Neurosurgery*. 2016;78(3):421-8; discussion 8.

IV. Asplund P, Linderöth B, Lind G, Winter J, Bergenheim AT. One hundred eleven Percutaneous Balloon Compressions for Trigeminal Neuralgia in a Cohort of 66 Patients with Multiple Sclerosis. *Operative neurosurgery*. 2019.

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Enkel sammanfattning på svenska

Trigeminusneuralgi (TN) är ett relativt ovanligt tillstånd av svåra smärtattacker i ena halvan av ansiktet. Sjukdomen beskrivs ofta som ett av de svåraste smärttillstånd vi känner till. Medicinsk behandling hjälper många patienter men långt ifrån alla. De mest verksamma medicinerna har också inte sällan besvärande biverkningar. För ett betydande antal patienter måste man därför gå vidare med kirurgisk behandling. De senaste decennierna har i huvudsak fem olika kirurgiska metoder använts mot TN, varav ballongkompression av trigeminusroten (PBC) möjligen är den minst omskrivna i litteraturen. Denna avhandling avser därför ge en bättre bild av PBCs behandlingseffekt och biverkningar.

Efter PBC blir 9 av 10 helt fria från smärta och mediciner. Med tiden återfår fler och fler patienter sin trigeminussmärta och måste åter börja ta mediciner eller genomgå en ny operation. Mediantiden till återfall är 28 månader för alla med TN, och efter ett återfall kan proceduren vid behov upprepas. En mindre grupp patienter har TN kopplad till multipel skleros (MS). Dessa patienter förefaller ha något sämre resultat av PBC, men mot bakgrund av att de generellt anses mer svårbehandlade och att deras MS gör de kirurgiska valmöjligheterna färre, kvarstår PBC som ett gott behandlingsalternativ.

För att PBC skall ge långvarig smärtfrihet är den kirurgiska tekniken viktig, och då i synnerhet en adekvat placering och fyllnad av ballongen. Denna framträder då under operationen, med hjälp av röntgen i sidoprojektion, som en päronformad ballong. Denna bild är, förutom bättre smärtfrihet, också associerad med en känselnedsättning i den opererade ansiktshalvan. En sådan känselnedsättning är förväntad och helt eller delvis övergående inom ett halvår, ofta mindre. Hornhinnans känsel påverkas nästan aldrig, vilket är viktigt för att undvika skador på densamma.

Övriga biverkningar är mindre vanliga, men enstaka till ett fåtal fall av tillfälligt hjärtstopp, hjärnhinneinflammation, obehagskänsla, försvagad tuggmuskulatur, dubbelseende, munsår, lockkänsla för örat, blödning i kinden och stickhål i munhålan har noterats. Vissa av dessa kan förebyggas, medan andra utgör en beräknad risk. De flesta biverkningar är övergående.

Biverkningsprofilen för PBC är fördelaktig jämfört med en operationsmetod som har vissa likheter med PBC, nämligen glycerolblockad av trigeminusroten. Den senare leder i högre utsträckning till obehagskänsla i ansiktshalvan och nedsatt känsel i hornhinnan. Den avsedda behandlingseffekten med smärtfrihet är dock jämförbar mellan de båda metoderna.

Sammantaget konstateras att PBC är en effektiv och relativt säker metod för behandling av de patienter med TN för vilka medicinsk behandling inte är tillräcklig, och att den förtjänar sin plats i den operativa standardrepertoaren mot detta fruktade smärttillstånd.

General Background

Imagine brushing your teeth one morning, the way you have done every morning for several decades now, when suddenly you experience an attack of chock-like excruciating pain in one side of your face – a pain the like of which you have never felt before, but will experience many times from now on. It may only last for a few seconds, but you will remember it for the rest of your life.

This is a typical presentation of trigeminal neuralgia (TN), often cited as one of the most painful conditions known to mankind. Before the introduction of effective treatment for TN, it was known as the “suicide disease”. Today, that sobriquet is all but a thing of the past due to advances in medical and surgical therapeutic options. This thesis will discuss important aspects of one of the latter – percutaneous balloon compression (PBC) of the trigeminal root fibers.

Historical Overview

Diagnosis and Pathogenesis

Although facial pain is mentioned in texts from ancient Egypt, Greece and medieval Persia, the first case description of what we can now be fairly certain was TN, was penned in detail by John Locke, as he had witnessed an attack of excruciating facial pain in the Countess of Northumberland.⁷¹ The comprehensive report included description of an episodic unilateral facial pain that also included the mouth and the tongue. The term *tic douloureux*, which for a long time was the most common term for what we today call TN, was coined by André in 1756, based on a report of five cases (of which probably only two would be diagnosed with TN today), and was used to not only describe the extreme pain, but also the grimaces associated with it.³⁸ Another synonym used for the disease has been Fothergill’s disease, after John Fothergill published an extensive, widespread and on many accounts accurate description of the disease in 1773 that in most regards holds true today for clinical diagnosis.⁷⁷ In the early 1820s, Bell succeeded to differentiate the functions of the trigeminal nerve and the facial nerve respectively, and thereby confining the disease to the trigeminal nerve, ultimately leading to the term trigeminal neuralgia.^{19,55}

“I have seen a case in which trigeminal neuralgia was one of the first and most permanent symptoms of sclerosis, and in which a sclerotic focus was found post-mortem at the point of emergence of the trigeminus.”¹⁸² This quote by Oppenheim from 1911 is notable not only for being one of the very first descriptions of a link between TN and what we now call multiple sclerosis (MS). It also contains a post mortem finding, however briefly described, of a

histopathological cause of the TN symptoms – an MS plaque in the trigeminal root entry zone.

Perhaps the most revolutionary finding regarding the pathogenesis of TN was presented by Dandy in the early 1930s.⁶² Initially mentioned only in passing in one of his meticulous descriptions of the surgical technique, he had noted a high frequency of gross lesions in association with the trigeminal root.⁶⁵ The most common lesion was an arterial loop, which was found in one third of the patients. This notion was later developed into theories on how pressure injures the nerve, thereby causing TN.²²³ By the late 1960s, the collective evidence for a peripheral etiology i.e., compression of the trigeminal root, was plentiful.¹¹⁹ It was however, for quite some time, rivaled by those advocating the theory of a central etiology.^{47,121} The subsequent surgical developments during the 1970s did however provide more evidence for a peripheral, or at least a first order sensory neuron, etiology than for a central one.

Medical Treatment

In the 18:th century, still long before the pathology behind TN was understood, Fothergill, who in total encountered at least 16 patients with TN, treated it with extract of hemlock.⁷⁷ In the 1820s, Hutchinson, who claimed to have seen 200 patients with TN, also claimed to have had considerable success treating them with large doses of iron carbonate.⁹⁵ He also provided a review of current medical treatments, including for example, mercury, ether, opium and arsenic.⁵⁵ In 1918, Plessner reported on a series of 17 TN patients treated with trichloroethylene. All patients were reported to have good effect on their TN, but the side effects were severe.⁵⁵ Modern medical treatment of TN began in 1942, when Bergouignan introduced anticonvulsant therapy in the form of diphenylhydantoin, based on the his belief that the episodic nature of TN resembled that of epilepsy.⁵⁵ Several different anticonvulsant drugs were used for TN until the 1960s, when Blom demonstrated carbamazepine to have a superior efficacy for TN, a drug that has to this day remained the mainstay of medical treatment for most patients.^{27,55}

Surgical Treatment – the Early Years

Hidden in the end of a book from 1756, dealing mainly with diseases of the urethra, is what is probably the first description of a successful surgical attempt to treat TN.³⁸ André describes two patients who can be assumed to have trigeminal neuralgia. The first of these patients was treated by decompressing the peripheral nerve using a cauterizing stone and mercury water, to create an open wound into the mental foramen. The patient was reported pain free until death from pneumonia 11 months later. While some unsuccessful attempts at surgery followed, it would take another century before the next documented

successful attempt to treat TN surgically was performed by Carnochan in 1856.⁴⁸ He made a postganglionic neurotomy of the trunk of the maxillary nerve, to treat a fellow physician with a severe case of second branch TN. Important scientific advances preceding and aiding the development of surgical treatment was the differentiation between the trigeminal nerve and the facial nerve by Bell in the 1820s described above, thereby establishing the association between tic douloureux the fifth cranial nerve, and significant advances in anesthesia in the mid 19th century, including the introductions of ether and chloroform.^{19,63,95} Throughout the second half of the 19th century, several procedures, often peripherally destructive ones, were performed, but not often with good long-term results. Curiously successful with regards to pain relief was a ligation of the ipsilateral carotid artery; first performed by von Nussbaum in 1858 to treat a severe bleeding from a neurectomy, it was incidentally also effective for treatment of the patient's TN.⁷⁸

Of the peripherally destructive procedures, one stood out as clearly more effective than the others; nerve avulsion.¹⁸² First performed in 1882 by Blum, the merit of this technique, as demonstrated in animal models two decades later, lied in the type of injury achieved by pulling the nerve. Not only were the peripheral axons severed, but the injury also extended into the ganglion and further back into the brain stem.²⁰⁰

Surgical Treatment – Intracranial Approaches

In 1890, Rose was the first to perform an intracranial surgery for TN, when he opened the skull base around the foramen rotundum to remove the ganglion.¹⁸⁷ The effect on the TN was very promising, but Rose's pterygoid approach was, however, very disfiguring to the face.²⁰⁰ In the following couple of years, a subtemporal extradural approach was developed independently in Germany and in the United States.¹⁰¹ Ganglionectomies soon gained widespread performance, but reviews of reported cases in the years before the turn of the century revealed a staggering high mortality of more than 20 %.²⁰⁰ The fate of ganglionectomies was in large part saved by the meticulous work by Cushing, who refined the technique to significantly reduce complications.^{60,200}

In all but Cushing's hands however, ganglionectomies still posed an unacceptable hazard to the patients.²⁰⁰ The subtemporal rhizotomy, a simpler procedure with less risk of tearing the cavernous sinus wall, was first performed (unsuccessfully) by Horsley in 1890.¹⁰⁰ During the first decades of the 20th century, the technique of open rhizotomy developed into a more targeted operation, eventually leading to sectioning of only the fibers of the affected branch or branches, and was considered a great success for surgery.^{63,200} One of the more important developments was the introduction of an access to the

trigeminal root through the posterior fossa, first described by Dandy in 1925.⁶⁴ Dandy initially performed full rhizotomies, but soon switched to partial rhizotomies to preserve some trigeminal function.⁶³ His early meticulous descriptions of the surgical technique also proved vital to the theories on the pathogenesis of TN, as described above.^{62,65}

In the 1930s and '40s, some surgeons pioneered more central lesional surgery for TN.⁹⁵ In 1938, Sjöqvist developed a method to section the nociceptive nerve fibers selectively through a medullary tractotomy.^{194,200} This was roughly concurrent with the introduction of a mesencephalic tractotomy and later followed by prefrontal lobotomy.⁹⁵ Even the theoretically attractive medullary tractotomy turned out to have limited efficacy, and all central lesional surgery was soon abandoned for superior medical and more peripheral surgical treatment options.¹⁶⁰

Rhizotomy arguably remained the most successful openly surgical option for TN up until 1976, when Jannetta first described what is now generally considered the most effective surgical treatment for TN, microvascular decompression (MVD).¹⁰⁸ While Gardner and Miklos had already in 1959 described one case in which TN was cured simply by separating a large arterial loop from the trigeminal root, Jannetta's use of the newly introduced operating microscope facilitated a vast improvement of this novel technique.^{81,109} In the microscope, it seemed as though all cases of TN were in some way symptomatic, and in most instances due to a neurovascular conflict. When he deemed it safe, he resolved the conflict by moving the offending artery without sectioning the nerve.¹⁰⁸ While meeting some initial resistance, not least due to Jannetta's young age and use of a microscope, MVD soon developed into a standard procedure worldwide.¹¹⁶

The Advent of Minimally Invasive Neuroablative Procedures

Many of the surgical procedures performed today for TN are minimally invasive. Most of the commonly used minimally invasive surgical techniques rely on the Härtel trajectory, an easy and relatively safe way of accessing the trigeminal ganglion and root, percutaneously through the cheek and foramen ovale using a cannula, first described in 1912.¹⁰³

Chemical Ablation

As described above, the first successful surgical attempt at treating TN was in fact a chemical ablation.³⁸ In the last decades of the 19th century, injection treatments of the peripheral trigeminal branches began to emerge.^{95,200} The first minimally invasive procedure of ablation of intracranial structures, however, was performed by Harris in 1910.^{93,96} He injected alcohol percutaneously into

the trigeminal ganglion through a lateral approach.¹⁰³ The approach developed by Härtel was first used in 1914 for a similar treatment.¹⁰⁴ Intraganglionic alcohol injections became an important option for the surgical treatment of TN during the first three quarters of the 20th century, especially in Europe.^{109,200} In 1940, Harris reported on the results from 1433 procedures, noting that the treatment was often efficient with regards to the TN, but that it carried a significant risk of a number of side effects related to trigeminal dysfunction.⁹⁴

The history of modern chemical ablative surgery for TN is overlapping with the one of stereotactic radiosurgery, described below. Before the advent of computed tomography (CT), the target for stereotactic radiosurgery was visualized using cisternography of Meckel's cave, whereby tantalum dust was used as a contrast medium, dispensed in glycerol. Accidentally, it turned out that the injection alone had an effect on the TN, a discovery that led Håkanson to develop the current form of chemical ablation, percutaneous retrogasserian glycerol rhizotomy (PRGR), first described in 1981.¹⁰² In retrospect, it is notable that glycerine (which is chemically identical to glycerol) had for decades before been used as a vehicle for other injected agents thought to be active in the treatment of TN.^{109,110}

Thermal Ablation

In 1913, Rethi described the first attempts at treating TN with electrocoagulation of the peripheral trigeminal branches.¹⁵⁹ Almost two decades later, in the early 1930s, Kirschner developed a technique for electrocoagulation of the trigeminal ganglion using a stereotactic frame.^{200,202} This technique got widespread use in Europe in the 1930s and '40s, but there was significant morbidity and mortality associated with it.¹⁷³ As something of an American curiosity, in the 1950s, Jaeger injected hot water into the trigeminal ganglion, a technique that similarly to Kirschner's was not without numerous side effects and complications, but without reported deaths.¹⁰⁶ In 1962 Thiry published improved results from electrocoagulation after having turned down the current somewhat compared to Kirschner.^{200,202} In 1965 the era of modern percutaneous treatment for TN was initiated when Sweet and Websic pioneered treatment with a radiofrequency electrode that gave precise control over the ablative temperature. Radiofrequency thermocoagulation (RFT) soon gained widespread use after the first publication appeared in 1974, and by 1986 over 14 000 cases were reported, and it is still one of the three standard percutaneous procedures for the treatment of TN.^{201,202}

Mechanical Ablation

The history of minimally invasive mechanical ablation begins with an effort to do the opposite. In 1952, Taarnhøj presented a new surgical technique for

treating TN; decompression of the trigeminal root by longitudinally dividing the dura of the porus trigeminus through a subtemporal intradural approach.²⁰³ Shelden et al. soon hypothesized that it was not the decompression, but the associated surgical trauma to the nerve, that caused pain relief.¹⁹¹ They therefore developed the technique of gently compressing the trigeminal root with a blunt instrument, through an incision in the dura small enough to not cause decompression. Inspired by the promising outcomes from the procedures performed by Shelden et al., Baker and Kerr demonstrated that compression of the trigeminal ganglion produced little injury to the ganglion cells, but moderate degeneration of the retroganglionic axons.¹⁶ While both compression and decompression were in use during the following decades, the overall results seem to have favored compression.^{84,167}

The first description of a minimally invasive technique utilizing compression of the trigeminal ganglion was published by Jelašić in 1959.¹¹¹ He advanced a blunt instrument, a surgical elevator, through the oral cavity and the foramen ovale, and once the tip was 12-15 mm beyond the outer margin of the foramen, the instrument was withdrawn slightly and rotated to traumatize the ganglion. This technique, however, seems to have disappeared from the literature after the original publication. Almost two decades later, in 1978, Mullan et al. began experimenting with compression of the trigeminal ganglion and root with a small embolectomy balloon catheter inserted through the Härtel trajectory.¹⁶⁶ Percutaneous balloon compression (PBC) was thoroughly introduced, along with promising results from the first 50 cases, by Mullan and Lichtor in 1983.¹⁶⁷ During the 1980s PBC gained widespread use and was established as one of three percutaneous techniques for treating TN. Still however, in 2004, Lopez et al. concluded that there was, at that point, insufficient good-quality data on PBC for evaluation of its results, in comparison to other surgical techniques.¹⁴⁹

Radiation Ablation

In 1897, only two years after the discovery of X-rays by Röntgen, the young orthopedic surgeon Gocht pioneered the treatment of TN with ionizing radiation, and he did so with good results.¹⁴ The history of modern radiation ablation, or stereotactic radiosurgery (SRS), begins with the invention of the stereotactic frame in the late 1940s and supplementing it with x-rays in the early 1950s.^{141,142} Development via proton radiation eventually led to the first stereotactic gamma radiation unit in Stockholm in 1968, a type of radiation still in use today. The first cases of trigeminal neuralgia were treated in 1953, but it was not until the 1970s that TN was more commonly treated in Stockholm.¹⁴³ The international breakthrough of this technique would however have to wait another two decades. With the development of CT and magnetic resonance imaging (MRI), targeting of the radiation was much improved, and eventually

dynamic allocation of the target allowed for the removal of the fixation of the patient.^{141,145}

This affection seems to be peculiar to persons advancing in years, and to women more than to men. I never met with it in any one much under forty, but after this period, no age is exempt from it. The case does not occur very frequently.

John Fothergill, 1773

Current State of Knowledge

First, let us conclude, that in some areas the science on TN has not advanced much in recent decades, while in others it is advancing more rapidly. Therefore, the following summary will refer to literature that, despite spanning several decades, is actually very important to our current understanding of these matters.

Epidemiology

Population-based studies indicate an incidence of TN of 4.7-26.7/100.000 person-years.^{90,115,123,153} This represents roughly one third of the incidence of all facial pain conditions (excluding toothache).¹²³ Women are affected more often than men by a factor of approximately 2:1.^{115,123} The maxillary branch is most commonly affected, while the ophthalmic branch is the least commonly affected, but the pain is often distributed over more than one branch.¹¹⁵ The incidence of TN is positively correlated to age, with a peak incidence in the eighth decade of life onwards, and since it is a chronic disease the prevalence can further be assumed to accumulate in the later decades.^{115,123} The lifetime prevalence has been reported to be 0.4-0.7 %.¹⁵³ There is an association between MS and TN. 4 % of the total incidence of TN occur in MS patients, meaning a relative risk of 20 for MS patients to develop TN.¹¹⁵ Conversely, the prevalence of TN among MS patients is 2 %, ^{99,196,212} TN can in a small number of patients be the first symptom of MS.⁹⁹ While MS is a risk factor for developing TN, TN is in turn a risk factor for developing depression, anxiety or sleeping disorder with a hazard ratio of approximately 2-3 for each.²²¹

Pathophysiology

The pathophysiology behind TN is incompletely understood. The current theories all require a basic understanding of the sensory trigeminal anatomy.^{113,190,220} Peripheral sensory stimuli is converged into, and conducted through, three principal trigeminal nerve divisions innervating an area from the anterior scalp to the chin; the ophthalmic nerve (V1), the maxillary nerve (V2) and the mandibular nerve (V3). Each of these contains the peripheral axons of pseudounipolar nerve cells. The axons are an even mixture of myelinated and unmyelinated ones, with the former measuring up to 1.3 micrometers in diameter and the latter measuring up to 11 micrometers in diameter. The nerves enter the intracranial space through the superior orbital fissure (for V1), the foramen rotundum (for V2) and the foramen ovale (for V3). The nerve cell bodies are located medially in the middle fossa in the trigeminal ganglion, organized in clusters, with a somatotopic organization, from V1 superomedially to V3 inferolaterally. The trigeminal ganglion is surrounded by a dural pouch,

Meckel's cave, which connects to the posterior fossa through the porus trigeminus, a dural tube riding over the petrous ridge. Centrally to the ganglion, the rootlets containing the axons of these same neurons gradually converge into the trigeminal root, which leads through the porus trigeminus and the prepontine cistern to the pons. Just before entering pons, in the trigeminal root entry zone, there is a transition from peripheral myelin (Schwann cells) to central myelin (oligodendrocytes). Within the brain stem, the axons extend to three different nuclei; the mesencephalic nucleus where muscular proprioception is directed, the principal nucleus where the majority of the tactile sensory signals are connected to second order sensory neurons, and the spinal nucleus, extending from pons to the upper spinal cord, where most of the thermal and nociceptive sensory signals are connected to second order sensory neurons. From there, signals are conducted to the third order sensory neurons in the contralateral thalamus and onwards to the primary somatosensory cortex. For our understanding of pathophysiological theories explaining TN, the most important part of this anatomy is the retroganglionic part of the first order sensory neurons and the structures surrounding it.

Two findings are strikingly often demonstrated in TN; demyelination in the trigeminal root and a vascular compression of the root.^{108,120} Often the former is assumed to be a result of the latter, and there is evidence of correlation between neurovascular conflicts and pathologic changes including demyelination in TN patients.^{70,150} Of all the cranial nerves, the trigeminal nerve is the one most frequently affected by a hyperactive dysfunctional syndrome (in this case TN), and it is also the cranial nerve with the largest portion of central myelin.⁸⁸ The central myelin has been reported to extend up to 9 mm from pons (mean 3½ mm).¹¹⁸ It has been suggested that it is the large volume of central myelin subjectable to compression that makes the trigeminal nerve particularly vulnerable to compression that in some cases leads to TN.⁸⁸ Neurovascular conflict involving the trigeminal root can be graded according to the Sindou classification: 0 = no contact, I = contact without affection, II = displacement, and III = indentation.¹⁹³ Arterial neurovascular conflict with the trigeminal nerve is most commonly caused by the superior cerebellar artery, followed by the anterior inferior cerebellar artery or an unspecified small artery.^{17,29} Though most neurovascular conflicts in TN involves arteries, there is also a significant number of patients with a venous contribution to the conflict, and in 8-16 % of the patients, a vein is the only offending vessel.^{17,74,76,136,233} These patients also have good effect from MVD, indicating causality.^{74,75} Case-control studies on MRI findings indicate that neurovascular contact in the root entry zone and/or anatomical changes have strong correlations to TN.¹¹ However, in studies on healthy subjects or on asymptomatic sides in TN patients, neurovascular conflicts involving the trigeminal root are very common compared to the low prevalence of TN.^{3,126,152} In other words, neurovascular conflicts are likely far

more commonly asymptomatic than associated with TN, which leads to the conclusion that it is not the only factor of importance for developing TN.

Demyelination of the trigeminal nerve has also been demonstrated in TN associated with compression of the nerve from a tumor in the cerebellopontine angle, resulting in TN.¹²⁹ Further, in the early years of decompressive surgery, it was suggested that nerve root compression could be caused by the trigeminal nerve riding over the petrous ridge, thereby causing TN.²⁰⁴ This theory has only recently been tested, generating preliminary evidence suggesting that the angle of the petrous ridge may be a factor associated with TN, with a more acute angle having a positive correlation with prevalence of TN.^{30,89}

Apart from compression, the other common cause of trigeminal demyelination is MS. Of MS patients with TN (MS-TN) At least 84 % of MS-TN patients have an MS-lesion on MRI that can explain their TN.^{57,212} MS-lesions associated with TN are confined to the first-order afferents, while lesions in the region of second-order neurons are associated with sensory disturbances other than TN.⁵⁷ Similar findings are however reported in a general MS population with a frequency of 23 %, without association to trigeminal neuralgia.¹⁵⁸ In addition to that, neurovascular conflicts are more common than expected in MS-TN, leading to the hypothesis of a dual concurrent mechanism explaining MS-TN.²¹²

The list of clinical characteristics of TN that must be explained by a hypothesis on the pathogenesis of TN on a physiological level is extensive, including for example the triggering by non-noxious stimuli, the length of the paroxysms and the response to various treatments. The ignition hypothesis elegantly explains nearly all characteristics of TN.⁶⁹ It builds on the revelation that oscillations in membrane potentials that normally occur in only a small portion of neurons are far more common in injured neuronal structures. This is what ignites a chain reaction, recruiting a large number of axons including nociceptors, based on two principles; 1) ephaptic cross-talk i.e., a spreading of electric discharge from one axon to the neighboring ones, aided by the lack of insulation in the demyelinated nerve, and 2) crossed afterdischarge, a non-synaptic release of potassium ions and/or neurotransmitters into the interstitial space, exciting neighboring neurons. The potassium ion release eventually causes a hyperpolarization, causing the discharge to stop followed by a refractory period. Afterdischarge has been recorded microneurographically in a TN patient.⁴⁵ While the ignition hypothesis is arguably the most interesting theory on the pathogenesis of TN, in that it is based on solid preclinical data and that it so comprehensively explains the disease, it also remains to be thoroughly verified in animal models or in TN patient. A verified animal model that reproduces the clinical characteristics of TN has not yet been presented in the literature.

While the ignition hypothesis explains the clinical features of TN, there are also unexplained structural and functional changes in the central nervous system associated with TN.^{68,178,208} These changes occur in gray and white matter in many parts of the brain that are directly or indirectly involved in various aspects of pain. To what extent these changes are the cause or the effect of TN remains to be investigated, but it is likely reasonable to expect them to in some way at least contribute to the perception of the TN pain.

It differs from the tooth-ach essentially in many respects. It affects some who, from age, have few or no teeth remaining.

John Fothergill, 1773

Diagnosis

Fothergill's description of the clinical characteristics of TN, first published in 1773, is considered to have stood the test of time.^{77,157} Add to this that the diagnosis (without regards for underlying cause) can be made almost entirely based on patient history, and it would seem that virtually no TN patient should have to be misdiagnosed.^{49,56} Yet, this has been frequently occurring, both historically and in modern days.^{46,182} In 69 patients who underwent MVD, 58 % had previously received dental treatment for the same condition, and of those initially seeing a dentist, only 7 % were directly referred to a physician.¹⁶⁹ Cluster headache is, despite its longer lasting pain and autonomous symptoms, sometimes also confused with TN, and in 144 patients with cluster headache, 22 % were initially diagnosed with trigeminal neuralgia.²¹⁸ Other differential diagnoses include glossopharyngeal neuralgia and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), both though with traits that clearly separates them from TN.^{12,219}

According to a recent consensus between the International Headache Society and the International Association for the Study of Pain, TN is diagnosed based on the following criteria in the International Classification of Headache Disorders, 3rd edition (ICHD-3):⁹⁷

- A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.
- B. Pain has all of the following characteristics:
 - 1. lasting from a fraction of a second to two minutes
 - 2. severe intensity
 - 3. electric shock-like, shooting, stabbing or sharp in quality
- C. Precipitated by innocuous stimuli within the affected trigeminal distribution.
- D. Not better accounted for by another ICHD-3 diagnosis.

In addition to that, some patients may exhibit sensory deficits in the affected region, ipsilateral muscle contractions and mild autonomic symptoms such as lacrimation. Following an attack of pain, there is usually a refractory period of time during which pain cannot be triggered. TN is further subdivided by demonstrated etiology:

- 1. Classical TN: no apparent cause other than neurovascular compression. Without or with persistent background facial pain.
- 2. Secondary TN: caused by an underlying disease. These causes include MS, space occupying lesion or other disease.

3. Idiopathic TN: no significant abnormalities on either MRI or electrophysiological tests.

This classification of etiology is however newer than the inclusion of patients in the cohorts in this study, and for all practical purposes in relation to PBC, the Burchiel classification from 2003 is more useful.⁴⁴ It subdivides TN into:

1. TN, Type 1 (TN-1): corresponding to classical or idiopathic TN with a persistent background pain of <50 %.
2. TN, Type 2 (TN-2): corresponding to classical or idiopathic TN with a persistent background pain of >50 %.
3. Symptomatic TN (MS-TN): corresponding to secondary TN in MS patients.

Of these, TN-1 (most often without any background pain at all) and MS-TN are considered for treatment with PBC. Clinically, MS-TN differs from TN-1 in at least three important regards; it is more often associated with sensory and electrophysiological disturbances, it is more often bilateral, and it presents significantly earlier, typically in the fifth decade of life.^{58,66,87,112,176,212} It is worth noting though, that with regards to age and to sensory and electrophysiological disturbances, there is considerable overlapping between the two groups.⁸⁷ The type of pain or the way it is triggered by stimuli does however not differ depending on the underlying cause, which again brings us back to talking to the patient.¹¹²

Modern workup also most notably includes an MRI, since the positive finding of a likely structural underlying cause, such as a severe neurovascular conflict, an MS-lesion or a tumor, is likely to have implications on the choice of treatment for a particular patient. A significant portion of the more current literature on TN relates to advancing the science on MRI protocols and findings. Factors other than the underlying cause e.g., trigeminal nerve atrophy, increased diffusion and reduced fractional anisotropy have been associated with TN, but there also seems to be a good amount of correlation between these factors, and it is therefore not currently clear which of these parameters that really add diagnostic value to the preoperative work-up.^{135,137}

Medical Treatment

The evidence for the treatment of TN is stronger in medical treatment than in surgery, and among the drugs, carbamazepine has the strongest evidence and is therefore considered the gold standard for the initial treatment of TN.²²⁸ The

use of oxcarbazepine for TN has, with the lack of high-quality randomized controlled trials (RCTs), weaker evidence, but there is consensus to support it as an alternative to carbamazepine as a first-line treatment.²²⁸ Both these drugs stabilize axonal membranes, by inhibiting voltage-gated sodium channels, and more so related to high-frequency trains of action potentials in neurons with depolarized action potentials.¹⁸⁵ The potential advantage of oxcarbazepine over carbamazepine is that the former may exhibit less adverse effects, a factor that often limits the use of carbamazepine.²²⁸ Common side effects include, but are not limited to, tiredness, dizziness, nausea, memory problems, headache, skin rash, leukopenia and hyponatremia.^{26,151}

Other drugs lack sufficient high-quality evidence of effect on TN, but are nonetheless considered as second- or third-line drugs. These include lamotrigine, baclofen and gabapentin.^{73,87,228} Anticonvulsants acting purely synaptically without a membrane stabilizing effect e.g., barbiturates, have not been proven to have an effect on TN.⁶⁹ Recently, evidence supporting the efficacy of injections of botulinum toxin A for the treatment of TN have emerged, but large well designed studies are needed to confirm these initial reports.^{73,165}

In MS-TN patients specifically, there is not enough evidence to support any drug over others, and therefore it has been recommended to use a similar first- and second-line treatment strategy as in a general TN population.²³² Drug therapy for MS-TN is complicated by MS patients being considered to be more sensitive to the side effects of antiepileptic drugs, especially carbamazepine.^{32,146} However, it is also in many TN-1 patients difficult to achieve adequate reduction of pain and frequency of attacks, while maintaining the side effects on acceptable levels. For carbamazepine, the numbers-needed-to-treat is 1.7-1.8 and the numbers-needed-to-harm is 3.4-24 (depending on the severity of harm).⁷³ After at least two failed attempts at sequential monotherapies and possibly one failed attempt at polytherapy, it is time to refer the patient for surgical intervention.^{54,177} The lifetime risk of TN patients having to undergo surgery has not been established for modern treatment modalities, but is likely a moving target due to advancements in therapy. There are further no high-quality studies comparing medical to surgical treatment.²³¹

Surgical Treatment

There are currently five different surgical procedures in widespread use for TN; MVD, SRS, RFT, PRGR and PBC. Evaluations of results after surgery vary in the literature. Most analyses use a dichotomous measure of an acceptable/unacceptable pain relief to evaluate efficacy. This is a statistical requirement both for reports of recurrence rate, which has become less

commonly used recently, and for survival/actuarial analysis, which has been used increasingly during the 21st century. As with the diagnosis itself, the evaluation of efficacy relies heavily on self-reports, but in interaction with a researcher or health care provider.²³¹

Based on observational data, MVD is considered the gold standard in surgery for TN, and it is the only procedure aimed at correcting the presumed pathology behind the pain i.e., a pathological neurovascular conflict.^{192,227} MVD is therefore often the first choice for TN patients suitable for open surgery. TN patients are often elderly, and while elderly patients often have more comorbidity, an advanced age is in itself no contraindication to MVD.¹⁸⁹ The success rate of MVD is dependent on the grade of neurovascular conflict, with more severe conflicts being correlated to better outcomes.¹⁹³ The existence of a neurovascular conflict on preoperative MRI has a very high positive predictive value, but the grade of conflict is often underestimated in comparison to operative findings.²⁹ A neurovascular conflict on preoperative MRI therefore speaks in favor of MVD, given that the patient is otherwise suitable for open surgery. According to the ignition hypothesis, the removal of mechanical stimulus from the injured trigeminal root, reduces the triggering of the ectopic pacemaker behind the pain paroxysms, which leads to an immediate pain relief, while also facilitating longer-term repair of the compressed neuronal tissue.⁶⁹ The mortality rate of MVD is 0.3-0.4 %.^{15,114} Since it is a non-ablative technique, side effects from lack of function of the trigeminal nerve are not expected, but they do occur.²⁵ Serious complications include cerebrospinal fluid leaks, infections, injuries to the cerebellum and affection of the seventh and eighth cranial nerve.^{17,76,226,230} There are, however, data supporting that some of these complications have decreased in recent decades, presumably due to a more refined technique and more experienced surgeons.¹⁰⁹

In the two most recent decades, publications on an endoscopic variant of MVD, so called E-MVD, have emerged. In a newly published meta-analysis, results after E-MVD are better than MVD when it comes to complications rates, while no significant difference can be found in published data on immediate pain relief and recurrence between the two techniques.²²⁶ While MVD is the only non-ablative technique for TN, it is sometimes combined with a partial sensory rhizotomy (PSR). The frequency of PSR in MVD was 3.4 % in the US in 1996-2000.¹¹⁴ Partial rhizotomies can also be performed without MVD, if no neurovascular conflict is found during posterior fossa exploration.¹⁰ The results in terms of pain-free rate are possibly lower than in MVD, and with the addition of a predictable sensory loss.^{206,230}

For many patients with TN, MVD is not the best option due to comorbidities making open surgery less suitable. Three ablative percutaneous techniques i.e.,

PBC, PRGR and RFT, have therefore been part of the standard repertoire for the treatment of TN since the early 1980s.^{102,167,202} They all have their advantages and disadvantages, but the several decades of parallel use is an indication that neither has turned out to be viewed as clearly superior or inferior to the others. Though there are obvious similarities in that they all access the trigeminal ganglion or root by cannulating the Härtel trajectory, their means of ablation have implications for slightly different effects and side effects. RFT is the most anatomically selective technique, while PBC is selective to large myelinated fibers. As they are all trigeminally ablative, they all carry a risk of hypoesthesia, masticatory weakness and dysesthesia.²⁰⁵

The least invasive surgical technique, in that it leaves no external scar, is SRS. Using a single-session radiation highly focused on the trigeminal nerve, it creates, just like the percutaneous techniques, a lesion that can potentially cure the symptoms of TN. A downside to SRS is that for a majority of patients it takes months for the treatment to have full effect.^{7,213} About half the patients undergoing SRS are pain free without medication when the treatment takes full effect, with a majority of the rest being able to control the pain with medication.²¹³ While there are different techniques for generating and delivering the radiation, none has so far proved more efficient than the other.²¹³ The main side effect is hypoesthesia, while other side effects and complications are rarely reported, though single cases have raised the suspicion of radiation damage to nearby vascular structures, mainly the superior cerebellar artery.²¹³

Other surgical techniques, some with a long history, such as peripheral alcohol injections and peripheral neurectomy, have been reported to some extent even in modern days, but they are not part of the standard repertoire at most neurosurgical centers.^{6,87,91,161,174} The current literature on these techniques does not seem to be strong enough to either discard them or to motivate a more widespread use of them. Deep brain stimulation of the posterior hypothalamus for the treatment of MS-TN has also been reported, but should be considered experimental.⁸⁰

High-quality studies comparing various surgical modalities for TN are lacking in the literature. For single center studies, patient selections for various modalities are almost always different or not reported, making accurate comparisons difficult. In addition to that, for pooled analyses, the inconsistency in reporting results poses a challenge. A first comprehensive comparison of ablative techniques i.e., excluding MVD, was published in 2004, but the efficacy analysis excluded PBC because of lack of studies meeting the inclusion criteria.¹⁴⁹ Although this study concludes that RFT seems to provide the longest pain relief and that SRS has the fewest complications, it fails to provide statistics supporting those conclusions. The first attempt at comparing all major surgical

modalities was published in 2008.²⁰⁶ In that study, no meta-analysis is performed due to the lacking quality of the data. The result is likely also skewed by the choice to only include studies with a more than 5-year follow-up time, a time span exceeding the median time to recurrence in many published series on all techniques but MVD. In a Cochrane review from 2011, available data was similarly found to be of insufficient coherence for a meta-analysis.²²⁷ Strikingly, no study on MVD met the inclusion criteria and little evidence was found to support one technique over another. A review from 2013 compares various surgical modalities in MS-TN, but the outcome measures of efficacy are not adequately reflecting the sequential accumulation of recurrences seen after PBC.¹⁶⁴

Specific Background to the Present Study

Percutaneous Balloon Compression

The Surgical Technique

PBC is performed under general anesthesia. The patient is placed in a supine position with an extended neck. Using intermittent fluoroscopy and the landmarks of the Härtel trajectory, a cannula (most often 14 gauge) is introduced into the foramen ovale. A 4 Fr embolectomy catheter is introduced through the cannula and beyond its tip, into Meckel's cave. Using an iodine contrast medium, the balloon is inflated until it deforms into a pear shape (as seen on lateral fluoroscopy), usually with about 0.7 ml and rarely more than 1 ml. The balloon is kept inflated for at least 1 minute, and then deflated and withdrawn together with the cannula. The patient is then taken out of general anesthesia.

This framework for how PBCs are currently performed has undergone only minor changes since the original description by Mullan and Lichtor in 1983.¹⁶⁷ The most important change relates to compression time. Originally, compression times usually between 5 to 7 minutes, and sometimes longer, were used, but these were soon shortened to avoid hypoesthesia and dysesthesia.¹⁴⁴ In the current literature, compression times outside of the 1-3 minute range are rare.

There are also other variations in how the procedure is performed at different centers and by different surgeons, often with little to no evidence in favor of either proposed strategy. The trigeminal depressor response (see below) and the risk of transient cardiac arrest that comes with it, has led some to advocate the use of atropine, while others regard the cardiovascular response to trigeminal compression a valuable indication of an adequately performed balloon placement and inflation, and instead keep atropine at hand in the operating room and use an external pacemaker if necessary.^{18,42,173} The use of biplanar fluoroscopy in an angiography suite has been described, but monoplanar fluoroscopy in a regular operating room seems to be the more common practice.^{24,43} Recordings of balloon pressure has been used by some, but producing little evidence to motivate its continued use.^{41,139,140,148} A guiding stylet to direct the balloon catheter inside the Meckel's cave, to thereby achieve some level of anatomical selectivity, has been described.^{35,122} A set inflation volume has been described, but is not common practice.¹⁹⁵ Local anesthetics are rarely discussed in relation to PBC, but a deep infiltration of local anesthetics has been promoted, and an intraganglionic injection of lidocaine has been

proven effective to stabilize cardiovascular parameters during the procedure.^{173,209} Twenty-first century advances include tomographic fluoroscopy, neuronavigation, multiple balloons and traction, but all of these techniques have yet to gain more widespread recognition.^{83,86,180,207,217,222}

Cause of Effect

Most studies of the effect of compression on, or crushing of, nerves do not concern the trigeminal system specifically. It is further difficult to assess from the studies that target the trigeminal system specifically, to what extent these findings are transferable to the specific conditions of PBC, regarding for example pressure, location and duration.¹⁶ An animal model using New Zealand White rabbits have therefore been developed to study the physiological and histological effects of PBC.^{98,184} Despite this surgical technique sometimes being referred to as balloon compression of the trigeminal ganglion, the ganglion cell bodies are mainly unaffected by the compression.³⁹ Instead, the compression leads to axonal injury with Wallerian and retrograde degeneration, followed by degeneration of myelin.¹⁸⁴ This result is typically seen also in compression injury of peripheral nerves.¹⁷⁹ Also typical for those injuries, as well as for the injury on the trigeminal root after PBC, is that large-diameter fibers are more susceptible to injury than small-diameter ones.^{39,179} This separates PBC from the other percutaneous techniques, which are more unselectively ablative. Unmyelinated fibers are spared from injury.³⁹ The compression is most destructive adjacent to the balloon, and in the rabbit model, this corresponds to the mandibular nerve.³⁹ In the months following PBC in rabbits, there is evidence of axonal remyelination and or collateral sprouting from surviving axons, but also for permanent loss of the destructed large myelinated axons.³⁹ It has been suggested that the pain-relieving effect of PBC is due to the reduction of the triggering sensory signal conducted through A β fibers.³⁹ According to the ignition hypothesis described above, the decreased number of A β fibers also reduces the recruitment of ectopic neuronal activity in the trigeminal root, and is therefore more effective than strictly trigger-reducing peripheral neurectomies.⁶⁹

PBC may also have additional effects beside the nerve compression. An anatomical study has demonstrated PBC to stretch the dura mater, and therefore potentially relieve any chronic dural compression on the nerve root.²¹⁶ A stretching of the nerve rootlets and root extending into the brainstem is also described.²¹⁶ To what extent the latter really contributes to the ablative effect remains to be demonstrated, but when considering the effectiveness of 19th century nerve avulsion (described above), that also caused stretching of the trigeminal root fibers, some contributing effect certainly seems possible.

Expected Results

One rationale behind this thesis is the wildly varying results from PBC in the literature. Since the introduction of survival analysis in reporting on PBC in the 1990s, reports of median time to recurrence of pain in patient populations including both TN-1 and MS-TN have ranged from just over a year to well over 15 years.^{1,37,40,41,46,51,124,125,163,172,181,198,199,225} Variations in reporting can account for at least some of these differences. After recurrence of pain PBC can be repeated, and the expected result is not significantly different after repeated procedures compared to after first procedures.⁵² The time to recurrence after PBC for MS-TN is generally shorter than for TN in general, with median pain free times after surgery ranging from a few months to a couple of years.^{154,161,162}

Side Effects and Complications

Apart from the challenge of safely inducing and maintaining general anesthesia in the elderly, a subject beyond the scope of this thesis, the first part of the surgical procedure is the cannulation along the Härtel trajectory. This trajectory includes, or is in close proximity to, several important anatomical structures of the face, including the parotid duct, the buccal nerve, the maxillary artery and the middle meningeal artery.⁸ Though these structures can theoretically be damaged, the practice of bluntly penetrating the trajectory, combined with various degrees of relatively freely movable structures, means they are unlikely to sustain clinically relevant injuries. Cheek hematomas are reported, but generally not serious.^{1,155,199} The pterygoid venous plexus is possibly frequently penetrated, seemingly without complication in most cases, but the formation of extracranial arteriovenous fistulas have been reported.⁸⁴ The mandibular nerve is part of the trajectory itself. Non-lasting injury to the mandibular nerve is possible (or even expected), but it may be difficult to separate from the ablative effect of the subsequent compression of the rootlets and root. Deviation from the intended trajectory may have more serious consequences. Accidentally puncturing the buccal mucosa contaminates the cannula with oral bacteria before advancing it into the foramen ovale, risking bacterial meningitis or even abscess formation.^{1,67,148} Directing the cannula too anteriorly carries the risk of injuring the optic nerve.^{4,8} Although sudden blindness have been reported as a very rare complication, no report mentions this being the result of a faulty trajectory.^{1,4} A posterior trajectory may lacerate the carotid artery, although an extracranial injury to the carotid artery seems yet to be reported. In PBC, as opposed to other percutaneous techniques, the cannula should never be advanced beyond the foramen ovale to avoid ending up outside of Meckel's cave. In one reported fatal case, the needle was introduced too deep, which resulted in a brainstem injury.²

Once at the level of the foramen ovale, a balloon catheter is introduced, by some surgeons preceded by a stylet, before the balloon is inflated.³⁷ The inflation of the balloon applies an ablative compression to the retroganglionic rootlets and root, affecting mainly large myelinated fibers.³⁹ This in turn generates in many patients, apart from the desired pain relief, predictable and often transient sensory and masticatory deficits.^{1,7,41,46,51,53,105,170,181,195} In peripheral nerves, there is evidence of remyelination in the months following compression.¹⁷⁹ This, together with collateral sprouting from surviving axons, may be the reason for the often described transient nature of neurological deficit e.g., sensory loss, after PBC.³⁹ In addition, a small number of patients develop trigeminal dysesthesia, presumably from the compression. The reported incidence of severe dysesthesia ranges from 0.7 % to 4 % in larger series.^{1,34,50,148,205} The compression also elicits the trigeminal depressor response, an autonomous cardiovascular depression that by many surgeons is used to verify a correct balloon position.^{42,128} In a small number of patients though, this response has been the cause of a transient cardiac arrest, and one case of intraoperative myocardial infarction has been reported.^{18,144,170,195,225} The management of the trigeminal depressor response in PBC has not been studied. One suggested strategy is to avoid premedication with atropine and to use an external pacemaker that triggers if the heart rate falls below 45 beats/minute.⁴¹ This allows for the reflex to be monitored but avoids an unnecessary relaxation of the cardiovascular system and the risk of transient general hypoperfusion. Reactivation of herpes simplex is also associated with the procedure, possibly from the compression, but is likely underreported in the literature due to usually mild and short-lasting symptoms presenting after discharge from the neurosurgical ward. Many authors report that approximately 1 in 10 is affected, but reports from those who have followed their patients closely for more than one day postoperatively indicate that as many as 1 in 3 or more may be affected.^{1,51,67,148,170,172,183} Compared to the other percutaneous techniques, corneal anesthesia is not often reported after PBC, and this has been suggested to be attributable to the relative sparing of the thin Aδ fibers and unmyelinated C fibers mediating corneal sensibility.^{39,59} There has however been one report of a postoperative corneal ulcer following PBC.¹⁴⁷

An unsatisfactory placement of the balloon catheter can cause further side effects and complications. The meningeal dura mater extends into the foramen ovale.¹⁰⁷ The balloon catheter can end up outside of the intended position in Meckel's cave if the meningeal dura is perforated by the cannula (or less likely the stylet or balloon catheter) at the level of, or beyond, the foramen ovale. Anatomical variants, such as a primitive foramen lacerum medius, may also theoretically complicate the balloon placement.^{13,85} Several sensitive structures are located medially to the Meckel's cave. Of the neural structures, the most proximate to the Meckel's cave, and that which is most frequently reported to be

affected, is the abducens nerve. Abducens nerve palsy, when it is reported, usually affects roughly 1-2.5 % in most large series, and it usually has a good regression within a few weeks or months.^{2,24,117,147,155,172,198} Rare instances of trochlear and oculomotor palsy have also been described.^{24,215} Abducens nerve palsy after compression with a seemingly correct balloon placement have been reported, indicating that the sheer proximity of structures to the inflated balloon may be the cause of side-effects on neural structures other than the fifth cranial nerve.²⁴

Intracranial vascular injuries have also been described. The formation of arteriovenous fistulas, including carotid cavernous ones, have occurred and in a few cases required endovascular treatment.^{82,127,134,171} Although extremely rare, intracranial bleedings are the only reported direct or indirect causes of death complicating PBC.^{1,13,197}

Percutaneous Treatments in Umeå

The Study Period 1986-2015

MVD for TN has been performed in Umeå since the 1980s, and is still the method of choice for the relatively young and healthy patients with TN-1 and a demonstrated neurovascular conflict.⁶¹ Before the 1980s, there was however no routine procedure in Umeå for the majority of patients who needed surgery, those with a medically refractory TN who were elderly and/or with significant comorbidity.

In the early 1980s, a stereotactic variant of RFT was introduced at the Umeå University Hospital, and with that, a modern minimally invasive technique for treating TN became available.^{92,131} This technique was however soon replaced, when in 1986, PRGR was introduced. This was in turn preceded by the development of a portable device for transcutaneous electrical stimulation, the ISSAL T-TNS 60 electrical stimulator and its successor the ISSAL 1412.^{23,92,133} Together with the stimulator, a protocol was developed for quantitative assessment of cutaneous sensibility, called sensimetry, but hereafter referred to as sensimetric testing.

The introduction of both these techniques led to the initiation of a database, with the rather successful ambition to, as a clinical routine, include every surgical procedure for trigeminal neuralgia performed in Umeå, including associated sensimetric testing and results from highly standardized clinical tests of sensibility to light touch and pinprick, and of corneal sensibility. The aim was to continuously assess the quality of the procedure and to allow improvement of the technique. The testing parameters included in this thesis are further

explained in the Clinical material and methods section. After 1997, a thorough examination of the available systems was performed to ensure that the database for PRGR included a truly consecutive series over the years 1986-1997.²⁸

In 1999 and 2000, PRGR was abandoned in Umeå in favor of PBC, in part due to the perceived advantage of being able to perform the latter under general anesthesia. For paper IV in this thesis, a new systemic revision was performed to ensure that the PBCs for MS-TN considered for inclusion were consecutive up until 2015.

Indication for Percutaneous Surgery

The indications for percutaneous surgery have remained virtually unchanged in Umeå since 1986, and are in line with international practice.^{9,31,33,41,50,102,122,172,173,188} All patients suffered from TN, and although they were not specifically diagnosed according to the Burchiel classification, percutaneous surgery was only considered for patients with primarily paroxysmal pain i.e., TN-1 or MS-TN. For all patients, the first line of treatment was medical, most often carbamazepine, sometimes with the addition of a second drug e.g., gabapentin or lamotrigine, and this was most often initiated by a neurologist, an internist or a general practitioner. In those patients where the pain was not controlled by drugs, or the drugs had intolerable side effects, surgery was considered through a referral to the neurosurgical clinic. It is beyond the scope of this thesis to examine whether all patients who should have been considered for surgery were referred for neurosurgical evaluation. The neurosurgical work-up included radiology, initially only a CT in patients eligible for MVD but in later years an MRI for all patients, to exclude underlying disease and to demonstrate any possible neurovascular conflict. Younger and healthier patients without MS and with a demonstrable neurovascular conflict if an MRI was performed, were offered an MVD. All other patients, as well as those who preferred a minimally invasive procedure, were offered percutaneous surgery. Considering that most patients with TN were elderly and often had comorbidity, or were MS patients, this resulted in a large majority of referred patients undergoing percutaneous surgery in Umeå.

Aims

- To evaluate the efficacy of PBC, both overall and in MS-TN patients specifically.
- To identify and evaluate pre- and intraoperative parameters associated with the efficacy of PBC.
- To investigate changes in sensory function after PBC.
- To identify side effects and complications associated with PBC.
- To evaluate how efficacy, side effects and complications differ between PBC and PRGR.

Clinical Materials and Methods

A summary, and in part an extended description, of the materials and methods used in this thesis is presented below. The papers in which these are used are referred to by their roman numerals.

Study design

The overall study design was a retrospective cohort study. For paper III, a comparison of two consecutive cohorts was performed. Inclusion in the cohorts was continuous as patients underwent surgery.

Patient Population

The PBC Database (I, II, III, IV)

All papers were wholly or partly based on the PBC database described above. In the database, each case represents a surgical procedure rather than a patient, and this is also reflected in the analyses. For all analyses, only actually executed surgical procedures were included, while excluding any of the few attempted procedures that for various reasons had to be aborted (with the exception of paper III, where only PRGRs were aborted). This approach ensures that the results represent the efficacy of the treatment, and that the side effects and complication rates from the treatment are not artificially lowered. For paper I, to evaluate the effect and side effects of PBC, the first 100 procedures of the PBC database, performed between October 1999 and April 2007 in 76 patients, were included, and none were excluded. For paper II, to evaluate the outcome and side effects of PBC in relation to intraoperative parameters, the evaluation required digitally stored radiographs, which was introduced in Umeå in 2002. Therefore, every procedure in the PBC database between January 2002 and May 2008 were eligible for inclusion, but 5 procedures from 2002 were excluded due to lack of stored radiographs, and the final analysis included 87 procedures in 69 patients. For paper III, comparing effects and side effects of PBC and PRGR, respectively, in patients who had no previous history of surgery for TN on the ipsilateral side, all such PBCs up until November 2013 were included from the database, except one that was excluded due to lack of informed consent, for a total of 82 procedures in as many patients. For paper IV, evaluating the results of PBC in MS-TN patients, every patient from the PBC database who was also diagnosed with MS and operated on no later than December 2015 was included, except one which was excluded due to lack of informed consent, resulting in 79 procedures in 34 patients.

Some PBCs performed in Umeå were included in more than one paper in this thesis. Of the 100 PBCs in paper I, 62 were also included in paper II, 44 in paper III and 21 in paper IV. Of the 87 PBCs included in paper II, 44 were also included in paper III and 18 in paper IV. Of the 82 PBCs included in paper III, 15 were also included in paper IV. The PBC database has also been used for one previously published study.²⁴

Additional Patients (III, IV)

For paper III, the PBCs were compared to every primary procedure in the PRGR database, except five that were excluded due to lack of informed consent. The recruitment therefore included 124 PRGRs, performed from October 1986 to March 2000. The PRGR database is, in this thesis, used for solely for paper III, but many of the 124 included PRGRs were also included in varying degrees in several previous publications.^{20-23,28,132} Finally the patient material for paper IV included, in addition to the PBCs from Umeå, 32 PBCs from Karolinska University Hospital, Stockholm, Sweden; a consecutive series of PBCs for MS-TN performed between October 2004 and December 2015. Some of these procedures were included in at least two previously published studies.^{124,125}

In total, 353 procedures performed in 280 patients were analyzed for this thesis.

Evaluation

There were three types of sources for data. Firstly, there were the PBC and PRGR databases. Secondly, there were patient records and radiographs, which were reviewed for additional information, information that in turn were used to expand the databases. Finally, telephone interviews conducted by a research nurse, were performed for follow-up data that could only be collected over time. The data from the latter two sources were more specifically a part of the research behind this thesis, but it continuously contributed to maintaining the databases.

The Standardized Clinical and Sensimetric Tests

The PBC and PRGR databases includes abundant data from tests performed on most patients one day before surgery and one day (or rarely up to three days) after surgery, and in many cases also at an outpatient follow up. The goal was to have this follow-up at three months postoperatively, but for some patients and for practical reasons, this was extended up to 6 months postoperatively (or rarely even longer). The purpose of these tests was to evaluate the clinical result of the treatment and possible sensory disturbances or other side effects to surgery for TN. The protocol for these tests has remained unchanged since 1986.

The tests were conducted with the patient sitting upright, in a calm environment and with only the examiner and the patient present. First, and for the preoperative examination only, the patient was asked to specify the maximum pain site (that information was later used also for the postoperative and late postoperative examinations). For some patients, this was initially difficult, but it could always be done with a little bit of patience and persistence from the examiner. Thereafter, the clinical sensory tests were conducted, and the results from these tests were recorded according to a scale with four steps: normal, slightly decreased, decreased and totally impaired sensibility. The first clinical test concerned sensibility to touch, and was performed by the examiner gently stroking his/her index fingertips bilaterally from top to bottom of first the patient's sides of the face, and then of the front of the face. The second clinical test concerned sensibility to pinprick. A metal or sharp wooden pin (standard instruments for neurological examinations) was used to prick test at six specific sites on each side of the face. The last clinical test was performed with a cotton swab to test for corneal sensibility. The test was performed bilaterally.

Thereafter, the sensimetric testing was conducted. The theory and technology behind this method has previously been described in detail.^{92,130,133} In short, a handheld adjustable constant current stimulator, the ISSAL T-TNS 60 or ISSAL 1412, delivered a unipolar alternating current of rectangular 0.2 ms pulses with a frequency of 100 Hz through a pair of electrodes conducting through saline soaked felt swabs 1 cm apart, held against the skin in the area of interest. These areas of interest were 6 symmetrical sites on each side of the face, two in the distribution area of V₁, three in the distribution area of V₂ and one in the distribution area of V₃. Before the test, the site best corresponding to the site of maximum pain during attacks of TN was identified. The test began with one trial round. The patient was informed to let the examiner know as soon as the first tingling sensation was felt, and then as soon as the sensation turned into a pinching feeling. Beginning on the side contralateral to the TN and on the top of the forehead (site 1), the electrodes were held to the skin and the current control was successively turned up, through the point of first sensation and up to the point of pain, without moving the electrodes. The trial round was continued sequentially with the same test on sites 2-6 and thereafter on sites 1-6 on the side ipsilateral to the TN. Thereafter, the actual test was conducted in exactly the same manner, except the examiner noted the value for current (mA) displayed at the moments of first sensation and first pain. Lastly, on the maximum pain site, turning up the current to the maximal endurable pain concluded the test, and that current was added to the record.

Main Outcome

*Anything other than complete relief is, in principle, a failure to achieve the initial goal of treatment.*²²⁹

This statement by Zakrzewska and Lopez in 2003, from a proposal for future research on evaluation of surgical treatment for TN, is in line with the choice of main outcome measure for this thesis. The main outcome was defined as the duration of complete relief from TN pain, without medication for TN, measured in months after surgery (allowing for a normal short postoperative period of tapering off any drugs for TN). Compared to other measures used in the literature, maintenance of pain relief without medication is: 1) in line with the goal of the treatment, 2) highly objective and easy to measure, and 3) a proposed standard making comparisons and pooled studies possible. The drawback is that this measure obscures an important aspect of the treatment effect. It is the experience at the neurosurgical departments in both Umeå and Stockholm that many patients with a recurrence of pain after PBC, can be managed with a small and completely tolerable dose of medication, thus enabling the report of “a satisfactory outcome” to reach a higher figure.

For all cases, patient records were reviewed to either verify the data in the database, or to obtain data. In many cases, the data was still incomplete, or, in case of no recurrence, could be improved. In these cases, and for patients who were still alive, the data was finally completed by telephone interviews. These interviews were performed in relation to each paper, to assess if the patient had a recurrence, and, if so, when, if the patients were free from medication for TN and to give the patients a chance to report on side effects and complications not previously reported.

All times on duration of pain relief were rounded off to whole months. In some instances, the statements on time were vague. Any values stated to be an approximate, was recorded as exactly that time e.g., about three years ago was recorded as 36 months before the date of the statement. If there was no way to pinpoint the timeframe to within a month, the middle of a longer stated timeframe was used e.g., 2008 was recorded as 1st of July 2008.

Additional Parameters

Patient characteristics were evaluated using the following parameters: age, sex, previous surgery (including data on different techniques), duration of TN, MS, duration of MS, TN side and main pain branch.

Data from sensimetric testing included preoperative, postoperative and late postoperative threshold values from six ipsilateral facial measurement sites (including the maximum pain site) and the site contralateral to the maximum pain site. Data from the clinical testing included ratings for sensibility to touch and pinprick at the maximum pain site, plus corneal sensibility from the same time points. Patient records were also actively scanned for all possible intra- and postoperative side effects and complications other than sensory deficits.

Intraoperative parameters included compression time, balloon inflation volume, balloon position in relation to sella turcica, and balloon shape. The latter two were derived from readings of digitally stored intraoperative lateral radiographs. The readings were performed according to a system, described in paper II, that was easy enough to not require radiological expertise, and they could be expected to be performed intraoperatively by any surgeon performing PBCs.

Statistical Analysis

As the previously proposed, and now emerging, standard for reporting outcome after surgery for TN, maintenance of pain relief was primarily analyzed using Kaplan-Meier analyses, many which compared levels of the factor using log rank tests i.e., univariate analyses.²²⁹ The number of censored cases was presented, and in paper IV also persons at risk at different time points. Multivariate analyses with maintenance of pain relief as outcome were performed using Cox regression. A graphical method for assessing violations to the assumption of proportional hazards was used.

Sensimetric data was tested for normal distribution. This data was then compared at different time points relative to surgery, mainly using paired samples t-tests. In instances with small subgroups, Wilcoxon signed ranks test was used. When analyzing thresholds on the side ipsilateral to surgery relative to the contralateral side, the data was not normal distributed, and Wilcoxon signed ranks test was used for differences over time, while Mann-Whitney U test was used for comparing groups.

Data from clinical tests of sensory disturbances were analyzed as the proportional distribution at different time points relative to surgery. Initially, for papers I and II, this was performed using the Chi² test. However, for papers III and IV, the Wilcoxon signed ranks test was adopted for the same purpose, to better account for the longitudinal aspect of the data and the fact that some cells in the distribution matrix contained only a very small number of cases.

The distribution of other side effects and complications between groups were analyzed using the Fisher exact test. Missing data was handled using available case analysis, except for the paired samples t-test, where pairwise deletion was used. For all tests, $p < 0.05$ was considered statistically significant. Analyses were performed using SPSS v.17 – v.23 (SPSS Inc., Chicago, IL, USA, and IBM Corp., Armonk, NY, USA).

Ethics

The content of this thesis was approved by the Regional Ethical Review Board, Umeå (2013/76-31).

Results and Discussion

The Efficacy of BPC

The Efficacy of BPC Overall (I, II, III)

In a non-selective series of PBCs, the initial success rate was 90 %. The median time of postoperative pain relief without medication was 28 months. In patients without previous surgeries on the treated side, the median time of postoperative pain relief was 20 months.

Many authors report results after PBC, but few report survival analyses on unselected patients pain free without medication after all included procedures and without retreatment. Kouzounias et al. report an initial success rate of 85 % and a median time of pain relief of 17 months, but they use PBC mainly on patients who demonstrated recurrent pain after previous surgeries.¹²⁴ A few reports have less clear descriptions of their respective outcome measures, but it is possible that it corresponds to pain-free without medication. A median time of >28 months of a somewhat unclear efficacy measure, can be derived from a report by Brown and Pilitsis, who report an initial success rate of 92 %.⁴¹ Omeis et al. report an initial success rate of 83 % and a median time to recurrence of 16 months.¹⁸¹ As a contrast, Abdennebi and Guenane report an initial success rate of 91 % and a median time of maintenance of pain relief without medication of around 16 years.¹

This highlights two important issues: 1) a clear statement of the outcome measure is vital for comparison and compiling of studies, and 2) there is a need for conformed reporting on the efficacy of PBC. This thesis can at least contribute to the first of these two. Until we have a more conformed reporting on PBC, it is not possible to know how much, if any, of the differences in reported outcome that can be attributed to variations in surgical skill, surgical technique or patient selection. The seemingly very varying median times to recurrence can probably in part be attributed to a pattern of survival curves after PBC often taking on an approximation of a negative logarithmic shape, with a relatively high rate of recurrence in the first months after surgery, and thereafter an increasingly slower recurrence rate. This makes small variations in initial success rate have a relatively large impact on the median time to recurrence, since a lower success rate will move the whole curve closer to the median, and the 50 % survival will therefore meet a more sharply declining curve close to the time of treatment. This pattern of gradually declining rate of recurrences over time also have another important implication; while possibly not relevant to the majority of treated patients, it seems that at least a minor

portion of patients can have a very long maintenance of pain relief after PBC, as demonstrated by some studies mentioned above.

The Efficacy of PBC in TN-1 (I)

Results after PBCs for TN-1 yielded an initial success rate of 91 % and a median maintenance of pain-relief of 33 months. In patients without previous surgeries on the treated side, the median time of postoperative pain relief was 48 months, but this was not significantly different from the results on previously treated patients.

Reports on TN-1 specifically are rare in the literature. A median time of pain relief of >10 years, can be derived from a report by Chen et al., and their initial success rate is 94 %.⁵¹ A notable difference in their report compared to what can be assumed to be transferable from paper II to paper I, is a higher frequency of pear-shaped balloons and a generally higher balloon inflation volume, presumably representing a more effective compression in a higher percentage of cases (see below). Ying et al. report an initial success rate of 99 % and a median pain free time of >5 years. Others report an initial success rate of 91-92 % but utilize no survival analysis to determine median time of pain relief.^{155,183}

In many reported series, the ratio of MS-TN to TN-1 is so low that it may not have a significant impact on the overall result, as was found in paper II. The discrepancy between the results reported by on one hand Chen et al. and Ying et al., and on the other the ones reported on PBC on a general TN population, are therefore striking, and there are possibly factors other than the surgical technique to consider.

The Efficacy of PBC in MS-TN (I, IV)

The initial success rate after PBC for MS-TN was 67 % and the median time of complete pain relief was 8 months. These numbers were higher in paper I, but as those 23 procedures were a subset of the 111 procedures in paper IV, the data from the latter paper should be considered more solid. No difference in efficacy was found between PBC for TN-1 and MS-TN, respectively, but as that analysis included the subset described above, this lack of difference may be due to a low statistical power.

Many reports on PBC for MS-TN are small and often buried in larger series, but a few larger series concerning MS-TN exclusively have been published. While none of them use pain-free without medication as outcome measure, their results are nevertheless in line with the ones in this study. Mohammad-Mohammadi et al. report an initial success rate of 71-95 % and a median time to recurrence of 8-29 months, while Mallory et al. report an initial success rate of

65 % and a median time to recurrence of 6 months. Taken together, these reports suggest that PBC may be less effective in MS-TN than in TN-1, which can help in managing expectations but offers no other advantage in the individual case.

The Correlation between Efficacy and Other Parameters

The Correlation between Preoperative Parameters and Efficacy (I, III, IV)

In an unselected consecutive series of PBCs, there was a tendency for first treatments to have better efficacy than repeated treatments, and for patients with TN-1 to have better results than patients with MS-TN, but neither of these results were statistically significant. In primary PBCs, sex was not a predictor of outcome. In MS-TN patients without a history of surgical treatments other than PBC, a history of 3-4 previous PBCs was a predictor of a less satisfactory outcome than without a history of previous surgeries. No other patient characteristics were found to influence the efficacy of PBC for MS-TN.

The importance of preoperative parameters lies in patient selection. The varying nature of the results reported in the literature, both within and between series, is unsatisfactory. It is therefore desirable to be able to better predict which patients will benefit most from the procedure. A slight tendency towards better results for previously untreated patients have been reported, but without statistical significance in the individual series, except for one.^{46,51,162,198} The prognostic importance of MS and duration of disease have been varying.^{125,163,198,214} Age and sex have been analyzed without finding a correlation to efficacy.^{125,162,198,214} A study on the correlation between various parameters deductible from preoperative MRI, found a high difference in diffusion directionality (fractional anisotropy) between the affected and the contralateral nerve root to be a predictor for recurrence after PBC, but these results need to be verified in further studies with actuarial analysis of efficacy.²¹⁴

The Correlation between Intraoperative Parameters and Efficacy (II, IV)

As postulated in the first description of PBC, the deformation of the balloon into a pear shape as seen on lateral intraoperative fluoroscopy, was associated with better efficacy than other balloon shapes. Craniocaudal balloon position, balloon inflation volume or compression time were not significantly correlated to efficacy. In MS-TN specifically, there was a tendency for pear-shaped balloons to be associated with higher efficacy than other balloon shapes, but the difference was not statistically significant.

Small variations in technique reflected in intraoperative parameters are reported within and between series, but the rationale behind these less frequently so. The possible correlations between these parameters and results after PBC are therefore important to study, to help surgeons refine their technique. Pear- and dumbbell-shaped balloons (the latter rather rare) are repeatedly reported to be associated with a better efficacy than other balloon shapes.^{125,162,183} This is to be expected, as these shapes indicate that the balloon is partly positioned within the porus trigeminus, where it can effectively compress the trigeminal root. No correlation between balloon inflation volume and efficacy has been found in the literature, and it is reasonable to think that as long as a pear-shaped balloon is achieved, the inflation volume should be adequate.¹²⁵ Within the compression time span normally used today of 1-3 minutes, different compression times have not been associated with efficacy, but compression times longer than 5 minutes are reported to be less effective.^{125,162} Intraoperative pressure recordings have yet to generate results that can be significantly correlated to efficacy.⁴¹

The Correlation between Postoperative Parameters and Efficacy (II)

No attempt was made to directly link postoperative parameters to efficacy. However, as stated above, pear-shaped balloons were strongly correlated to higher efficacy, and can therefore be considered an indirect intraoperative measurement of treatment efficacy. One day after surgery, a significant proportion of patients had decreased sensibility to touch and pinprick after compression with pear-shaped balloons, but not after compression with other balloon shapes. Likewise, the sensimetric thresholds for perception and pain were significantly raised only after compression with pear-shaped balloons on the first postoperative day. At follow-up, all these sensory deficits were partly or fully normalized. Interestingly, and likely correlated to the selective destruction of thick myelinated fibers associated with this technique, there were no significant postoperative changes of corneal sensibility, irrespective of balloon shape.

The importance of postoperative parameters e.g., as in this case side effects, lies in the possibility for the surgeons and patients to be satisfied rather than alarmed if these effects are noted. The literature is limited with the regards to evidence on this aspect, but there is some data indicating that postoperative hypoesthesia may be associated with better efficacy.⁴⁶

Side Effects and Complications

Postoperative Changes of Sensory Function (I, II, III, IV)

On a group level, the sensibility to touch was decreased directly after surgery, both in TN-1 and MS-TN patients. Sub-group analyses according to the shape of the balloon during compression revealed that this only held true if the patient was treated with a pear-shaped balloon. At a later follow-up, often performed after 3-6 months, the initially decreased sensibility to touch was normalized, except in a sub-group analysis of patients treated with pear-shaped balloons where it was only partially normalized. The sensibility to pinprick was similarly generally decreased directly after surgery, except in the groups that contained only MS-TN patients and patients treated with non-pear-shaped balloons respectively. At the later follow-up, there was a trend towards normalization also of sensibility to pinprick in TN-1 patients and in patients treated with pear-shaped balloons, but not as convincing as for touch. Corneal sensibility was not significantly affected on a group level, even though there were a very small number of patients with transiently decreased sensibility.

The trends for changes of perception to touch and pinprick was, on a group level, virtually mirrored by the average results from the sensimetric testing. The day after surgery, thresholds for perception and pain were significantly raised, and after 3-6 months they were partly or fully normalized. The postoperatively raised thresholds were particularly high for pain in the area of V2, and in the area directly inferior to the eye, they also remained high after 3-6 months.

Considering that PBC is an ablative technique targeting the trigeminal nerve, ipsilateral hypoesthesia is to be expected, and highlighting this can be important to manage the expectations of surgeons and patients. Indeed, immediate postoperative hypoesthesia is often reported in the range of 80-90 %, ^{1,7,41,46,170,172,195,214} The vast majority of cases are reported to be mild, with cases of severe hypoesthesia being rare. ^{40,51,167,172} Compared to the earliest accounts of PBC, with compression times ranging up to 15 minutes, modern day compression times are usually shorter, typically 1-3 minutes. Compression times were reduced to lower the frequency of, among other things, severe hypoesthesia, but convincing data supporting this strategy has yet to be reported. ^{41,144,161} New or accentuated hypoesthesia after PBC for MS-TN is reported in 29-54 % of cases. ^{154,161} At follow-up of varying lengths, the frequency of persisting hypoesthesia is generally much lower than directly after surgery, in line with the results of this thesis, but reported with a very wide range of 5-72 %, ^{7,41,51,144,170,181,195,205} This dynamic of a transient hypoesthesia that partly or fully resolves faster than the recurrence of pain is generally acknowledged but previously not analyzed statistically. There are also published data that could

possibly support postoperative hypoesthesia being correlated to a successful pain relief, but not accompanied with the statistical analysis to support conclusions.²²⁵ The tendency for PBC to spare A δ -fibers means that this technique is relatively spared from side effects in terms of corneal hypoesthesia.³⁹ This is supported by neurophysiological assessment having shown no significant difference in latency or amplitude of the corneal reflex between the operated and the contralateral side at a mean of 3 months after PBC.⁵⁹

Other Side Effects and Complications (III, IV)

Apart from hypoesthesia, a small number of other side effects and complications were reported. Among the intraoperative complications, the most severe were arguably two cases of transient cardiac arrest during PBCs performed in Stockholm, where atropine was not routinely used preoperative to block the trigeminal depressor response. Other intraoperative side effects included four cheek hematomas, two buccal perforations and one balloon rupture. Postoperative side effects and complications were slightly more common. One patient developed streptococcal meningitis secondary to a buccal perforation, leading to cognitive and balance impairment on follow-up. Dysesthesia, usually mild, developed in 3-4 % of the cases. One case of severe dysesthesia developed after a severe case of postoperative herpetic eruption. Herpetic eruptions were noted in 4-6 % of the cases. Transient diplopia developed in 2 % of the cases. Other minor and rare postoperative side effects included transient masseter dysfunction and muffled hearing. No fatal complications occurred.

Side effects and complications are important to consider in relation to any surgical procedure, not only to manage expectations, but also to value benefit versus potential cost (both financially and in suffering) of the procedure. Also, side effects such as sensory changes have important clinical implications. In the case of recurrent pain, persisting hypoesthesia may leave the surgeon reluctant, from clinical experience, to perform additional percutaneous procedures due to the potential risk of dysesthesia. The low frequency of each complication requires large or pooled studies to get representative numbers. The complications (other than hypoesthesia) from three published series of at least 400 procedures are presented in Table 1.

TABLE 1: Complication rates in three PBC series

	Abdennebi & Guenane ¹	Skirving & Dan ¹⁹⁵	Yadav et al. ^{*224}
Procedures (n)	901	496	400
Masticatory weakness (%)	10.8	3.4	11.0
Dys-/paresthesia (%)	2.9	3.8	6.3
Diplopia (%)	1.2	1.6	5.0
Cheek hematoma (%)	2.9	1.0	-
Corneal hypo-/anesthesia (%)	0.9	-	2.8
Otalgia/hypoacusis (%)	10.2	-	-
Temporomandibular joint pain (%)	2.2	-	-
Rhinorrhea (%)	0.3	-	-
Unilateral blindness (%)	0.2	-	-
Death (%)	0.1	-	-

*Only report common complications

There are discrepancies between series in the reported rate of some side effects and complications. Several factors may possibly explain these discrepancies e.g., the experience and technique of the surgeon, the routine for postoperative evaluation and the threshold for reporting complications.

PBC versus PRGR

The Efficacy of PBC and PRGR (III)

In patients without a previous history of ipsilateral surgery for TN, there was no statistically significant difference in efficacy between PBC and PRGR. The initial success rate was 82 % for PBC and 85 % for PRGR. The median time to recurrence was 20 months for PBC and 21 months for PRGR. For both techniques, the median time to recurrence was shorter for men than for women in these series, but the differences were not significant.

PBC and PRGR have since the early 1980s been potential treatment options for the same patient category i.e., patients with a medically refractory TN unsuitable for major intracranial surgery. Despite this fact, the literature has previously been devoid of good comparisons between these techniques on equal terms on a general TN population, except for one study.¹⁷² That study indicates PBC having a better efficacy than PRGR. All the other literature is severely limited by procedure selection criteria being unreported or different for the two techniques, or by shortcomings in statistics or design.^{79,124,154,161,206} Taken

together, there is not yet indisputable support for choosing one technique over the other based on efficacy.

Side Effects and Complications of PBC and PRGR (III)

A small minority of patients (12-24 %) had decreased sensibility to touch and pinprick before surgery with either PBC or PRGR. One to 3 days postoperatively, a majority of patients (52-66 %) had decreased sensibility, a significant change in all four categories. After 3 to 6 months, generally the frequency of normal sensibility was partially normalized. This improvement over time was significant for all categories except for pinprick after PRGR, and after PBC the distribution of sensory disturbances was no longer significantly different compared to the preoperative distribution. After PRGR though, the frequency of patients with sensory deficits (57-58 %) was still significantly higher than before surgery. PRGR also led to a decreased corneal sensibility in a significant number of patients, with an increase from 3 to 32 %, and this was virtually unchanged after 3 to 6 months. PBC had no significant impact on corneal sensibility. Sensimetric testing of thresholds for perception and pain after PBC and PRGR respectively, generated average results in line with the clinical tests of touch and pinprick i.e., significantly raised thresholds directly after surgery and partially normalized thresholds at follow-up.

Concerning side effects and complications other than sensory deficit, one result stood out; dysesthesia (often mild) was significantly more common after PRGR (23 %) than after PBC (4 %). No other side effect was significantly different between the two techniques, but we know that some less common side effects are intrinsically associated with each respective technique e.g., 2 % diplopia after PBC and 4 % chemical meningitis after PRGR.

As there was no discernable difference in efficacy between PBC and PRGR, the difference in side effects profiles becomes all the more important for surgeons and patients to decide between the two techniques. The higher rates of decreased corneal sensibility and of dysesthesia after PRGR speak clearly in favor of PBC in this material. The previously published literature is more conflicted with regards to complication rates for the two techniques.^{79,124,149,154,161,206} The current series were however comparable, both in composition and in indication for surgery, something that, as stated above, is often unclear or lacking in the literature.

Limitations

This thesis is not without its limitations. Firstly, a limitation that it shares with all other literature evaluating results after surgery for TN, is based on an unpredictable feature of the course of the disease. It is well known that the disease is often cyclic in nature, with pain free remissions lasting weeks, months and sometimes years.^{49,72} How these natural pain free intervals interact with the attempted measurement of the efficacy of the surgery remains to be studied, but it is likely that some of the long term maintenance of pain relief after surgery that we observe is due to the natural course of the disease. The initial success rate should however not be affected by this limitation, as all patients in this thesis were operated on while they had an existing pain problem, making the immediate effect of surgery possible to evaluate.

Secondly, the procedures analyzed in this thesis have been performed over approximately three decades, and two potential sources of bias in patient selection over that time can be identified. The increased availability of MRI may possibly have selected a few more cases for percutaneous treatment in later years, from patients otherwise suitable for MVD but where no neurovascular conflict was found at the MRI, and this should then have changed gradually over time. Further, PRGR is performed as awake surgery, while PBC is performed under general anesthesia, potentially preventing uncooperative patients from undergoing PRGR, and patients in very poor general condition from undergoing PBC. To which extent, if any, these factors have actually influenced patient selection, have, however, not been systematically examined within the framework of this thesis.

Thirdly, the data on which this thesis relies has been collected from evaluations performed over an equally long period of time, by several examiners, not least for paper III. The consistence of these examinations over time, and their intra-rater reliability, has not been systematically evaluated in relation to the management of the database. However, clinical tests of sensibility to touch and pinprick, and of corneal sensibility, are familiar to anyone with experience with clinical neurological examinations. For the PBC database, the responses to these tests were encoded into four easily comprehensible categories, which, although out of control for the research in this thesis, should leave relatively little room for subjectivity.

Fourthly, sensimetric testing with the ISSAL 1412 according to the database protocol has not been validated against clinical tests or loss of nerve fibers. Similar, but more cumbersome, technology has, however, showed that there is a good correlation between pain thresholds in electrical stimulation and clinical

findings, and that transcutaneous electrical stimulation is a valuable technique for collecting quantitative data.¹³⁰ The data from the PBC database gives the impression that single sensimetric thresholds are, because of the large individual variation illustrated by wide standard deviations, of little value on their own. However, previous research has shown good intraindividual reproducibility, making individual evaluations over time possible.¹³⁰ Further, on a group level over time, the current data shows a trend that is very consistent with that of the clinical tests. The sensimetric tests should primarily be considered a complement to the clinical tests, and a potential advantage of this is the truly quantitative nature of the data from the sensimetric tests.

Suggestions for Future Research

As time goes by, more and more patients will have been treated with PBC. This will, as long as there are no major changes in surgical technique, allow for retrospective studies on larger and larger series, which in turn will make it possible to analyze parameters with more categories and to make more elaborate multivariate analyses, without losing statistical power, than today. However, high quality retrospective studies require structured, meticulous and continuous work in the clinical departments, with regards to documentation of pre-, intra- and postoperative anamnesis and clinical status, as with the structured testing and telephone interviews that this thesis is based upon. If performed correctly, this will also, in most cases, be directly beneficial to the individual patient, and should therefore be uncontroversial to implement.

A consideration for the future should be the implementation of more structured pain scales, possibly even in clinical routine, to continuously evaluate trigeminal pain, and also to have a structured timeline for the follow-up. The Barrow Neurological Institute (BNI) pain scale was developed to evaluate results after radiosurgery for TN, but has since been widely adopted in different forms to evaluate also other surgical techniques for TN.^{5,186} This scale standardizes to some extent the otherwise wide variation of possible outcome measures. The outcome measure “pain free without medication” corresponds perfectly to BNI score I. Some authors have opted to present successful results after PBC as BNI score I-II.^{163,172,225} While this allows for a fair description of the actual merits of the surgical procedures, it also again makes comparisons between studies difficult, unless a separate analysis for BNI score I is also included, which is therefore advisable. An advantage to the BNI pain scale is that it can be used for both retrospective and (more easily) prospective studies. For prospective studies, it may be complemented with multidimensional pain scales, such as the Penn Facial Pain Scale or the Brief Pain Inventory, to get a deeper understanding of how patients experience pain, how it affects their lives, and

how these aspects in turn are affected by surgery.^{5,138,211} As the decades go by, more and more patients will have longer series of repeated treatments, and they will eventually pass away due to causes unrelated to their TN or their PBCs. While this is in no way desirable, it does offer an opportunity to study the longitudinal effects of repeated treatments in a way that is currently not possible with the partly censored data used in this thesis. In centers that have treated patients with PBC since the 1980s, this may already be a possibility.

The real opportunity to advance future science in surgical treatment of TN, however, lies prospectively, in RCTs, especially on percutaneous techniques, but possibly also on other techniques. The three commonly used percutaneous techniques (PBC, PRGR and RFT) are often used for the same group of patients, and are all minimally invasive with obvious similarities in approach, being ablative and using a cannula for accessing the trigeminal ganglion or the trigeminal root through the Härtel trajectory. Their mechanisms of ablation are however very different from each other.^{36,102,167,188,202} Previous studies, including paper III, have provided evidence of differences in therapeutic effect and side effects between the percutaneous techniques (although these differences vary between studies, especially with regards to side effects).^{124,149,154,161,172,188,205,206} Despite this, these three percutaneous techniques have existed in parallel with each other since the early 1980s, without scientific consensus on one being clearly better than the others. Therefore, one or more well designed RCTs are needed to advance the scientific evidence on this matter from the current weak and middle level study designs, and to eventually form the basis for systematic reviews and meta-analyses.¹⁶⁸

RCTs in surgery are no trivial task, and they require an effort to in fact be an improvement on lower-level designs.^{156,175} They can never be blinded to the surgeon and only rarely to the patient. While the percutaneous procedures all leave only a small wound on the cheek, they require different levels and methods of intraoperative sedation and/or cooperation, which make blinding impossible. Learning curves for different techniques is another matter that can complicate analyses, but there are today neurosurgical centers with long experiences regarding more than one percutaneous technique, where this challenge could be overcome. Possibly the most obvious challenge is, however, time. The frequency of percutaneous procedures at a single center is a product of the prevalence of correctly diagnosed TN (a quite rare disease), the proportion of those with TN who need surgery, the proportion of those patients who are actually referred for surgery, the proportion of those referred for whom a percutaneous procedure is the preferred option, and finally the proportion of those remaining who actually can and are willing to undergo surgery. These proportions are not well studied, and may indeed differ between different cultures, regions and healthcare systems, but they present an opportunity for

future research. We do however know that out of a lifetime prevalence of 0.4-0.7 % (and it is not clear how transferrable this is to the 0,9 million people serviced by the Umeå University hospital), paper I includes 100 procedures over a time of approximately 7 1/2 years, or only 13 procedures/year. Add to that several decades of science being undecided on which percutaneous treatment that has the highest efficacy and the lowest frequency of side effects and complications, meaning the number of participants in each treatment arm would probably have to be significant to reach an adequate statistical power threshold. Further subdividing patients with multivariate analysis will also have a direct multiplicative impact on time required to maintain statistical power. For a good RCT at a single center, this would probably mean the study time would amount to decades, and at the end of such a trial, the currently available techniques may have been superseded by an as of yet undeveloped technique. The prospect of RCTs on percutaneous techniques therefore lies in multicenter trials, which would have the added positive effect of conforming the patient selections, procedures and reporting, something that could hopefully also spill over onto the rest of the future literature on results after surgery for TN.

Future analyses of data pooled from multiple RCTs or other high quality studies, need to take into consideration that the continuously accumulated recurrences after surgery, as analyzed by survival analysis, is now the de facto standard in modern reporting on results after surgery for TN.²²⁹ Therefore, the standard models used in meta-analysis cannot be utilized, but fortunately specific models for meta-analysis of survival data have been developed.²¹⁰ However, these put requirements on presented data in the included studies that very few studies on surgery for TN currently live up to e.g., patients at risk at different time points, but as long as these requirements are acknowledged, they should not pose a problem for future research.

Conclusions

PBC is rightly one of the standard surgical procedures for the treatment of both TN-1 and MS-TN. Its efficacy, while varying on an individual basis, lasts for years for most patients, especially when treating TN-1. In the case of postoperative recurrence of pain, the procedure can be repeated.

A properly placed and inflated balloon, intraoperatively seen as a pear-shaped balloon, is crucial to achieve a long-lasting pain relief, but is also associated with postoperative hypoesthesia in a significant number of patients. As the surgeon can compress with a properly placed balloon in most patients, postoperative hypoesthesia can be expected. This is however partly or fully normalized in many patients within 6 months. Corneal sensibility is generally not affected.

Apart from hypoesthesia, other side effects and complications are less common, but include transient cardiac arrest, meningitis, dysesthesia, masticatory weakness, diplopia, herpetic eruptions, muffled hearing, cheek hematoma, buccal perforation and balloon rupture. Preventive measures can be taken against some of these, while others are a calculated risk but often self-limiting.

The side effects profile of PBC is advantageous when compared to that of PRGR, as PRGR carries a significantly higher risk of dysesthesia and of corneal hypoesthesia. The pain-relieving efficacy of these two techniques is however comparable.

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